36th Annual ANS Meeting Hobart

4th – 7th December 2016

HNNA organised symposium at ANS December 2016

Title: The genetic dissection of hypothalamic neural networks

Symposium organisers:

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Presentation 1: Using Mouse Genetics to Unravel the CNS Pathways Controlling Energy Balance and Glucose Homeostasis

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Presentation 2: Optogenetic and chemogenetic analysis of the hypothalamic neural network controlling fertility

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Presentation 3: Population-specific deletion of hypothalamic prolactin receptors identifies a critical role for maternal behaviour

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Presentation 4: Central neural control of brown fat thermogenesis - is beige the new brown?

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Speaker 1 – Professor Joel Elmquist

Professor Elmquist is the Carl H. Westcott Distinguished Chair in Medical Research, Professor of Internal Medicine, Pharmacology, and Psychiatry, and the Maclin Family Professor in Medical Science at the University of Texas Southwestern Medical Center. He is the founding Director of the Hypothalamic Research Center at the University of Texas Southwestern Medical School in Dallas, Dr. Elmquist recruited a group of faculty investigators working to understand brain pathways controlling body weight and metabolism. He currently serves on the editorial boards of several major scientific journals. He has served on numerous NIH study sections and chaired the NIH Integrative Physiology of Obesity and Diabetes study section. Dr. Elmquist is currently a member of the NIDDK Advisory Council and is the principal investigator on several NIH grants, including a MERIT award from the NIDDK. In 2008, The Endocrine Society announced him as the recipient of the Ernest Oppenheimer Award. In 2014, Dr. Elmquist was the recipient of the Stange Award from Iowa State University. In 2014, he was chosen by the American Diabetes Association as the recipient of the Outstanding Scientific Achievement Award supported by Eli Lilly and Company. In 2014, Dr. Elmquist received the Mentor of the Year Award from the National Postdoctoral Association given in recognition of exceptional mentoring or postdoctoral scholars. Professor Elmquist pioneered the use of the cre recombinase/loxP system in the neural control of appetite when at Harvard medical School in the early 2000's. His work has set the standard in the field and this lecture will discuss how his team has used the cre/lox system to understand how CNS leptin receptors mediate melanocortin receptor signalling to control body weight and glucose homeostasis.

Presentation title: Using Mouse Genetics to Unravel the CNS Pathways Controlling Energy Balance and Glucose Homeostasis

Relevant Recent Publications

1: Kohno D…**Elmquist JK**. Dnmt3a in Sim1 neurons is necessary for normal energy homeostasis. *JNeurosci*. 2014 34(46):15288-96.

2: Williams KW…**Elmquist JK**. Xbp1s in Pomc neurons connects ER stress with energy balance and glucose homeostasis. *Cell Metab*. 2014 20(3):471-82.

3: Berglund ED…**Elmquist JK**. Melanocortin 4 receptors in autonomic neurons regulate thermogenesis and glycemia. *Nat Neurosci*. 2014 17(7):911-3.

4: Liu C…**Elmquist JK**. PPARγ in vagal neurons regulates high-fat diet induced thermogenesis. *Cell Metab*. 2014 Apr 1;19(4):722-30.

5: Berglund ED…**Elmquist JK**. Serotonin 2C receptors in pro-opiomelanocortin neurons regulate energy and glucose homeostasis. *J Clin Invest*. 2013 12):5061-70.

6: Sohn JW, **Elmquist JK**. Melanocortin 4 receptors reciprocally regulate sympathetic and parasympathetic preganglionic neurons. *Cell*. 2013 31;152(3):612-9.

7: Kim KW….**Elmquist JK**. FOXO1 in the ventromedial hypothalamus regulates energy balance. *J Clin Invest*. 2012 (7):2578-89.

8: Berglund ED….**Elmquist JK**. Direct leptin action on POMC neurons regulates glucose homeostasis and hepatic insulin sensitivity in mice. *J Clin Invest*. 2012 (3):1000-9.

9: Sohn JW, Xu Y, Jones JE, Wickman K, Williams KW, **Elmquist JK**. Serotonin 2C receptor activates a distinct population of arcuate pro-opiomelanocortin neurons via TRPC channels. *Neuron*. 2011 (3):488-97.

10: Hill JW..**Elmquist JK**. Direct insulin and leptin action on pro-opiomelanocortin neurons is required for normal glucose homeostasis and fertility. *Cell Metab*. 2010 (4):286-97.

Speaker 2 – Allan Herbison

Professor Allan Herbison received a Commonwealth Scholarship to undertake a PhD in neuroendocrinology at the University of Cambridge. Allan then spent a further 12 years as Principal Investigator at The Babraham Institute and Fellow, Pembroke College, University of Cambridge before returning in 2002 to the Department of Physiology, University of Otago supported by the Wellcome Trust as Professor of Neuroendocrinology. He is Director of the University of Otago, Centre for Neuroendocrinology. He has received multiple fellowships and prizes including the Lister-Jenner Fellowship of the Lister Institute, Benoit Prize of the French Société de Neuroendocrinologie Expérimentale, Liley Medal from the NZ Health Research Council, Triennial Medal of the Physiological Society of NZ and the Distinguished Research Medal of the University of Otago. Allan was elected Fellow of the Royal Society of New Zealand in 2007. He has published over 200 research papers and has an H-index of 63.
Professor Herbison is the world-leading expert in the neural control of fertility. By generating and using different genetic mouse models and a variety of molecular, cellular and in vivo experimental approaches, his laboratory has made significant progress in unravelling the complex hypothalamic neuronal network repsonsible for controling the gonadotropin-releasing hormone (GnRH) neurons. His work has focused primarily upon understanding how the network generates episodic activity and how circulating gonadal steroids modulate GnRH secretion.

Presentation title: Optogenetic and chemogenetic analysis of the hypothalamic neural network controlling fertility.

His presentation at ANS will detail the laboratory's use of brain slice electrophysiology and GCaMP calcium imaging, optogenetic and chemogenetic strategies that have begun to elucidate the pulsatile nature of GnRH secretion.

Relevant publications
1: Cheong RY…..**Herbison AE**. Expression of ESR1 in Glutamatergic and GABAergic Neurons Is Essential for Normal Puberty Onset, Estrogen Feedback, and Fertility in Female Mice. *J Neurosci.* 2015 8;35(43):14533-43.
2: Han SY….**Herbison AE**. Selective optogenetic activation of arcuate kisspeptin neurons generates pulsatile luteinizing hormone secretion. *PNAS*. 2015;112(42):13109-14.
3: Piet R….Herbison AE. Estrogen permits vasopressin signaling in preoptic kisspeptin neurons in the female mouse. *J Neurosci*. 2015 ;35(17):6881-92.
4: Campos P, **Herbison AE**. Optogenetic activation of GnRH neurons reveals minimal requirements for pulsatile luteinizing hormone secretion. *PNAS* 2014 111(51):18387-92.
5: Clarkson J….**Herbison AE**. Sexual differentiation of the brain requires perinatal kisspeptin-GnRH neuron signaling. *J Neurosci*. 2014 34(46):15297-305.
8: Herde MK….**Herbison AE**. GnRH neurons elaborate a long-range projection with shared axonal and dendritic functions. *J Neurosci*. 2013 ;33(31):12689-97.
9: Piet R….**Herbison A**E. Estrous cycle plasticity in the hyperpolarization-activated current ih is mediated by circulating 17β-estradiol in preoptic area kisspeptin neurons. *J Neurosci*. 2013 33(26):10828-39.
10: Constantin S, Iremonger KJ, **Herbison AE**. In vivo recordings of GnRH neuron firing reveal heterogeneity and dependence upon GABAA receptor signaling. *J Neurosci*. 2013 33(22):9394-401.
11: Kirilov M….**Herbison AE**. Dependence of fertility on kisspeptin-Gpr54 signaling at the GnRH neuron. *Nat Commun*. 2013;4:2492.

Speaker 3 - Rosemary Brown

Dr Rosemary Brown is a Research Fellow at the Centre for Neuroendocrinology and Department of Anatomy, at the University of Otago, New Zealand. Following completion of her PhD in 2010, she has been a part of Professor Dave Grattan's research team and her research focuses on the actions of the pituitary hormone, prolactin, in the brain. Current projects include investigating; the role of prolactin in infertility, how prolactin accesses the brain from the peripheral circulation, and the role of prolactin in initiating maternal behaviour.

Recent Publications;

Brown RSE, Wyatt AK, Herbison RE, Knowles PJ, Ladyman SR, Binart N, Banks WA, Grattan DR. Prolactin transport into mouse brain is independent of prolactin receptor. *The FASEB Journal (in print 2016).*

Brown RSE, Herbison AE, Grattan DR. Effects of prolactin and lactation on A15 dopamine neurones in the rostral preoptic area of female mice. *Journal of Neuroendocrinology* 27; 708-717 (2015).

Brown RSE, Herbison AE, Grattan DR. Prolactin regulation of kisspeptin neurones in the mouse brain and its role in the lactation-induced suppression of kisspeptin expression. *Journal of Neuroendocrinology* 26; 898-908 (2014).

Liu X*, **Brown RSE***, Herbison AE, Grattan DR. Lactational anovulation in mice results from a selective loss of kisspeptin input to GnRH neurons. *Endocrinology* 155 (1); 193-203 (2014).

Brief synopsis of proposed presentation

"Population-specific deletion of hypothalamic prolactin receptors identifies a critical role for maternal behaviour"

During pregnancy and lactation, a critical adaptation that occurs in the maternal brain is the establishment of appropriate behaviour to enable the mother to feed and nurture offspring. Prolactin is known to be involved in stimulating the onset of maternal behaviour, but the mechanism and the site of action is unknown. The medial preoptic area (MPOA) of the hypothalamus is important for maternal behaviour, and we have shown prolactin receptor expression and an increase in prolactin responsive neurons in this region during lactation. Therefore, we deleted prolactin receptors from the MPOA of adult female mice by injecting an adeno-associated virus expressing Cre-recombinase into the MPOA of prolactin receptor flox transgenic mice. Although fertility, length of gestation and parturition was unaffected in these mice, no litters survived beyond day 2 of lactation, due to a complete failure of maternal care. We have shown that prolactin acting in the MPOA plays an essential role in the initiation of maternal behaviours.

Speaker 4 – Brian Oldfield

Professor Brian Oldfield is an NHMRC Principal Research Fellow with an appointment in the Department of Physiology, Monash University. He is the current President of the Australian and New Zealand Obesity Society, immediate past Chair of the Victorian Obesity Consortium and holds positions on a number of Obesity related Boards and Advocacy groups including the Scientific Advisory Board of Novo Nordisk.

He has an interest in the central neural regulation of energy balance with a focus on energy expenditure, particularly in brown adipose tissue and the newly identified, recruitable form of brown fat, so-called beige fat. His standing in this area is evidenced by his numerous invitations to speak nationally and internationally on the topic and by invitations from the NIH, NHMRC, Stock conferences and other peak bodies to join thought leaders in discussions of the potential of brown and brown-like fat as a therapeutic target. His research in this area has been driven over a number of years by the utlilisation of genetically-modified neurotropic viruses to identify the central neural pathways involved in the innervation of brown adipose tissue (BAT). More recently, these approaches have been supplemented by combination with laser microdissection of single identified BAT – directed neurons and RNA seq to elucidate potential candidates to augment the energy expenditure capabilities of BAT and other brown-like fat cells.

His presentation in the proposed symposium at ANS will focus on the topical issue of the specific innervation of beige fat, an area that has received much fanfare as the necessary intermediate step in the recruitment of brown–like fat - a possible therapeutic approach to combat obesity.

Recent review:

Stefanidis, A.; Wiedmann, N. M.; Adler, E. S.; **Oldfield, B. J.** Hypothalamic control of adipose tissue Best Pract Res Clin Endocrinol Metab (2014) 28 5 685- 701

Selected relevant publications:

Lockie SH, Stefanidis A, Tschop MH, **Oldfield B.J.** (2015) Combination cannabinoid and opioid receptor antagonists improves metabolic outcomes in obese mice. Molecular and Cellullar Endocrinology 417: 10-19

Adler, E.S., Hollis, J.H., Clarke, I.J., Grattan, D.R. and **Oldfield, B.J.** Neurochemical characterization and sexual dimorphism of projections from the brain to abdominal and subcutaneous white adipose tissue in the rat. J Neurosci. 2012 Nov 7;32(45):15913-21

Kampe J, Stefanidis A, Lockie SH, Brown WA, Dixon JB, Odoi A, Spencer SJ, Raven J, **Oldfield B.J.** 2012. Neural and humoral changes associated with the adjustable gastric band: insights from a rodent model. International Journal of Obesity 36: 1403–1411

Verty, A. N. A., Allen, A.M. and **Oldfield, B.J.** (2010) The endogenous actions of hypothalamic peptides on brown adipose tissue thermogenesis in the rat Endocrinology. 2010 Sep;151(9):4236-46