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HNNA organised symposium at ANS December 2017

Title: Novel neural circuits and plasticity regulating stress and stressor responses

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Presentation 1: Endocannabinoid signaling and glucocorticoid effects in the brain

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Presentation 2: Identification of pathways involved in the autonomic responses to interoceptive stressors.

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Presentation 3: Plasticity in hypothalamic stress circuits.

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Presentation 4: Optogenetic dissection of novel pathways controlling the HPA axis

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Speaker 1: Cecilia Hillard

Title of the presentation: Endocannabinoid signaling and glucocorticoid effects in the brain

Dr. Hillard's research focuses on the biochemistry and function of the endocannabinoid-mediated signaling in the brain, particularly in the context of stress. Accumulated data from our laboratory and others strongly supports the hypothesis that endocannabinoid/CB1 cannabinoid receptor signaling is a vital stress effector in the brain [1, 2]. For example, glucocorticoids affect synaptic plasticity in the prefrontal cortex [3], hippocampus [4], hypothalamus [5] and raphe via mobilization of endocannabinoid signaling. This mechanism has been shown to be essential for long-loop feedback regulation of the hypothalamic-pituitary-adrenal axis by CNS glucocorticoids. Recent work from our laboratory in collaboration with John Mantsch demonstrates that there is a "dark side" to this mechanism. In particular, stress potentiates reinstatement to cocaine seeking behavior in rats with a history of cocaine self-administration [6]. We have shown that stress-induced potentiation of cocaine seeking is blocked by CB1 receptor antagonism. Further, our data support a model in which stress-mobilized glucocorticoids activate endocannabinoid signaling in the medial prefrontal cortex, which results in inhibition of GABA release, which disinhibits an excitatory projection from the mPFC to the nucleus accumbens. Activation of this circuit, in combination with a small priming dose of cocaine, results in robust reinstatement of seeking behavior in rats that have extinguished previously. In addition to animal studies, our laboratory has also explored the effects of stress on endocannabinoid signaling in humans [7]. Recent studies in this area include investigations of the role of the endocannabinoids in exercise-induced hyperalgesia [8, 9] and in cyclic vomiting syndrome [10]. Given the topic of this symposium, I will focus on data supporting a role for endocannabinoid signaling in the regulation of the hypothalamic-pituitary adrenal axis.

Some papers (referenced in the summary) from the Hillard laboratory in this research area:

1. Hillard, C.J., *Stress regulates endocannabinoid-CB1 receptor signaling.* Semin Immunol, 2014. **26**(5): p. 380-8.
2. Hillard, C.J., *Endocannabinoids and the Endocrine System in Health and Disease.* Handb Exp Pharmacol, 2015. **231**: p. 317-39.
3. Hill, M.N., et al., *Recruitment of prefrontal cortical endocannabinoid signaling by glucocorticoids contributes to termination of the stress response.* J Neurosci, 2011. **31**(29): p. 10506-15.
4. Wang, M., et al., *Acute restraint stress enhances hippocampal endocannabinoid function via glucocorticoid receptor activation.* J Psychopharmacol, 2012. **26**(1): p. 56-70.
5. Evanson, N.K., et al., *Fast feedback inhibition of the HPA axis by glucocorticoids is mediated by endocannabinoid signaling.* Endocrinology, 2010. **151**(10): p. 4811-9.
6. McReynolds, J.R., et al., *CB1 receptor antagonism blocks stress-potentiated reinstatement of cocaine seeking in rats.* Psychopharmacology (Berl), 2016. **233**(1): p. 99-109.
7. Dlugos, A., et al., *Acute stress increases circulating anandamide and other N-acylethanolamines in healthy humans.* Neuropsychopharmacology, 2012. **37**(11): p. 2416-27.
8. Brellenthin, A.G., et al., *Endocannabinoid Responses To Exercise In Low, Moderate, And High Active Individuals: 3765 Board #204 June 4, 8: 00 AM - 9: 30 AM.* Med Sci Sports Exerc, 2016. **48**(5 Suppl 1): p. 1052-3.
9. Koltyn, K.F., et al., *Mechanisms of exercise-induced hypoalgesia.* J Pain, 2014. **15**(12): p. 1294-1304.
10. Venkatesan, T., et al., *Endocannabinoid-related lipids are increased during an episode of cyclic vomiting syndrome.* Neurogastroenterol Motil, 2016. **28**(9): p. 1409-18.

Speaker 2: Andrew Allen

Research area

Andrew Allen's laboratory is interested in homoeostatic regulation of autonomic function with an emphasis on neural regulation of the sympathetic nervous system. Whilst basic in nature this research seeks to understand the neurobiological contributions to hypertension and cardiovascular diseases.

Recent accomplishments

The laboratory has developed expertise in the ability to modulate the activity of different neuronal populations in adult animals, using recombinant viruses, to target neurochemically-defined sub-groups of neurons, precise stereotaxic injections and opto- and chemo-genetic molecules to regulate activity. This has enabled us to define the function of specific neuronal cell groups, for example the catecholaminergic C3 group, understand the basis for the amplified respiratory modulation of sympathetic activity that underpins some forms of hypertension and define all of the synaptic inputs to specific neuronal populations.

Relevant papers (selection from last 5 years)

Chen D, Jancovski N, Bassi, JK, Nguyen-Huu TP, Choong Y-T, Palma-Rigo K, Davern P, Gurley SB, Thomas WG, Head GA, Allen AM. Angiotensin type 1A receptors in C1 neurons of the rostral ventrolateral medulla modulate the pressor response to aversive stress. J. Neuroscience, 2012; 32: 2051-2061.

Menuet C, Sevigny SP, Connelly AA, Bassi JK, Jancovski N, Williams DA, Anderson CR, Llewellyn-Smith IJ, Fong AY, Allen AM. Catecholaminergic C3 neurons are sympathoexcitatory and involved in glucose homeostasis. J. Neuroscience 2014; 34: 15110-15122.

Dempsey B, Le S, Turner A, Bokiniec P, Ramadas R, Bjaalie JG, Menuet C, Neve R, Allen AM, Goodchild AK, McMullan S. Mapping and analysis of the connectome of sympathetic premotor neurons in the rostral ventolateral medulla of the rat using a volumetric brain atlas. Front. Neural Circuits 2017 (in press).

Menuet C, Le S, Dempsey B, Connelly AA, Kamar J, Jancovski N, Bassi JK, Walters K, Simms AE, Hammond A, Fong AY, Goodchild AK, McMullan S, Allen AM. Excessive respiratory modulation of blood pressure triggers hypertension. Cell Metabolism 2017 (in press)

Stamp LA, Gwynne RM, Foong JPP, Lomax AE, Hao MM, Kaplan DI, Reid DA, Petrou S, Allen AM, Bornstein JC, Young HM. Optogenetic demonstration of functional innervation of mouse colon by neurons derived from transplanted neural cells. Gastroenterology 2017 (in press).

Brief Lecture Synopsis

Interoceptive stressors, such as glucoprivation, induce behavioural, neuroendocrine and autonomic response patterns via activation of multiple brain pathways. The presentation will discuss research involving viral-mediated chemo- and opto-genetic approaches designed to unravel these pathways and understand the roles for different brain regions.

Speaker 3

Dr Karl Iremonger

Centre for Neuroendocrinology

Department of Physiology, University of Otago

Dunedin, New Zealand

Presentation title: *Plasticity in hypothalamic stress circuits.*

Research area: The hypothalamus is an area of the brain that contains neural circuits that are essential for survival. I am specifically interested in one cell type within the hypothalamus; the corticotropin-releasing hormone (CRH) neuron. CRH neurons are activated in response to many different types of stress and in turn release neuropeptides both within the brain and into the circulation to control the body's stress response. We use electrophysiology, in vivo calcium imaging and other techniques to understand how CRH neural circuits within the hypothalamus are regulated. We are specifically interested in determining how these neural circuits process information and adapt across different physiological and behavioral states.

Recent accomplishments: I am currently a Sir Charles Hercus Health Research Fellow (2015-18). In addition, my research laboratory is supported by a Marsden Fast-Start project grant (2015-18). In 2014 I established an independent research laboratory at the University of Otago and in the same year was awarded the Prime Minister's MacDiarmid Emerging Scientist Prize. In 2015 I was awarded the University of Otago Early Career Award for Distinction in Research.

Lecture synopsis: Hypothalamic corticotropin-releasing hormone (CRH) neurons control the neuroendocrine stress response. These neurons secrete CRH peptide from their nerve terminals to control pituitary adrenocorticotropic hormone secretion and hence circulating levels of corticosteroid stress hormones. Once blood corticosteroid levels are elevated, corticosteroids can feedback and inhibit both the pituitary and adrenal gland. Corticosteroids also feedback to the brain and have complex actions on neural circuits via the glucocorticoid receptor. Here we have studied the actions of corticosteroids on CRH neurons both in vitro and in vivo using electrophysiology and calcium imaging. Our data reveal that corticosteroids regulate both the structure and function of CRH neurons over diverse time scales.

Recent publications

Iremonger KJ, Bains JS. Asynchronous glutamate release enhances neuronal excitability during the post-spike refractory period. *The Journal of Physiology*, 2016; 594: 1005-15.

Iremonger KJ, Herbison AE. Multitasking in Gonadotropin-releasing hormone neuron dendrites. Neuroendocrinology. 2015;102(1-2):1-7.

Herde MK*, Iremonger KJ*, Constantin S and Herbison AE. GnRH neurons elaborate a long-range projection with shared axonal and dendritic functions. *Journal of Neuroscience.* 2013; 33(31): 12689-97. *co-first authors

Iremonger KJ*, Wamsteeker Cusulin JI* and Bains JS. Changing the tune: Plasticity and adaptation of retrograde signals. *Trends in Neurosciences*. 2013; 36(8): 471-9. *co-first authors

Constantin S, Iremonger KJ and Herbison AE. In vivo recording of GnRH neuron firing reveal heterogeneity and dependence on GABA receptor signalling. *Journal of Neuroscience*. 2013; 33(22): 9394-401.

Iremonger. KJ, Herbison, AE. Initiation and propagation of action potentials in GnRH neuron dendrites. *Journal of Neuroscience*. 2012; 32(1):151-8.

Speaker 4: Chris Dayas

Recent accomplishments: I was recently appointed to Associate Professor and serve as Deputy Director of the Centre for Brain and Mental Health and Co-Director of the Preclincal Neurobiology Group at University of Newcastle. My lab is funded by NHMRC grants and has received philanthropic support for major neuroscience infrastructure from the Hunter Medical Research Institute and Glencore Xstrata. This includes a Laser Applied Stimulation and Uncaging System (LASU, Scientifica) to perform Channel Rhodopsin Assisted Circuit Mapping in stress and reward pathways.

Title of the presentation: Optogenetic dissection of novel pathways controlling the HPA axis

I hold a BSc Hons and PhD degrees from the University of QLD. After my PhD I undertook post-doctoral training at the Scripps Research Institute in CA San Diego USA on a CJ Martin Fellowship from NHMRC. My work focuses on brain pathways controlling stress and motivation in the context of addiction and mood disorders. A particular focus has been on how stress and addictive drugs impact the lateral hypothalamic orexin system. Orexin neurons are important for a number of basic physiological functions including sleep-wake transitions, reactivity to stress and drug-seeking. Our work has shown that chronic stress or drugs of abuse can produce long lasting changes in LH orexin circuit function. We are currently exploring pharmacological and non-pharmacological mechanisms to restore normal function in these circuits. We are also interested in basic HPA axis control mechanisms and how chronic stress can impact reward processes. Currently our work in this area involves studying how parts of the amygdala control HPA axis responses to psychological stress. In this regard, the present talk will focus on medial amygdaloid control of HPA axis responses through direct projections to the PVN. This work involves electrophysiological and ontogenetic dissection of distinct MeA→ hypothalamic pathways and recruitment of PVN CRF cells.

Recent publications

James MH, Campbell EJ, Dayas CV. Role of the Orexin/Hypocretin System in Stress-Related Psychiatric Disorders. **Curr Top Behav Neurosci**. 2017 Jan 13. doi: 10.1007/7854_2016_56.

James MH, Quinn RK, Ong LK, Levi EM, Smith DW, Dickson PW, Dayas CV. Rapamycin reduces motivated responding for cocaine and alters GluA1 expression in the ventral but not dorsal striatum. **Eur J Pharmacol**. 2016 Aug 5;784:147-54.

Quinn, R. K., Brown, A. L., Goldie, B. J., Levi, E. M., Dickson, P. W., Smith, D. W., Cairns., M.J., **Dayas, C. V.** (2015). Distinct miRNA expression in dorsal striatal subregions is associated with risk for addiction in rats. ***Translational Psychiatry***, *5*, e503.

James, M. H., Campbell, E. J., Walker, F. R., Smith, D. W., Richardson, H. N., Hodgson, D. M., **Dayas, C. V.** (2014). Exercise reverses the effects of early life stress on orexin cell reactivity in male but not female rats. ***Frontiers in Behavioral Neuroscience***.

Yeoh, J. W., James, M. H., Graham, B. A., & **Dayas, C. V.** (2014). Electrophysiological characteristics of paraventricular thalamic (PVT) neurons in response to cocaine and cocaine- and amphetamine-regulated transcript (CART). ***Frontiers in Behavioral Neuroscience***, *8*.

Yeoh JW, James MH, Jobling P, Bains JS, Graham BA & **Dayas C.V.** (2012). Cocaine potentiates excitatory drive in the perifornical/lateral hypothalamus. ***Journal of Physiology*** 590:3677-89.

James M.H., Charnley J.L., Levi, E.M., Yeoh, J.W., Smith, D.W. and Dayas C.V. 2011 Orexin-1 receptor signaling within the ventral tegmental area, but not the paraventicular thalamus, is critical to regulating cue-induced reinstatement of cocaine-seeking. ***Int J Neuropsychopharmacology***.