AWCBR
Australasian Winter Conference on Brain Research

VIRTUAL AWCBR SUMMER MEETING

TUESDAY 8 DECEMBER 2020

Locations	Otago	St Davids Complex Seminar Rooms A and B
	Auckland	Room 503-028, Grafton Campus
	Wellington	Easterfield 407 VUW, Kelburn Campus
	Christchurch	Room 707/8, 7th floor, UOC, 2 Riccarton Ave

Zoom Link https://otago.zoom.us/j/97035870636?pwd=aFZERDgreTlSUU9uaGt6RHVIU0h3Zz09#success
Meeting ID: 970-3587-0636 Password: 119855

8.45-9.00 am Opening remarks

1. SESSION HOSTED BY OTAGO:
CHAIR: ANURAG SINGH

9.00 am	1.1	**Shane Ohline, *University of Otago*** Tracking the activity of adult-born neurons as they age: Intrinsic versus molecular excitability
9.15 am	1.2	**Yukti Vyas, *University of Auckland*** Looking inside the brain of freely-behaving rodents using miniscopes
9.30 am	1.3	**Tim David, *University of Canterbury*** Parameter optimisation in models of neurovascular coupling: The problem of complexity
9.45 am	1.4	**Rhys Livingstone, *University of Otago*** The role of calcium-permeable AMPA receptors in secreted amyloid precursor protein alpha-mediated plasticity

2. PLENARY LECTURE:
CHAIR: RUTH EMPSON

10.00 am	2	**Gordon Shepherd, *Northwestern University, USA*** Circuit organization of mouse motor cortex

11.00-11.30 am		Tea/Coffee break

3. GODDARD PRIZE SESSION:
CHAIR: INDRANIL BASAK / KYLA-LOUISE HORNE

11.30 am	3.1	**Jaya Prasad, *University of Auckland*** Promoting IGF-1 signalling to treat inflammation-related brain injury in newborn rats
11.45 am	3.2	**Emma Deeney, *University of Otago*** Voluntary exercise normalises brain-derived neurotrophic factor expression to restore motor behaviour in a mouse model of spinocerebellar ataxia type 1
12.00 pm	3.3	**Shruthi Sateesh, *University of Otago*** Transregional and synapse-specific regulation of hippocampal long-term potentiation by prior synaptic activity
12.15 pm	3.4	**Taylor Stevenson, *University of Auckland*** α-synuclein is not an inflammatory stimulus to human brain pericytes and microglia
12.30 pm	3.5	**Aisha Sati, *University of Otago*** The role of microglia in polycystic ovary syndrome
12.45 pm	3.6	**Karan Govindpani, *University of Auckland*** Characterising a novel GABA signalling system in the human cerebral vasculature
1.00-2.00 pm		Lunch break
1.30-2.00 pm		ANNUAL GENERAL MEETING All conference participants are invited to attend

4. SESSION CO-HOSTED BY WELLINGTON & CHRISTCHURCH:
CHAIR: SUE SCHENK / NADIA MITCHELL

2.00 pm	4.1	**Anne La Flamme, *Victoria University of Wellington*** Understanding how neuroinflammation alters clozapine-mediated effects
2.15 pm	4.2	**Leon Smyth, *University of Otago, Christchurch*** Oxidant-mediated disruption of the BBB in Alzheimer's disease
2.30 pm	4.3	**Samantha Murray, *Lincoln University*** Combined intracerebroventricular and ocular gene therapy in a sheep model of CLN5 Batten disease
2.45 pm	4.4	**Kelly Paton, *Victoria University of Wellington*** Targeting remyelination and recovery in multiple sclerosis

3.00-3.30 pm	Tea/Coffee break

5. Session Hosted by Auckland:
Chair: Simon O'Carroll

3.30 pm	5.1	**Victor Dieriks, *University of Auckland*** Parkinson's disease: Time for a different perspective
3.45 pm	5.2	**Louise Bicknell, *University of Otago*** An unexpected requirement for histones in brain development
4.00 pm	5.3	**Samantha Holdsworth, *University of Auckland*** Amplified MRI as a tool for detecting altered brain pressure
4.15 pm	5.4	**Denise Taylor, *Auckland University of Technology*** Non-invasive brain stimulation: Potential for a real impact?
4.30-4.45 pm		Closing remarks and student prize presentation

Goddard Prize Abstracts

1.4

The role of calcium-permeable AMPA receptors in secreted amyloid precursor protein alpha-mediated plasticity

R. W. LIVINGSTONE, W. C. ABRAHAM, and J. M. WILLIAMS
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The orchestrated regulation of the AMPA-subtype of glutamate receptors (AMPARs) by neuronal activity and neuromodulators is critical to the expression of both long-term potentiation (LTP) and memory. In particular, Ca^{2+}-permeable AMPARs (CP-AMPARs) comprise a unique role in these processes due to their transient, activity-regulated expression at the synapse. Importantly, many of the mechanisms which govern these processes are negatively affected in neurodegenerative disorders such as Alzheimer's disease, suggesting that understanding the mode of action of neuromodulatory molecules may reveal much needed novel therapeutic interventions. Secreted amyloid precursor protein-alpha (sAPPα), a metabolite of the parent amyloid precursor protein (APP) has been previously shown to enhance hippocampal LTP and facilitate memory formation. Accordingly, we hypothesised that sAPPα may act via modulation of AMPAR synthesis and cell surface expression. Using cultured primary hippocampal neurons, we found that sAPPα (1 nM) regulates the synthesis and cell surface expression of CP-AMPARs which underlies the enhancement of LTP in acute hippocampal slices. Additionally, we found that sAPPα further regulates the expression of existing GluA2-, and GluA3-containing AMPARs, indicating that sAPPα facilitates a dynamic exchange of AMPARs at the neuronal cell surface. Together, these findings suggest that regulation of AMPAR composition and expression are central to how sAPPα regulates plasticity in hippocampal neurons. These experiments expand upon our current knowledge underlying mechanisms of plasticity in both health and disease.

3.1

Promoting IGF-1 signalling to treat inflammation-related brain injury in newborn rats

J.D. PRASAD[1], Y. LOOIJ[2], S. SIZONENKO[2], J. GUAN[4], M. J. BERRY[5], L. BENNET[1], A.J. GUNN[1], and J.M. DEAN[1].
[1] Department of Physiology, Faculty of Medical and Health Sciences, University of Auckland, New Zealand, [2]Division of Child Development and Growth, Department of Pediatrics, University of Geneva, Geneva, Switzerland, [4]Department of Pharmacology, Faculty of Medical and Health Sciences, University of Auckland, New Zealand, [5]Department of Paediatrics and Health Care, University of Otago, Dunedin, New Zealand

Preterm born infants have high rates of postnatal infection and non-specific inflammation, which are strongly associated with white matter injury and adverse neurodevelopmental outcomes. Critically, preterm infants with evidence of inflammation at birth show reduced circulating insulin-like growth factor-1 (IGF-1) concentrations, which were associated with poor neurological outcomes. Therefore, we hypothesised that postnatal systemic inflammation impairs central IGF receptor (IGF-IR) signalling during white matter development, and that restoring IGF-IR signalling during postnatal inflammation would reduce associated white matter injury. Neonatal rats received single daily intraperitoneal injections of sterile saline or lipopolysaccharide (LPS; 0.3 mg/kg) from postnatal day (PND)1–3, with concomitant subcutaneous injections of sterile saline, recombinant human IGF-1 (rhIGF-1; 0.5mg/kg), or cyclic-glycine proline (cGP; 0.01mg/kg). Brain IGF-IR signalling was assessed from PND2-21 by western blot. Oligodendrocyte cell death was assessed at PND4. Motor (accelerating rotarod), cognitive (novel object recognition), and brain microstructural (diffusion MRI) outcomes were assessed at PND21. LPS animals showed persisting reduction in central IGF-IR signalling. Both rhIGF-1 and cGP treatment could reduce acute oligodendrocyte cell death at PND4 and partially improved motor outcomes at PND21 when administered at low equimolar doses, while only cGP treatment improved cognitive outcomes and subcortical white matter microstructure. Thus, cGP may represent a novel therapeutic intervention for treatment of inflammation-related preterm brain injury.

3.2

Voluntary exercise normalises brain-derived neurotrophic factor expression to restore motor behaviour in a mouse model of spinocerebellar ataxia type 1

E. A. DEENEY[1], S. M. HUGHES[2], and R. M. EMPSON[1]
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Spinocerebellar ataxia type 1 (SCA1) is a progressive, incurable, autosomal-dominantly inherited neurodegenerative disease. SCA1 is characterized by loss of motor coordination of limbs, speech, and eye movements, due to cerebellar degeneration. This study aimed to determine whether voluntary exercise could be used a therapy for mouse models of SCA1. SCA1 154Q/2Q mice (ataxic) and wild-type (WT) controls (non-ataxic) were individually housed from 4 weeks of age (early-stage of SCA1 disease progression) with or without a running wheel for 4 weeks. At 8 weeks, mice were tested on an accelerating rotarod (4 trials per day, for 4 consecutive days). Our findings show that SCA1 non-exercised (NE) mice had reduced latency to fall scores, compared to WT NE mice ($P<0.01$). Latency to fall scores of SCA1 mice that exercised for 4 weeks were indistinguishable from WT NE mice ($P>0.05$). Fluorescent immunohistochemistry performed on cerebellar sagittal vermal sections (30μm thick) taken from folia X, a region which receives vestibular and ocular information, showed that molecular layer BDNF (ml-BDNF) expression in 9-week-old SCA1 NE mice was significantly elevated when compared to age-matched WT NE mice ($P<0.01$). 9-week-old exercised SCA1 mice had ml-BDNF expression levels that were reduced back to 9-week-old WT levels ($P>0.05$). These findings indicate that 4 weeks of voluntary exercise can restore motor coordination and balance on an accelerating rotarod and that these behavioural improvements may be a consequence of normalising ml-BDNF expression levels.

3.3

Transregional and synapse-specific regulation of hippocampal long-term potentiation by prior synaptic activity

S. SATEESH, A. SINGH, O. D. JONES, and W. C. ABRAHAM
Department of Psychology, University of Otago, Dunedin

Synaptic plasticity is vital for neural health and cognition, however unregulated plasticity compromises learning and, in the extreme, may be injurious. Mechanisms must therefore be in place to prevent excessive long-term potentiation (LTP) and long-term depression (LTD). Such regulation comes in part through processes termed "metaplasticity" which regulates both LTP and LTD through processes that are initiated by "priming" activity that precedes a later bout of plasticity-inducing synaptic activity. Here we tested the spatial spread of a previously described metaplastic effect across various synaptic pathways of the hippocampal network. Field potential recordings were undertaken from *in vitro* rodent hippocampal slices. Following electrical "priming" stimulation delivered to the stratum oriens (SO) of area CA1, there was an inhibition of subsequent LTP at pyramidal cell synapses in the stratum radiatum ($p<0.0001$). Surprisingly, the inhibition of LTP was also evident at granule cell synapses in the dentate gyrus (DG, $p<0.01$), a neighboring region ~800 µm away and across the hippocampal fissure. However, priming did not affect LTP at CA1 pyramidal cell apical tuft dendrite synapses in stratum lacunosum-moleculare nor at basilar dendrite synapses in SO. Similar synapse-specific effects were obtained by pharmacological priming using bath-application of the cytokine tumour necrosis factor-alpha. These effects required activation of TNFα receptor-1. Thus, this mode of metaplasticity has the novel property of exerting a specific spatial spread that spares some synapses on cells in one region while extending to entirely different cells of a neighboring region. Understanding why some synapses are selectively impaired by such activity and some protected may open new targets for combating neurological disorders in which plasticity and memory are impaired.

3.4

α-synuclein is not an inflammatory stimulus to human brain pericytes and microglia

T. J. STEVENSON[1], R. P. JOHNSON[1], L. BOUSSET[2], J. RUSTENHOVEN[1], L. C. D. SMYTH[1], Z. WOOLF[1], H. C. MURRAY[1], R. L. M. FAULL[1], E. MEE[1], P. SCHWEDER[1], P. HEPPNER[1], C. TURNER[1], R. MELKI[2], B. V. DIERIKS[1], M. A. CURTIS[1], and M. DRAGUNOW[1]
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Neuroinflammation is a prominent feature of Parkinson's disease, marked by the activation of glial cells, infiltration of blood-derived inflammatory cells and increased expression of inflammatory cytokines. The presence of α-synuclein (α-syn) aggregates is a hallmark of Parkinson's disease and extracellular α-syn has been shown to trigger the release of pro-inflammatory cytokines by glial cells in *in vitro* and *in vivo* rodent models. However, the use of human brain cells for the study of α-syn induced inflammation has been limited. In this study, we treated primary human brain pericytes and microglia with seven different human recombinant α-syn preparations produced in *Escherichia coli* from three independent sources. Additionally, two α-syn preparations were co-treated with Toll-like receptors ligands. Inflammatory responses were measured in both cell types using cytometric bead arrays, cytokine/chemokine proteome profiler arrays and high content imaging analysis. Five of the seven α-syn preparations did not induce measurable inflammatory responses in either cell type. Two α-syn preparations that did induce inflammation were discovered to be contaminated with high levels of bacterial endotoxins. In addition, the endotoxin-free α-syn preparations did not augment Toll-like receptor activation when co-treated with Toll-like receptor ligands. These data suggest that α-syn that is free of contaminants, does not induce inflammation in primary human pericytes and microglia. The findings from this study have important implications for understanding the role of inflammation in Parkinson's disease.

3.5

The role of microglia in polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility worldwide. Accumulating evidence suggests that the brain plays a key role in the pathophysiology of PCOS. In a well-characterised prenatally androgenised (PNA) mouse model of PCOS, aberrant neuronal wiring associated with PCOS deficits are detected as early as postnatal day (P) 25, prior to disease onset. However, the mechanisms by which prenatal androgen exposure alters brain wiring remains unknown. Microglia, the immune cells of the brain, are active sculptors of neuronal wiring across development, regulating the formation and removal of neuronal inputs. This project aims to understand whether microglia play a role in driving the abnormal wiring that leads to PCOS-like features in the PNA brain. Microglia population and activation state, which can be used as a proxy of cellular function, were used to assess whether microglia are altered in the brain of PNA mice across developmental stages associated with PCOS. Microglia were immunolabelled for a microglia-specific marker and quantified in hypothalamic regions implicated in fertility regulation across development (Embryonic day 17.5, P0, P25, P40 and P60 (n=7–14/group)). Although PNA treatment did not alter microglia at E17.5, at P0, PNA mice had significantly fewer "activated" microglia compared to controls (P<0.05). Later in development at P25, PNA mice exhibited significantly fewer "sculpting" microglia (P<0.001), whereas at P60, PNA mice possessed a greater number of "activated" microglia (P<0.01). These findings demonstrate time-specific changes in the central microglia population and activation state in a mouse model of PCOS, suggesting a role for microglia in driving the brain wiring abnormalities associated with PCOS.

3.6

Characterising a novel GABA signalling system in the human cerebral vasculature

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H.J. WALDVOGEL[1], R.L.M. FAULL[1], and A. KWAKOWSKY[1]
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γ-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the mammalian brain, playing a central role in the regulation of cortical excitability. However, there is evidence from rodent studies that GABA may also play a role in cerebrovascular functions including vascular contractility and angiogenesis. This implies the existence of a functional cerebrovascular GABA signalling apparatus, but this has never been demonstrated in the human brain. We conducted NanoString nCounter analysis, Western blot and immunocytochemistry studies using post-mortem human middle temporal gyrus (MTG) tissue, primary human brain pericytes and human cerebral microvascular endothelial cells (hCMVECs) to examine the expression and distribution of GABA receptor subunits, transporters, and synthesising and metabolizing enzymes. We then conducted *in vitro* functional studies with pericytes and endothelial cells, including live-cell calcium imaging, electrical cell-substrate impedance sensing (ECIS) and potentiometric dye assays. We detected robust cerebrovascular expression of the beta3, gamma3 and epsilon GABAA receptor (GABAAR) subunits in the human MTG vasculature and in cerebrovascular cells, indicating the existence of a vascular GABAAR subtype with a distinct subunit configuration. However, we did not detect GABA-mediated effects on pericyte contractility, vascular calcium signalling or membrane potential. In conclusion, we have demonstrated for the first time that GABAARs are expressed in the human cerebral vasculature, but the pharmacological relevance of these receptors remains to be determined.