



23rd International Symposium on Regulatory Peptides

RegPep23

Proceedings

August 2021

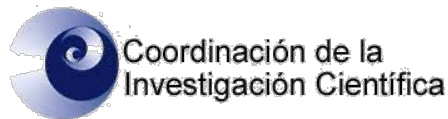
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Final posting of RegPep23 Proceedings of August 9-11, 2021 (Virtual Segment) and August 15-19, 2021 (Hybrid Segment)

RegPep23

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Welcome note from the IRPS Co-Presidents

Dear colleagues and friends,

Welcome to RegPep23, the 23rd International Symposium on Regulatory Peptides, with the specific theme of regulatory peptides in brain-body interactions, under the auspices of the International Regulatory Peptide Society (IRPS).

RegPep biennial meetings have been unique venues for basic and clinician scientists studying the physiology and pathophysiology of peptide actions, integrated from a brain-body-behavior perspective in health and disease. At RegPep, researchers, scholars, students, and medical professionals can learn about and discuss cutting-edge findings across all aspects of peptide function, in translationally relevant areas of research, and advocate for strengthening scientific research traditions, international cooperation for education and training, and cross-cultural understanding.

This conference was convened as soon as possible after its postponement from September 19th, 2020, due to COVID-19. It is organized as both a real-time/virtual segment, and as a hybrid/face-to-face segment, because our Society recognizes the urgency of science, and the vital need of scientists to communicate with each other spontaneously and openly by whatever means possible, with the most humane and effective being the sharing of a physical space over a sufficient period to generate the trust and openness required for real scientific exchange.

As recently as a few weeks ago, we feared that the second, so-called delta wave of COVID-19 might forbid convening this meeting, as one where participants on the ground would spark the scientific spirit required to sustain those who could not be physically present. But here we will be, in Acapulco Diamante, to celebrate the importance of the mission of the IRPS to share basic, translational, and clinical advances in regulatory peptides, and at this moment, to accomplish it.

Lee E. Eiden and Limei Zhang, the IRPS Co-Presidents

August 8th, 2021

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Mario A. Zetter

Elba Campos-Lira

Omar Rangel Rivera

Andrés Molina Torres Arpi

Lee E. Eiden

Advisory Committee

Ruud. M. Buijs (Chair, RegPep2020)

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Luis de Lecea (Stanford Uni., USA)

Valery Grinevich (Uni. Heidelberg, Germany)

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Preface

RegPep23 represents contributions from the international regulatory peptides research community from Australia, Austria, Brazil, Canada, Chile, China, Denmark, France, Germany, Hungary, Israel, Japan, Mexico, The Netherlands, New Zealand, South Africa, Sweden, the United Kingdom, and the United States.

RegPep23 is the first RegPep World Conference organized solely and directly under the auspices of the International Regulatory Peptide Society, incorporated as a non-profit scientific organization for the first time in its long history, in 2019. Continuing in the long tradition of RegPep conferences, RegPep23 features the Society's Victor Mutt Invested Lectureship, which honors the historic contributions of Dr Mutt to advancing peptide research through the discovery of gut peptides including cholecystokinin, pancreastatin, bombesin and many others. The work of Diego Bohorquez, the RegPep23 Mutt honoree, in exploring the frontier of brain-gut interaction in regulatory peptide physiology resonates particularly harmoniously with the pioneering work of Victor Mutt.

This conference is organized, uniquely, into two segments. One is entirely virtual, conducted in the Gather Town environment, running from August 9-11, and preceding the actual convening of RegPep23 in Acapulco Diamante on August 15, 2021. The second is a face-to-face/virtual hybrid meeting at which the welcoming/convening ceremony, the Mutt Lecture, the recognition of our Distinguished Members, and the General Assembly of the IRPS, and the presentation of lectures by those physically attending RegPep23, will be conducted. This extraordinary format is a product of our extraordinary times, and the realization that science, especially regulatory peptide science, must go on, and that science is always speeded by the intellectual impetus of intense and open collegial communication.

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Virtual Segment

*Scientific
Program*

August 9th - 11th, 2021 *live*
August 9th to September 4th, *online*

(Time: Mexican time = US CDT, Chicago)
Monday 9th, August 2021

08:00 - 09:00	Keynote lecture 1: Gil Levkowitz (<i>Weizmann Institute of Science, Israel</i>). Role of oxytocin in the developmental acquisition of sociality.
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Virtual Scientific Session (V-SS) 1 Chair: Lee E. Eiden	
09:00 - 09:30	V-SS 1.1: Corinne Bousquet (<i>INSERM UMR-1037, Cancer Research Center of Toulouse (CRCT), France</i>). Somatostatin and its analog signaling to stromal cells in pancreatic cancer.
9:30 - 10:00	V-SS 1.2: Helene Castel (<i>Normandie Univ, UNIROUEN, INSERM, DC2N, France</i>). Pleiotropic functions and biased signaling of the urotensin II receptor: actionable mechanisms in glioblastoma.
10:00 - 10:30	V-SS 1.3: Wenqin Xu (<i>National Institute of Mental Health, USA</i>). The neuroendocrine cell-selective guanine nucleotide exchanger NCS-RapGEF2 as a cyclic AMP sensor in an ERK-dependent GLP1R signaling pathway.
10:30 - 11:00	V-SS 1.4: William J Giardino (<i>Stanford University School of Medicine, USA</i>). Extended amygdala neuropeptide circuits driving anxiety and addiction.

11:00 - 16:00

Poster viewing and networking

16:30 - 17:30	Keynote lecture 2: Luis de Lecea (<i>Stanford University, USA</i>). Neuropeptides in control of sleep stability.
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Virtual Scientific Session 2 (V-SS2) Co-Chairs: Ernie Blevins & Pawel Olsewski	
17:30 - 18:00	V-SS 2.1: James E Blevins (<i>University of Washington School of Medicine/VA Puget Sound Health Care System, USA</i>). Oxytocin as a therapeutic strategy to treat obesity in diet-induced obese rodents and nonhuman primates.
18:00 - 18:30	V-SS 2.2: Luis Paiva (<i>Universidad Austral de Chile, Valdivia, Chile</i>). Insulin signalling on oxytocin neurones.
18:30 - 19:00	V-SS 2.3: Emily Noble (<i>University of Georgia, Athens, USA</i>). Central oxytocin and eating behavior.
19:00 - 19:30	V-SS 2.4: Pawel K Olszewski (<i>University of Waikato, NZ.</i>). Oxytocin as a potential pharmacological tool to curb overeating.
19:30 - 20:00	V-SS 2.5: Yoichi Ueta (<i>University of Occupational and Environmental Health, Japan</i>). Transgenic approaches to reveal the physiological role of the central vasopressin system.

Tuesday 10th, August 2021

08:00 - 09:00 **Keynote lecture 3: Chun-Xia Yi (*University of Amsterdam, The Netherlands*). Hypothalamic neuron-glia interaction in metabolic disorders.**

09:00 - 11:00	Scientific session 3 (V-SS3) Chair: Limei Zhang
09:00 - 09:30	V-SS 3.1: Jing Lu (<i>Zhejiang University School of Medicine, China</i>). Changes of hypocretin (orexin) system in schizophrenia: from plasma to brain.
9:30 - 10:00	V-SS 3.2: Erik Hrabovszky (<i>Institute of Experimental Medicine, Hungary</i>). The kisspeptin system in reproduction and emotions.
10:00 - 10:30	V-SS 3.3: Matthew J. Paul (<i>University at Buffalo, USA</i>). Vasopressin and social development.
10:30 - 11:00	V-SS 3.4: Alexa Veenema (<i>Michigan State University, USA</i>). Implications of sex differences in the juvenile and adult vasopressin system for the regulation of social behavior.

11:00 - 16:00

Poster viewing and networking

16:30 - 17:30 **Keynote lecture 4: Victor M. Navarro (*Harvard Medical School / Brigham and Women's Hospital, USA*). Upstream neuropeptides in HPG axis pulse generation.**

17:30 - 20:00	Scientific session 4 (V-SS4) Chair: Vito Hernández
17:30 - 18:00	V-SS 4.1: Peng Li (<i>University of Michigan, USA</i>). The peptidergic control circuit for sighing.
18:00 - 18:30	V-SS 4.2: Sunny Z Jiang (<i>NIMH, NIH-IRP, USA</i>). Endocrine and behavioral effects of conditional ablation of PACAP projections in mouse brain.
18:30 - 19:00	V-SS 4.3: Valentina Sabino (<i>Boston University School of Medicine, USA</i>). Neuropeptides and anxiety: actions of CRF and PACAP in central amygdala.
19:00 - 19:30	V-SS 4.4: Sung Han (<i>Salk Institute for Biological Studies, USA</i>). Divergent brainstem opioidergic pathways that mediate pain-breathing interaction.
19:30 - 20:00	V-SS 4.5: Rosemary S E Brown (<i>University of Otago, New Zealand</i>). Prolactin as a modulator of maternal aggression.

Wednesday 11th, August 2021

08:30 - 11:00	Scientific session 5 (V-SS5) Chair: Lee E. Eiden
08:30 - 9:00	SS 5.1: Geert Van den Bogaart (<i>University of Groningen, Netherlands</i>). Chromogranin A and its cleavage product catestatin A control gut immune homeostasis and microbial composition.
09:00 - 09:30	SS 5.2: Peter J Duncan (<i>University of Edinburgh, Edinburgh, UK</i>). Corticotroph plasticity in stress: at the brain-endocrine interface.
9:30 - 10:00	SS 5.3: Wei Ying (<i>University of California, San Diego, USA</i>). CR1g+ macrophages prevent gut microbial DNA-containing extracellular vesicle-induced tissue inflammation and insulin resistance.
10:00 - 10:30	SS 5.4: Mario Perello (<i>Instituto Multidisciplinario de Biología Celular (IMBICE), CONICET/CIC-PBA/UNLP, Argentina</i>). Ghrelin and LEAP2: The yin and yang controlling the growth hormone secretagogue receptor activity.
10:30 - 11:00	SS 5.5: Teresa Morales (<i>Universidad Nacional Autónoma de México, México</i>). Protective effects of prolactin in neurotoxin-induced hippocampal injury.

11:00 - 16:00

Poster viewing and networking

13:30 -14:20 **Keynote lecture 5: Joanna Dabrowska (*Rosalind Franklin University of Medicine and Science, USA*). Oxytocin, fear memory, and the bed nucleus of the stria terminalis (BNST).**

	Scientific session 6 (V-SS6) Chair: André Mecawi
14:30 - 15:00	V-SS 6.1: Paul J. Marvar (<i>George Washington University, USA</i>). Brain angiotensin II as a mediator of emotional memory.
15:00 - 15:30	V-SS 6.2: Ki. A Goosens (<i>Icahn School of Medicine, USA</i>). A role for ghrelin in stress-induced vulnerability to affective psychiatric disorders.
15:30 - 16:00	V-SS 6.3: Melissa Chee (<i>Carleton University, Canada</i>). Melanin-concentrating hormone receptor 1-mediated control of hyperactivity.
16:00 - 16:30	V-SS 6.4: Alastair V Ferguson (<i>Queen's University, Canada</i>). Circumventricular organs as sensors and integrators of regulatory peptides controlling ingestive behaviors.
16:30 - 17:00	V-SS 6.5: Andrew L Gundlach (<i>The University of Melbourne, Australia</i>). Central relaxin-3/RXFP3 systems and peptidergic modulation of integrated autonomic, neuroendocrine and higher circuits.

Posters

Poster 01	Dana Bakalar (<i>National Institute of Mental Health, USA</i>). Relationship between constitutive and acute gene regulation, and physiological and behavioral responses, mediated by the neuropeptide PACAP.
Poster 02	Emily Brown (<i>University of Otago, New Zealand</i>). Mechanotransduction of heteromeric ΔN-TRPV1 and TRPV4: implications for vasopressin neuron activity.
Poster 03	Tays A Camilo (<i>Universidade Federal de São Paulo, Brazil</i>). Molecular profile of brain serotonin, galanin and dynorphin systems in rats with and without limbic recruitment induced by audiogenic kindling.
Poster 04	Sam Dahlke (<i>National Institute of Mental Health, USA</i>). Beyond PKA: cAMP-dependent GLP-1 Signaling to ERK Requires NCS-RapGEF2.
Poster 05	Vito Hernández (<i>National Autonomous University of Mexico, Mexico</i>). ACE2 expression in rat brain: implications for COVID-19 associated neurological manifestations.
Poster 06	Gabriela Hurtado-Alvarado (<i>Universidad Nacional Autónoma de México, México</i>). Acute sleep restriction induces hyperglycemia and changes SCN activity.
Poster 07	Alex R Johnston (<i>The University of Edinburgh, UK</i>). Short-term fasting is associated with food seeking behavior and increased hypothalamic neuropeptide Y mRNA expression in Japanese quail chicks.
Poster 08	Adrian Limón-Mendoza, (<i>Universidad Autónoma de Aguascalientes, México</i>). Role of N-methyl-D-aspartate receptor (NMDA-R) in the pathophysiology of schizophrenia.
Poster 09	Michael R Perkinson (<i>University of Otago, New Zealand</i>). Visualising the changes in oxytocin neuron population activity in virgin and lactating freely-behaving mice.
Poster 10	Angus Reid (<i>The University of Edinburgh, UK</i>). Evolution of DPP4 susceptibility in vertebrate peptide YY.
Poster 11	Mitchell T Ringuet (<i>University of Melbourne, Australia</i>). Functional GPCR interactions in parasympathetic preganglionic neurons (PGNs) in rat spinal cord.
Poster 12	Verónica Trujillo (<i>Universidade Federal de São Paulo, Brazil</i>). Vasopressin secretion is modulated by estrogen levels in female rats.
Poster 13	Verónica Trujillo (<i>Universidade Federal de São Paulo, Brazil</i>). Oxytocin receptor signaling at the central amygdala does not mediate dehydration-induced exploration reduction in rats.
Poster 14	Mario A. Zetter (<i>National Autonomous University of Mexico, Mexico</i>). Microglial pruning on axon initial segment spines at dentate gyrus granule cells: effects of early life stress and vasopressin in adult fear responsiveness.
Poster 15	Limei Zhang (<i>National Autonomous University of Mexico, Mexico</i>). Hindbrain parabrachial complex PACAP containing projection forms Calyx-like synapses at GABAergic neurons of CeC project to ventral pallidum and LPO modulating defensive locomotion.
Poster 16	Wen Zhong (<i>KTH-Royal Institute of Technology, Sweden</i>). The neuropeptide landscape of human prefrontal cortex.

Virtual segment
Abstracts



Keynote lecture (V-K 1) **Role of oxytocin in the developmental acquisition of sociality**

Nunes, Ana Rita 1, 2; Gliksberg, Michael 2; Varela, Susana A.M. 1, 3; Teles, Magda 1; Wircer, Einav 2; Blechman, Janna 2; Petri, Giovanni 4; Oliveira, Rui F. 1, 3; **Levkowitz, Gil 2**

1 Instituto Gulbenkian de Ciência, Portugal; 2 Weizmann Institute of Science, Israel; 3 ISPA- Instituto Universitário, Portugal; 4 ISI Foundation & ISI Global Science Foundation, Italy

Social behavior is an age-dependent phenomenon with young animals showing it to a very limited extent, and developing it throughout their lives until reaching maturity. The neuropeptide oxytocin modulates social behaviors across vertebrate species, and is associated with neurodevelopmental social deficits such as autism. However, whether oxytocin plays a role in the developmental maturation of neural systems that are necessary for social behavior remains poorly explored. We show that proper behavioral and neural response to social stimuli in zebrafish depends on a developmental process orchestrated by oxytocin neurons. Zebrafish whose oxytocin system is ablated during early development show blunted neuronal and behavioral responses to social stimuli as well as wide-ranging disruptions in the functional connectivity of the social brain. We propose that oxytocin neurons have an organizational role, namely to shape forebrain neuroarchitecture during development and to acquire an affiliative response towards conspecifics.

Reference:

Nunes, A. R., , et al. (2020). Developmental effects of oxytocin neurons on social affiliation and processing of social information. *bioRxiv*, 2020.10.08.330993. doi: <https://doi.org/10.1101/2020.10.08.330993>



V-SS 1.1 Somatostatin and its analog signaling to stromal cells in pancreatic cancer

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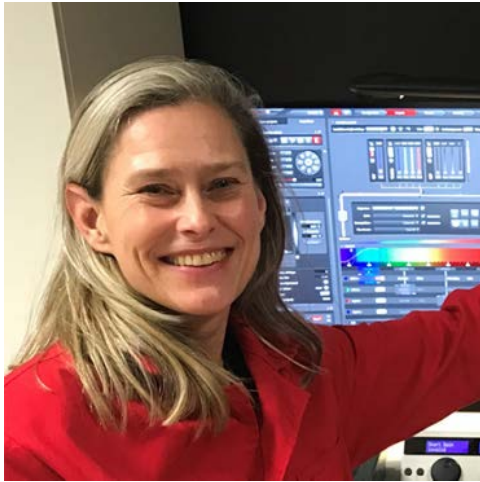
Pancreatic ductal adenocarcinoma (PDA) remains a lethal malignancy. Therapeutic strategies aimed at targeting pancreatic cancer cells have failed. We hypothesized that pitfalls are due to the functional heterogeneity of this tumor, which comprises both cancer and stromal cells.

Cancer-Associated Fibroblasts (CAFs) are the most abundant cells present in PDA stroma. We showed that human activated (α SMA-expressing) pancreatic CAFs (primary cultures isolated from human tumor resections) express the somatostatin receptor subtype sst1, but not the other receptor subtypes (sst2-sst5), in contrast to non-activated (α SMA-negative) pancreatic fibroblasts (PaSC, pancreatic stellate cells isolated from normal pancreas).

Somatostatin receptors are highly expressed in neuroendocrine tumor cells where they are therapeutic targets due to their antisecretory and antitumoral role. However, these receptors are not expressed in pancreatic cancer cells (PDA). Data regarding the expression of somatostatin receptors in the tumor stroma are scant at best.

We observed hyperactivation of the PI3K-mTORC1 pathway in CAFs as compared to PaSC, which was blunted by the somatostatin analog SOM230 (pasireotide) through activation of sst1, but not by octreotide. The observed elevated protein synthesis rates in CAFs were also dramatically decreased by SOM230 treatment, resulting in protein secretion inhibition. Chemoprotection provided by the CAF secretome on cancer cells was blunted by SOM230 treatment. Athymic or immunocompetent mice orthotopically co-xenografted with pancreatic cancer cells and CAFs of human or mouse origin, respectively, developed tumors, the growth of which was dramatically reduced upon mouse treatment with the combination SOM230+gemcitabine (chemotherapy of reference for PDA), but not by each single drug. Interestingly also, we showed that most untreated or gemcitabine-treated mice developed metastases (lungs and liver), but none of the SOM230-treated or SOM230+gemcitabine-treated mice did. We identified using proteomic analyses on SOM230-treated CAF conditioned media and mouse plasma, the molecular mechanism underlying SOM230 therapeutic benefit, which involves the disruption of a pro-metastatic crosstalk between CAF and myeloid cells through colony-stimulating factor 1 (CSF1).

Our results highlight a novel promising anti-tumor activity for SOM230 indirectly targeting pancreatic cancer cell chemoresistance, invasion and metastasis through pharmacological inhibition of stromal CAFs.



V-SS 1.2 Pleiotropic functions and biased signaling of the urotensin II receptor: actionable mechanisms in glioblastoma

Castel, Helene 1,2

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During the past decade, complex cellular pleiotropic G protein coupled receptor (GPCR) signaling has been unveiled through selectivity/biased agonism effects. Various studies have attempted to link such complex signaling regulation to cellular and physiological behaviors but gaps remain in the understanding of

GPCR activation by biased ligands in pathological situations. The urotensinergic system is currently suspected of being linked to numerous pathological states including atherosclerosis, heart failure, hypertension, pre-eclampsia, diabetes, renal disease, vascular inflammation and cancer. The vasoactive peptide urotensin II (UII) and its paralog urotensin-related peptide (URP) are both endogenous ligands of the GPCR urotensin (UT) receptor, and display nonsystematic identical functional implications. We previously demonstrated common and distinct mechanisms of UII and URP in reactive astrocytes, and specific UII-relaying pleiotropic roles in glioma cells migration and angiogenesis, not mimicked by URP. This strongly suggested a non-ubiquitous promising therapeutic target specifically constituted by the UII-UT system and its associated signaling pathways.

To elucidate the potential differential capacity of UII and URP and the antagonist/biased role of some synthetic UII-analogs at regulating the pleiotropic UT coupling, a collaboration with Dr L. Prézeau (IGF, Montpellier) and Pr R. Leduc (University of Sherbrooke, Quebec, Canada) was initiated to investigate, on HEK293 cells expressing UT, six different signaling pathways (Gq, Gi1, Goa, G13, β -arrestins 1 and 2, and Gs), downstream events such as ERK1/2, NF κ B phosphorylation and receptor internalization, and cell behaviors. Interestingly, we did not observe any coupling differences for UII and URP, leaving open the question about the differential effects of these peptides in native cells. However, synthetic peptide ligands such as urantide induced different UT receptor-dependent pathway profiles, not only behaving as full or partial agonists but also displaying biased signaling of specific pathways.

Then, the biased ligand “urantide” was evaluated on glioma cell migration and angiogenesis accompanying gliomagenesis. In culture, urantide blocked the UII-induced tubulogenesis of two human endothelial lineages. In vivo, while UII accelerated the development and angiogenesis of xenografted GBM cells in nude mice, urantide showed greater efficacy than a ‘classical antagonist’ at inhibiting tumor growth and angiogenesis, leading to prolonged animal survival. We will also demonstrate here how we can use a local delivery system based on a biocompatible hydrogel within the brain containing the chemopeptide urotensin II (UII) or the biased synthetic analog urantide with the aim of “trapping” GBM cells and/or controlling immune cells. These interventions led to GBM recurrence prevention and neurological rehabilitation in a mouse model of orthotopic GBM growth after resection.

Together, the useful role of a pharmacological UT biased ligand on GBM growth and angiogenesis in vivo is clearly established in a preclinical animal model. However, how this peptide analog regulates UT signaling cascades in the different neural and immune cells in this pathological context remains unknown. Nevertheless, we strongly believe that these receptor biased ligands can constitute true therapeutic options, when delivered in novel modes, to tackle such an aggressive cancer.

Supported by Ligue contre le cancer Normandie, Géfluc, Région Normandie, Fondation ARC, Université de Rouen Normandie and Inserm.



V-SS 1.3 The neuroendocrine cell-selective guanine nucleotide exchanger NCS-RapGEF2 as a cyclic AMP sensor in an ERK-dependent GLP1R signaling pathway

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The secretin family (class B) of G-protein coupled receptors (GPCRs) contain receptors for fifteen peptide hormones which share 21-67% sequence identity. Previous studies in neuroendocrine NS1 cells have demonstrated that ligands that activate Gs-coupled GPCRs signal to three separate cAMP sensor-effectors: protein kinase A (PKA), Epac, and the neurotogenic cAMP sensor NCS-RapGEF2. Activation of the Gs-coupled PACAP (Adcyap1) receptor PAC1 (Adcyap1r1) by PACAP leads to cAMP-dependent neurite formation via an NCS-RapGEF2-->Rap-->Braf-->MEK-->ERK pathway. We sought to learn whether this pathway is a common activation mechanism shared by other class B GPCRs such as glucagon-like peptide 1 receptor GLP1R, which is an important drug target for treatment of diabetes. Using NS1 cells as a model we first analyzed the correlation of family B GPCR expression with cognate agonist-induced neuritogenesis and cAMP elevation. In accordance with the robust cAMP production and neurite formation after stimulation with PACAP, microarray analysis revealed its receptor PAC1R was expressed at much higher than VIPR1, VIPR2 and GLP1R, for which the respective agonist VIP (for VIPR1 and 2) and Exendin-4 (for GLP1R) did not induce a significant increase of cAMP and neuritogenesis, in NS1 cells. Furthermore, exogenous expression of VIPR1, VIPR2 and GLP1R in NS1 cells induced a neurotogenic response upon exposure to VIP (for VIPR1 and VIPR2) and Exendin-4 (for GLP1R). GLP1R is expressed in the rodent insulinoma cell lines MIN6 and INS-1, and in human pancreatic islets. Using INS-1 insulinoma cells as a model, we demonstrated that ERK phosphorylation after exposure to exendin-4 is attenuated by shRNA-mediated NCS-RapGEF2 knockdown. Transcriptomic analysis of INS-1 cells treated with exendin-4 revealed cohorts of both ERK-dependent (sensitive to inhibition by the MEK inhibitor U01126) and ERK-independent immediate early genes (IEGs). The latter are presumably regulated via the cyclic AMP sensors PKA or Epac, previously demonstrated to be present, and also activated by exendin-4, in INS-1 cells. These results suggest that multiple cAMP sensors participate in signaling to the transcriptome, through the Gs-coupled GPCR GLP1R, in pancreatic beta cells, and that RapGEF2 is a novel signaling pathway for incretin action, albeit its role in overall physiological regulation of beta cell function including insulin secretion remains to be determined.



V-SS 1.4 Extended amygdala neuropeptide circuits driving anxiety and addiction

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Negative emotional states linked to addiction arise from neuroplasticity within neuronal networks of the hypothalamus and amygdala. These circuits encompass an enormous diversity of cell types that display specialized connectivity patterns and innumerable forms of signaling. Specifically, lateral hypothalamus (LH) neurons containing the neuropeptide Hypocretin (Hcrt; orexin) profoundly influence arousal (wakefulness) and motivated behavior. I previously identified connectivity between Hcrt-LH neurons and “extended amygdala” neurons of the bed nuclei of stria terminalis (BNST) containing the prototypical stress peptide corticotropin-releasing factor (Crf). I then characterized Hcrt-LH and Crf-BNST neurons as tightly coupled nodes in a stress-promoting circuit, suggesting their involvement in addiction.

Here, we investigated Hcrt-LH neurocircuits in free-choice binge alcohol drinking by performing genetically defined physiological monitoring, optical manipulations, and molecular perturbations in neurons of freely behaving mice. First, we identified Hcrt-LH activation during alcohol withdrawal-enhanced anxiety behavior and used *in vivo* Ca²⁺ recordings to reveal withdrawal-dependent sensitivity of Hcrt-LH neurons to aversive stimuli. We next revealed the necessity of Hcrt for behavioral avoidance driven by Crf-BNST stimulation and focused on BNST-projecting Hcrt-LH neurons with the hypothesis that BNST Hcrt receptors drive excessive alcohol drinking. We developed a CRISPR/Cas9 gene editing system, finding that disruption of Hcrt Receptor1 (*hcrt1*) in Crf-BNST neurons reduced alcohol intake, anxiety, and avoidance of stressful stimuli.

These studies advanced prior work by identifying the mechanisms through which LH-->BNST pathways promote excessive alcohol consumption. We posit an essential role for Crf-BNST-HcrtR1 signaling in alcohol addiction via dysregulated hyperarousal. These outcomes have major implications for developing effective strategies to treat addiction through modulating neuropeptide circuit function.

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V-KL 2 Neuropeptides in control of sleep stability

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The arousal construct underlies a spectrum of behaviors that include sleep, exploration, feeding, sexual activity and adaptive stress. Pathological arousal conditions include stress, anxiety disorders, and addiction. In the past few years we have used optogenetics to interrogate neuronal circuits underlying transitions between arousal states. Here I will present causal evidence of a critical period during adolescence in which disruption of sleep/wake cycles associated with increased dopaminergic tone results in deficits in social interactions in adult mice. I will also present a new mechanism underlying sleep fragmentation during aging. Hcrt neurons are hyperexcitable in aged mice. We identify a potassium conductance known as the M-current, as a critical player in maintaining excitability of Hcrt neurons. Genetic disruption of KCNQ channels in Hcrt neurons of young animals results in sleep fragmentation. In contrast, treatment of aged animals with a KCNQ channel opener restores sleep/wake architecture. These data point to multiple circuits modulating sleep integrity across the lifespan.



V-SS 2.1 Oxytocin as a therapeutic strategy to treat obesity in diet-induced obese rodents and nonhuman primates

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Previous studies indicate that CNS administration of oxytocin (OT) reduces body weight (BW) in high fat diet-induced obese (DIO) rodents by reducing food intake (FI) and increasing energy expenditure (EE). We recently demonstrated that hindbrain [fourth ventricular (4V)] administration of OT elicits weight loss and elevates interscapular brown adipose tissue temperature (TIBAT; surrogate marker of increased EE) in DIO rats (1) and mice (2). What remains unclear is whether OT-elicited weight loss requires increased sympathetic nervous system (SNS) outflow to IBAT. We hypothesized that OT-induced stimulation of SNS outflow to IBAT contributes to its ability to elicit weight loss in DIO rats. To test this, we determined the effect of disrupting SNS activation of IBAT on the ability of 4V OT to elicit weight loss in DIO rats. We initially determined whether bilateral surgical SNS denervation to IBAT was successful as defined by a 60% reduction in IBAT norepinephrine (NE) content in DIO rats. NE content was selectively reduced in IBAT at weeks 1, 6 and 7 post-denervation by 95, 97 and 86% ($P < 0.05$), respectively, and was unchanged in inguinal white adipose tissue or liver. We subsequently measured the effects of chronic 4V OT (16 nmol/day) or vehicle infusions on BW, adiposity and FI in DIO rats following bilateral surgical (or sham) SNS denervation to IBAT. Chronic 4V OT reduced weight gain and fat mass in both sham and denervated rats ($P < 0.05$) with no difference in response between groups ($P = NS$). These effects were attributed, in part, to reduced FI ($P < 0.05$). Together, these data are consistent with the hypothesis that hindbrain OT treatment evokes sustained weight loss through a mechanism that does not require SNS innervation to IBAT in DIO rats. To determine if OT elicits weight loss in a more translational pre-clinical model, we tested the effects of OT on BW, FI and EE in DIO rhesus monkeys (17.6±1.1 kg; 38±2% fat) fed fructose-sweetened beverages (75 g/300 kcal/day) (3). DIO monkeys initially received 2x daily subcutaneous vehicle treatment over 1 week. Chronic 2x daily subcutaneous OT administration for 4 weeks [0.2 mg/kg (2 weeks); 0.4 mg/kg (2 weeks)] reduced BW by 3.3±0.4% (≈0.6 kg; $P < 0.05$). Moreover, OT (0.2 mg/kg) suppressed 12-h chow intake by 26±7% ($P < 0.05$). The higher dose of OT (0.4 mg/kg) suppressed 8- and 12-h chow intake by 13±9% and 27±5% ($P < 0.05$), respectively, and suppressed 8-h beverage intake by 18±8% ($P < 0.05$). OT also increased EE (as determined using indirect calorimetry) during the dark cycle by 14±3% ($P < 0.05$). Together, these data suggest that 1) OT reduces BW in DIO rodents and nonhuman primates by decreasing FI and increasing EE and 2) OT-elicited reductions in weight gain and adiposity do not require SNS innervation to IBAT in DIO rats.

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1. Roberts et al., *Am. J. Physiol.*, 313: R357-R371, 2017.
2. Edwards et al., *Am. J. Physiol.*, 320: R471-R487, 2021.
3. Blevins et al., *Am. J. Physiol.*, 308: R431-R438, 2015.



V-SS 2.2 Insulin signalling on oxytocin neurones

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Insulin is widely known for its role in glucose homeostasis on peripheral tissues, but its central effects are not yet fully elucidated. Once secreted into circulation, insulin is transported into the brain by a saturable transport mechanism. In the brain, several regions have been reported to be sensitive to insulin, including the prefrontal cortex, hippocampus, and hypothalamus. The insulin receptor is abundantly expressed in the supraoptic nucleus of the

hypothalamus (SON) which exclusively contains magnocellular oxytocin and vasopressin neurons. In addition to its classical roles in reproduction, oxytocin is also involved in energy homeostasis: both central and peripheral administration exerts anorexigenic effects and increases energy expenditure. Interestingly, clinical reports indicate that patients with diabetes mellitus exhibit lower plasma oxytocin, suggesting a potential relationship between insulin and the secretory activity of magnocellular neurons.

Here, we have investigated the effect of systemically administered insulin on the electrical activity of oxytocin neurons *in vivo*. To achieve this, fasted male Sprague-Dawley rats were anaesthetized with an intraperitoneal injection of urethane, then a recording microelectrode was placed into the right SON to record the extracellular activity of single neurons and a stimulating electrode was positioned in the pituitary stalk for antidromic identification of SON neurons. Oxytocin neurons were distinguished from vasopressin neurons by their firing pattern and by their opposite response to intravenous (i.v.) cholecystokinin (CCK). Our results show that i.v. administration of insulin induced a prolonged activation of oxytocin neurons, and that this response was greater in fasted than non-fasted rats. We also show that this activation of oxytocin neurons was independent of changes in blood glucose concentration but was completely blocked by the intracerebroventricular administration of the insulin receptor antagonist S961. Vasopressin cells were also activated, but these show less consistent responses. Finally, we replicated the previously published finding that oxytocin cells are activated by gavage of sweetened condensed milk, and show that this response also was completely blocked by central administration of the insulin receptor antagonist. We conclude that the response of oxytocin cells to both sweet food administration and exogenous i.v. insulin is mediated by activation of central insulin receptors.

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V-SS 2.3 Central oxytocin and eating behavior

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Central oxytocinergic signaling has a potent anorexigenic effect in both human and animal experimental models, however the mechanisms by which oxytocin reduces eating are not completely understood. We investigated forebrain mechanisms for oxytocin-mediated food intake reductions, focusing on various reward-based and motivated aspects of feeding behavior. Our data suggest that oxytocin modulates several distinct appetitive domains, including food seeking in the absence of consumption, impulsive responding for food, and effort-based appetitive decision making. Given these findings, we further examined oxytocin's effect on phasic dopamine neuron responses to sucrose-predictive Pavlovian cues using in vivo fiber photometry in ventral tegmental area (VTA) dopamine neurons. Results reveal that ICV oxytocin significantly reduces food cue-evoked dopamine neuron activity. As there is a paucity of preclinical research investigating the effectiveness of oxytocin to reduce feeding behaviors in females, we further studied whether biological sex and estrous hormones impact the effectiveness of lateral ICV oxytocin to reduce food intake. In females, oxytocin was less effective at reducing food intake, however these differences are likely due to estrogen surges during proestrus reducing overall food intake independent of oxytocin signaling. Overall, these data support a role for oxytocin as a promising candidate therapeutic for obesity pharmacotherapy.



V-SS 2.4 Oxytocin as a potential pharmacological tool to curb overeating

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The past three decades of extensive research have defined the neuropeptide oxytocin (OT) as a potent anorexigenic molecule. It has been shown that the release of OT and activation of hypothalamic OT neurons coincide with meal termination. Plasma hyperosmolality and excessive stomach distension—typically arising from avid consumption of large food loads—also result in OT secretion. Central and peripheral administration of OT decreases meal size in deprived animals as well as in free-feeding individuals when injected just prior to the onset of the nocturnal feeding phase. Reduced food consumption has been shown after OT treatment in humans. Importantly, OT appears to be particularly effective in reducing consumption of carbohydrates and sweet tastants. Yet, despite these promising basic research data, attempts to use OT in the clinical setting to combat obesity and overeating have generated somewhat mixed results. Here, we present studies that shed light on the nature of the limitations as well as on the benefits of OT as a therapeutic molecule. We focus on findings in humans and laboratory animals that delineate effectiveness of OT in decreasing a drive to eat in the hunger-satiation continuum. We also point to a relationship between the magnitude of OT's anorexigenic action and the composition of ingested diet, its energy density, and the current (patho)physiological state of an individual.



V-SS 2.5 Transgenic approaches to reveal the physiological role of the central vasopressin system

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A transgenic rat that expresses the arginine vasopressin (AVP)-eGFP fusion gene was generated to identify a living AVP neuron (Ueta et al., *Endocrinology* 2005). Then, transgenic rats that express the AVP-hM3Dq-mCherry fusion gene were generated to activate endogenous AVP neurons selectively by peripheral administration of clozapine-N-oxide (CNO) (Yoshimura et al., *Sci. Rep.* 2017). Peripheral administration of CNO selectively activated AVP neurons in the paraventricular nucleus, the supraoptic nucleus and the suprachiasmatic nucleus, as measured using immunohistochemistry for Fos protein. Plasma AVP levels were significantly increased 10-120 min after peripheral administration of CNO. Cumulative food intake, water intake and urine volume during a 12h/12h light/dark cycle were decreased significantly after peripheral administration of CNO. Furthermore, locomotor activity and core body temperature were disturbed three days after peripheral administration of CNO. Intracerebroventricular (icv) administration of nesfatin-1/NucB2-neutralizing antibody caused significant attenuation of CNO-induced suppression of cumulative food intake without alteration of water intake. On the other hand, i.c.v. administration of nesfatin-1/NucB2-neutralizing antibody did not affect CNO-induced disturbance of the locomotor activity and core body temperature. These results suggest that activation of endogenous AVP neurons may suppress feeding but not drinking via a central nesfatin-1 pathway. A transgenic rat line employing the AVP-DREADD system is a powerful tool to reveal the physiological role of endogenous AVP mediating various behavioral changes.



V-K 3 Hypothalamic neuron-glia interaction in metabolic disorders

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Brain microglia are long-surviving and self-renewing innate immune cells that are crucial for scavenging cell debris and pathogens to maintain brain tissue homeostasis. The hypothalamus contains highly heterogeneous and condensed populations of peptidergic neurons in different regions. The mediobasal hypothalamus (MBH) functions as an important “brain window” for sensing blood-borne substances. It is reasonable that this region constantly produces cell debris and metabolic waste during different metabolic states. In order to keep a healthy and clean microenvironment for the hypothalamic neurons to function, the microglial activity in the MBH needs to match the high demands for immune surveillances and phagocytizing/clearances of debris. This was demonstrated by the fact that microglia in the MBH showed a significantly higher reactivity than in other hypothalamic regions when experimental animals were exposed to a high-fat high-sugar (HFHS) diet, and that this occurs rapidly after receiving a HFHS diet. One of the metabolic wastes produced by the MBH neurons is advanced glycation end-products (AGEs), with their receptors highly expressed by microglia. AGEs are potent inflammatory stimuli to activate microglia. In the reactive microglia, TNF is one of the major cytokines produced. TNF acts on the neighboring pro-opiomelanocortin (POMC) peptidergic neurons and induces mitochondrial stress, which might eventually result in POMC neural dysfunction. This POMC neural loss is not only observed in the diet-induced obese animals, but also in postmortem hypothalamic tissue of type 2 diabetic patients. The reactive microglia in the MBH upon HFHS diet is not only characterized by increased cytokine production, but also impaired phagocytic capacity. In microglia, besides governing lipid uptake for fueling, the lipoprotein lipase (LPL)-gated phospholipid production is also crucial for phagolysosome formation and function. HFHS diet might impair microglial phagocytosis in the MBH, whereas a compensatory mechanism drives more LPL expression and phospholipids production in order to maintain the phagocytic capacity. Not surprisingly, in HFHS diet-fed mice that had lack of LPL in microglia, phagocytic capacity was worsened and associated with fewer POMC neurons and more vulnerability to diet-induced metabolic disorders. Microglial activity is not only affected by microenvironmental immune factors, but also controlled by intrinsic biological clock. Interestingly, in microglia lacking core clock gene Brain and Muscle ARNT-Like 1 (Bmal1), the phagocytic capacity was significantly enhanced when mice were subjected to an HFHS diet. Enhanced microglial phagocytosis was associated with significant retention of POMC-immunoreactivity in the MBH in mice on the HFHS diet. This response ultimately protected mice from HFHS diet-induced obesity. Thus, loss of the rigorous control implemented by the intrinsic clock machinery increases the extent to which microglial phagocytosis can be triggered by neighboring neurons under metabolic stress. Overall, these data suggest that sufficient microglial phagocytosis is essential for hypothalamic neural survival upon metabolic stress. Moreover, since in obesogenic diet-activated microglia the increased pro-inflammatory cytokines oppose phagocytic capacity, targeting microglial pathway in treating obesity and type 2 diabetes needs to tackle both inflammatory and phagocytic pathways.



V-SS 3.1 Changes of hypocretin (orexin) system in schizophrenia: from plasma to brain

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Hypocretin (also called orexin) regulates various functions, such as sleep-wake rhythms, attention, cognition, and energy balance, which show significant changes in schizophrenia (SCZ). We aimed to identify alterations in the hypocretin system in SCZ patients. We measured plasma hypocretin-1 levels in SCZ patients and healthy controls and found significantly decreased plasma hypocretin-1 levels in SCZ patients, which was mainly due to a significant decrease in female SCZ patients compared with female controls. In addition, we measured postmortem hypothalamic hypocretin-1-immunoreactivity (ir), ventricular cerebrospinal fluid (CSF) hypocretin-1 levels, and hypocretin receptor (Hcrt-R) mRNA expression in the superior frontal gyrus (SFG) in SCZ patients and controls. We observed a significant decrease in the amount of hypothalamic hypocretin-1 ir in SCZ patients, which was due to decreased amounts in female but not male patients. Moreover, Hcrt-R2 mRNA in the SFG was decreased in female SCZ patients compared with female controls, while male SCZ patients showed a trend of increased Hcrt-R1 mRNA and Hcrt-R2 mRNA expression compared with male controls. We conclude that central hypocretin neurotransmission is decreased in SCZ patients, especially female patients, and this is reflected in the plasma.



V-SS 3.2 The kisspeptin system in reproduction and emotions

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Kisspeptin neurons are key elements of the hypothalamic neuronal networks that regulate the onset of puberty, account for the pulsatile secretion of gonadotropin-releasing hormone (GnRH) and mediate negative and positive estrogen feedback signals to GnRH neurons. Being directly connected anatomically and functionally to the hypophysiotropic GnRH system, the major kisspeptin cell groups of the preoptic area/rostral hypothalamus and the arcuate nucleus, respectively, are ideally positioned to serve as key

nodes which integrate various types of environmental, endocrine and metabolic signals that influence fertility.

In this talk we provide an overview of the current state of knowledge on the anatomy, functions and plasticity of brain kisspeptin systems based on literature available from different species. Then, the species-specific features of human hypothalamic kisspeptin neurons will be discussed. Topography, morphology, unique neuropeptide content, plasticity, connectivity to hypophysiotropic GnRH neurons and estrogen-regulated transcriptome of kisspeptin neurons will be covered. Some newly emerging roles of central kisspeptin signaling in behavior and clinical perspectives will be discussed.



V-SS 3.3 Vasopressin and social development

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Vasopressin has been implicated in a variety of social behaviors in many species and across all stages of development. It is often assumed that vasopressin regulates these behaviors through actions on social motivation, but this hypothesis is rarely tested. Alternative hypotheses have proposed that vasopressin influences social behavior via its actions on stress, autonomic function, and behavioral state. We have begun to address this question within a developmental framework using Brattleboro rats, which lack vasopressin due to a spontaneous mutation in the vasopressin gene and exhibit diabetes insipidus (excessive drinking and urination) due to the absence of peripheral vasopressin action on the kidney. We have found that male and female juvenile Brattleboro rats exhibit an atypical social behavior profile characterized by decreased social play and prosocial ultrasonic vocalizations, but increased huddling behavior. Initial experiments using operant conditioning and social approach testing paradigms have found only modest support for the social motivation hypothesis within this animal model. Notably, the atypical social behavior profile of juvenile Brattleboro rats is associated with a hypoaroused, low anxiety-like phenotype, which is consistent with the hypothesis that vasopressin influences social behavior through its regulation of behavioral state. This hypoaroused phenotype persists after restoration of peripheral vasopressin action by viral rescue of vasopressin production within magnocellular cells of the paraventricular nucleus of the hypothalamus. Hence, the hypoaroused phenotype is not a side-effect of diabetes insipidus and is likely due to the loss of vasopressin actions within the brain. Further testing of these hypotheses using different behavioral paradigms and more targeted vasopressin manipulations is needed. Uncovering the mechanism by which vasopressin regulates social behavior will inform the development of vasopressin as a treatment for disorders of social development such as Autism Spectrum Disorders.



V-SS 3.4 Implications of sex differences in the juvenile and adult vasopressin system for the regulation of social behavior

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Sex differences in the brain are highly prevalent, yet, we know little about their impact on behavior. For example, the sex difference in vasopressin (AVP) fiber projections from the medial amygdala (MeA) and bed nucleus of the stria terminalis (BNST) to the lateral septum (LS) is one of the best-characterized sex differences in the vertebrate brain. Yet, we know little about its functional consequences. We recently demonstrated that this sex difference is already present at juvenile age in rats, suggesting a sex-specific role of the MeA/BNST-to-LS AVP pathway across the lifespan. In support, we showed that the LS-AVP system regulates juvenile social play behavior in sex-specific ways. In detail, pharmacological blockade of AVP 1a receptors (V1aR) enhances social play in males but reduces it in females. We further demonstrated that the sex-specific regulation of social play by the LS-AVP system involves sex differences in dopaminergic neurotransmission. Moreover, we found a sex difference in vasopressin (AVP) fiber density in the ventral pallidum that was similar to the LS. These AVP fibers also originated in the MeA and BNST. Also similar to the LS, pharmacological blockade of V1aR in the ventral pallidum enhances social play in males but reduces it in females. This suggests a broader AVP neural circuitry involved in the sex-specific regulation of social play with AVP suppresses social play in males while facilitating it in females. Finally, we showed that pharmacological blockade of V1aR reduces opposite sex preference in adult male rats but enhances it in adult female rats. This suggests that AVP facilitates sociosexual motivation in males while suppressing it in females. Overall, these findings demonstrate that sex differences in the AVP system have functional implications for the sex- and age-specific regulation of social behaviors. These findings may be relevant for the sex and age-specific use of therapeutic drugs targeting the AVP system in the treatment of social dysfunction in autism spectrum disorder.



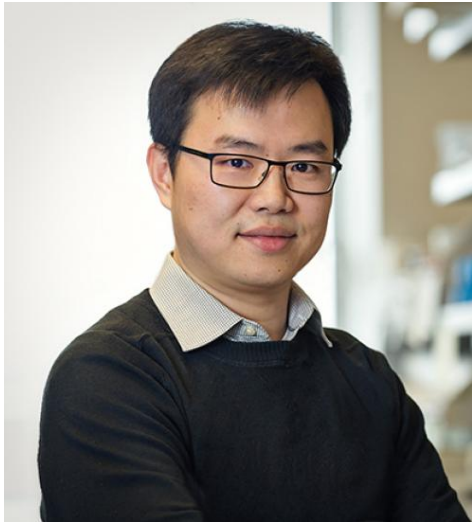
V-K 4 Upstream neuropeptides in HPG axis pulse generation

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KNDy neurons, expressing kisspeptin, neurokinin B (NKB, stimulatory) and dynorphin (Dyn, inhibitory), have been proposed to drive the pulsatile release of GnRH and vasomotor symptoms (VMS), a.k.a. hot flashes, in conditions of low circulating sex steroids, e.g. menopause. Humans bearing inactivating mutations in the genes encoding NKB and its receptor, NK3R (TAC3/Tac2 and TACR3/Tacr3, respectively in humans/mice) display hypogonadotropic hypogonadism (HH); however, this reverses spontaneously in many cases, resembling the fertile

phenotype of the equivalent knockout (KO) mouse models. Our studies in ovariectomized (OVX) Tac2KO mice showed reduced, but not absent, frequency of LH pulses compared to WT OVX. Moreover, blockade of dynorphin action in these mice induced an LH pulse within 20 min and Kiss1-specific kappa opioid receptor (KOR) KO mice still present normal LH pulses. This demonstrates that pulsatile LH release is still present in the absence of NKB and Dyn signaling. To investigate if other tachykinins: neurokinin A (NKA) and substance P (SP)—which also stimulate LH release, compensate for the absence of NKB signaling leading to fertility in humans and mice, we generated double KO mice for Tac1 (encoding NKA and SP) and Tac2 (Tac1/Tac2KO). Male and female Tac1/Tac2KO mice presented delayed puberty onset. In females, fertility was severely disrupted (80% infertile) in clear contrast with each KO model separately (all animals are fertile). However, they still presented evident low frequency LH pulses. Corpora lutea were absent in the ovaries of females, suggesting an ovulatory defect. By contrast, males retained normal fertility. While LH pulses occur in the absence of KOR signaling, we have demonstrated that the use of KOR agonists inhibit LH pulsatility and decreases body temperature, thus indicating that KNDy neurons are inhibited by KOR activation. Altogether, these results depict a highly complex mechanism of action of tachykinins and dynorphin in the regulation of GnRH pulses and thermoregulation and position KNDy neurons as a therapeutic target for the treatment of fertility disorders and VMS.



V-SS 4.1 The peptidergic control circuit for sighing

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Sighs are long, deep breaths with a bimodal inspiration that occur spontaneously every several minutes to reverse the alveolar collapse (atelectasis) and maintain normal lung function. Not only essential for life, sighing is regulated by emotional and physiological stimuli, and increases under hypoxia, stress, and certain psychiatric conditions. We recently identified the specific

expression of the bombesin family neuropeptides, neuromedin B (Nmb) and gastrin releasing peptide (Grp), and their cognate receptors, in a couple of hundred neurons in the ventral medulla of the mouse brain. These neurons and the neuropeptide pathways they express comprise the core of a dedicated sigh control circuit in the brain. Next, tracing upstream from these sigh control neurons, we identified a dozen high-order brain regions containing their direct presynaptic neurons. Among them is a subpopulation of neurons in the hypothalamus expressing another neuropeptide, hypocretin, which mediate the stress-induced sighing. More recently, we also found the neural circuit in the medulla that mediates hypoxia-induced sighing. Overall, our work demonstrates the peptidergic control circuitry for sighing, and its emotional and physiological control, and paves the way for potential pharmacologic approaches for treating breathing disorders.



V-SS 4.2 Endocrine and behavioral effects of conditional ablation of PACAP projections in mouse brain

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The neuropeptide PACAP is implicated in stress responding throughout the nervous system. PACAP in brain mediates both endocrine and behavioral responses to stress. Our previous studies indicated that PACAP deficiency in mouse has no effect on CORT elevation after 1-2 hr of restraint stress or even for 1 hr restraint stress repeated for 7 days, but does attenuate CORT elevation when stress occurs continuously for 2-3 hr of restraint stress repeated over several days (Jiang and Eiden, *STRESS* 19: 374, 2016). On the other hand, CRH mRNA elevation and Fos activation in PVN are PACAP-dependent even after just 1 hr of restraint. We deduce that PACAP is required not to release CRH, but rather to sustain the ability of CRH neurons to produce and secrete CRH by augmenting CRH mRNA production, thus allowing a higher rate of CRH peptide biosynthesis during stress. However, restraint-induced hypophagia even after 1 hr restraint is PACAP-dependent, indicating that this effect requires PACAP actions within circuits other than those controlling the HPA axis.

In addition to activation of CRH PVN neurons, restraint stress also activates neurons of the centrolateral amygdala (CeL) and oval nucleus of BNST (ovBNST) that receive PACAPergic inputs from the extended lateral parabrachial nucleus (elPBn). PACAP terminals appear to synapse predominantly on PKC⁻ and to some extent on CRH-expressing neurons of extended amygdala. Fos activation in ovBNST and CeL after 2 hr restraint is abolished in PBnAAV-Cre::PACAPfl/fl mice, in which PACAP is ablated in nerve terminals of ovBNST and CeL, concomitant with attenuation of restraint-induced hypophagia. Fos activation in PVN, and CORT elevation after chronic restraint stress were maintained in PBnAAV-Cre::PACAPfl/fl mice. Additional PACAPergic circuits participate in restraint stress responses. Sim1-Cre::PACAPfl/fl mice, in which PACAP expression throughout hypothalamus is ablated, showed attenuated hypophagic response to acute restraint stress. Camk2 α -Cre::PACAPfl/fl mice, in which PACAP expression is ablated in forebrain, but not in hypothalamus and brain stem, did not show attenuation of restraint-induced hypophagia, but did exhibit deficits in restraint stress-induced HPA axis activation. Thus, Fos activation and CRH mRNA increase in PVN at 2 hr of acute restraint stress was attenuated in Camk2 α -Cre::PACAPfl/fl mice, and this is reflected cumulatively in attenuated CORT elevation after chronic restraint stress (2 hr restraint stress repeated over 4 days). These results suggest that anatomically distinct PACAPergic circuits separately control endocrine and behavioral responses to stress.

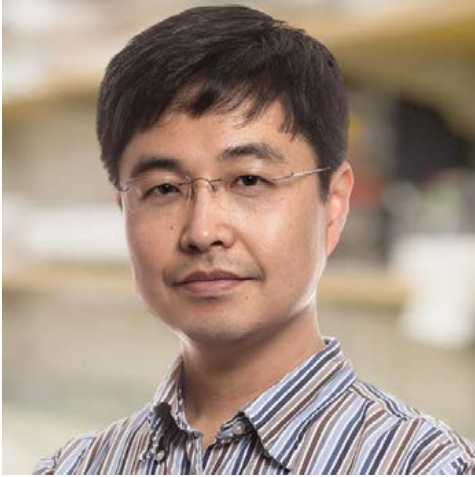


V-SS 4.3 Neuropeptides and anxiety: actions of CRF and PACAP in central amygdala

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The neuropeptide and neurohormone pituitary adenylate cyclase-activating polypeptide (PACAP) and its receptor PAC1 (PAC1R) are expressed in the hypothalamus as well as in extra-hypothalamic brain regions, including the central nucleus of the amygdala (CeA) and the bed nucleus of the stria terminalis (BNST). The PACAP/PAC1R system plays a fundamental role in the orchestration of the various aspects of the stress response. We will provide evidence that the exposure to acute stressors, such as restraint stress or footshock stress, causes an increase in PACAP levels in the extended amygdala, and that the resulting activation of PAC1R in these areas is responsible for the behavioral effects of stress. In the CeA, electrophysiological evidence shows that PACAP is able to augment GABAergic transmission onto inhibitory output neurons with a presynaptic mechanism of action, via the activation of PAC1R. Furthermore, we will show evidence that the continuous activation of the PACAP/PAC1R system in the CeA is responsible for the detrimental effects of chronic stress in a model of chronic social defeat stress. The involvement of corticotropin-releasing factor (CRF) in the pro-stress effects of PACAP will be discussed. These data suggest that reversing the dysregulation of the PACAP/PAC1R system of the CeA stress circuit may represent a novel target for the treatment of anxiety and mood disorders.



V-SS 4.4 Divergent brainstem opioidergic pathways that mediate pain-breathing interaction

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Breathing and pain perception seem to be unrelated critical brain functions, yet they influence each other. Severe pain induces hyperventilation, whereas paced slow breathing alleviates pain perception. However, a neural circuit-based understanding of pain-breathing interaction is lacking. Here we report that Oprm1 (μ -opioid receptor)-expressing neurons in the lateral parabrachial nucleus (PBL) are crucial for regulating breathing, pain, and their interaction. The PBL-Oprm1 activity is tightly correlated with the breathing rhythm, and noxious stimuli simultaneously elevate both. Manipulating PBL-Oprm1 activity collectively modulates breathing rhythm and negative affects, such as pain and anxiety. Furthermore, we find that the association of pain and breathing is mediated by two non-overlapping but reciprocally connected Oprm1 subpopulations in the core and shell of the PBL, which diverge to the central amygdala and medullary respiratory center, respectively. These results uncover the role of the parabrachial opioidergic pathways in regulating basal respiratory rhythm and pain-breathing interaction.



V-SS 4.5 Prolactin as a modulator of maternal aggression

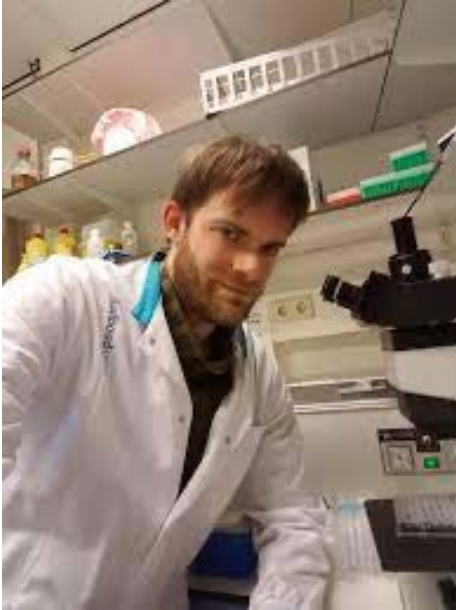
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Social interactions between a mother, her child and her family members are influenced by hormones acting on complex neural circuitry, with different regions of the brain regulating specific aspects of behaviour. Maternal aggression, a component of maternal behaviour, is conserved across many species including humans, and enables a mother to respond to and protect her young from danger or a perceived

threat. It is currently unclear how the hormonal changes of pregnancy and lactation contribute to this behavioural change. Previously we have shown that the hormone prolactin acts throughout the neural network that governs maternal behaviour, to promote the onset of maternal nursing behaviour after offspring are born (1). With high levels of Prlr expression in the hypothalamic ventromedial nucleus (VMN), a region known to be important in regulating aggressive behaviour, we hypothesised that prolactin might also play a role in mediating increased maternal aggression. The Prlr was specifically deleted from neurons in the VMN, using an adeno-associated virus to deliver Cre recombinase into the VMN of female Prlr flox mice. Surprisingly, deletion of Prlr specifically from the VMN resulted in lactating mice that were hyper-aggressive towards male intruders. This suggests that prolactin has a modulatory role in limiting the intensity of intruder-directed aggression during lactation. Subsequent work has revealed that prolactin acts on a population of prolactin-sensitive glutamatergic neurons in the VMN which project to multiple brain regions implicated in regulating different aspects of maternal responses. These data demonstrate a novel role for prolactin, and suggest that prolactin through specific actions on discrete regions of the maternal neural network, is able to influence a range of maternal behaviours.

1 Brown, R. S. E. et al. Prolactin action in the medial preoptic area is necessary for postpartum maternal nursing behavior. *Proc Natl Acad Sci U S A* 114, 10779-10784, doi:10.1073/pnas.1708025114 (2017).



V-SS 5.1 Chromogranin A and its cleavage product catestatin A control gut immune homeostasis and microbial composition

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High levels of the prohormone chromogranin A (CgA), which is cleaved into several bioactive peptides, have been associated with cancer, inflammatory bowel disease (IBD) and diabetes. The CgA anti-inflammatory cleavage peptide catestatin (CST) is also increased in IBD. Here we show that gut microbial composition is lower in both CgA and CST knockout mice. Moreover, the gut morphology and barrier function are oppositely affected in both KO mice. CgA stimulation in vitro led to increased Tumor Necrosis Factor- α (TNF- α) macrophage responses, whereas CST had the opposite effect. CD and UC patients had higher blood levels of CgA when compared to healthy controls whereas CST levels increased during disease remission, suggesting that the contrasting activities of CgA and CST link to IBD activity. Thus, CgA and its counteracting cleavage product CST are key modulators of intestinal health and disease.



V-SS 5.2 Corticotroph plasticity in stress: at the brain-endocrine interface

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Stress and stress-related disorders represent a significant burden on health and society. Following an acute stress, glucocorticoids mediate the hormonal stress response of the organism and provide negative feedback to limit hypothalamic-pituitary-adrenal (HPA) axis activity to facilitate recovery. However, following chronic stress the HPA axis is typically characterized by alterations in HPA sensitivity to stressors and

glucocorticoid negative feedback.

Anterior pituitary corticotrophs are an integral component of the HPA axis and sit at the brain-endocrine interface, receiving input from hypothalamic neuropeptides CRH and AVP while regulating glucocorticoid output from the adrenal cortex. Corticotrophs are electrically excitable and stimulation with CRH and AVP results in a characteristic a transition from spiking to bursting activity. Bursting is more efficient in raising intracellular calcium activity than spiking and is proposed to drive secretagogue-evoked ACTH secretion.

Mice expressing GFP under the proopiomelanocortin (POMC) promoter (POMC-GFP) were used to identify corticotroph cells in a mixed anterior pituitary culture. The effects of CS were investigated by subjecting male mice to a 14-day CS paradigm using a daily restraint stress (30 min per day). Pituitary glands were collected at the end of the stress period (day 15) or after a one- or four-week recovery period (day 22 or day 43 respectively). Corticotrophs were isolated using trypsin digestion and either cultured on glass coverslips for electrophysiological recordings, or FAC sorted for RNA-seq experiments.

Control cells (CON) display predominantly single-spike action potentials at rest and an almost exclusive transition to bursting with CRH stimulation. CS induces significant changes in patterns of corticotroph excitability, including an increase in both spontaneous and CRH-induced bursting activity. Surprisingly, rather than a return to baseline, a one-week recovery period (CS-1R) results in a significant suppression of spontaneous and CRH-evoked activity. This phenotype persists in the four-week recovery group (CS-4R).

Corticotrophs from CON, CS and CS-4R mice were isolated using FACS for bulk RNA-seq experiments. We reveal that CS causes no major changes in gene expression at the transcriptional level. However, corticotrophs from CS-4R mice show a large down-regulation of gene expression (5.4% genes) compared to controls. Identification of genes altered by CS, in particular those regulating electrical excitability, may represent potential targets for pharmacological intervention

In conclusion, a two-week exposure to stress results in significant changes to corticotroph physiology that persist after a four-week recovery period. Whether the effects of chronic stress are fully reversible, or cause lifelong changes to corticotroph and HPA axis physiology, remain important questions in the field. Corticotrophs are located at the brain-endocrine interface, which makes them an ideal target for therapeutic intervention. Further study of the effects of CS on corticotrophs may lead to novel treatments for stress and stress-related disorders.



V-SS 5.3 CRIG⁺ macrophages prevent gut microbial DNA-containing extracellular vesicle-induced tissue inflammation and insulin resistance

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Liver CRIG⁺ (complement receptor of the immunoglobulin superfamily) macrophages play a critical role in filtering bacteria and their products from circulation. Translocation of microbiota-derived products from an impaired gut barrier contributes to the development of obesity-associated tissue inflammation and insulin resistance. However, the critical role of CRIG⁺ macrophages in clearing microbiota-derived products from bloodstream in the context of obesity is largely unknown. We performed studies with CRIG^{-/-}, C3^{-/-}, cGAS^{-/-}, and their wildtype littermate mice. CRIG⁺ macrophage population and bacterial DNA abundance were examined in both mouse and human liver by either flow cytometric or immunohistochemistry analysis. Gut microbial DNA-containing extracellular vesicles (mEVs) were adoptively transferred into CRIG^{-/-}, C3^{-/-}, or WT mice, and tissue inflammation and insulin sensitivity were measured in these mice. After coculture with gut mEVs, cellular insulin responses and cGAS/STING-mediated inflammatory responses were evaluated. Gut mEVs can reach metabolic tissues in obesity. Liver CRIG⁺ macrophages efficiently clear mEVs from the bloodstream through a C3-dependent opsonization mechanism, while obesity elicits a marked reduction in CRIG⁺ macrophage population. Depletion of CRIG⁺ cells results in the spread of mEVs into distant metabolic tissues, subsequently exacerbating tissue inflammation and metabolic disorders. Additionally, *in vitro* treatment of obese mEVs directly triggers inflammation and insulin resistance of insulin target cells. Depletion of microbial DNAs blunts the pathogenic effects of intestinal EVs. Furthermore, the cGAS/STING pathway is crucial for microbial DNA-mediated inflammatory responses. Treatment with catenastatin restored CRIG⁺ cell population in obese mice, concomitant with less microbial DNA abundance and tissue inflammation in key metabolic tissues. Therefore, CRIG⁺ macrophages are key players preventing microbial DNAs-induced tissue inflammation and metabolic diseases.



V-SS 5.4 Ghrelin and LEAP2: The yin and yang controlling the growth hormone secretagogue receptor activity

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The growth hormone secretagogue receptor (GHSR) has emerged as a fascinating molecule from the perspective of neuroendocrine control. GHSR is mainly expressed in the pituitary and the brain, and plays key roles regulating not only

growth hormone secretion but also food intake, adiposity, body weight, glucose homeostasis and other complex functions. Quite atypically, GHSR is regulated by two digestive system-derived peptide hormones: the octanoylated peptide ghrelin and the liver-expressed antimicrobial peptide 2 (LEAP2). The existence of two peptide ligands with contrary actions indicates that GHSR activity can be tightly regulated and that the receptor displays the capability to integrate such opposing inputs in order to provide a balanced intracellular signal. Here, we will provide an update of the current understanding of the biology of ghrelin, LEAP2 and GHSR and discuss the reconceptualization of the cellular and physiological implications of this neuroendocrine system.



V-SS 5.5 Protective effects of prolactin in neurotoxin-induced hippocampal injury

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Prolactin (PRL) is a pleiotropic hormone with multiple functions in several tissues and organs, including the brain. PRL treatment decreases neuronal loss induced by kainic acid (KA) in the hippocampus of female and male rodents, which is associated with decreased astrogliosis and attenuation of cognitive impairment due to KA lesioning. Also, PRL decreases lesion-induced microgliosis and modifies gene expression related to microglial functions in the hippocampus, thereby providing a possible mechanism through which it might participate in neuroimmune modulatory responses diminishing neuronal cell damage. However, the direct contribution of microglial cells to PRL-mediated neuroprotection is still unclear and no studies have yet documented whether PRL can directly activate cellular pathways in microglial cells.

Recent *in vivo* work aimed to investigate whether treatment with PRL decreases astro- and microgliosis in the dorsal hippocampus, and how it modulates the expression of some important inflammatory factors after an excitotoxic lesion, showed that PRL reduced the astro- and micro-gliosis in CA1, CA3, and CA4 hippocampal subfields induced by KA. Morphometric analysis of microglial cells in CA4 revealed a PRL effect in reducing their activation. PRL-increased immunoreactivity for IL-10 and IL-4 was detected in neurons, accompanied by a decrease in the expression of TNF α and iNOS in lesioned rats. These results indicated anti-inflammatory actions of PRL in the hippocampus, both by decreasing the astrogliosis and microglial activation and by reducing the level of pro-inflammatory cytokines probably through the upregulation of neuronal IL-10 and IL-4. By using the immortalized SIM-A9 microglia cell line, we have analyzed actions of PRL in basal and LPS-stimulated conditions. PRL treatment alone induced a time-dependent ERK1/2 activation, while pretreatment with PRL attenuated LPS stimulated pro-inflammatory markers: nitric oxide levels, iNOS, IL-6, IL-1 β and TNF- α expression. PRL suppressed LPS-induced NF- κ B p65 subunit phosphorylation and its upstream p-ERK1/2 activity. Thus, PRL exhibits anti-inflammatory effects in LPS-stimulated SIM-A9 microglia by downregulating pro-inflammatory mediators corresponding to suppression of LPS-activated ERK1/2 and NF- κ B phosphorylation and is an endogenously produced candidate for the regulation of inflammatory responses in the brain microglia, a mechanism that could protect against CNS injury and other neurodegenerative disorders.

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V-K 5 Oxytocin, fear memory, and the bed nucleus of the stria terminalis (BNST)

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Oxytocin (OT) is a hypothalamic hormone and a neuromodulator, which has been shown to be involved in mediating fear- and anxiety-like behaviors. The dorsolateral bed nucleus of the stria terminalis (BNSTDL) has high expression of OT fibers and OT receptors (OTR), which were shown to facilitate fear to predictable, discrete signals (cued fear). Furthermore, cued fear conditioning has been shown to increase extracellular levels of OT in the BNSTDL. However, the role of OTR in the modulation of BNSTDL activity and the mechanisms of fear regulation via OTR remain elusive. BNSTDL contains GABAergic neurons classified based on intrinsic membrane properties and firing pattern into three types (Type I-III neurons). Using *ex vivo* patch-clamp recordings in male adult rats, we demonstrated that OT selectively excites and increases spontaneous firing rate of Type I BNSTDL neurons. As a result, OT increases the frequency, but not amplitude, of spontaneous inhibitory post-synaptic currents (sIPSCs) selectively in Type II neurons, an effect abolished by OTR antagonist or tetrodotoxin. OT also reduces spontaneous firing of Type II neurons. These results suggest an indirect effect of OT in Type II neurons, which is mediated via OT-induced increase in firing of Type I interneurons. As it was recently shown that the majority of Type II BNSTDL neurons project to the central amygdala (CeA), we also recorded from retrogradely labeled BNST→CeA neurons after microbead injection into the CeA. We show that OT increases the frequency of sIPSC in these Type II BNST→CeA projection neurons. In contrast, in Type III BNSTDL neurons, OT reduced the amplitude, but not frequency, of both sIPSCs and evoked IPSCs via a postsynaptic mechanism without changing their intrinsic excitability. We present a model of fine-tuned and cell-type specific modulation of BNSTDL activity by OT, which selectively excites Type I BNSTDL, interneurons, reduces GABAergic inhibition of Type III neurons and inhibits Type II BNST→CeA projection neurons. Based on the dominant role of the CeA in mediating cued fear, our results suggest that OTR in the BNSTDL might facilitate cued fear by inhibiting the BNST→CeA neurons.



V-SS 6.1 Brain angiotensin II as a mediator of emotional memory

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Post-traumatic stress disorder (PTSD) is a strong predictor of cardiovascular disease (CVD), the leading cause of death in men and women in the U.S. However, the biological, behavioral and other causal mechanism(s) and pathways linking PTSD with CVD co-morbidity are unclear. This lack of understanding of the mechanisms involved in PTSD-CVD co-morbidity severely limits treatment strategies, mandating continued research on the mechanisms of this co-morbidity.

The renin-angiotensin system (RAS), regulating both cardiovascular homeostasis and arousal as well as emotional responses to stress, has emerged as a potentially important mechanistic link between these disorders. We have previously shown that pharmacological inhibition of the angiotensin (Ang) II type 1 receptor (AT1R) or genetic deletion of the AT1R from select neuronal populations facilitates fear memory extinction—a process that is impaired in PTSD. Using angiotensin receptor reporter mice, we demonstrate that AT2R projecting neurons in the central medial division (CeM) are involved in the expression (i.e., freezing behavior) of learned fear, while a separate population of AT1R neurons, restricted to the central lateral division (CeL), modulate extinction learning. These new data have improved our understanding of the neuropeptidergic actions of Ang II in fear-related learning, and suggest that actions of AT1R and AT2R differentially modulate stages of fear learning. Our working hypothesis is that local synthesis of Ang-II activates brain AT1R / AT2Rs, differentially modulating fear circuits required for both the expression (i.e., freezing, blood pressure, heart rate) and encoding of fear (or threat) memory.

In this presentation I will provide an up-to-date review of these data combined with recent translational clinical evidence supporting a role for angiotensin II in fear-related learning and their therapeutic relevance for anxiety-related disorders such as PTSD.



V-SS 6.2 A role for ghrelin in stress-induced vulnerability to affective psychiatric disorders

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A history of exposure to intense stressors increases the risk of multiple psychiatric illnesses, such as post-traumatic stress disorder (PTSD), for decades after stressor exposure ceases. Recent work from my laboratory and others has shown that one endocrine change that persists long after stress ceases is an increase in circulating ghrelin. I will present data showing that this increase in ghrelin is a conserved response to chronic stress exposure: our studies show it occurs in mice, rats, and humans. I will also present a

series of experiments showing that this produces an insensitivity to ghrelin in brain circuits that regulate aversion, and I will describe our recent experiments showing that stress-induced elevation of ghrelin predicts both PTSD risk and severity in humans. I will also show data that link stress-induced changes in ghrelin to suicidal risk. Collectively, our studies suggest that ghrelin is one hormone that may play a causal role in a long-term vulnerability to affective disorders following exposure to intense stressors.



V-SS 6.3 Melanin-concentrating hormone receptor 1-mediated control of hyperactivity

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Melanin-concentrating hormone (MCH) is a key player underlying energy balance. Deleting MCH or its MCH receptor MCHR1 results in lean mice that are resistant to diet-induced obesity. This protection is related to their hyperactivity and increased energy expenditure. Given the prominent expression of *Mchr1* mRNA at GABAergic cells, such as within the accumbens, we determined if MCH would act via GABAergic cells marked by *Vgat* mRNA to regulate energy expenditure. We selectively deleted *Mchr1* from *Vgat* neurons and observed robust hyperactivity in our *Vgat-Mchr1-KO* mice. This hyperactivity was recapitulated by restricting *Mchr1* deletion to the accumbens. Amperometry recordings from within the accumbens showed that *Mchr1* deletion was associated with a hyperdopaminergic state and suggested that MCH could suppress dopamine release. Indeed, we showed that MCH application reversibly reduced dopamine content in the accumbens, thus ongoing work will determine whether MCH could also act on dopaminergic cells to regulate dopamine release. Taken together, we surmised that the interaction between the MCH and dopamine or GABA network comprise critical neural circuits supporting the effects of MCH on energy expenditure.



V-SS 6.4 Circumventricular organs as sensors and integrators of regulatory peptides controlling ingestive behaviors

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Central nervous system (CNS) structures involved in the regulation of energy and fluid balance gather information from the variety of different peripherally derived signaling molecules that we now believe provide an integrated perspective of autonomic state of the organism. However, the existence of the blood brain barrier means that the CNS is theoretically unable to directly monitor many of these circulating signals such as adiponectin, amylin, angiotensin II, cholecystokinin, GDF-15, glucose, ghrelin, leptin, and peptide YY which do not freely diffuse across this barrier. A number of mechanisms have been suggested to play important roles in facilitating the ability of the CNS to monitor this essential sensory information. My presentation will focus primarily on the potential roles of specialized CNS structures which lack the blood brain barrier known as the sensory circumventricular organs (CVOs). In particular I will highlight the complex sensory abilities of single CVO neurons in monitoring multiple circulating peptides signals and also describe the efferent projections of these neurons to essential autonomic control centers behind the blood brain barrier.



V-SS 6.5 Central relaxin-3/RXFP3 systems and peptidergic modulation of integrated autonomic, neuroendocrine and higher circuits

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Complex neural circuits within the brain regulate autonomic and neuroendocrine processes, and related cognitive and motor behaviors, by engaging amino acid, monoamine, peptide, gaseous and lipid transmitters/modulators, and specific G-protein-coupled receptors (GPCRs) and associated cell-signaling pathways. Relaxin-3 is a newly-identified neuropeptide (c. 2001), that is highly conserved and is the ancestral member of the broader relaxin-peptide family [1]. Extensive anatomical data from rodents and non-human primates reveal that relaxin-3-expressing GABA neurons in the hindbrain broadly innervate the brain, including strong projections to the limbic system (septum, hippocampus, amygdala), hypothalamus, thalamus, and regions of cerebral cortex [2]. Relaxin-3 is thought to predominantly act in vivo via a Gi/o-associated receptor, RXFP3 [1], but exogenous relaxin-3 activates related receptors (RXFP4 and RXFP1), and RXFP3-selective agonist peptides are preferred for in vivo pharmacological studies [2-4]. In a RegPep22 presentation, the emergence of the relaxin-3/RXFP3 system as an extrinsic regulator of the neuroendocrine axis was highlighted by a review of its neuroanatomy and links to arousal-, stress-, and feeding- behaviors and associated neural networks. The regulatory and functional studies in rats and wildtype/transgenic mice reviewed revealed relaxin-3/RXFP3 signaling has effects on neuroendocrine/peptide systems associated with stress responses/(CRF), motivation and reward/(orexin), and metabolism and social behavior/ (oxytocin) [2,5,6]. This presentation will review more recent data from laboratories investigating the relaxin-3/RXFP3 system as a regulator of interdependent modalities, including spatial and emotional memory, and normal vs binge-feeding, and the gender-based differences observed [7-11]. Anatomical studies in rats have mapped the reciprocal interactions between relaxin-3 neurons in nucleus incertus (NI) and the parahippocampal cortex [7], in line with effects of altered endogenous RXFP3 signaling on learning and memory [8]. Neurophysiological studies further characterised the impact of RXFP3 on oxytocin magno/parvocellular neuron activity [9], actions associated with regulation of binge-eating in female rats observed after RXFP3 antagonist injections into PVN. Studies also implicated the relaxin-3/RXFP3 system in food intake fluctuations across the estrous cycle in female rats [10]. In male rats, sustained stimulation of RXFP3 on heterogeneous GABA neurons in ventral hippocampus or medial amygdala led to differential anxiogenic and anxiolytic profiles and differential effects on social interaction, respectively [11]. In this regard, co-expression of RXFP3 and oxytocin receptor mRNA in the amygdala suggest that further investigations of the interaction between these systems will provide novel insights into the peptidergic modulation of essential homeostatic neural circuits.

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V-Posters

Poster 01 Relationship between constitutive and acute gene regulation, and physiological and behavioral responses, mediated by the neuropeptide PACAP

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The role of neuropeptides in brain function has been investigated both via the use of pharmacological agonists and antagonists to provoke or inhibit outputs and using mice deficient in the peptide or its receptor(s) (knockout mice). Functional deficiencies in adult neuropeptide-deficient mice could be due to genetic or non-genetic immediate effects at the time of experimentation, or genetic effects occurring prior to the experiment, even in development. These differences in turn could reflect developmental or neuromodulatory roles for a given neuropeptide. Here, we demonstrate that in the constitutively (from conception) *Adcyap1* (PACAP) knockout mouse there is a cohort of genes (constitutively PACAP-Regulated Genes, or cPRGs) whose basal expression is altered in PACAP-deficient mice, and additional genes (acutely PACAP-Regulated Genes, or aPRGs) whose basal expression is the same in wild-type and knockout mice, but whose alteration in response to a physiological challenge is impaired in the absence of PACAP expression. We identify a behavioral phenotype (repetitive jumping) which is dramatic in constitutive *Adcyap1* KO mice, but is not phenocopied by either the PACAP receptor *PAC1* KO or by post-natal knockout of *Adcyap1*, indicating a developmental rather than acute role of PACAP that may be reflected in the expression of cPRGs, such as *Pttg1* and *Xaf1*. On the other hand, blunted responses to restraint stress (hypophagia and corticosterone elevation) seen in PACAP-deficient mice, and phenocopied in *PAC1* deficient mice, are accompanied by corresponding alterations in the expression of genes in hypothalamus (CRH) and elsewhere in brain. This suggests a ‘real-time’ (neuromodulatory) role for PACAP-*PAC1* signaling in the regulation of these genes (aPRGs). Distinguishing constitutive and acute effects of neuropeptide deficiency reveals the changing functions of neuropeptides through the lifespan.

Poster 02 Mechanotransduction of heteromeric Δ N-TRPV1 and TRPV4: implications for vasopressin neuron activity

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The hormone, vasopressin, is synthesised by hypothalamic neurons and is secreted into the circulation from the posterior pituitary gland in response to action potential firing. Vasopressin maintains body fluid homeostasis by promoting renal water retention in response to increased plasma osmolality. Vasopressin neurons respond directly to changes in osmolality through expression of an N-terminal truncated variant of the transient receptor potential vanilloid (TRPV)-1 channel, Δ N-TRPV1, which is mechanically activated by osmotically-induced membrane shrinkage. Δ N-TRPV1 activation increases the probability of action potential firing by depolarising the neurons towards action potential threshold. Vasopressin neurons also express TRPV4 but the role of TRPV4 in vasopressin neuron function is unknown. While TRPV1 can form heteromers with TRPV4, it is unknown whether Δ N-TRPV1 can form heteromers with TRPV4.

To test the hypotheses that Δ N-TRPV1 and TRPV4 heteromerise and that this heteromerisation modulates mechanical activation of Δ N-TRPV1, single-channel patch-clamp electrophysiology was used to determine channel biophysical properties and mechanosensitivity in Δ N-TRPV1 and TRPV4 co-transfected HEK293 cells. All Δ N-TRPV1+TRPV4 expressing HEK293 cells had distinct single-channel properties compared to Δ N-TRPV1 homomer and to TRPV4 homomers, revealing that heteromers had formed. Single-channel conductance of Δ N-TRPV1+TRPV4 was larger at positive holding potentials (49.3 ± 3.4 pS) compared to negative holding potentials (10.6 ± 1.4 pS). Δ N-TRPV1+TRPV4 were mechanically activated by positive pressure, which increased open probability ($p = 0.006$; paired t-test) and maximum current amplitude ($p = 0.04$; paired t-test) at +60 mV holding potential. 5/14 heteromers were also activated by negative pressure, a property neither homomer expressed (maximum current amplitude $p = 0.01$ paired t-test).

Taken together, these results suggest that Δ N-TRPV1 and TRPV4 form functional heteromeric channels that have broader mechanosensitivity than homomeric Δ N-TRPV1. Hence, the Δ N-TRPV1 and TRPV4 could form heteromers in vasopressin neurons, providing a mechanism that might allow plasticity in the osmosensitivity of vasopressin neurons evident in different (patho) physiological states such as pregnancy and hypertension.

Poster 03 Molecular profile of brain serotonin, galanin and dynorphin systems in rats with and without limbic recruitment induced by audiogenic kindling

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Epilepsy is a complex neurological disorder that affects over 70 million people worldwide. In the present study, we used the Wistar audiogenic rat (WAR) strain as an animal model of genetic epilepsy predisposition, where the seizures are induced by acoustic stimulation. In those animals, repeated seizures or the audiogenic kindling (AK) can induce limbic seizures, associated with the recruitment of the hippocampus, amygdala, and cortex. The dysregulation of serotonergic neurons from the mesencephalic dorsal raphe nucleus (DRN) was demonstrated to be involved in the physiopathology of epilepsy and its comorbidities, including the sudden unexpected death. Moreover, we have recently demonstrated molecular and functional changes in the hypothalamic-neurohypophysial system in WARs, which are also involved in the synthesis and release of galanin and dynorphin, neuropeptides with demonstrated anti-seizure effects. Thus, we aimed to understand the molecular profile of brain serotonin, galanin, and dynorphin systems in WARs, with and without limbic recruitment (LiR) induced by AK. Thus, at the end of the AK protocol (10 days with two sessions of acoustic stimulation per day) male Wistar and WARs were euthanized and their brains were collected for RT-qPCR. We evaluated the mRNA expression of genes related to serotonin production/secretion regulation (Tph1, Tph2, Slc6a4, and Htr1a) in the DRN; to dynorphin (Pdyn) and galanin (Gal) synthesis in the hypothalamic supraoptic nucleus (SON); and their receptors (Htr1a, Htr1b, Htr2a, Htr2c, Galr1, Galr2, Oprk1, and Oprm1) in limbic structures (hippocampus and amygdala). We found a significant reduction in Htr1a ($p=0.006$) expression in the DRN of WARs compared to Wistar rats. Moreover, the AK induces the increase in Tph1 ($p=0.012$), Slc6a4 ($p<0.001$), and Htr1a ($p<0.001$). A significant interaction between strain and AK was found for Slc6a4 expression ($p=0.009$), with a more prominent impact of AK in Wistar (in fact chronic stimuli, not seizures) than in WARs. In the SON, we found a significant increase in both Gal ($p=0.002$) and Pdyn ($p=0.023$) expression in WARs compared to Wistar rats, with no effect of AK. No significant differences were found in the DRN or SON gene expression according to LiR. Concerning receptors mRNA expression, there was a reduction of Htr1b ($p=0.018$) in the hippocampus, Htr2c ($p=0.031$) in the basolateral amygdala, and Htr2c ($p=0.037$) in Galr1 ($p=0.040$) in the central amygdala of WARs compared to Wistar. The AK increases the Htr2c ($p=0.003$) expression in the hippocampus. WARs submitted to AK but without LiR show a significant increase in Htr1b and Htr2c ($p<0.05$) compared to WAR naive in both basolateral and central amygdala. We also performed a Spearman correlation analysis between score means of mesencephalic and limbic seizures scales with gene expression. We found a negative correlation between Pdyn expression and mesencephalic scores ($p=0.049$; $r=-0.59$), besides a trend for negative correlation with limbic scores ($p=0.055$; $r=-0.57$). Our data point for a possible role of molecular profile related to serotonin, galanin, and dynorphin and its receptors in WARs with impact in their susceptibility to develop seizures and activate mesencephalic structures and/or recruit limbic ones.

Poster 04 **Beyond PKA: cAMP-dependent GLP-1 Signaling to ERK Requires NCS-RapGEF2**

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Family B GsPCRs canonically signal to PKA via activation of adenylyl cyclase and elevation of cAMP. Recently, alternate cAMP sensors have been identified and shown to be involved in GPCR signaling. The Rap guanine nucleotide exchange factor 2 (NCS-RapGEF2) is required for differentiation initiated by the neuropeptide Pituitary Adenylate Cyclase-activating Peptide (PACAP), via the Gs-protein coupled receptor (GsPCR) PAC1, in Neuroscreen-1 (NS-1) neuroendocrine cells. Here, we assess the expression of other GsPCRs in NS-1 cells and evaluate their coupling through NCS-RapGEF2. Exposure of NS-1 cells to the VIPR1/2 agonist vasoactive intestinal polypeptide, or the GLP1R agonist exendin-4, did not induce neuritogenesis, or elevation of cAMP, presumably as a result of insufficient receptor protein expression. Vasoactive intestinal polypeptide and exendin-4 did induce neuritogenesis after transduction of human VIPR1, VIPR2 and GLP1R into NS-1 cells. Exendin-4/GLP1R-stimulated neuritogenesis was MEK-ERK-dependent (blocked by U0126), indicating its use of the cAMP→RapGEF2→ERK neuritogenic signalling pathway previously identified for PACAP/PAC1 signalling in NS-1 cells. NCS-RapGEF2 is expressed in the rodent insulinoma cell lines MIN6 and INS-1, as well as in human pancreatic islets. As in NS-1 cells, exendin-4 caused ERK phosphorylation in INS-1 cells. Reduction in RapGEF2 expression after RapGEF2-shRNA treatment reduced exendin-4-induced ERK phosphorylation. Transcriptome analysis of INS-1 cells after 1 hour of exposure to exendin-4 revealed an immediate early-gene response that was composed of both ERK-dependent and ERK-independent signalling targets. We propose that cAMP signalling initiated by glucagon-like peptide 1 (GLP-1) in pancreatic beta cells causes parallel activation of multiple cAMP effectors, including NCS-RapGEF2, Epac and protein kinase A, to separately control various facets of GLP-1 action, including insulin secretion and transcriptional modulation.

Poster 05 ACE2 expression in rat brain: implications for COVID-19 associated neurological manifestations

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We examined cell type-specific expression and distribution of rat brain angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV-2, in the rodent brain. ACE2 is ubiquitously present in brain vasculature, with the highest density of ACE2 expressing capillaries found in the olfactory bulb, the hypothalamic paraventricular, supraoptic, and mammillary nuclei, the midbrain substantia nigra and ventral tegmental area, and the hindbrain pontine nucleus, pre-Bötzinger complex, and nucleus of tractus solitarius. ACE2 was expressed in astrocytes and astrocytic foot processes, pericytes and, endothelial cells, key components of the blood-brain barrier. We found discrete neuronal groups immunopositive for ACE2 in brainstem respiratory rhythm generating centers, including the pontine nucleus, the parafascicular/retrotrapezoid nucleus, the parabrachial nucleus, the Böttinger, and pre-Böttinger complexes and the nucleus of tractus solitarius; in the arousal-related pontine reticular nucleus and gigantocellular reticular nuclei; in brainstem aminergic nuclei, including substantia nigra, ventral tegmental area, dorsal raphe, and locus coeruleus; in the epithalamic habenula, hypothalamic paraventricular and supramammillary nuclei; and in the hippocampus. Identification of ACE2-expressing neurons in rat brain within well-established functional circuits facilitates prediction of possible neurological manifestations of brain ACE2 dysregulation during and after COVID-19 infection.

Highlights

- ACE2 is present in astrocytes, pericytes, and endothelia of the blood-brain barrier.
- Neuronal ACE2 expression is shown in discrete nuclei through the brain.
- Brainstem breathing, arousal-related, hypothalamic and, limbic nuclei express ACE2.
- ACE2 is expressed in circuits potentially involved in COVID-19 pathophysiology

Poster 06 Acute sleep restriction induces hyperglycemia and changes SCN activity

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Chronic sleep restriction is a common problem in modern society. Despite the clear role of chronic sleep restriction as a risk factor for developing metabolic and cardiovascular disease there is no clear evidence about the specific brain-controlled mechanisms which drive the metabolic impairments. Previous studies have shown that the suprachiasmatic nucleus (SCN) is involved in the regulation of wakefulness, contributing to the sleep-wake cycle. Further, circadian disturbances such as shift work also promote metabolic imbalance. Here, we propose that acute sleep restriction can modify the neuronal activity of the SCN, resulting in alterations in systemic glycemia. Male Wistar rats (300-350g) were exposed to forced activity in their rest-phase in a rotating wheel (one lap each 3 minutes). After 2 hours in the rotating wheel, rats exhibited higher glucose levels. After 12 hours in the rotating wheel, rats were allowed to sleep 2 hours. We found that even after 2 hours of sleep opportunity high glucose levels remained.

Interestingly we did not find changes in food intake. Further, we analysed the differences in SCN activity, and we evaluated possible changes in neuropeptides (vasopressin, vasoactive intestinal peptide) under acute sleep restriction. Finally, because it is known that SCN communication with the arcuate nucleus, is in a pivotal position for involvement in the central control of glucose homeostasis, we evaluated arcuate nucleus activity and hypothalamic barrier characteristics. Those data provide novel information about the early mechanisms which drive metabolic disturbances induced by sleep restriction and that appear to be controlled by the SCN.

The group is supported by grants PAPIIT IG-201321 and Conacyt 279293.

Poster 07 Short-term fasting is associated with food seeking behavior and increased hypothalamic neuropeptide Y mRNA expression in Japanese quail chicks

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The regulation of feeding is a complex interaction between central and peripheral signalling governed centrally by the melanocortin system comprising of specific neuronal populations and circuits in the hypothalamus and brainstem. Little is known about the central mechanisms regulating the onset of appetite in birds in early life and here we investigated how changes in nutritional status and food availability effect the hypothalamic pathways modulating appetite in young Japanese quail (*Coturnix japonica*). Nine-day old chicks (both sexes) kept on (19L:5D) were randomly assigned to FED (control, ad libitum feeding) or FASTED (4h fast from lights on, food removed at lights off) groups. Food seeking behaviour and appetite-related hypothalamic gene expression was compared between groups and chick sex was determined from a terminal blood sample by PCR. FASTED chicks exhibited significantly lower body and gut weights as well as lower blood glucose levels compared to FED controls. No sex differences were observed; n=22-26/group/sex. Behavioural analysis of video recordings (Hikvision, UK), and RFID PIT tagged (Eccel Technology, UK) showed that FED and FASTED chicks rested and rarely fed or drank during darkness. Following lights on chicks immediately exhibited food-seeking behaviour. The feeding station was visited with increased frequency during the first 2h of lights on. FASTED chicks showed increased food seeking behaviour at the empty feeding station compared to the FED chicks. At 4h following lights on chicks were killed and blood, tissue and brain samples were collected on dry ice. RT-qPCR analysis of appetite-related hypothalamic gene expression, showed a significant increase in hypothalamic neuropeptide-Y (NPY), but not agouti-related peptide (AgRP), Proopiomelanocortin (POMC), cocaine-and-amphetamine-regulated transcript (CART) or gonadotropin-inhibitory hormone (GnIH) mRNA or their receptors, GnIH-R1, NPYR1 or NPYR2 in FASTED quail compared to the FED control chicks. Thus, negative energy balance caused by food restriction enhances food-seeking behaviour in male and female chicks, and this was associated with increased hypothalamic NPY mRNA expression but not AgRP mRNA. Despite conserved peptide signalling among vertebrates, these findings suggest that there are some functional differences in the neuropeptide mechanisms regulating food intake in chicks. All work was performed under UK Home Office licence, ARRIVE guidelines and local ethical review. Research supported by BBSRC (BB/5015760/1).

Poster 08 Role of N-methyl-D-aspartate receptor (NMDA-R) in the pathophysiology of schizophrenia

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Schizophrenia is a serious mental disorder characterized by distortion of thought, perceptions, emotions, language, self-consciousness, and behavior; as well as the presence of auditory hallucinations and delusions. The global prevalence of schizophrenia ranges from 0.9% to 1.9%. Despite the severity of this disorder, only 0.05% of patients receive adequate psychiatric treatment and follow-up.

In pathophysiology of schizophrenia multiple factors are involved: genetic, psychophysiological and structural changes, functional and neurochemical disorders. Here we review and integrate mainly studies on the role of the N-methyl-D-Aspartate receptor (NMDA-R) in the pathophysiology of schizophrenia in order to provide and broaden the scientific perspectives for new links in the pathogenesis of this disorder.

NMDA-R are glutamate-activated ion channels, and form part of one of the most important excitatory systems of the nervous system; its dysfunction generates psychiatric and neurological alterations by generating changes in neuronal functional regulation.

It has been shown that hippocampus, limbic system and basal ganglia are involved in the pathogenesis of schizophrenia, where regulation of neuronal excitation is deficient because in these areas the NMDA-R are dysfunctional due to the interaction between the autoantibodies (IgG) with the NR2 subunit of the receptor (glutamate-sensitive).

Evidence also suggests that IgG autoantibodies bind to NMDA-R by inducing reversible receptor internalization in synaptic membranes; the loss of receptors on neuronal surface correlates with a decrease in synaptic currents in the affected areas generating dysfunction in local neuronal excitation. Being these regulatory zones of the prefrontal cortex generates inability to fulfill this function this causes the prefrontal cortex to lose this regulation and therefore begins to produce dopamine abnormally which induces the symptomatology of schizophrenia.

These findings could completely revolutionize the way we understand pathogenesis and the way we treat schizophrenia; However, the evidence still does not determine whether these autoantibodies are actually reactive only to this receptor or also to others present in this area, so it is necessary to continue expanding our knowledge on this mechanism of the disease.

Poster 09 Visualising the changes in oxytocin neuron population activity in virgin and lactating freely-behaving mice

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Oxytocin is synthesised by magnocellular neurons of the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus and is essential for stimulating milk let down during lactation. Oxytocin is secreted into circulation at the posterior pituitary gland in response to action potential firing. Oxytocin secretion is relatively low and constant in virgin mice due to the low basal firing rate of oxytocin neurons. However, when pups suckle during lactation, milk is ejected in discrete episodes due to high-frequency bursts of action potentials (milk-ejection burst) in oxytocin neurons, which is coordinated across the oxytocin neuron population. The purpose of this current study was to record the oxytocin neuron population activity in freely-behaving mice to determine how oxytocin neural activity changes across virgin and lactating reproductive states. We hypothesised that during lactation the frequency of milk-ejection bursts are dependent on the intensity of the suckling stimulus. Here, we developed and validated GCaMP6s fibre photometry to optically measure PVN oxytocin neuron activity in freely-behaving mice. In virgin mice, oxytocin neurons exhibited low and constant tonic fluorescence with occasional small increases in fluorescence. By contrast, large peaks in fluorescence were evident every 2 – 10 min during lactation in the same mice, reflecting the occurrence of milk-ejection bursts, which preceded milk let-down (determined from video recording of vigorous pup movement) by ~15 s during suckling. These bursts were often preceded by smaller peaks of coordinated activity, like the fluorescence in virgin mice, that did not trigger milk ejection. Reducing the number of pups suckling, thereby reducing the suckling stimulus, reduces burst frequency. Furthermore, when pup numbers were reduced below approximately 30% of the original pup number, no milk-ejection peaks were recorded. When pup number was reduced below this threshold, there were still the smaller peaks that typically precede milk-ejection bursts but these were never followed by a milk-ejection burst. Hence, a threshold number of pups simultaneously suckling is required to generate milk-ejection bursts in oxytocin neurons. Furthermore, reintroducing hungry pups to enhance the suckling stimulus, increases milk-ejection burst frequency compared to natural feeding frequency, suggesting suckling intensity determines burst frequency. Overall, oxytocin neuron activity patterns switch from low tonic activity to episodic bursts, to generate milk let-down in lactating mice and the frequency and generation of these bursts are gated by pup suckling intensity.

Poster 10 Evolution of DPP4 susceptibility in vertebrate peptide YY

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PP-fold peptides fulfil complex and diverse signalling roles in vertebrate energy homeostasis. The satiety action of peptide YY (PYY) is classically potentiated by dipeptidyl peptidase-4 (DPP4) cleavage of PYY1-36 to PYY3-36 altering receptor specificity. Examinations of non-mammalian PYY molecules are limited, but DPP4 resistance is evidenced in some species. As this distinction might explain intricate contrasts in energy balance, we aimed to characterise cleavability of PYY across vertebrates.

Known and presently-derived vertebrate PYY precursor sequences were examined for susceptibility to DPP4 cleavage. Parallel phylogenetic analysis was performed to describe evolution of DPP4 cleavage.

Other than few spurious examples, DPP4-cleavable PYY seems to be an exclusively mammalian trait, affecting all mammalian clades. Susceptibility of PYY to DPP4 cleavage therefore likely arose around the time of mammalian divergence, representing a relatively novel development of the involvement of PP-fold signalling in vertebrate energy homeostasis.

Ancestral vertebrate PYY was clearly resistant to cleavage by DPP4. This resistance persists in most extant non-mammalian vertebrates. The satiety action of DPP4-cleaved PYY3-36 is therefore exclusive to mammals and might explain some unique features of mammalian energy homeostasis, for example comparatively low glucose tolerance and susceptibility to type 2 diabetes (T2D). These findings broadly support recent observations of a critical pancreatic signalling role for PYY in mammalian glucose homeostasis. Aberrant regulation of PYY cleavage and signalling may therefore play a role in progression of T2D and somewhat explain the antidiabetic action of DPP4 inhibitor drugs. Exploration of the role of PYY in glucose homeostasis might yield novel therapeutic approaches for T2D.

Poster 11 **Functional GPCR interactions in parasympathetic preganglionic neurons (PGNs) in rat spinal cord**

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Background and Objectives: Both dopamine (DA) and ghrelin activate the lumbosacral defecation centres (parasympathetic preganglionic neurons; PGNs) and cause propulsive contractions of the colorectum in vivo. Dopamine, but not ghrelin, is found in nerve terminals in the defecation centres, where GPCRs, Dopamine D2 receptor (DRD2) and ghrelin receptor (GHSR1a) transcripts have been identified. There is evidence that DRD2 and GHSR1a form heteromers in lipid membranes and transfected cells, resulting in altered agonist-activated signalling pathways. Our studies investigated whether altered signaling/ GPCR interaction is observed in native cells of the defecation centre.

Methods: In vivo colonic motility experiments were conducted in anaesthetized rats. DRD2 and GHSR1a transcripts were located in rat spinal cord using RNAscope. For electrophysiology recordings, neonatal rats (p4-11) were injected i.p. with retrograde tracer, Fast DiI, to label PGNs. After 3-7 days of transport, animals were euthanised, spinal cords removed by dorsal laminectomy and lumbosacral regions cut into 300 μ M slices in ice-cold sucrose aCSF, followed by incubation in NMDG hepes- buffered recovery solution for 10 minutes at 32°C. Tissue was left in aCSF at RT for 1 hour before recording at 32°C. All recordings were made in open, whole cell patch configuration under voltage clamp using an Axopatch 200A or Multiclamp 700B amplifier. Dopamine hydrochloride (DA, 30 μ M), Capromorelin (10nM), and GHSR1a receptor blockers, JMV2959 (1 μ M) and YIL781 (100nM) were washed onto slices (3-5mL/ min) and current (pA) changes were calculated relative to baseline values.

Results: A DRD2 agonist, quinpirole, applied directly to the defecation centres of rats in vivo, stimulated colorectal propulsion that was antagonized by systemic ghrelin receptor antagonist, YIL781, indicating that activation of DRD2 of the defecation pathway requires interaction with an agonist-activatable GHSR1a. In situ hybridization revealed Ghsr in neurons of the defecation centres, but not in down-stream neurons. Moreover, 80% of neurons in the centres that expressed Drd2 also expressed Ghsr. Both Capromorelin and DA caused an inward current and increased excitability of a subpopulation of DiI labelled PGNs. Pre-incubation with ghrelin receptor blocker, JMV2959, and inverse agonist/ blocker, YIL781, for 5-10 minutes did not change the excitability of PGNs, suggesting that baseline constitutive activity of GHSR1a is tissue specific, not occurring in these neurons. Furthermore, the presence of either GHSR1a blocker significantly reduced the excitability of the neurons to DA. Repeat DA applications in separately recorded PGNs did not show a comparable decrease in response. Thus, our results using pharmacological techniques in native spinal cord slices suggest that DRD2 signalling can be switched from its normal inhibition to excitation, dependent on interaction with the GHSR1a receptor.

Conclusions: DRD2 and GHSR1a are in the same neurons of the defecation centres and are functionally involved in the defecation control pathways. Our pharmacological and localisation studies are consistent with these receptors forming heteromers and with dopamine being the physiological activator of the heteromeric DRD2/ GHSR1a complex. The complex can be activated by both dopamine and ghrelin, but only dopamine has a physiological role.

Poster 12 Vasopressin secretion is modulated by estrogen levels in female rats Trujillo, Verónica 1,2; Camilo, Tays A 1; Reis, Luís C 3; Rorato, Rodrigo C 1; Mecawi, André S 1,3

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The hypothalamic magnocellular neurons produce and secrete vasopressin (AVP) in response to hyperosmolality. Once at the circulation, this neuropeptide act at the kidney and blood vessels to increase water reabsorption and blood pressure. The hypothalamus-neurohypophyses system is known to be sexually dimorphic, mainly due to sexual hormones regulating magnocellular neurons function. Recent studies have shown that the estrogen receptor of type β (ER β) increases the sensitivity of magnocellular neurons to water deprivation-induced hyperosmolality. The estrogen action to regulate AVP synthesis and secretion become especially important considering that the hypersecretion of AVP during pregnancy (when estrogen levels are high) seems to be involved in the physiopathology of preeclampsia, the main cause of maternal-fetal deaths worldwide. This work aims to evaluate the sex dimorphism and the role of estrogen on thirst and AVP secretion induced by acute hyperosmolality in rats. For that, we used adult Wistar rats divided into the following groups: 1) intact males; 2) intact females at proestrus/estrus; 3) intact females at metaestrus/diestrus; 4) ovariectomized female treated with oil (OVX+Oil); and 5) ovariectomized female treated with estradiol (10 μ g/0.1 ml per rat; OVX+E2). The efficiency of ovariectomy was confirmed by the lowest weight of the uterus of OVX+Oil females, whose uterus were even lighter than in metaestrus/diestrus group (all p 's<0.01), and by lower plasmatic estrogen levels in metaestrus/diestrus intact and OVX+Oil comparing with proestrus/estrous and OVX+E2 groups. A set of rats were adapted in metabolic cages and administrated with a hypertonic (1.5 M NaCl, i.p.) solution to induce intracellular dehydration and thirst. After hypertonic injection, rats remained for 1 h without water access, and then animals were allowed to drink for 24h. Acute hyperosmolality induced a robust water intake response in all groups, without significant changes according to sex or estrogen replacement. The second set of rats were decapitated 30 min after received an injection (i.p.) of hypertonic (1.5 M NaCl) or isotonic (0.15 M NaCl) solution and plasma was collected to assess AVP levels, osmolarity, and Na⁺ concentration. As expected, the hypertonic solution administration increases plasma AVP levels, osmolarity, and Na⁺ concentration in all groups (all p 's<0.0001). However, we found that, after hypertonic stimulus, intact females in metaestrus/diestrus stages and OVX+Oil females showed lower AVP plasma levels than males, intact females in proestrus/estrus stages, and OVX females treated with estrogen (all p 's<0.001), with no significant differences on plasma osmolality and Na⁺ levels. In summary, high estrogen levels seem to be necessary for female rats to achieve a full hyperosmolality-induced AVP secretion, compared to males. The modulation produced by estrogen on AVP levels could be related to the ER β activation due to its known effect on magnocellular neurons. Therefore, to better understand how estrogen modulates AVP secretion future works will be performed to evaluate the role of ER β on gene expression and activity modulation of magnocellular neurons in response to acute osmotic stimulation.

Poster 13 Oxytocin receptor signaling at the central amygdala does not mediate dehydration-induced exploration reduction in rats

Trujillo, Verónica 1,2; Felintro, Viviane 3; dos-Santos, Raoni C. 3; da Silva Almeida, Claudio 3; Rocha, Fábio F 3; Reis, Luís C 3; Mecawi, André S 1,3

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Vasopressin (AVP) and oxytocin (OXT) are neuropeptides produced by magnocellular neurons (MCNs) of the hypothalamus and secreted through neurohypophysis to defend mammals against dehydration. It was recently demonstrated that MCNs also project towards limbic structures modulating several behavioral responses. Thus, the present work evaluates the effect of dehydration (water deprivation or 0.3M salt loading) on locomotor and anxiety-like behaviors in Wistar male rats. Twenty-four hours of water deprivation or salt loading did not change exploration or anxiety-like behaviors in the elevated plus maze (EPM). However, after 48h of dehydration, water-deprived rats showed fewer entries into closed arms of EPM compared to control ($p=0.0085$) or salt loading ($p=0.0185$) groups associated with a reduction on the total EPM entries (open + closed arms) compared to control rats ($p=0.0514$). Despite an increase in the number of quadrants crossed in the light area of the light/dark box ($p=0.0129$) after 48h of water deprivation, no further behavioral alterations were produced by dehydration in the open field and light/dark box tests. In accordance, our results show an increase in plasma osmolality ($p=0.0063$) and hematocrit ($p<0.0001$) after 48h, but not 24h, of water deprivation. Thus, we evaluate glutamate decarboxylase 1 (Gad1), vesicular glutamate transporter 2 (Slc17a6), AVP (Avpr1a), and OXT (Oxtr) receptors expression at the lateral habenula, basolateral and central amygdala (CeA) after 48h of water deprivation or salt loading. Water deprivation, but not salt loading, for 48h was able to significantly increase Oxtr mRNA expression at the CeA ($p=0.0103$). Thus, we performed a bilateral pharmacological blockade of OXTR at the CeA (L-371,257, 1.6 pmoles) to evaluate its possible role in regulating the EPM exploration and/or water intake induced by 48h of water deprivation. The antagonization of OXTR at CeA did not reverse the hypoactivity response in EPM nor change water intake induced by water deprivation. Meanwhile, the negative correlation between closed arm entries in EPM and water intake found in vehicle-treated rats ($p=0.043$; $r=-0.49$) was reverted by OXTR antagonization at the CeA ($p=0.151$; $r=-0.15$). In conclusion, we confirm that water deprivation modulates exploratory behaviors in rats, but this response is not mediated by oxytocin receptor signaling at the CeA despite receptor mRNA expression up-regulation in that structure under 48h of water deprivation.

* Verónica Trujillo and Viviane Felintro contributed equally to this work

Poster 14 **Microglial pruning on axon initial segment spines at dentate gyrus granule cells: effects of early life stress and vasopressin in adult fear responsiveness**

Zetter, Mario A

Zetter, Mario A. 1; Hernandez, Vito S. 1; Eiden, Lee E. 4; Zhang, Limei 1.

Early life stress (ELS) modifies memory and stress susceptibility in both human and rodents. The mechanisms have yet to be fully understood. We have previously reported abnormal increase of peptidergic innervation in hippocampal formation (HF) and amygdala under ELS, as well as significant increase of their metabolic activities detected by PET tomography. Microglial cells exert crucial synaptic pruning activities during early development and neuropeptide vasopressin (VP) has been reported to suppress macrophage phagocytic activity. Thus, we asked whether microglia could have abnormal activity under ELS and whether VP could play a role on synaptic pruning during postnatal neurodevelopment. We report that somatic and axon initial segment (AIS) spines are present at granule cells of DG during early postnatal life (postnatal day 5, PND5) that are progressively eliminated (towards PND15 and 15). The exposure to daily maternal separation (MS) delayed the pruning of AIS spines, with marked effects in females than male rat pups, that retained abundant AIS spines, observed through Golgi-Cox staining. This was associated with hyper-ramified morphology of microglial cells (immunopositive for Iba1) associated to GC axon initial segments (positive for Ankyrin G) which featured increased engulfment of synaptic spines (measured as the number of PSD-95 positive puncta which overlapped with Iba1 at cell cytoplasm) at PND15. These morphological features were correlated with enhanced behavioral response of MS-exposed animals to a two-step auditory fear test and increased neuronal activation of DG granule cells (measured by cFos positive nuclei) at rat adolescence (PND50). To assess whether neuropeptide VP could be functionally associated with these observations, acute brain slices were incubated with VP analog for 2 hours, which mimicked the morphological rearrangements of microglial cells at DG. Our results suggest that the exposure to ELS induces abnormalities of synaptic pruning through the exposure of microglial cells to neuropeptides like VP, changing the excitatory status of neurons such as the DG granule cells and thus, changing at long-term, the behavioral response of individuals.

Poster 15 Hindbrain parabrachial complex PACAP containing projection forms Calyx-like synapses at GABAergic neurons of CeC project ventral pallidum and LPO modulating defensive locomotion

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Defensive locomotion can be triggered by processive stressors which require an appraisal of the situation to make the correct movement. This stress response involves high-level cognitive processing of incoming sensory information. Neuropeptide PACAP-PAC1 signaling has been reported to be crucially involved in this category of stress response. The circuit interaction have yet to be described. We report here a direct PACAP-glutamatergic projection from the hindbrain parabrachial complex (PBC) to the central amygdala (CeC) PAC1 expressing GABAergic neurons. This projection established perisomatic glutamatergic Calyx-like synapses observed at EM level. By using in vivo single cell juxtacellular labeling, anatomical reconstruction and immunohistochemistry, we found the targeted GABAergic neurons to project to ventral pallidum and lateral preoptic hypothalamus where the locomotor initiator and controller centers are reported in rodent. We recently developed a rodent model for simple defensive locomotion assessment. Animals were placed in a two-chamber wooden box with a glass-lidded chamber containing a sample of cat urine within a flask whose lid can be opened remotely. In between the 2 chambers there is a semi-opened escape door toward the chamber without the predator scent. Predator odor triggered defensive locomotion behaviors defined here as object exploration/retreat, pushing the escapedoor and freezing in which the PACAP-ko mice showed significantly decreased defensive behaviors, but increased purposeless movement compared with control. Bi-lateral GABAA agonist muscimol injection to PBC mimicked the gait and behavior of PACAP-ko subjects. Our results identify the PACAP-PAC1 signalling in PBC>CEC>LPO pathway as a "high fidelity" circuit interaction required for critical defensive locomotion.

Poster 16 The neuropeptide landscape of human prefrontal cortex

Zhong, Wen 1; Barde, Swapnali 2; Mitsios, Nicholas 2; Adori, Csaba 2; Oksvold, Per 1; Von Feilitzen, Kalle 1; O'Leary, Liam 3,4; Csiba, László 5; Hortobágyi, Tibor 6; Szocsics, Péter 7,8; Mechawar, Naguib 3,4; Maglóczky, Zsófia 8; Renner, Éva 9; Palkovits, Miklós 9; Uhlén, Mathias 1,2; Mulder, Jan 2; Hökfelt, Tomas 2

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The human prefrontal cortex (hPFC) is a complex brain region involved in cognitive and emotional processes, and psychiatric disorders. However, genome-wide maps of the chemical neuroanatomy, especially the modulating neuropeptide transmitter systems, are still lacking. Here, we describe a comprehensive analysis of gene expression profiles for 17 hPFC subregions complemented with three cortical reference regions. We used microdissection followed by genome wide transcriptome analysis, integration with data from single cell analysis and RNAscope for cellular expression. We found that anatomically neighboring regions of the prefrontal cortex have distinct molecular compositions, and we explored gene-coding proteins related to chemical signaling, in particular the neuropeptide systems. We present a complete peptidergic transcriptomic PFC landscape, where closely located and functionally different subregions are heterogeneous with unique peptide/transmitter-related transcript profiles, including microcircuits, involving local glutamatergic neurons co-expressing hypocretin/orexin, galanin or oxytocin. Here the peptide may represent a co-transmitter agonist (hypocretin/orexin) or antagonist (galanin). Specific neuropeptide receptors have been identified as targets for neuronal afferents, like neurotensin, and for peripheral blood-borne peptide hormones, like leptin, adiponectin and GIP, as well as growth hormone and prolactin. Peptide-rich PFC subregions are also enriched in transcripts for e.g., monoaminergic and nitroergic markers. These results support the concepts that the slow and long lasting neuropeptide signaling may both help stabilize circuit connectivity and fine-tune/modulate PFC functions executed during health and disease. The results may also advance our understanding of hPFC basic physiology as well as facilitate efforts to identify novel therapeutic strategies of relevance for human brain disorders.

Hybrid: virtual-f2f Segment

Scientific Program

Princess Mundo Imperial
Resort and Conference Center
Riviera Diamante, Acapulco, Mexico
August 15-19, 2021

Sunday 15th, August 2021	
15:00 - 15:10	Lee E. Eiden and Limei Zhang: Welcome
15:10 - 16:00	Lay Lecture: Dick Swaab (<i>Netherlands Institute for Neuroscience, The Netherlands</i>). Sexual differentiation of our brains: basis for diversity.
16:00 - 16:15	<i>Music interlude I</i>
16:15 - 17:00	Victor Mutt Lecture: Diego Bohorquez (<i>Duke University, USA</i>). A gut sense for calories.
17:00 - 17:15	<i>Music interlude II</i>
17:30 - 18:15	History Lecture: George Fink (<i>Florey Institute of Neuroscience, Australia</i>). External layer of the median eminence: a neurovascular synapse.
<i>Welcome Reception</i>	

Monday 16th, August 2021	
07:00 - 10:00	Keynote symposium 1 (H-KS 1) Chair: Geert De Vries (<i>Georgia State University, USA</i>).
07:00 - 07:45	H-KS 1.1: Carmen Sandi (<i>Brain Mind Institute, EPFL, Switzerland</i>). Neural circuits linking stress, anxiety, and motivation.
07:45 - 08:30	H-KS 1.2: Patrick Sexton (<i>Monash University, Australia</i>). Mechanisms of signaling by peptide-activated G protein-coupled receptors.
08:30 - 09:15	H-KS 1.3: Geert DeVries (<i>Georgia State University, USA</i>). Sex differences in the brain seen from a whole-body perspective.
09:15 - 10:00	H-KS 1.4: Robert Millar (<i>University of Pretoria, South Africa</i>). Rescue of function of mutant human GPCRs in the reproductive hormone axis.
10:00 - 11:00	<i>Buffet breakfast</i>
11:00 - 13:00	Scientific session 1 (H-SS 1): Chair: Lee E. Eiden (<i>National Autonomous University of Mexico, Mexico</i>).
10:00 - 11:30	H-SS 1.2: Sarah Melzer (<i>Harvard Medical School, USA</i>). Mechanisms and functions of GRP-GRPR peptidergic signaling in the auditory cortex.

11:30 -12:00	H-SS 1.2: Tom Cunningham (<i>UNT Health Science Center at Fort Worth, USA</i>). Renin-angiotensin-aldosterone system in cardiovascular regulation.
12:00 - 12:30	H-SS 1.3: André Mecawi (<i>Federal University of São Paulo, Brazil</i>). Osmoregulation of the transcriptome of the hypothalamic supraoptic nucleus.
12:30 - 13:00	H-SS 1.4: Limei Zhang (<i>National Autonomous University of Mexico, Mexico</i>). Calyx of Held-like synapse in rodent forebrain: A short story of a serendipitous observation
13:00 - 15:00	<i>Box lunch + posters viewing + networking</i>
15:00 - 17:30	Scientific session 2 (H-SS 2): Chairs: Xiaoke Chen (Dept Biology, Stanford University, Stanford, CA)
15:00 - 15:30	H-SS 2.1: Colin Brown (<i>University of Otago, New Zealand</i>). Plasticity in α-melanocyte stimulating hormone modulation of oxytocin neuron activity in pregnancy and lactation.
15:30 - 16:00	H-SS 2.2: Alexandra Castillo-Ruiz (<i>Georgia State University, USA</i>). Effects of birth mode on vasopressin and oxytocin neurons of the hypothalamus.
16:00 - 16:30	H-SS 2.3: Mario Zetter (<i>National Autonomous University of Mexico, Mexico</i>). Early life stress and neuropeptides-microglial role in neurodevelopment.
16:30 - 17:00	H-SS 2.4: Andrés Quintanar-Stephano (<i>Universidad Autonoma de Aguascalientes, Aguascalientes, Mexico</i>). Effects of arginine vasopressin (AVP) deficiency or blocking of the V1a-V2 AVP receptors on liver functions and fibrosis in chronic portocaval anastomosis rats.

Tuesday 17th, August 2021	
07:00 -10:00	Keynote Symposium 2 (H-KS-2) Chair: Javier Stern (<i>Georgia State University, USA</i>).
07:00 - 07:45	H-KS 2.1: John Furness (<i>The Florey Institute for Neuroscience, Australia</i>). An essential interaction of the dopamine D2 and the ghrelin receptor for the physiological control of colo-rectal function
07:45 - 08:30	H-KS 2.2: Valery Grinevich (<i>University of Heidelberg, Germany</i>). How does a single neuropeptide elicit pleiotropic behavioral and metabolic effects? oxytocin as an example.

08:30 - 09:15	H-KS 2.3: Marisela Morales (<i>National Institute on Drug Abuse, USA</i>). Fast and slow co-transmission in the modulatory system.
09:15 - 10:00	H-KS 2.4: Javier Stern (<i>Georgia State University, USA</i>). Real-time two-photon imaging of the hypothalamus in vivo.
10:00 - 11:00	Buffet breakfast
11:00 -13:00	Scientific session 3 (H-SS 3): Chair: Rebeca Mendez (<i>National Autonomous University of Mexico, Mexico</i>).
10:00 - 11:30	H-SS 3.1: Mike Ludwig (<i>University of Edinburgh, UK</i>). Exploring novel neuronal populations of vasopressin expressing neurones using transgenic rat models and viral transfection systems.
11:30 -12:00	H-SS 3.2: Simone L. Meddle (<i>University of Edinburgh, UK</i>). Seasonal breeding in birds: environmental regulation of the neuroendocrine and behavioural systems.
12:00 - 12:30	H-SS 3.3: Mary Lee (<i>Veterans Affairs Medical Center, Washington, DC, USA</i>). Central signaling after systemic administration of oxytocin.
12:30 - 13:00	H-SS 3.4: Danilo Lustrino (<i>Federal University of Sergipe, Brazil</i>). Anabolic and anti-catabolic effects of oxytocin on skeletal muscle protein metabolism.
13:00 - 15:00	Box lunch + posters viewing + networking
15:00 - 17:15	Scientific session 4 (H-SS 4): Chair: Sushil Mahata (<i>University of California, San Diego, USA</i>).
15:00 - 15:30	H-SS 4.2: Margarita Curraz-Collazo (<i>University of California, Riverside, USA</i>). Dysregulation of hypothalamic gene expression and the oxytocinergic system by diabetogenic soybean oil diets in mice.
15:30 - 16:00	H-SS 4.3: Vito S. Hernández (<i>National Autonomous University of Mexico, Mexico</i>). Aging and GABAergic transmission in limbic system: testosterone and neuropeptides.
16:00 - 16:30	H-SS 4.4: Sushil K. Mahata (<i>University of California, San Diego, USA</i>). Catestatin's role in immunometabolism and insulin sensitivity.
16:30 - 17:15	H-SS 4.5: George Fink (<i>University of Melbourne, Australia</i>). Gonadotropin Releasing Hormone (GnRH), a pluripotent neuropeptide: significance of GnRH self-priming and tachyphylaxis.

Wednesday 18th, August 2021

07:00 - 10:00	Keynote Symposium 3 (H-KS-3) Chair: George Fink (<i>University of Melbourne, Australia</i>)
07:00 - 07:45	H-KS 3.1: Kokaia Merab (<i>Lund University, Sweden</i>). Neuropeptides for gene therapy In epilepsy.
07:45 - 08:30	H-KS 3.2: Arpád Dobolyi (<i>Eotvos Lorand University, Hungary</i>). Tuberoinfundibular peptide 39: an emerging new social neuropeptide.
08:30 - 09:15	H-KS 3.3: Francesco Ferraguti (<i>Medical University of Innsbruck, Austria</i>). Cortical Vasoactive Intestinal Polypeptide (VIP)-expressing interneurons and the broadcasting of salience.
09:15 - 10:00	H-KS 3.4: Xiaoke Chen (<i>Stanford University, USA</i>). Thalamic control of opiate-associated memory.
10:00 - 11:00	<i>Buffet breakfast</i>
11:00 -13:00	Scientific session 5 (H-SS 5): Chair: Alexandra Castillo-Ruiz (<i>GSU, USA</i>).
11:00 - 11:30	H-SS 5.1: Ryoichi Teruyama (<i>Louisiana State University, USA</i>). Sexually dimorphic oxytocin receptor expressing neurons in the MPOA regulate maternal behavior.
11:30 - 12:00	H-SS 5.3: Lee E. Eiden (<i>National Institute of Mental Health, USA</i>). PACAP-glutamate co-transmission in brain circuits.
12:00 - 12:30	H-SS 5.4: Carolina Escobar (<i>Universidad Nacional Autónoma de México, México</i>). The importance of circadian rhythms for metabolic health.
13:00 - 15:00	<i>Box lunch + posters viewing + networking.</i>
15:00 - 17:00	IRPS General Assembly
	<i>Conference dinner (formal dress)</i>

Thursday 19th, August 2021

07:00 - 07:30	<p>Distinguished Member recognition Co-Chairs: Lee E. Eiden & Limei Zhang (<i>National Institute of Mental Health, USA & National Autonomous University of Mexico</i>).</p>
07:30 - 08:15	<p>Special Event 1 (SE 1): Julian Mercer (<i>University of Aberdeen, UK</i>). Scientific publishing: obligations and opportunities</p> <p><i>An exploration of how our scientific community can support the journals that truly fulfill the mission of advancing science communication for all scientists</i></p> <p>Lead discussants: Julian Mercer, Bob Millar, Dave Grattan, Gareth Leng: current and past editors-in-chief, Journal of Neuroendocrinology, <u>the IRPS official journal</u>.</p> <p>Willis K (Rick) Samson, Ex-Editor-in-Chief, American Journal of Physiology -Regulatory, Integrative, and Comparative Physiology (APS), Deputy Editor-in-Chief, Physiological Review (APS), and incoming Distinguished Member of IRPS</p>
08:15 - 09:00	<p>Neuroscience Special Lecture:</p> <p>Xiao-Dong Wang (<i>Zhejiang University, China</i>). Exploring joy and worry in the tactile world.</p>
09:00 - 09:30	<p>Special Event 2 (SE 2): Greti Aguilera (<i>National Institute of Child Health and Human Development, USA</i>). Old and new challenges for basic and clinical research on regulatory peptides: a physiological perspective.</p>
09:30 - 10:15	<p>Special Event 3 (SE 3): Willis K. Samson (<i>Saint Louis University School of Medicine, USA</i>). Peptides as therapeutics: orphan GPCR – ligand matching is just the beginning.</p>
10:15 -10:30	<p>Closing ceremony and group photograph</p>

Hybrid segment
Abstracts



Lay Lecture

Sexual differentiation of our brains: basis for diversity

Swaab, Dick F

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Neuropsychiatric disorders, Amsterdam, The
Netherlands*

Sexual differentiation of our brains is a clear example of one of the mechanisms that is the basis for the huge diversity in our brain and behavior. Our feeling of being a man or a woman (gender-identity),

or everything in between, and our sexual orientation (hetero- homo- or bisexuality) have already been permanently programmed in our brain circuits before birth. These processes are dependent on a direct interaction of testosterone with the developing neurons, in contrast to rodents where aromatization of testosterone is crucial for the male differentiation of the brain. There are permanent structural and functional gender differences in the human brain, and reversals of such differences that are related to their gender-identity are found in transsexual people. The “mosaic” hypothesis states that there is a high variability in the degree of ‘maleness’/‘femaleness’ of different features within a single brain. This is indeed true for many brain areas, but we think from recent observations much less so for systems that are involved in gender-identity and sexual orientation. This topic has social consequences for people with gender identity disorders in relation to their name in the birth certificate and passport, and their participation in top-sports and for homosexual people in relation to adoption of children.

Sex differences in our brain are accompanied by sex differences in the vulnerability for particular neuropsychiatric disorders. In addition, sex differences are found in systems affected in neuropsychiatric disorders. For instance, in mood disorders sex differences are present in the activation of the stress-related neuropeptides CRH, oxytocin and hypocretin (=orexin). In schizophrenia, a different sex difference is present in hypocretin, and in preclinical Alzheimer patients a sex difference is present in somatostatin neurons in the entorhinal cortex, that is affected early in the Alzheimer process.

Well documented human postmortem brain is available for the neuroscientific community. It is necessary to validate animal models for neuropsychiatric disorders, and it can reveal valuable functional information in relation to novel therapeutic strategies.

Swaab DF, Wolff SEC, Bao AM. Sexual differentiation of the human hypothalamus: Relationship to gender identity and sexual orientation. *Handb Clin Neurol.* 2021;181:427-443. doi: 10.1016/B978-0-12-820683-6.00031-2. PMID: 34238476.



Victor Mutt Lecture

A gut sense for calories

Bohórquez, Diego V

Departments of Medicine and Neurobiology, Duke University, Durham, NC, USA

Our motivation to consume sugars is thought to arise at the surface of the gut. However, the neural circuits are unknown. The Bohórquez Laboratory discovered a neural circuit linking gut to brain in one synapse. The circuit begins with a type of sensory epithelial cell that synapses with the vagus nerve. These epithelial cells are called neuropod cells. In the mouse small intestine, monosynaptic rabies virus infects neuropod cells and spreads onto vagal neurons that project to the nucleus tractus solitarius in the brainstem. This neural circuit is necessary and sufficient to transduce sensory signals from sugars. Silencing neuropod cells silences the ability of the animal to distinguish the caloric content in sugars. This gut sensor for caloric sugars is a portal for nutrients to drive our motivation to eat.



History Lecture

External layer of the median eminence: a neurovascular synapse

Fink, George

Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville 3010, Melbourne, Victoria, Australia

The external layer of the median eminence is comprised of nerve fibres that terminate on the primary plexus of the hypophysial portal vessels. This system is a unique neurovascular synapse which can be used as a window through which may be studied the characteristics of central neurotransmission. The heterogeneity of the neuropil of the external layer of the median eminence, in terms of neurotransmitter types, carries the advantage that interactions between different classes of neurons can be investigated. These points are illustrated by physiological and pharmacological studies on the release into hypophysial portal blood of several regulatory neuropeptides, by way of the transpharyngeal method devised by G Fink and C Worthington Jr (1965). Examples, include studies of the characteristics of gonadotropin releasing hormone, thyrotropin releasing hormone, vasoactive intestinal peptide, somatostatin 14, 28 (1-12), corticotropin releasing factor (CRF-41), vasopressin, oxytocin, atrial natriuretic peptide, and PACAP. The portal vessels convey these neurohormones to the anterior pituitary gland where they stimulate or inhibit the release of pituitary hormones. The pituitary gland may be used to investigate the "post synaptic" effects of regulatory neuropeptides. In particular the portal-pituitary system has established the relative importance of CRF-41 and vasopressin in the control of adrenocorticotropin (ACTH) and the glucocorticoid negative feedback control of ACTH. Similarly, the portal-pituitary system has established the positive and negative feedback systems involved in the release of gonadotropin releasing hormone and the pituitary gonadotropins. In addition to "established" neurohormones, the portal-pituitary has also helped to discover previously unknown regulatory peptides and their functions. Examples include plasminogen activator, thyrocalcitonin and the calcitonin gene related peptide. In addition to regulatory neuropeptides, the neurovascular synapse has also facilitated studies on other neurotransmitters such as dopamine, for example, which plays a key inhibitory role in the control of prolactin release.

H-KS 1.1 Neural circuits linking stress, anxiety, and motivation



Sandi, Carmen

Brain Mind Institute, EPFL, Lausanne, Switzerland

There is important inter-individual variation in stress coping responses and motivated behavior, and trait anxiety is revealing as a key moderator of this variation. Our work in animals and humans identifies the involvement of mitochondrial function and metabolism in the brain's motivation hub, the nucleus accumbens, in the link between stress, anxiety and motivated actions. I will present work in rodents and humans; the latter one involving virtual reality, magnetic resonance spectroscopy and neuroimaging. Our findings have implications for the understanding of the mechanisms involved in individual differences in vulnerability to stress and comorbidity between anxiety and depression.



H-KS 1.2 Mechanisms of signaling by peptide-activated G protein-coupled receptors

Sexton, Patrick M 1,2; Zhang, Xin 1,2; Belousoff, Matthew J 1,2; Zhao, Peishen 1,2; Piper, Sarah J. 1,2; Liang, Yi-Lynn 2; Christopoulos, Arthur 1,2; Wootten, Denise 1,2

1 ARC Centre for Cryo-electron Microscopy of Membrane Proteins, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia; 2 Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia.

G protein-coupled receptors (GPCRs) are the largest family of cell surface drug targets. Among these, peptide-activated receptors play major roles in systems level physiology, including metabolic, cardiovascular and immunological regulation. Consequently, there is high interest in understanding the structure of members of this receptor superfamily and molecular detail of how ligands and transducer proteins interact with the receptors. Our laboratory has been applying single particle cryo-EM to determination of active GPCR structures, using minimally modified receptors, to understand the structural basis for receptor activation by peptide and small molecule ligands. This work has provided molecular insight into the pharmacology of partial and biased agonists, and into promiscuous G protein coupling to individual receptors. Moreover, cryo-EM can access the spectrum of conformations present during vitrification allowing 3D reconstruction of conformational dynamics of GPCR complexes along principal components. This new insight into receptor dynamics has been critical to understanding differences in the pharmacology of different ligands that can interact with the same receptor or receptor family.



H-KS 1.3 Sex differences in the brain seen from a whole-body perspective

De Vries, G J

*Department of Biology, Georgia State University,
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Vasopressin (AVP) innervation shows some of the most consistently found sex differences among vertebrates, with males having denser AVP projections from, the bed nucleus of the stria terminalis and medial amygdaloid nucleus in males than in females.¹ Parsimony dictates that sex differences in sex chromosomal gene expression, gonadal hormones, and environmental interactions act directly on the brain to cause these and other neural sex differences. However, these

factors act on peripheral structures as well. Neural sex differences may therefore develop in part because brains reside in fundamentally different bodies. Brains may generate different output autonomously, but if they are wired up to different bodies, similar output will have different consequences for function. To generate similar behaviors, the nervous system may have to compensate by giving different commands. This interaction between body and brain has to be taken into account for a full understanding of the development as well as function of sex differences in the brain.² Within the brain, similar rules may apply as individual neurotransmitter systems, dimorphic or not, may interact with sexually dimorphic circuits.

We are interpreting the role of sex differences in AVP expression from this perspective. A growing number of studies demonstrate manipulating AVP signaling has different, and sometimes opposite, effects on social behavior and anxiety in male and female animals, for example reference.³ Recently, we have directly tested the function of sexually dimorphic AVP innervation, taking advantage of two different strains of AVP Cre mice and the existence of different Cre-dependent viral vectors to specifically manipulate AVP-expressing cells. We find, for example, that ablation of BNST AVP cells affected social and anxiety-related behavior stronger in males than in females.⁴⁻⁵ Interestingly, ablation of PVN AVP, which do not show marked sex differences shown, have more pronounced effects in females.⁶⁻⁷ The consequences of these effects will be discussed. The case will be made that in some cases sex differences in AVP expression function to compensate for other differences in the brain or body to reach similar behavioral and physiological endpoints.

1. De Vries GJ, Panzica GC. (2006). Sexual differentiation of central vasopressin and vasotocin systems in vertebrates: different mechanisms, similar endpoints. *Neuroscience* 138: 947-955.

2. De Vries GJ, Forger NG (2015) Sex differences in the brain: a whole-body perspective. *Biol Sex Differences* 6:15

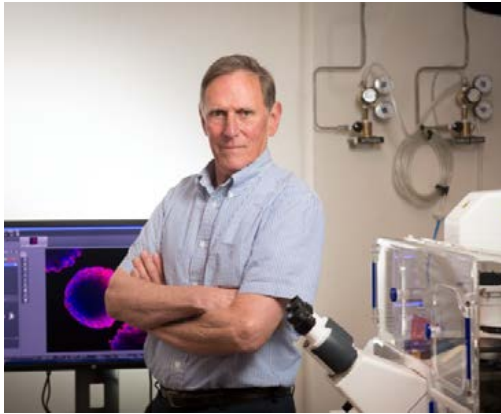
3. Veenema AH, Bredewold R, De Vries GJ (2013) Sex-specific modulation of juvenile social play by vasopressin. *Psychoneuroendocrinology*. 38: 2554-2561.

4. Rigney N, Whylings J, Mieda M, de Vries GJ, Petrusis A. (2019) Sexually dimorphic vasopressin cells modulate social investigation and communication in sex-specific ways. *eNeuro* 6: e0415-18.

5. Whylings J, Rigney N, Peters NV, de Vries GJ, Petrusis A. (2020). Sexually dimorphic role of BNST vasopressin cells in sickness and social behavior in male and female mice, *Brain, Behavior, and Immunity* 83: 68-77

6. Rigney N, Whylings J, de Vries GJ, Petrusis A. 2020. Sex Differences in the Control of Social Investigation and Anxiety by Vasopressin Cells of the Paraventricular Nucleus of the Hypothalamus. *Neuroendocrinology* 111: 521-535

7. Whylings J, Rigney N, de Vries GJ, Petrusis A. 2020. Removal of vasopressin cells from the paraventricular nucleus of the hypothalamus enhances lipopolysaccharide-induced sickness behaviour in mice. *Journal of Neuroendocrinology* 33 (1), e12915



H-KS 1.4 Rescue of function of mutant human GPCRs in the reproductive hormone axis

Millar, Robert P 1,2; Newton, Claire L 1, Anderson Ross C 1

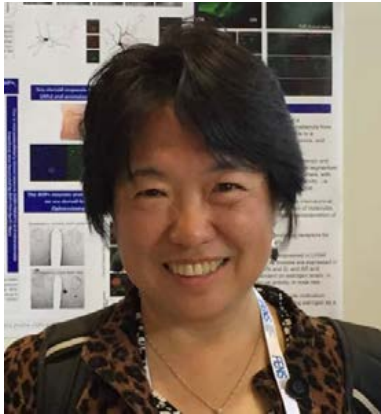
1 Centre for Neuroendocrinology, Departments of Immunology and Physiology, University of Pretoria, Pretoria, South Africa; 2 Institute for Infectious Diseases, University of Cape Town, Cape Town, South Africa

Reproduction in vertebrates is driven by hypothalamic peptides, kisspeptin and neurokinin B which stimulate gonadotropin releasing hormone (GnRH), which in turn stimulates luteinizing hormone (LH) and follicle stimulating hormone (FSH) which regulate testis and ovarian function.

Inactivating mutations in G-protein coupled receptors (GPCRs) at all levels of this axis give rise to incomplete reproductive development and adult infertility. The majority of the mutations in these GPCRs cause misfolding of the receptor and a failure to traffic to the cell surface. We have therefore sought for cell permeant small molecules which can bind orthosterically or allosterically to stabilize the nascent GPCR in the endoplasmic reticulum and chaperone the mutant GPCR to the cell membrane.

We have successfully identified cell-permeant small molecules targeting receptors at all levels of the axis and demonstrated rescue of cell surface expression and restoration of function for NKB, GnRH, LH and FSH receptors. Moreover we have also been able to allosterically activate binding deficient and signalling deficient LHR with an LHR small molecule

These discoveries represent an advance towards personalized medicine for GPCR inactivating mutations in the human reproductive hormone axis. As GPCRs constitute 80% of signalling in humans, inactivating mutations are likely to be a major contributor of disease and hence targets for small molecule rescue of function. The existence of vast numbers of GPCR-targeted small molecules from pharma data bases, many of which have already entered the clinic but abandoned, provides a rich source for treating GPCR human mutations and is more viable than a gene repair approach



H-SS 1.1 Calyx of Held-like synapse in rodent forebrain: *A short story of a serendipitous observation*

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Kolliker (1886) - Fuse (1913) described a nucleus located in the dorsolateral pons in human that today carries their names (KF_n). In rodent, it is located on the latero-ventral side of the superior cerebellar peduncle (scp) and comprises one of the three parabrachial subdivisions. It sends signals to the lower medulla oblongata, the spinal cord, the extended amygdala, and the lateral hypothalamus. The KF_n is more developed in humans than in other animal species. Chronic stimulation of the KF_n region has resulted in relief of intractable pain in patients and the effect is comparable to that of PAG/periventricular stimulation. Using duplex and multiplex ISH, we report here a distinct neuronal population in the KF_n that co-expresses VGLUT1, VGLUT2, PACAP, CGRP and neurotensin (NT) RNA. Using *in vivo* juxtacellular labeling, we observed that some of these neurons send long-range monosynaptic projections to the central amygdala (capsular division, CeC) and to bed nucleus of stria terminalis, oval division (BNST_{ov}), making contact with PKC δ immunopositive neurons co-expressing VGAT, PAC1 and VPAC2 mRNA, which were seen to project to lateral preoptic region, detected by *in vivo* labeled single neuron reconstruction. Using focused ion beam electron microscopy (FIBSEM) and transmission electron microscopy (TEM), we demonstrate for the first time that the PACAP-glutamatergic pathway from hindbrain establishes Calyx of Held-like synapses in extended amygdala and Gray type I synapse from PACAP immunopositive axons to GABAergic neuron somata. Fos activation was evaluated after formalin injection in the paws of urethane anesthetized rats. Strong neural activation was observed in the PBN / KF_n and its targets in BNST_{oval} and CeC. Our results suggested the PACAP signaling pathway in KF_n>CEC/BNST_{ov}>LPO may serve as a "high-fidelity (HiFi)" circuit interaction for critical defensive locomotion toward survival.



H-SS 1.2 Mechanisms and functions of GRP-GRPR peptidergic signaling in the auditory cortex

Melzer, Sarah

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Inhibitory neurons throughout the mammalian cortex are powerful regulators of circuit excitability and plasticity and allow for the adaption of cortical processing to changing environments and experiences. All major inhibitory cortical cell types are marked by differential expression of neuropeptide receptors, suggesting highly diverse context- and experience-dependent peptidergic modulation of cortical processing. We found that the bombesin-like neuropeptide gastrin-releasing peptide (GRP) serves as an important regulator of cortical memory formation through selective targeting of one specific inhibitory neuronal cell type. Using novel in vivo imaging approaches, CRISPR/Cas9-mediated knockout of the GRP receptor and a combination of anterograde and retrograde tracing techniques, we aimed at gaining a detailed understanding of the peptidergic circuit, signaling mechanisms and in vivo functions. Our data establish peptidergic regulation of cortical disinhibitory microcircuits as a mechanism to regulate circuit functions and auditory fear memory.



H-SS 1.3 Osmoregulation of the transcriptome of the hypothalamic supraoptic nucleus

Mecawi, André S 1*; **Pauža, Audrys G** 2*; **Paterson, Alex** 2; **Hindmarch, Charles C T** 3; **Greenwood, Mingkwan** 2; **Murphy, David** 2#; **Greenwood, Michael P** 2#.

1 Laboratory of Molecular Neuroendocrinology, Department of Biophysics, Paulista School of Medicine, Federal University of São Paulo, São Paulo, Brazil; 2 Molecular Neuroendocrinology Research Group, Bristol Medical School: Translational Health Sciences, University of Bristol, Bristol, England; 3 Queen's

Cardiopulmonary Unit (QCPU), Translational Institute of Medicine (TIME), Department of Medicine, Queen's University, Kingston, Ontario, Canada.

The hypothalamic supraoptic nucleus (SON) is a core osmoregulatory control centre that deciphers information about the metabolic state of the organism and orchestrates appropriate homeostatic (endocrine) and allostatic (behavioural) responses. We have used RNA sequencing to describe the polyadenylated transcriptome of the SON of the male Wistar Han rat. These data have been mined to generate comprehensive catalogues of functional classes of genes (enzymes, transcription factors, endogenous peptides, G protein coupled receptors, transporters, catalytic receptors, channels and other pharmacological targets) expressed in this nucleus in the euhydrated state, and that together form the basal substrate for its physiological interactions. We have gone on to show that fluid deprivation for 3 days (dehydration) results in changes in the expression levels of 2247 RNA transcripts, which have similarly been functionally catalogued, and further mined to describe enriched gene categories and putative regulatory networks (Regulons) that may have physiological importance in SON function related plasticity. We hope that the revelation of these genes, pathways and networks, most of which have no characterised roles in the SON, will encourage the neuroendocrine community to pursue new investigations into the new 'known-unknowns' presented in this study.

* Equal first authors; #Equal senior authors.

H-SS 1.4 Renin-angiotensin-aldosterone system in cardiovascular regulation



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1 Department of Physiology and Anatomy, Graduate School of Biomedical Sciences, UNT Health Science Center at Fort Worth, Fort Worth, TX, 76107

The Renin-angiotensin-aldosterone system (RAAS) is one of the primary therapeutic targets for cardiovascular disease. However, the existence of independent tissue RAAS remains controversial. Hypertension associated with chronic intermittent hypoxia (CIH), an animal model of the hypoxemia related to sleep apnea, is angiotensin dependent. Seven days of CIH produce increases in the expression of angiotensin related genes in the lamina terminalis region of adult male rats. This includes increases in the expression

of ace1, ace2, and agtr1a in the median preoptic nucleus (MnPO). Manipulations that target angiotensin receptors in the CNS, such as intracerebral or local paraventricular nucleus infusions of losartan block CIH hypertension. Furthermore, AAV mediated angiotensin receptor knockdown in either the MnPO or the subfornical organ (SFO) prevent the development of CIH hypertension. While the SFO is a circumventricular organ that can be directly influenced by circulating angiotensin, the MnPO and paraventricular nucleus are inside the blood-brain-barrier. Together, these results indicate a role of a brain RAAS in CIH hypertension.

To investigate the role of a brain RAAS, our lab has generated angiotensin sensitive “sniffer” cells by transfecting Chinese Hamster ovary cells with agtr1a and a genetically based calcium indicator like RGECO. These cells have been placed on the MnPO in a sagittal brain slice preparation containing an intact SFO to MnPO pathway. Angiotensin sensitive sniffer cells placed on the MnPO demonstrate spontaneous and SFO evoked activity. These responses can be blocked by losartan (10 μ M) and tetrodotoxin (1 μ M). Incubating the slices with captopril (10 μ M), an ACE inhibitor, also reduces the spontaneous activity of angiotensin sniffer cells over the MnPO.

To test the role of renin in these responses, we used male and female (2-6 mo) SS.SS Ren1-m1 renin heterozygous (Het) and homozygous (Ho) knock out rats. Bath application of aliskerin (10 μ M), a renin inhibitor, produced a moderate reduction in sniffer cell activity in wild type males, while it induced a more robust reduction in activity in wild type females. Baseline activity in male Het KO was reduced compared to female Het KO. Aliskerin reduced sniffer cell activity in slices from both males and females but there was no difference in the aliskerin effects between Het KO males and females. In slices from Ho KO, baseline activity was still present in both male and female. There were no differences in basal sniffer cell activity between males and females and aliskerin did not reduce sniffer cell activity in the male and female Ho KO. Furthermore, there were no estrous cycle differences in the baseline activity and the effects of aliskerin in female Het KO and Ho KO slices.

These results indicate that the brain RAAS may be independent of the peripheral RAAS in Renin KO rats and there are sex differences in renin-independent angiotensin synthesis. Future experiments will test the effects of CIH on angiotensin signaling in MnPO.

Supported by P01HL088052, R01HL155977



H-SS 2.1 Plasticity in α -melanocyte stimulating hormone modulation of oxytocin neuron activity in pregnancy and lactation

Brown, Colin H 1,2,3; **Perkinson, Michael R** 1,2,3; **Augustine, Rachael A** 1,2,3; **Kirchner, Matthew K** 4; **Zhang, Meng** 4; **Stern, Javier E** 4

1 Brain Health Research Centre, 2 Centre for Neuroendocrinology, 3 Department of Physiology, University of Otago, Dunedin, Aotearoa New Zealand; 4 Center for Neuroinflammation and Cardiometabolomic Diseases, Georgia State University, Atlanta, GA, USA.

The peptide hormone, oxytocin, is secreted into the circulation from the posterior pituitary gland to stimulate uterine contraction during birth and milk ejection during suckling. Oxytocin is synthesized by magnocellular neurons of the hypothalamic supraoptic nucleus (SON) and paraventricular nucleus (PVN), and its secretion into the circulation is triggered by action potential firing. Oxytocin neuron activity is governed by a complex interplay of intrinsic and extrinsic regulators, each of which is modified during pregnancy to increase oxytocin secretion.

We recently reported that inhibition of oxytocin neuron firing rate by the neuropeptide, α -melanocyte stimulating hormone (α -MSH), is lost by mid-pregnancy as part of a general attenuation of hypothalamic responsiveness to α -MSH. However, we noted that α -MSH inhibited some neurons but excited others. Therefore, we hypothesised that α -MSH inhibition of oxytocin neuron activity would switch to excitation in late-pregnancy and lactation. To test this hypothesis, we made extracellular single-unit recordings from SON oxytocin neurons in urethane-anesthetized non-pregnant, late-pregnant and lactating rats during local administration of α -MSH for 30 min through a microdialysis probe placed on the surface of the SON. Intra-SON microdialysis administration of α -MSH progressively decreased oxytocin neuron firing rate over 30 min in non-pregnant rats. By contrast, α -MSH progressively increased oxytocin neuron firing rate in late-pregnant rats and lactating rats. These effects of α -MSH were specific to oxytocin neurons because intra-SON α -MSH administration had no effect on the firing rate of SON vasopressin neurons in non-pregnant, late-pregnant and lactating rats.

In addition to secretion into the circulation from the posterior pituitary gland, magnocellular neurons also secrete oxytocin into the brain from axon collaterals as well as from their soma and dendrites, and this somato-dendritic secretion can occur independently of axon terminal secretion. Central oxytocin is anorexigenic and is thought to mediate the satiety effects of α -MSH. Remarkably, in parallel with decreasing the firing rate of oxytocin neurons in non-pregnant rats, α -MSH simultaneously increases somato-dendritic secretion. While oxytocin is anorectic in non-pregnant rats, it increases food intake in pregnant rats. Therefore, we hypothesised that α -MSH stimulation of somato-dendritic oxytocin secretion would be maintained into lactation to support increased food intake required to cope with the metabolic demands imposed by the offspring. To test this hypothesis, we used oxytocin receptor-expressing sniffer (snifferOT) cells to monitor changes in somato-dendritic oxytocin secretion from oxytocin neurons in brain slices from non-pregnant and lactating rats during superfusion of α -MSH. The latency and amplitude of snifferOT cell intracellular calcium responses to α -MSH were similar in PVN slices from non-pregnant and lactating rats, although the duration of the oxytocin-induced calcium response was longer in slices from lactating rats.

Taken together, our results show that α -MSH inhibition of oxytocin neuron firing rate switches to excitation over pregnancy, while α -MSH stimulation of somato-dendritic oxytocin secretion is maintained (or prolonged) into lactation. Hence, plasticity in α -MSH regulation of oxytocin neuron activity might facilitate secretion into the circulation for birth and milk ejection while maintaining somato-dendritic oxytocin secretion to increase food intake.



H-SS 2.2 Effects of birth mode on vasopressin and oxytocin neurons of the hypothalamus

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Birth is an extraordinary event for placental mammals and occurs at a time when key developmental processes, such as neuronal cell death, are shaping the brain. Little is known about the contributions of birth to brain development and whether birth mode (vaginal vs. Cesarean) alters neurodevelopmental trajectories. To study these questions, we manipulated birth mode in mice (matched for gestation length and birth time) and found that, on the day of birth, Cesarean birth caused greater cell death across many brain regions, with the most dramatic effect observed in the hypothalamic paraventricular nucleus (PVN). Intriguingly, this effect was associated with reduced vasopressin (VP) neuron number at weaning. We next investigated whether the effect of birth mode on VP neurons of the PVN extends to adulthood and whether birth mode also affects oxytocin (OT) neurons. We found that Cesarean birth reduced VP neuron numbers, specifically in magnocellular regions of the PVN. Cesarean birth also reduced VP and OT soma size and VP efferent projections in the PVN. No effect of birth mode was found in other prominent VP and OT hypothalamic populations. Thus, Cesarean delivery causes long-term effects on the VP and, to a lesser extent, OT systems in the PVN, suggesting that this region is particularly sensitive to the effects of birth mode. Because VP is neuroprotective *in vitro*, and a massive VP surge follows a vaginal but not a Cesarean birth, we provided VP treatment to Cesarean-born mice at birth, and found that this rescued the effects of birth mode on cell death in the PVN. It remains to be established whether this manipulation can also rescue the VP and OT deficits seen at later ages. Taken together, our findings may help explain the altered behavior reported for Cesarean-born mice and provide insights on the role of VP at birth. This is also of clinical significance given the widespread practice of Cesarean births across the world.



H-SS 2.3 Circadian gating of the liver-spinal axis initiates an anti-inflammatory reflex

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The autonomic nervous system (ANS) modulates the immune response through the engagement of an anti-inflammatory reflex.

There is controversy regarding which efferent branch of the ANS, sympathetic or parasympathetic, downregulates the intensity of the inflammatory response. Furthermore, how information about the immune status of the body reaches the CNS to engage this reflex remains unclear. The present study demonstrates the existence of a liver-spinal axis that conveys early circulating inflammatory information to the CNS in response to lipopolysaccharide (LPS) and serves as the afferent arm of a sympathetic anti-inflammatory reflex. Furthermore, brainstem and spinal cord visceral sensory neurons show a circadian sensitivity to the incoming inflammatory information, in particular, prostaglandins (PG). Consequentially, the liver-spinal axis promotes the retention of tumor necrosis factor α (TNF α) in the liver and spleen during the resting period, resulting in low plasmatic TNF α levels. Consistently, low sensitivity for LPS during the active period promotes the release of TNF α from the organs into the circulation, resulting in high plasmatic TNF α levels. The present novel findings illustrate how the circadian activation of the liver-spinal axis contributes to the daily fluctuations of the inflammatory response.

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H-SS 2.4 Early life stress and neuropeptides-microglial role in neurodevelopment

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The exposure to adverse experiences during early life (early life stress, ELS) imprint profound and long-term changes in the brain, but how the multimodal sensory information from early life is transduced from environment to nervous tissue remains to be answered.

In recent years, the microglia, resident immune cells of the brain previously recognized for their role in neuroinflammation, have gained attention in these processes as they participate in the remodeling of neuronal connections during neurodevelopment, either by strengthening synapses or by eliminating excessive synaptic spines in an activity-dependent manner. Recently we have shown that daily maternal separation (MS), as a model of ELS during the first two postnatal weeks, was correlated with the presence of a hyper-ramified phenotype of a novel population of these cells named axon initial segments (AIS)-associated microglia. This morphological feature observed in microglia was associated with an abnormal pruning of synaptic spines that are present at immature axon initial segments (AIS) of granule cells in the dentate gyrus (DG), resulting in increased neuronal activation at ventral and dorsal DG and enhanced fear responsiveness of animals towards repeated auditory stimuli. The morphological rearrangement of microglial cells was mimicked *ex vivo* with vasopressin incubation, resembling those featured in stressed rats.

This data suggests that AVP, OT and other neuropeptides that are up- or down-regulated in response to ELS could act as transducing messengers of information from the environment to microglial cells for shaping neural circuits excitability in response to external stimuli during early life, making in turn, sharper and adaptive individuals.



H-SS 2.5 Effects of arginine vasopressin (AVP) deficiency or blocking of the V1a-V2 AVP receptors on liver functions and fibrosis in chronic portocaval anastomosis rats

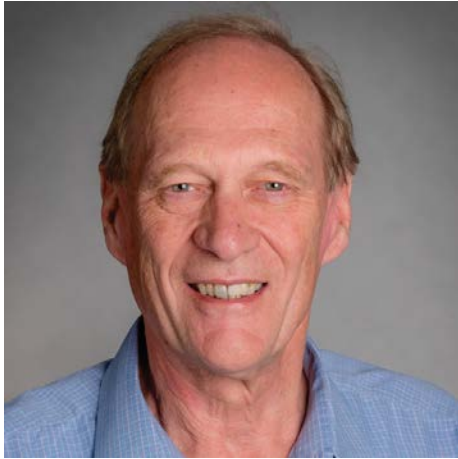
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Liver fibrosis is due to the over-deposition of collagens on the extracellular matrix, causing fibrotic septa and liver failure. Portocaval anastomosis (PCA) is a model of liver disease. AVP stimulates fibrogenesis. We have described the restoring effects of the AVP deficiency (neurointermediate pituitary lobectomy (NIL)-induced) on liver functions and cirrhosis. Here we hypothesize that blocking the AVP receptors with conivaptan (CV) (a V1a-V2 AVP receptors antagonist), will induce the same restoring effects of NIL on liver fibrosis and functions. Male Wistar rats were divided in 6 groups (8-10 each): Sham surgery (SHAM), PCA, NIL, PCA+NIL, CV and PCA+CV. SHAM, NIL and the 4 groups with PCA were operated at week 0, whereas NIL surgery to PCA+NIL group was done at week 8. CV treatments (30 mg/day/i.m./8 weeks) to CV group started at week 0, whereas in the PCA+CV group treatment started at week 8. NIL and CV groups were sacrificed at week 8, whereas SHAM, PCA, PCA+NIL and PCA+CV were sacrificed at week 16. At sacrifice, serum levels of ALT, AST, total and unconjugated bilirubin, urea, albumin, glucose and blood NH₄ were assessed. Livers were weighed and tissue samples were processed for glycogen content and for light microscopy study (slide tissues stained with H-E, Masson trichome and Sirius red). Table 1 summarizes results of the effects of the several experimental conditions on liver wet weights, liver glycogen content and the mentioned serum and blood biochemical parameters of liver functions.

Liver histopathology. In the PCA group, mainly in the periportal areas, small inflammatory infiltrates and big deposits of collagen were developed. Compared with the PCA the PCA+NIL and PCA+CV groups showed less inflammatory areas and much less collagen deposits. Conclusions. Results showed that: 1) AVP deficiency restores to normality the liver physiology and histology in the protracted liver disease, 2) Except the alterations in glycemia and NH₄ metabolism, similar restored effects on liver functions and histopathology were induced by CV, suggesting that similar cell signaling pathways are involved, 3) Results strongly support that AVP plays an important role in the pathophysiology of the liver fibrosis and possibly other non-liver fibrotic diseases.

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H-KS 2.1 An essential interaction of the dopamine D2 and the ghrelin receptor for the physiological control of colo-rectal function

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Background: Here we bring together two puzzles. The ghrelin receptor (GHSR1a), but not ghrelin, is expressed in the central nervous system and effects through the dopamine receptor 2 (DRD2) are generally inhibitory, but in the lumbo-sacral spinal cord are excitatory. We present evidence that a function of GHSR1a in the CNS is as a modulator of other GPCRs, and that it switches dopamine signalling at DRD2 from inhibition to excitation in the lumbosacral defecation centres.

Methods and key results: We found that the receptor genes *Drd2* and *GHSR1a* were expressed together in autonomic preganglionic neurons at the level of the defecation centres in rat. The receptors were also expressed together in neurons in the region of the defecation centres in human spinal cord. We found that dopamine, and the DRD2 agonist, quinpirole, directly applied to the lumbosacral cord, caused defecation. The effect of intrathecal dopamine was inhibited by the GHSR1a antagonist, YIL781, given systemically. The DRD2 agonist, pramipexole, administered systemically caused colorectal propulsion that was prevented if the pelvic nerves were cut. Behaviourally-induced defecation (caused by water avoidance stress) was reduced by the DRD2 antagonist, sulpiride and by YIL781. Electrophysiological recording from the autonomic preganglionic neurons, identified by retrograde tracing, showed that dopamine and a GHSR1a agonist, capromorelin, excited the same neurons and the effect of dopamine was antagonised by YIL781.

Conclusions: Dopamine is in nerve terminals surrounding autonomic neurons of the defecation centre, whereas ghrelin is not present anywhere in the spinal cord. Dopamine is a transmitter of the defecation pathways whose actions are exerted through interacting dopamine (D2) and ghrelin receptors on lumbo-sacral autonomic neurons that project to the colorectum.



H-KS 2.2 How does a single neuropeptide elicit pleiotropic behavioral and metabolic effects? Oxytocin as an example

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The neuropeptide oxytocin has attracted great attention of the general public, basic neuroscience researchers, psychologists and psychiatrists due to its profound pro-social, anxiolytic and “anti-stress” behavioral, homeostatic, and physiological effects. During the last decade, a substantial progress has been achieved in understanding the complex neurobiology of the brain oxytocin system. However, the picture of oxytocin actions remains far from being complete, and the central question remains: “How does a single neuropeptide exert such diverse actions?”. In this lecture, I will tackle this question, demonstrating the anatomical divergence of oxytocin neurons and their numerous central projections. In conjunction, I will describe unique compositions of distinct oxytocin-sensitive neurons in different brain regions, modulating distinct forms of behaviors. Further, I will introduce new oxytocin-sensitive cell types – astrocytes, which are critically involved in oxytocin-mediated emotional responses to fear and pain. Next, I will touch intra-cellular signaling pathways elicited by oxytocin, which determines the specific responses of cellular ensembles and thus behavioral changes. At the end, I will discuss uncertainties with permeability of exogenous oxytocin and its analogs through the blood-brain barrier and will summarize results of oxytocin application in human patients afflicted with mental and metabolic disorders, highlighting caveats and perspectives for clinical use of this neuropeptide.



H-KS 2.3 Fast and slow co-transmission in the modulatory system

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Dopamine neurons distributed within the ventral tegmental area (VTA) play crucial roles in different aspects of motivated behavior. Studies of VTA information processing have been focused on resident dopamine neurons for over fifty years. This talk will provide an overview of evidence showing that the VTA has glutamatergic neurons that establish both local and long-range connections, and provide excitatory regulation within different brain areas. In addition, it will cover data on subpopulations of VTA neurons that co-release dopamine and glutamate. It will also provide evidence indicating that in common with the VTA, the DR has neurons that co-release serotonin and glutamate, synapse on VTA dopamine neurons and that play a role in reward. The discovery of the complex neuronal diversity of the VTA and the DR offers new scientific challenges and opportunities towards having a better understanding on neuronal mechanisms underlying brain disorders related to motivated behavior.



H-KS 2.4 Real-time two-photon imaging of the hypothalamus in vivo

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The hypothalamus plays critical roles in the regulation of bodily homeostasis, including the generation of coordinated neurosecretory and autonomic responses during challenges to energy, fluid and electrolyte balance, among others. Some unique functional and cytoarchitectural features of the hypothalamus include the diverse expression of functional neuropeptides and the presence of a rich and plastic astroglial network. Strikingly, the hypothalamus is one of the most vascularized regions in the brain. Still, a detailed characterization of the hypothalamic neurovascular unit, and the functional significance of this uniquely rich vascularization remains puzzling. The classical model of neurovascular coupling (NVC) implies that activity-dependent axonal glutamate release at synapses evokes the production and release of vasoactive signals from both neurons and astrocytes, which dilate arterioles, increasing in turn cerebral blood flow (CBF) to areas with increased metabolic needs. One limitation in the field is that *In vivo* imaging of neurovascular coupling has largely been limited to dorsal superficial brain areas, which has led to the conventional view that this modality of NVC is common to all brain regions. However, whether this model is also applicable to deep brain areas that use less conventional neurotransmitters, such as neuropeptides, and which generally process information at a very different spatio-temporal scale, is currently unknown. To start addressing some of these critical gaps in the field, we developed a surgical approach to allow *in vivo* two-photon imaging from the ventral surface of the hypothalamus. Using this approach, we aimed to measure NVC in the supraoptic nucleus (SON) in response to a systemic homeostatic challenge. Using a transgenic rat expressing eGFP driven by the vasopressin promoter, in conjunction with the delivery of intravascular fluorescent dyes, we were able to successfully image SON neurons and the local microvasculature *in vivo* in anesthetized rats. During my presentation, I will summarize the results obtained thus far using this novel approach, which overall support the presence of an unconventional, neuropeptide-mediated NVC modality in the SON. Furthermore, I will discuss the potential functional implication for this form of NVC within the context of fluid/electrolyte homeostasis.



H-SS 3.1 Exploring novel neuronal populations of vasopressin expressing neurones using transgenic rat models and viral transfection systems

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Neural vasopressin is a potent modulator of physiology and behaviour in vertebrates. It acts at both sensory processing regions and within larger regulatory networks to mediate changes in social recognition, affiliation, aggression, communication, and regulates our biological clock. Using transgenic rat lines, immunohistochemistry, tracer injection and viral transfection systems we identified multiple populations of vasopressin neurons and their projection targets within the brain, including groups in olfactory and visual processing regions. Based on the interconnectivity of vasopressin-producing and sensitive brain areas, and in consideration of autocrine, paracrine and neurohormone-like actions associated with somato-dendritic release, I will discuss how these different neuronal populations affect neuronal networks and may interact on behaviour.



H-SS 3.2 Seasonal breeding in birds: environmental regulation of the neuroendocrine and behavioural systems

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For most bird species reproduction is seasonal and breeding is regulated by environmental cues including photoperiod, food availability, temperature and social interactions. My research interests lie in understanding how these environmental factors coordinate the both the timing and the progression of reproduction and associated behaviour. I will give an overview of recent research giving examples from both wild free living passerines and domesticated species. The change in day length is one key environmental factor used by birds to determine the time of year to breed. Birds use extra retinal photoreceptors and their circadian system to interpret the light:dark signal. Gonadal development is under the control of gonadotrophin secretion from the pituitary gland and under increasing day lengths thyrotrophin triggers a flow of molecular events in the mediobasal hypothalamus to increase the synthesis of triiodothyronine which ultimately leads to gonadotrophin releasing hormone synthesis and release until photorefractoriness. Nonetheless there is inherent flexibility for precisely when birds transition from their reproductive states. Recent investigations into the neural mechanisms underlying complex social and parental care have highlighted the importance of the central mesotocin and vasotocin systems. Neurophysiological studies in zebra finches and Silkie bantam chickens have been particularly useful in elucidating brain mechanisms responsible for behaviours such as nest building, incubation and care of the chicks. There is also evidence that neuroendocrine adaptations underlie the unique behaviour required to maximize survival and reproductive success in capricious environments, e.g. in arctic-breeding passerines like the socially monogamous white-crowned sparrow. This species rapidly modulates its stress response and adapts behaviour to optimise reproductive success in a very short breeding season which is often fraught with inclement weather events. With such wonderful examples of environmental adaptations and regulation, avian behavioural neuroendocrinologists are entering an exciting period. Using the annotation of many more avian species genomes to devise comparative genomic approaches and species-specific genetic tools, the identification of the genes responsible for integrating environmental information, neuroendocrine signals and reproductive behaviour is within our reach.



H-SS 3.3 Evidence of central signaling after systemic administration of oxytocin

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Preclinical studies suggest that central endogenous signaling of the nine amino acid peptide, oxytocin (OT) is altered in drug and alcohol addiction. There are preliminary preclinical and clinical studies indicating that administration of OT reduces addiction-related behaviors such as self-administration, conditioned place preference and withdrawal symptoms. As such, OT may represent a novel treatment for alcohol and drug dependence. However, there are still many unanswered questions that limit further clinical development of this promising treatment, such as the brain penetrance of OT when given systemically via intranasal or intravenous routes. Another question relates to its mechanism of action to mediate processes related to addiction such as its modulation of DA signaling in mesocorticolimbic pathways. We have conducted a series of nonhuman primate studies to investigate the brain tissue penetrance of labelled OT administered intravenously and intranasally, measuring labelled and endogenous OT by mass spectrometry. We have also measured endogenous and administered labelled OT in the CSF over a prolonged time course (2 hours). In a series of rodent studies, we quantified the concentration and distribution pattern of [125I]-radiolabeled OT in the brains and peripheral tissues of rats after intranasal delivery using gamma counting and autoradiography, respectively. In nonhuman primates and rats, administration of intranasal OT resulted in a physiologically significant concentrations of OT in brain regions along the trajectory of the trigeminal and olfactory nerves, as well as in the striatum. We also conducted an [11C] raclopride positron emission tomography (PET) study in nonhuman primates (N= 6 male rhesus macaques) to investigate the effect of intravenous OT (80 IU) on [11C] raclopride binding potential in the striatum after an IV methylphenidate challenge. In the caudate and putamen, there was a significant main effect of methylphenidate ($p < 0.001$), as well as a significant OT x methylphenidate interaction ($p = 0.025$) where OT attenuated the methylphenidate induced reduction in raclopride binding potential. These results indicate a possible mechanism underlying the effect of OT to reduce the rewarding effect of psychostimulants as reported in previous preclinical studies. The demonstration of this effect in nonhuman primates has translational relevance particularly as the brain receptor distributions of OT vary considerably between rodents and primate species.



H-SS 3.4 Anabolic and anti-catabolic effects of oxytocin on skeletal muscle protein metabolism

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Oxytocin (OT) is a neuropeptide with recognized action on the smooth and cardiac muscles. However, recent studies have demonstrated that OT receptor (OTR), a G protein coupled receptor, is also expressed in skeletal muscles and its stimulation was able to activate AKT signaling. Although this signaling pathway is involved in the control of muscle protein turnover and consequently of muscle mass, the role of OTR activation in the regulation of protein metabolism in skeletal muscles is still poorly understood. Therefore, the present work aimed to determine OT's effects on skeletal muscle protein metabolism. For that, total proteolysis, proteolytic system activities and protein synthesis were assessed in isolated soleus muscle from prepubertal female rats incubated with WAY-267,464 (WAY), a selective non-peptide OT receptor (OTR) agonist. In in vivo experiments, rats received 3-day OT treatment or saline, and muscles were harvested for mass-gain assessment. All procedures were approved by the Animal Research Ethics Committee (CEPA) of Sergipe Federal University, Brazil, under protocol number 62/2017. The results were expressed as means \pm SEM. Normality of the data was assessed with the Shapiro-Wilk test and statistical significance was assessed with the Student t-test, Mann-Whitney test or one-way analysis of variance (ANOVA) followed by Bonferroni's test. $p \leq 0.05$ was taken as the criterion for significance. In vitro OT receptor stimulation reduced total proteolysis (24% vs. control group), specifically through attenuation of the lysosomal and proteasomal proteolytic systems (38% and 46% vs. control group, respectively), and in parallel increased the Akt/FoxO phosphorylation levels by 60% and 110%, respectively as measured by western blotting. To substantiate these results, the rats were submitted to a three-day motor denervation (DEN)-induced atrophy model and the soleus were incubated with WAY. As expected, DEN resulted in protein upregulation expression of atrophy markers (MuRF-1 and atrogin-1) and this effect was attenuated by WAY (76% and 106%, respectively), in comparison with DEN free-WAY muscles. While the protein synthesis was not altered by in vitro treatment with the OT receptor selective agonist, in vivo short-term OT treatment enhanced this process (~65% vs. saline-treated rats), resulting in soleus mass gain (~9%), probably through an indirect effect. The soleus hypertrophy was confirmed by a ~12% increase in its fiber cross-section area. Interestingly, mRNA expression of atrophy markers was not altered in soleus obtained from OT-treated rats compared to controls. Taken together, these data show for the first time that OTR activation promotes anti-catabolic and anabolic effects on rat oxidative skeletal muscle protein metabolism, probably through crosstalk with the Akt/FoxO signaling pathway.



H-SS 4.1 Sex differences in modulation of traumatic stress by NPY

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The susceptibility to stress-elicited disorders is markedly influenced by sex. Women are twice as likely as men to develop posttraumatic stress disorder (PTSD), depression, anxiety disorders, and social impairments following exposure to traumatic stress. However, most of the studies in animal models examining putative therapeutics for stress-triggered impairments, including single prolonged stress (SPS), were performed predominantly with males. Previous studies in males demonstrated that intranasal neuropeptide Y (NPY) can provide therapeutic relief of many PTSD-associated maladaptive behaviors. However, it was ineffective in females at the same dose. Thus, females may need a higher dose of exogenous NPY to attain a therapeutically significant concentration since the overwhelming majority of studies found that NPY levels in females in many brain regions are lower than in male rodents. Therefore we examined SPS as an appropriate model to elicit many PTSD-associated symptoms in females and whether intranasal NPY at higher doses than with males is able to alter the development of SPS-triggered behavioral impairments. Sprague Dawley female rats were exposed to SPS only, or in a separate cohort after SPS stressors were immediately infused intranasally with one of several doses of NPY, starting with 600 μ g/rat - 4 times the dose effective in males. In a third cohort of animals, females were infused intranasally with either 600 μ g NPY, omarigliptin (a dipeptidyl peptidase IV [DPP4] inhibitor), or both right after the SPS stressors. After 19 days they were tested on several behavioral tests. SPS elicited significant depressive/despair like behavior on the forced swim test (FST), anxiety behavior on the elevated plus maze (EPM), as well as impaired social interaction. On the FST, there was a dose-response effect of intranasal NPY, with 1200 μ g, but not 600 μ g, preventing development of the SPS-elicited depressive-like behavior. The omarigliptin and 600 μ g NPY combined treatment, but neither alone, was also sufficient at preventing depressive-like behavior on the FST. The results demonstrate that: (1) SPS elicits several behavioral manifestations of PTSD in females; (2) early intervention with a high dose of intranasal NPY has therapeutic potential also for females; (3) NPY cleavage by DPP4 may play a role in the higher dose requirement for females. Furthermore, addition of DPP4 inhibitors, such as omarigliptin, may help in therapeutic intervention with NPY.

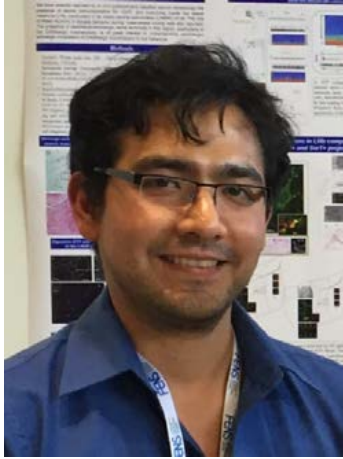


H-SS 4.2 Dysregulation of hypothalamic gene expression and the oxytocinergic system by diabetogenic soybean oil diets in mice

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Soybean oil consumption has increased greatly in the U.S. in the past half-century and is linked to obesity and diabetes in rodent models. To determine whether the hypothalamus might play a role in these metabolic effects, we performed RNA-seq analysis of the hypothalamus of male mice fed isocaloric, high-fat diets (HFD) based on conventional soybean oil, which is high in linoleic acid (LA), a genetically modified, low-LA soybean oil (Plenish), and coconut oil (lacking endogenous LA). The two soybean oil diets had similar, albeit non-identical, effects on the hypothalamic transcriptome, whereas the coconut oil HFD had a negligible effect compared to a low-fat control diet. Hypothalamic genes related to obesity, diabetes, lipid metabolism, inflammation, neuroendocrine and neurochemical pathways and neurological disorders were dysregulated by both conventional soybean oil and Plenish diets. *Oxt*, which encodes the neuropeptide oxytocin (OXT), was the only gene with metabolic, inflammatory and neurological significance in our selected categories that was upregulated by both soybean oil diets. Immunohistochemistry showed that mice on both soybean diets had reduced OXT protein in the supraoptic and paraventricular nuclei of the hypothalamus, while a plasma immunoassay revealed increased circulating OXT, suggesting both central and peripheral effects on oxytocin. These central and peripheral effects of soybean oil diets were correlated with glucose intolerance but not body weight. Notably, alterations in OXT levels were not observed in a coconut oil diet enriched in stigmasterol, a phytosterol found naturally in soybean oil, suggesting that neither this phytosterol nor LA is responsible for the effects on the oxytocin system. Given the ubiquitous presence of soybean oil in the American diet, the observed effects of soybean oil on hypothalamic gene expression in mice could have important public health ramifications.



H-SS 4.3 Aging and GABAergic transmission in the limbic system: testosterone and neuropeptides

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We have previously reported the existence of a novel neuronal population in the medio-central subdivision of the lateral habenula (LHbMC) of the rat, in which *Slc32a1*, and *Esr1*, the mRNAs coding for the vesicular GABA transporter and the estrogen receptor α respectively are co-expressed. These GABA and estrogen receptor-expressing neurons (thus, GERNs) receive inputs from hypothalamic vasopressinergic and orexinergic neurons and midbrain serotonergic and dopaminergic neurons. These projection neurons in turn express the enzyme aromatase, and thus are capable of converting estrogens to androgens. Rats in which testosterone levels were upregulated had an increased density of GERNs in the LHbMC and the density of GERNs correlated with extent of active escape behaviors of rats in the face of predator stress. Here, we investigated whether or not GERNs exist in other brain areas, including anterior and posterior hypothalamus and limbic (BNST, septum, amygdala, cingulate cortex, and hippocampus) regions of the brain, and whether or not testosterone modulates their density. Using the RNAscope technique, we compared the effect of testosterone up-regulation (testosterone supplementation) or downregulation (castration and aging) on the density of GERNs in male rats. The results indicate a direct correlation between testosterone levels and the expression of *Slc32a1* in hypothalamic and limbic peptidergic regions. We also compared two regions (anterior hypothalamus and BNST) in which the majority of *Esr1* neurons were *SLC32a+* and one region (hippocampus CA3) where the majority of *Esr1* neurons were negative for *Slc32a1*. We found that reduction in the levels of testosterone caused a significant reduction in the percentage of *Esr1/Slc32a1* neurons only in the anterior hypothalamus and BNST.



H-SS 4.4 Catestatin's role in immunometabolism and insulin sensitivity

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Background and Objectives: Cells of the innate immune system produce inflammatory cytokines and other factors that affect insulin signaling and result in the development of insulin resistance (IR) and Type 2 diabetes (T2D). In obesity-induced IR, Kupffer cells (KCs), the liver resident M2-type macrophage, are activated, followed by recruitment of M1-type monocyte (Mc)-derived recruited macrophages (McMΦs) in the liver. Most of the KCs express a complement receptor of the immunoglobulin superfamily (CRIg), which efficiently bind and phagocytize complement C3-opsonized bacterial products. Diet-induced obese (DIO) mice exhibit a “leaky gut” that facilitates the influx of microbial extracellular vesicles (mEVs) containing microbial DNAs into the portal system and translocate to the liver. Recent studies implicate that translocation of mEVs to liver and insulin-sensitive tissues results in the development of tissue inflammation and IR. Since Catestatin (CST: human Chromogranin A352-372) knockout (CST-KO) mice are obese and insulin-resistant and have leaky guts, we sought to determine whether CST improves insulin sensitivity in DIO mice.

Methods and Results: Plasma CST levels were low in DIO mice and treating of DIO mice with CST decreased lipid and plasma insulin levels, diminished expression of gluconeogenic genes, attenuated expression of pro-inflammatory genes, increased expression of anti-inflammatory genes in McMΦs, and inhibited infiltration of McMΦs, which led to an improvement of insulin sensitivity. Consistent with low plasma CST in DIO mice, CST-KO mice on normal chow diet (NCD) displayed IR. Supplementation of CST to NCD-CST-KO mice improved insulin sensitivity as evidenced by the improvement in glucose tolerance during glucose tolerance test (GTT), and insulin tolerance during insulin tolerance test (ITT). Testing of FACS-sorted F4/80+Ly6C⁻ cells (representing KCs) and F4/80-Ly6C⁺ cells (representing McMΦs) on hepatic glucose production (HGP) revealed that both basal and glucagon-induced HGP was markedly increased in hepatocytes co-cultured with KCs and McMΦs from NCD-CST-KO mice, and the effect was abrogated upon pre-treatment of CST-KO-MΦs with CST. While transfer of bone marrow from NCD-CST-KO mice to NCD-WT mice made NCD-WT mice insulin resistant, transfer of NCD-WT bone marrow to NCD-CST-KO mice made them sensitive to insulin, reinforcing the importance of immune cells in glucose metabolism as well as their regulation by CST. Of note, NCD-WT bone marrow recipient NCD-CST-KO mice show significant amounts of circulating CST, indicating release of CST from the immune cells. In fact, peritoneal macrophages express CST. Like DIO mice, NCD-CST-KO mice exhibit a leaky gut. While CRIg-expressing KCs were decreased in DIO mice, treatment with CST increased this macrophage population. Likewise, NCD-CST-KO mice displayed decreased CRIg-expressing KCs, which were restored after supplementation with CST leading to improvement in GTT and ITT.

Conclusions: We conclude that immune cells regulate glucose metabolism and that CST produced by the immune cells are mostly responsible for immunometabolism. Furthermore, CST improves insulin sensitivity in insulin-resistant DIO and NCD-CST-KO mice by (i) attenuating infiltration of McMΦs in liver, (ii) decreasing entry of mEVs through the gut barrier, and (iii) increasing CRIg-expressing KCs. Thus, the present studies provide solid evidence that CST plays crucial roles in immunometabolism.



H-SS 4.5 Gonadotropin releasing hormone (GnRH), a pluripotent neuropeptide: significance of GnRH self-priming and tachyphylaxis

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Gonadotropin releasing hormone (GnRH) is a decapeptide that mediates the central nervous control of the synthesis and release of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH). The peptide is remarkable in that in addition to stimulating gonadotropin release, long exposure of pituitary gonadotropes to GnRH results in tachyphylactic inhibition of gonadotropin release. Furthermore, GnRH is capable of self-priming, thereby increasing pituitary responsiveness to itself. The self-priming effect of GnRH is a powerful servomechanism that potentiates by several fold pituitary responsiveness to GnRH so that it synchronizes GnRH release from the hypophysial portal vessels with pituitary responsiveness to GnRH, thereby enhancing the magnitude of gonadotropin release as is required to induce ovulation. With the exception of the oxytocin-uterine contraction system, the ability of GnRH to self-prime seems to be unique among peptides. We showed in the early 1970s that the self-priming effect of GnRH, which occurs in the human and other species, is crucial for triggering the ovulatory gonadotropin surge (Fink G *Frontiers in Neuroendocrinology* 16: 183-190: 1995). In addition The self priming effect of GnRH probably also plays a role in the induction of puberty, in that GnRH self-priming enables a series of GnRH pulses, too small by themselves to evoke LH release, to trigger LH pulses large enough to induce puberty (Fink et al 1976; *J Endocrinol.* 69, 359-372; Fink 2018 *Molec.Cell Endocrinol.* 470, 34-35).

The self-priming effect of GnRH can also be elicited *in vitro*, and this has enabled a comparison to be made between the mechanisms of the self-priming effect and the releasing action of GnRH. The key differences between the releasing and self-priming actions of GnRH are that: (i) GnRH priming, but not releasing, is dependent on protein synthesis, (ii) in contrast to the GnRH releasing action, GnRH self-priming cannot be mimicked by potassium depolarisation or calcium ionophores. Priming involves potentiation of the IP₃ intracellular Ca²⁺ mechanisms, protein kinase C, activation of mitogen-activated protein (MAP) kinase and effects on the cytoskeleton that lead to the migration of gonadotrope secretory granules to the marginal zone close to the cell membrane.

Turning to tachyphylaxis, GnRH binds to specific receptors on pituitary gonadotropes. These receptors belong to the family of G protein-coupled receptors. Their activation leads to phosphoinositide breakdown with generation of inositol 1,4,5-trisphosphate (Ins(1,4,5)P₃) and diacylglycerol. These second messengers initiate Ca²⁺ release from intracellular stores and activation of protein kinase C, both of which are important for gonadotropin synthesis and secretion. Prolonged activation of GnRH receptors by GnRH, and especially more potent GnRH agonists leads to desensitization and consequently to suppressed gonadotropin secretion. The tachyphylaxis induced by GnRH agonists, which results in a profound decrease in gonadotropin secretion is the basis for using the GnRH agonists as “puberty blockers”, and in the treatment of precocious puberty, gender dysphoria, prostate cancer, some types of breast cancer and several gynaecological disorders.

H-KS 3.1 Neuropeptides for gene therapy in epilepsy



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Epilepsy is one of the most devastating neurological diseases, affecting at least 60 million people worldwide. Despite certain progress in antiepileptic drug development, available pharmacological treatments are only symptomatic, have side effects and fail to adequately control seizures in a third of patients. Recently, neuropeptides emerged as strong regulators of synaptic transmission in the CNS, offering a potent tool to counteract the seizure activity. However, it is not clear yet what the role of these agents is in mechanisms of epileptogenesis. We do research to develop gene therapy strategies based on neuropeptides, particularly NPY as a target molecule. In the presentation I will discuss the preclinical research conducted in my lab as a translational basis for developing novel gene therapy approaches based on NPY to counteract seizure activity in patients with drug-resistant epilepsy.



H-KS 3.2 Tuberoinfundibular peptide 39: an emerging new social neuropeptide

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Tuberoinfundibular peptide of 39 residues (TIP39), or parathyroid hormone 2, was originally purified from bovine hypothalamus (Usdin et al., 1999) as ligand of the parathyroid hormone 2 receptor. Recently, the role of TIP39 as a social neuropeptide was suggested as its expression was induced by conspecifics in the zebrafish (Anneser et al. 2020, Nature). We previously demonstrated that

TIP39 is induced in mother rats in the posterior intralaminar thalamic nucleus (PIL), and innervates oxytocin neurons (Dobolyi et al., 2018). Here, we describe evidence that TIP39 and the thalamo-hypothalamic pathway containing TIP39 is involved in the regulation of maternal as well as direct contact adult social behavior.

TIP39 expression is increased in the PIL of female rats kept together with other females while social isolation reduced TIP39 levels, a finding consistent with the reduction of TIP39 in mother rats following removal of her litter. PIL TIP39 neurons demonstrated c-Fos activation in response to conspecifics but only if direct contact was allowed between the animals. Chemogenetic activation of PIL neurons increased the number of social touches between rats. Since TIP39 neurons also contain calbindin and glutamate but not vesicular GABA transporter (VGAT), calbindin-Cre and VGAT-Cre mice were used to study cell type specific functions. While activation of calbindin (TIP39) neurons increased maternal motivation, manipulation of GABAergic PIL neurons was without effect. The physiological importance of PIL TIP39 neurons was demonstrated by the reduction of maternal motivation when the cells were chemogenetically inhibited. Furthermore, an antagonist of the PTH2 receptor also reduced maternal motivation. To reveal which projections of TIP39 PIL neurons are involved in social behavior, cell specific neuronal tracing was performed, which revealed distinct projection pattern of calbindin (TIP39) and GABAergic (VGAT+) PIL neurons. The most intense projection of calbindin (TIP39) neurons was to the medial preoptic area (MPOA). The selective chemogenetic stimulation of the PIL-MPOA pathway was performed using double viral injections (a retrogradely virus expressing Cre injected into the MPOA coupled with a Cre dependent virus into the PIL) and also by using local CNO administration directly into the MPOA. The selective stimulation of the PIL-MPOA projection increased direct interactions during social behavior. In addition, direct contact during social interaction caused increase in neuronal activity in the MPOA.

The results suggest that posterior thalamic PIL neurons convey socially relevant information to a variety of different forebrain centers, among which the MPOA is involved in the processing of social touch. Thus, we identified an important novel component of the social brain network, which may increase the motivation for affiliative direct contact interactions.

Support: The work was supported by NKFIH via NKFIH-4300-1/2017-NKP_17, TKP2020-IKA-05, OTKA K134221 and EFOP-3.6.3-VEKOP-16-2017-00009 research grants.

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H-KS 3.3 Cortical Vasoactive Intestinal Polypeptide (VIP)-expressing interneurons and the broadcasting of salience

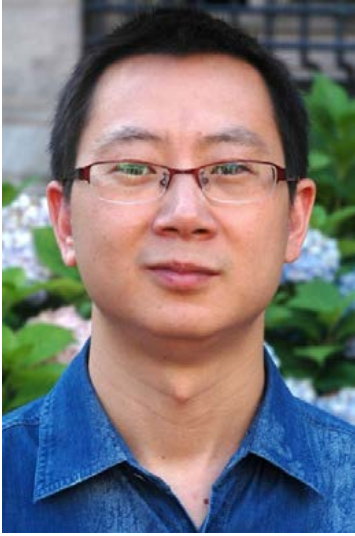
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Adaptive behavior critically depends on the detection and attribution of salience. The anterior insular cortex (aIC) has long been proposed as a key player in the detection of behaviorally relevant stimuli, as part of the brain system known as the “salience network”. However, to date, little is known about the contribution of aIC interneurons to the processing of salient stimuli.

Based on a multidisciplinary approach including whole-brain connectivity tracing, imaging of neural calcium dynamics and optogenetic modulation in freely moving mice across different experimental paradigms, we propose a role for vasoactive intestinal polypeptide-expressing (VIP+) interneurons in the aIC in mediating adaptive behaviors in response to salient events of aversive and positive nature. Our findings enlighten novel cellular mechanisms underlying salience processing in the aIC and show that VIP+ interneurons are centrally positioned within the salience network to participate to the broadcasting of salience.



H-KS 3.4 Thalamic control of opiate-associated memory

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Disrupting memories that associate environmental cues with drug experiences holds promise for treating addiction, yet accessing the distributed neural network that stores such memories is challenging. Here, we show that the paraventricular nucleus of the thalamus (PVT) orchestrates the acquisition and maintenance of opiate-associated memories via projections to the central nucleus of the amygdala (CeA) and nucleus accumbens (NAc). PVT→CeA activity associates morphine reward to the environment, whereas transient inhibition of the PVT→NAc pathway during retrieval causes enduring protection against opiate-primed relapse. Using brain-wide activity mapping, we revealed distributed network activities that are altered in non-relapsing mice, which enabled us to find that activating the downstream NAc→lateral hypothalamus (LH) pathway also prevents relapse. These findings establish the PVT as a key node in the opiate-associated memory network and demonstrate the potential of targeting the PVT→NAc→LH pathway for treating opioid addiction.



H-SS 5.1 Sexually dimorphic oxytocin receptor expressing neurons in the MPOA regulate maternal behavior

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Oxytocin is involved in the regulation of social behaviors including parental behaviors in a variety of species. Oxytocin triggers social behaviors by binding to oxytocin receptors (OXTRs) in various parts of the brain. OXTRs are present in the preoptic area (POA) where hormone-sensitive sexually dimorphic nuclei exist. The present study was conducted to examine whether sex differences exist in the distribution of neurons expressing OXTRs in the POA. Using OXTR-Venus (an enhanced variant of yellow fluorescent protein) mice, the distribution of OXTR-Venus cells in the POA was compared between sexes. The total number of OXTR-Venus cells in the medial POA (MPOA) was significantly greater in females than in males. No detectable OXTR-Venus cells were observed in the anteroventral periventricular nucleus (AVPV) within the MPOA in most of the brain sections from males. We further examined the total number of OXTR-Venus cells in the AVPV and the rest of the MPOA between the sexes. The total number of OXTR-Venus cells in the AVPV in females was significantly greater than that in males, whereas the total number of OXTR-Venus cells in the rest of the MPOA did not differ significantly between the sexes. Thus, the sexually dimorphic expression of OXTR-Venus specifically occurred in the AVPV, but not in the rest of the MPOA. We also examined whether the expression of OXTR in the AVPV is driven by the female gonadal hormone, estrogen. Immunocytochemistry and single-cell RT-PCR revealed the presence of the estrogen receptor α in OXTR-Venus cells in the female AVPV. Moreover, ovariectomy resulted in the absence of OXTR-Venus expression in the AVPV, whereas estrogen replacement therapy restored OXTR-Venus expression. Lastly, we tested if the OXTR neurons in the AVPV are involved in regulation of maternal behavior. Specific inactivation of the OXTR neurons using a chemogenetic approach impaired some maternal behaviors such as pup retrieval and crouching over the pups. These results demonstrate that the expression of OXTR in the AVPV is primarily female specific and estrogen dependent. In addition, the sexually dimorphic expression of OXTR in the AVPV is necessary for induction of maternal behavior.



H-SS 5.2 Role of vasopressin in daily setting of the outputs of the SCN clock

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Vasopressin (VP) is an important hormone produced in the supraoptic (SON) and paraventricular nucleus (PVN) with antidiuretic and vasoconstrictor functions in the periphery. As one of the first discovered peptide hormones, VP was also shown to act as a neurotransmitter, where VP is produced and released under the influence of various stimuli. VP is one of the core signals via which the biological clock, the suprachiasmatic nucleus (SCN), imposes its rhythm on its target structures and its production and release is influenced by the rhythm of clock genes and the light/dark cycle. This is contrasted with VP production and release from the bed nucleus of the stria terminalis and the medial amygdala, which is influenced by gonadal hormones, as well as with VP originating from the PVN and SON, which is released in the neural lobe and central targets. The release of VP from the SCN signals the upcoming resting phase in rodents and prepares their physiology accordingly by down-modulating corticosterone secretion, influencing the reproductive cycle and locomotor activity. All these circadian variables are regulated within very narrow boundaries at a specific time of the day, where day-to-day variation is less than 5% at any particular hour. However, the circadian peak values can be at least ten times higher than the circadian trough values, indicating the need for an elaborate feedback system to inform the SCN and other participating nuclei about the actual levels reached during the circadian cycle. In short, the interplay between SCN circadian output and peripheral feedback to the SCN is essential for the adequate organization of all circadian rhythms in physiology and behavior.



H-SS 5.3 PACAP-glutamate co-transmission in brain circuits

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Neurons that express and release neuropeptides often, perhaps even invariably, contain and release co-transmitter substances, including GABA and glutamate, with well-known inhibitory or excitatory post-synaptic effects. The circuit functions of identified peptidergic neurons are increasingly reported to be mimicked or inhibited by optogenetic maneuvers that increase or decrease firing their firing rates and are likely to effect the release of all transmitters contained in the neuron (e.g., Yap et al., *Nature*, 590:115, 2021). This raises the question of whether the co-release of neuropeptides and classical transmitters are mutually permissive or instructive for each other's post-synaptic functions in a given circuit. Neuropeptide function could be exerted during construction of specific circuits during development, or to ensure that excitatory/inhibitory synaptic events are time-locked and stimulus-intensity gated during circuit activation in the adult brain. The latter is likely, given that GABA and glutamate are released from small synaptic vesicles (SSVs) while neuropeptide release occurs from large dense-core vesicles (LDCVs), with quantal release probabilities as a function of stimulus intensity (firing rate) unique for each vesicle type (Hökfelt et al., *Lancet Neurology* 2: 4763, 2003).

PACAP is expressed throughout the nervous system. Peripherally, PACAP contributes uniquely to both sympathetic and parasympathetic function upon release, with acetylcholine, from pre-ganglionic neurons (see Eiden and Zhang, *Cell Tissue Res.* 375: 103, 2019). PACAP co-release from glutamatergic melanopsin-expressing neurons of the retina likewise imparts unique characteristics to these neurons, allowing them to transduce dependent phase changes in the brain circadian pacemaker of the suprachiasmatic nucleus during the photoperiod around dawn, as well as the photoperiod around dusk (Lindberg et al., *Front. Neurosci.* 13: 1281, 2019). Recent systematic investigation of co-expression of PACAP mRNA with glutamatergic and GABAergic markers in the CNS has revealed some general features of PACAP-classical transmitter co-expression in CNS that may shed light on the shared roles of PACAP and classical transmitters in information transmission from neurons that contain and release both. PACAP is expressed in both GABA- and glutamatergic neurons throughout the brain, but GABA (VGAT) co-expression is far less frequent than glutamate (VGLUT1 or VGLUT2) co-expression. Neocortical PACAPergic neurons are predominantly glutamatergic, as are PACAPergic neurons throughout the diencephalon and brain stem (Zhang et al., *eLife* 10: 61718, 2021). In contrast, PACAP expression in cerebellum is confined mainly to Purkinje cells, which are GABAergic.

Neuronal activation (increased fos expression) in response to threat (predator odor) in extended amygdala targets of PACAP/glutamate neurons of the brain stem (parabrachial nucleus) in wild-type, but not PACAP-deficient mice, indicate a specific role for PACAP co-transmission in permitting or effecting post-synaptic neuronal activation (Zhang et al., *ibid*). Constitutive PACAP knock-out in mice reveals (Bakalar et al., *BioRxiv* doi.org/10.1101/2021.03.29.437579) that PACAP is required both for transcriptional effects triggered by stress in adult mice, but also for constitutive regulation of specific transcripts during development. Thus, PACAP may have dual roles as a co-transmitter in adult brain in both excitatory and inhibitory neurons, and as an instructive factor during brain development.

The Section on Molecular Neuroscience is supported by the NIMH Intramural Research Program, via MH002386.



H-SS 5.4 The importance of circadian rhythms for metabolic health

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1 Departamento de Anatomía, Facultad de Medicina, Universidad Nacional Autónoma de México, Ciudad de México; 2 Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Ciudad de México

Shift-work, frequent transmeridional traveling, shifted sleep time and light at night are conditions that lead to circadian disruption and loss of behavioral and physiological homeostasis. Individuals exposed constantly to such disruption are at risk to develop overweight and metabolic disturbance.

In order to better understand the mechanisms that lead to the loss of homeostatic balance we have developed experimental models with rodents, that mimic such disrupting conditions. A main effect observed with all models is an increased adiposity and dyslipidemia. We have observed that animals exposed to protocols of circadian disruption, shift their feeding schedules to the hours when they are forced to be awake, even when this timing is in conflict with the light-dark cycle.

Therefore, we have tested restricted feeding schedules of 12 h fasting – 12h food as a synchronizing strategy in order to prevent or revert the circadian disruption. When food is scheduled to the normal activity phase, which is night for rodents, the feeding schedule restores circadian rhythmicity and prevents overweight and dyslipidemia. However, when food is scheduled out of phase from the normal light-dark cycle, it enhances deleterious effects on metabolism and body weight.

We will present experimental evidence of deleterious effects of disrupted circadian rhythms on metabolism and bodyweight and will point out the relevance of the timing of food intake. We will further discuss the benefits and limitations of feeding schedules to ameliorate the metabolic burden in shift workers and other individuals affected by circadian disruption.

The group is supported by grants PAPIIT IG-201321 and División de Investigación, Facultad de Medicina UNAM.



SE 1.1 Old and new challenges for basic and clinical research on regulatory peptides: a physiological perspective

Greti Aguilera

National Institute of Child Health and Human Development

Acting as endocrine, paracrine, autocrine factors or as neurotransmitters, peptides are key physiological regulators in health and disease. During the last two decades, significant progress on the identification of new regulatory peptides, deorphanization of GPCR, the elucidation of biopeptide biosynthesis and signaling transduction mechanisms, identification of peptidergic neural pathways, as well as technological advances for peptide analogs synthesis and design have facilitated the use of peptides as therapeutic and diagnostic tools. In spite of tremendous advances, challenges remain concerning the mode of peptide administration and the occurrence of side effects and unexpected responses, especially during chronic peptide administration. This derives from the complexity of the physiological actions of regulatory peptides, including pleotropic actions of the majority of peptides, with central and peripheral actions, activation of different receptor subtypes by a single peptide, genetic diversity, rhythmic and pulsatile physiological patterns of secretion and the modulation of peptide action through interaction with other peptide or steroidal hormones. Addressing these problems will require multidisciplinary approaches with the participation of clinical researchers, basic cellular and molecular biologists, physiologists, bioinformatic and bioengineering experts. In addition to deepen our knowledge of peptide physiology and neurobiology, the development of technology for peptide hormone delivery mimicking physiological patterns will be important for optimizing the therapeutic use of peptides. The ability of modifying intracellular signaling using synthetic small peptides, which interfere with protein-protein interaction, has potential for application for modulating peptide hormone action in a receptor independent manner. Therapeutic applications of such peptides would depend on the feasibility of developing technology for allowing cell specific targeting and cell membrane penetration of these interfering peptides. Overall, coordinated efforts of basic scientists and clinical researchers leading to a better understanding of the cell biology and pathophysiology of peptide regulated functions, as well as perfecting existent and developing new technology for designing function-specific peptides and peptide delivery will be needed to maximize the efficacy and minimize adverse effects in the clinical use of peptides.



SE 1.2 Peptides as therapeutics: orphan GPCR – ligand matching is just the beginning

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Once a novel, endogenous peptide is discovered the race toward establishing therapeutic relevance begins. Isoforms of the nascent peptide must be examined for pharmacologic activity in vitro and in vivo, processing of the prohormone must be understood, site of action and biologic potency/stability must be elucidated and appropriate reagents developed with which to begin establishing physiologic relevance. This later task typically involves the use of antibodies to neutralize the endogenous peptide, molecular tools to abrogate or exaggerate endogenous production and in silico approaches at structure function relationships.

Some researchers choose the minimalist approach, embryonic gene compromise, to indicate the importance of the peptide, but compensatory mechanisms and problems with embryonic lethality have handicapped this approach. Post-differentiation gene compromise techniques have jumpstarted the process; however, for the issue of “sufficiency” and/or “necessity” to be established, a cognate receptor needs be identified. This is an important first step, but then the really difficult work begins. How one develops an efficacious, safe and action-specific analog becomes an effort best suited for very large research groups, perhaps even only industrial entities. This presentation will give examples of what in the end becomes the most difficult step: how to deliver the agent to just the desired site of action so that only one of the biologic actions of the endogenous peptide can be mimicked or interrupted.



SE 2 Scientific publishing: obligations and opportunities

Mercer, Julian

University of Aberdeen, UK

An exploration of how our scientific community can support the journals that truly fulfill the mission of advancing science communication for all scientists

Panelists: J. Mercer, R. Millar, S. Grattan, G. Leng, (JNE), Rick Samson (The Physiological Review).

Neuroscience Special Lecture

Exploring joy and worry in the tactile world



Wang, Xiaoi-Dong

Department of Neurobiology and Department of Psychiatry of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, 310058 Hangzhou, China; and NHC and CAMS Key Laboratory of Medical Neurobiology, MOE Frontier Science Center for Brain Research and Brain-Machine Integration, School of Brain Science and Brain Medicine, Zhejiang University, 310058 Hangzhou, China.

Touch can positively influence memory function and emotional responses, but the underlying mechanisms remain unclear. Recently, we found that non-social tactile experience enrichment improves memory and alleviates anxiety by remodeling neurons along the dorsoventral axis of the dentate gyrus (DG) in adult male mice. Tactile enrichment modulates behavior in a temporally specific manner and induces differential activation and structural modification of neurons in the dorsal DG (dDG) and ventral DG (vDG). In addition, tactile enrichment increases the presynaptic input from the lateral entorhinal cortex (LEC), which is reciprocally connected with the primary somatosensory cortex (S1), to tactile experience-activated DG neurons. Chemogenetic activation of tactile experience-tagged dDG and vDG neurons is sufficient to enhance memory and reduce anxiety respectively, whereas inactivation of these neurons or S1-innervated LEC neurons abolishes the memory-enhancing and anxiolytic effects of tactile enrichment. Moreover, adulthood tactile enrichment attenuates early-life stress-induced memory deficits and anxiety-related behavior. These findings suggest that enriched tactile experience retunes the S1>LEC>DG pathway and enhances DG neuronal plasticity to modulate cognition and emotion. In this talk, I will present a brief historical overview of touch-related studies, and then discuss our recent findings.

Recognition

Distinguished Members of the *International Regulatory Peptide Society*

We wish to recognize the contributions of our Distinguished Members to the development of fundamental morphological, biochemical, cytological, and molecular insights generating concepts useful in the integration of regulatory peptide function in systems biology, and translation into medical practice and treatments. The achievements of our Distinguished Members serve to inspire new students and practitioners in the field alike, that curiosity disciplined by the scientific method allows experimentation that is its own reward, and can lead to the betterment of human health, and an improved perspective on the proper place of humankind within the animal kingdom.

It is also our wish to express our gratitude to all our Distinguished Members for their strong connection to and generous support of the IRPS-RegPep.

Greti Aguilera

Recognized for her contributions to understanding how physiological and signaling mechanisms by corticotropin releasing hormone and other hormones regulate cardiovascular and HPA axis activity.

José Antunes-Rodrigues

Recognized for his pioneering explorations of the physiology of mineral and water balance by neurohypophyseal hormones.

Sue Carter

Recognized for her pathbreaking explorations of the role of oxytocin, vasopressin and other hormones in mammalian reproductive and social behavior.

Richard Di Marchi

Recognized for his translational breakthroughs in incretin pharmacology and medicinal chemistry.

George Fink

Recognized for expanding the concept of temporal endocrine regulation through pulsatile secretion of reproductive hypophysiotropic hormone, and the characterization of the release of hypothalamic neuropeptides into the hypophysial portal vessels.

John Furness

Recognized for pioneering work in defining the functional chemoanatomy of the enteric nervous system.

Hal Gainer

Recognized for integrating dynamics of hormone processing and axonal transport in neurosecretory cells.

Tomas Hokfelt

Recognized for revealing the extent and meaning of neuropeptide and aminergic co-transmission in neurons and neuronendocrine cells in mammalian brain.

Jens Holst

Recognized for providing principles guiding the translation of incretin action into therapeutic intent.

Robert T. Jensen

Recognized for defining regulatory peptide hormone receptor expression in endocrine tumor cells, and its use in tumor detection, characterization and anti-tumor treatment.

Luis de Lecea

Recognized for his discovery of the hypothalamic hormone hypocretin/orexin, and its role in the transduction of convergent physiological stimuli into altered behavioral states.

Gareth Leng

Recognized for his insights into paracrine and autocrine mechanisms that tune neurosecretory cell electrophysiology for optimal homeostatic performance.

Maurice Manning

Recognized for perfecting chemical tools for synthesis of peptide analogs for oxytocin, vasopressin, and other neuropeptides, and dissecting their structure-function properties.

Robert Millar

Recognized for determining the ribosomal synthesis of GnRH, identification of novel GnRH structures, design of novel analogues and cloning of the GnRH receptor, leading to development of peptide and small molecule analogs employed in treating hormone-dependent diseases such as prostate cancer.

John Morris

Recognized for astute morphological observations at the ultrastructural level leading to a refined understanding of the function and diversity of peptide-secreting neuroendocrine cells.

Quentin Pittman

Recognized for electrophysiological and pharmacological investigation of synaptic behavior and its modulation by regulatory peptides as well as steroid hormones and inflammatory mediators.

Jens Rehfeld

Recognized for exploration of peptide and peptide receptor co-evolution, providing insights into the evolutionary basis for ligand specificity and receptor specialization to physiological purpose.

Rick Samson

Recognized for innovative approaches to peptide receptor deorphanization and understanding of peptide receptor participation in physiological regulation.

Carmen Sandi

Recognized for her work in identifying the roles of regulatory peptides in the neurobiological processes that determine individual differences in behavior and personality, and of brain bioenergetics in the regulation of stress and anxiety.

Dick Swaab

Recognized for his pathbreaking work in experimental contextualization of the crucial importance of regulatory peptides and other hormones in influencing brain development.

Summary

We thank all of our Distinguished Members for providing inspiring example, and intellectual and practical encouragement to the members of our Society and their many other colleagues at their own institutions, and throughout the world.

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