FROM MOLECULES TO NEURONAL DISEASE Bristol 2013

PROCEEDINGS OF

THE UK-KOREA NEUROSCIENCE CONSORTIUM

The 6th UK-KOREA
Neuroscience Symposium

bristol neuroscience

Brain+inspire

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The 6th UK-KOREA Neuroscience Symposium

Royal Marriott Hotel,
Bristol,
United Kingdom

18 July - 19 July 2013

Programme - Thursday 18th July

Morning Session

08:30	Registration: Merchant Foyer 2nd Floor		
	Location: Merchant 1, 2nd Floor		
09:00	Opening Address	**Kei Cho**, *University of Bristol*	
09:10	Congratulate Address & British Neuroscience History	**Tim Bliss**, *NIMR*	
09:20	**Plenary Lecture 1**: *TBC*	**John O'Keefe** *UCL*	*Chair: **Tim Bliss***
10:10	***Refreshments: Tea, Coffee, Sweet & Savory snacks*** *(Merchant Foyer 2nd Floor)*		
	Session - 1 (Chair: Tim Bliss): *Merchant 1, 2nd Floor*		
10:30	Synaptic mechanisms in the hippocampus relevant to neurodegeneration	**Graham Collingridge**, *University of Bristol*	
10:50	LTD signals and microtubule associated protein tau: Physiological and pathological synaptic plasticity	**Kei Cho**, *University of Bristol*	
11:10	Evolution of cerebral cortical development	**Zoltan Molnar**, *University of Oxford*	
11:30	Activity-dependent modulation of the interaction between CaMKIIα and Abi1 and its involvement in spine maturation	**Dong Eun Park**, *Seoul Nat. University*	
11:50	Synaptic scaffolding proteins, NMDA receptor function, and ASDs	**Eunjoon Kim**, *BIS-KAIST*	
12:10	***Long Lunch including sight-seeing open top bus tour of Bristol: Pickup at 13:15, return at 14:45***		Walter's, Ground Floor

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Afternoon Session

	Session - 2 (Chair: Graham Collingridge): *Merchant 1, 2nd Floor*		*Session - 3 (Chair: Elek Molnar):* *Merchant 5, 2nd Floor*	
15:00	Functional diversity in the midbrain dopamine system	**Mark Ungless** *Imperial College*	Peripheral pain pathways	**John Wood** *UCL*
15:20	Molecular mechanisms for polarized distribution of NCKX2 in rat hippocampal neurons	**Suk-Ho Lee** *Seoul Nat. Univ.*	Function of ERM proteins in migration of neuroblasts following traumatic brain injury	**Woong Sun** *Korea University*
15:40	Circuit alterations and compensations in the Fmr1-KO mouse model of Fragile X syndrome	**John Issac** *Eli Lilly*	NeuroD, a proneural bHLH transcription factor, relays metabolic signals to nuclei	**Hae Young Suh** *Ajou University*
16:00	Ca2+ binding proteins and sensory regulation in Caenorhabditis elegans	**Sun-Kyung Lee** *Hanyang University*	The birth and death of the synapse: a role for Wnt signalling.	**Patricia Salinas** *UCL*
16:20	***Refreshments: Tea, Coffee, Sweet & Savory snacks*** *(Merchant Foyer, 2nd Floor)*			
16:40	**Plenary Lecture 2** Imaging Pain and Relief in the Human Brain	**Irene Tracey** *University of Oxford*	*Chair: John Wood*	*Merchant 1, 2nd Floor*
17:30	*End of Day 1 Scientific Programme*			
18:30	*Delegate Dinner - Bordeaux Quay - Invited guests ONLY*			

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Programme - Friday 19th July

Morning Session

09:00	***Plenary Lecture 3*** *Thalamocortical circuits in control of consciousness and cognition*	**Hee-Sup Shin** *IBS, Daejeon* ***Chair: John Wood***	Merchant 1, 2nd Floor
09:50	***Refreshments: Tea, Coffee, Sweet & Savory snacks*** *(Merchant Foyer)*		
	Session - 4 (Chair: Michael Owen): *Merchant 1, 2nd Floor*		
10:20	Cognition in preclinical models of dementia	**Lisa Saksida**, *University of Cambridge*	
10:40	Early functional impairments caused by Ca^{2+} dysregulation in dentate granule cells of Tg2576 mice	**Wonkyung Ho**, *Seoul Nat. Univ.*	
11:00	NGF and BDNF: Their roles in Alzheimer's disease and as therapeutic targets	**Shelley Allen-Birt**, *University of Bristol*	
11:20	A role for microRNA-188 in synaptic function: Implications for Alzheimer's disease	**Hye-Sun Kim**, *Seoul Nat. Univ.*	
11:40	Synaptic receptor interplay in Aβ-driven pathophysiology in the perirhinal cortex	**Daniel Whitcomb**, *University of Bristol*	
12:00	The effects of repeated seizures on ionotropic glutamate receptors	**Elek Molnar**, *University of Bristol*	
12:20	***Buffet lunch - Bristol Royal Marriott (Walter's, Ground Floor) - Registered delegates ONLY***		

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Afternoon Session

	Session - 5 (Chair: Patricia Salinas): *Merchant 1, 2nd Floor*		*Session - 6 (Chair: John O'Keefe):* *Merchant 5, 2nd Floor*	
14:30	Regulation of homeostatic and experience-dependent synaptic plasticity by MSK1	**Bruno Frenguelli** *University of Warwick*	The amplitude modulation of the HPA code	**Stafford Lightman** *University of Bristol*
14:50	The role of glutamate autoreceptors in plasticity	**Nigel Emptage** *University of Oxford*	Role of dopamine D2 receptors in plasticity of stress-induced addictive behaviours	**Ja Hyun Baik** *Korea University*
15:10	Spartin Regulates Synaptic Growth and Neuronal Survival by Inhibiting BMP-Mediated Microtubule Stabilization	**Seong Bok Lee** *Seoul Nat. Univ.*	Acute Stress and Synaptic Plasticity (UK-Korea joint presentation): **Jihoon Jo** *(Chonnam Nat. Univ.)* & **Garry Whitehead,** *(University of Bristol)*	
15.30	***Refreshments: Tea, Coffee, Sweet & Savory snacks*** *(Merchant Foyer, 2nd Floor)*			
15:50	Genetics and the nature of schizophrenia	**Michael Owen** *University of Cardiff*	Is hippocampal LTP really the basis of long-term spatial memory?	**David Bannerman** *University of Oxford*
16:10	A positive feedback loop between Sox2 and Sox6 inhibits neuronal differentiation in the developing central nervous system	**Jae Sang Kim** *Ewha Womans University*	Hippocampus and decision making	**Min-Whan Jung** *Ajou University*
16:30	To be or not to be (standing), that is the question: neuronal regulation of a dispersal behavior in nematodes	**Jun Ho Lee** *Seoul Nat. Univ.*	A novel sleep maintenance pathway composed of myoinhibitory peptide and sex peptide receptor in Drosophila	**Joon Ho Choe** *KAIST*
16:50	A Novel Function of DISC1 related to ER	**Sang-Ki Park** *Postech*	Brain circuits involved in selection of avoidance response under threat	**June Seek Choi** *Korea University*
17:10	***Closing Remarks: John Wood*** *(UCL),* ***Kyungjin Kim*** *(Seoul Nat. Univ.)* ***and Eunjoon Kim*** *(IBS-KAIST)*			
18:30	***Symposium Dinner*** *(Palm Court Marriott)* - Congratulate Address (**Dr Byeong-Jun Bae**, *Director General, Korea MOHW*; **Dr Mark Palmer**, *Director of International Strategy , UK MRC*)			

FROM MOLECULES TO NEURONAL DISEASE Bristol 2013

Proceedings of the UK-Korea Neuroscience Consortium vol. 1, *2011:1*

Synaptic mechanisms in the hippocampus relevant to neurodegeneration

Graham Collingridge

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Synaptic plasticity is a major neural process used for information storage in the CNS. The two most extensively studied forms of synaptic plasticity in the vertebrate brain are long-term potentiation (LTP) and long-term depression (LTD). These are involved in a variety of physiological functions, such as learning and memory. We are interested in the molecular mechanisms of LTP and LTD at hippocampal synapses. Recently we have obtained evidence that molecules that are strongly associated with neurodegenerative conditions, such as Alzheimer's disease, are important components of the LTD process. We believe, therefore, that aberrant LTD may be the cause of the synaptic degeneration that is a core feature in such pathological conditions. In this talk, I will summarise the state of knowledge of LTD in the hippocampus.

Proceedings of the UK-Korea Neuroscience Consortium vol. 1, *2011:2*

LTD signals and microtubule associated protein tau: Physiological and pathological synaptic plasticity

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As a prominent form of synaptic plasticity, long-term depression (LTD) is expressed as a controlled deconstruction and elimination of synaptic connections, primarily through the internalization of excitatory receptors and an associated downregulation in synaptic transmission. We have previously shown that a novel signalling pathway, central components of which form the caspase-apoptosis cascade, is critically required for LTD. Our study suggests that caspase-3-mediated cleavage of Akt-1 plays a key role in LTD and AMPAR endocytosis, without inducing apoptosis. We also found that Aβ induces synaptic elimination and aberrant synaptic plasticity in a specific manner, blocking LTP but actually enhancing LTD signals, such as caspase-3 and glycogen synthase kinase-3β (GSK-3β). We now bring these two findings together; given that Akt-1 ordinarily serves to down-regulate GSK-3β activity, the caspase cleavage of Akt-1 leads to the activation of GSK-3β. Very recently, we found that the induction of LTD is associated with the GSK-3β-mediated phosphorylation of tau, another key pathophysiology of Alzheimer's diase. These observations demonstrate that tau has a critical physiological function in LTD. The primary importance of understanding the molecular details of these LTD-signal pathways is to determine the interplay between physiology and pathophysiology in the brain.

Supported by MRC, The Wellcome Trust and Wolfson Research Merit Award, the Royal Society London.

Proceedings of the UK-Korea Neuroscience Consortium vol. 1, *2011:3*

Evolution of cerebral cortical development

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Understanding how the mammalian isocortex (neocortex) evolved to its present complex state is a fascinating topic for neuroscience, genetics, bioinformatics and comparative biology. To gain further insights we study the development of various extant species. Our aim is to correlate cortical cell numbers and neuronal cell types with the elaboration of cortical progenitor populations and their modes of proliferation in different species. There are several progenitors, i.e. the ventricular radial glia, the subventricular intermediate progenitors and subventricular (outer) radial glia types, but the contribution of each to cortical layers and cell types through specific lineages is not fully understood. Recent comparisons of the proportions of these progenitors in various species during embryonic neurogenesis have revealed the elaboration and cytoarchitectonic compartmentalization of the germinal zone, with alterations in the proportions of various types that can be included among the intermediate progenitors. Across species, larger and more diverse intermediate progenitor populations correlate with brain size and cortical cell diversity. The challenge is to relate the radial and tangential expansion of the neocortex with the changes in the proliferative compartments during mammalian evolution and with the analysis of transcriptomes and clones derived from the various sectors of the developing brain. Increased knowledge of neuronal numbers, cell types and their molecular taxonomy is redefining anatomy. The “fractal-like” progression of cortical sub-compartmentalization is potentially induced and modulated by local and distant signals during neocortical development and this result in relative amplification or diminution of selected neurogenetic events that drive forebrain evolutionary changes. Understanding the molecular and cellular interactions regulating the divisions of these intermediate progenitors not only has implications for cortical evolution but also relates to stem cell biology and illuminates the pathomechanisms of several cortical developmental disorders.

Supported by MRC, BBSRC, The Wellcome Trust. NAV is a Goodger Scholar, FGM is a HFSP Fellow.

Proceedings of the UK-Korea Neuroscience Consortium vol. 1, *2011:4*

Activity-dependent modulation of the interaction between CaMKIIα and Abi1 and its involvement in spine maturation

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Remodeling of dendritic spines through regulation of actin dynamics is a key event in activity-dependent structural plasticity. However, the molecular mechanism underlying this process is poorly understood. Here, we show that activity-dependent modulation of the Abi1-CaMKIIα interaction is important for regulation of spine morphology in cultured rat hippocampal neurons. Abi1 interacts with CaMKIIα at resting conditions through its tSNARE, which harbors striking homology with the CaMKIIα regulatory domain. The interaction of the two proteins results in the simultaneous inhibition of CaMKIIα activity and Abi1-dependent Rac activation. This functional impediment is subsequently removed upon protein dissociation by Calmodulin binding through glutamate receptor activation. Prior to dissociation, Abi1 is phosphorylated by CaMKIIα at Serine 88. Furthermore, Abi1 affinity for CaM increased with Ser 88 phosphorylation inducing dissociation from CaMKIIα. Ser 88 phosphorylation is also needed for Rac activation. Spine maturation was attenuated by GFP-Abi1^{S88A} and tSNARE-deletion mutants similar to dendritic phenotype in Abi1 knockdown rat hippocampal neurons implying a substantial role of the tSNARE domain and CaMKIIα-mediated phosphorylation of Abi1 in spine maturation. Our results suggest that modulation of the interaction between Abi1 and CaMKIIα, through the glutamate receptor pathway, may be a molecular mechanism underlying activity-regulated structural plasticity.

Proceedings of the UK-Korea Neuroscience Consortium vol. 1, *2011:5*

Synaptic scaffolding proteins, NMDA receptor function, and autism spectrum disorders

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A growing number of synaptic proteins have recently been associated with diverse neuropsychiatric disorders including schizophrenia, autism spectrum disorders, attention deficit hyperactivity disorder (ADHD), and mood disorders. Autism spectrum disorders (ASDs) represent a group of neurodevelopmental disorders characterized by symptoms including impaired social interaction, impaired social communication, repetitive behaviors, and restricted interests. Although a large number of ASD-related genetic variations have been identified, only a small number of them have been verified by approaches including mouse genetics. In addition, neural mechanisms underlying the development of ASDs have largely remained unknown, explaining the lack of efficient medications for ASD treatment. Synaptic scaffolding proteins at excitatory synapses interact with various synaptic proteins including receptors and signaling molecules, and couple receptor activations with downstream signaling events. In this presentation, I will discuss how defects in some of the synaptic signaling scaffolds are associated with alterations in NMDA receptor function and autism-like behavioral abnormalities in mice.

Proceedings of the UK-Korea Neuroscience Consortium vol. 1, *2011:6*

Functional diversity in the midbrain dopamine system

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Midbrain dopamine neurons play a central role in reward processing and it is often assumed that they form a functionally homogeneous group. However, evidence is emerging, using a broad range of techniques, indicating that subgroups of dopamine neurons play distinct roles in information coding, particularly with respect to aversive events. Moreover, these subgroups also exhibit diversity of long-term synaptic adaptations in response to drugs of abuse and aversive events. I will present our findings, using single-cell labelling in vivo, that relate anatomical diversity to differential coding for aversive events, and discuss recent data concerning the functional properties of dorsal raphe dopamine neurons and synaptic adaptations in this subgroup in response to social isolation."

Proceedings of the UK-Korea Neuroscience Consortium vol. 1, *2011:7*

Molecular mechanisms for polarized distribution of NCKX2 in rat hippocampal neurons

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Distribution of K^+-dependent Na^+/Ca^{2+} exchanger (NCKX) activity is polarized to the axon in central neurons. Investigating molecular mechanisms underlying the axonal polarization of NCKX2, we identified NCKX2 as the first neuron-specific cargo molecule of KIF21A. We present here compelling evidence supporting the view that interaction of NCKX2 and KIF21A is essential for axonal transport of NCKX2. Despite the axonal polarization of the NCKX activity and surface NCKX2, both somatodendritic (SD) and axonal regions were immunoreactive to NCKX2. Surface NCKX2 on the SD compartment was significantly increased by inhibition of endocytosis. We noted that NCKX2 has two putative tyrosine motifs (YxxΦ), which can be recognized by the μ2 subunit of AP-2, a clathrin adaptor molecule. We found that the ^{365}YGKL motif is essential for interaction with the μ2 subunit and for the endocytosis of NCKX2. Furthermore, interaction between the ^{365}YGKL motif and μ2 subunit was regulated by tyrosine phosphorylation induced by Src family kinase (SFK). These results indicate that KIF21A-mediated axonal transport and selective somatodendritic endocytosis underlie the axonal polarized surface expression of NCKX2 and that the surface expression of NCKX2 in the SD region is regulated by SFK.

Proceedings of the UK-Korea Neuroscience Consortium vol. 1, *2011:8*

Circuit alterations and compensations in the *Fmr1-KO* mouse model of Fragile X syndrome

John Issac*, Peter Kind and Aleks Domanski

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Fragile X syndrome (FXS) is an hereditary developmental disorder caused by a single gene mutation in the fragile X mental retardation protein (FMR1) and is the single largest genetic cause of autism spectrum disorder. Symptoms include cognitive impairment, deficits in sensory gating and abnormal sleep. Studies in the Fmr1-KO mouse model of FXS have demonstrated several developmentally-regulated changes to cortical neuronal anatomy, physiology and plasticity. With relevance to sensory gating deficits, a number of studies have shown alterations in primary sensory circuits in Fmr1 KO mice; however, the circuit basis for such deficits is poorly understood. Using a combination of electrophysiology, functional imaging and modeling in barrel cortex slices, we demonstrate elevated neuronal excitability in layer 4 of Fmr1-KO mice and show that, despite pronounced reciprocal reductions in excitatory-inhibitory connectivity, the efficacy of feed forward inhibition is increased. We also observe changes in short-term plasticity at excitatory and inhibitory synapses. Together these effects produce alterations in circuit dynamics that lead to a loss of spike-timing precision in the circuit, a critical feature for encoding sensory information that could underlie the deficits in sensory gating observed in FXS. Interestingly, modeling suggests that many of the alterations of synaptic and neuronal function are compensatory to one another, thus minimizing the impact of the genetic lesion. Thus, our work shows than an accumulation of effects at the synaptic and cellular level in the Fmr1 KO mouse produce circuit level dysfunction; however, our work also highlights the challenge of understanding which of these changes are pathological and which are compensatory.

Proceedings of the UK-Korea Neuroscience Consortium vol. 1, *2011:9*

Ca^{2+} binding proteins and sensory regulation in *Caenorhabditis elegans*

Changhoon Jee, Taewoo Choi, Karunambigai Kalichamy, Joohong Ahnn
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Calcineurin is a Ca^{2+}/calmodulin-dependent protein phosphatase involved in calcium signaling pathways. In *Caenorhabditis elegans*, the loss of calcineurin activity, causes pleiotropic defects including hyperadaptation of sensory neurons, hypersensation to thermal difference and hyper-egg-laying when worms are fed after starvation. *arrd-17* is *calcineurin interacting protein-1* (*cnp-1*), which is a novel molecular target of calcineurin. CNP-1 interacts with the catalytic domain of the *C. elegans* calcineurin A subunit, TAX-6, in a yeast two-hybrid assay, and is dephosphorylated by TAX-6 *in vitro*. *cnp-1* is expressed in ASK, ADL, ASH, and ASJ sensory neurons as TAX-6. It acts downstream of *tax-6* in regulation of locomotion and egg-laying after starvation, and lysine chemotaxis, which is known to be mediated by ASK neurons. Calreticulin and calnexin, the molecular chaperones in endoplasmic reticulum, control intracellular Ca^{2+} homeostasis and facilitate the proper folding of newly synthesized proteins in the lumen of ER. In order to study the function of calreticulin and calnexin in chemosensation, we investigated the chemosensory behavior of calreticulin (*crt-1*) and calnexin (*cnx-1*) mutants in *Caenorhabditis elegans*. Both *crt-1* and *cnx-1* mutants exhibited normal chemotaxis responding to some AWC sensed odorants such as isoamyl alcohol, benzaldehyde and butanone. The *crt-1* mutants exhibited hyperadaptation to AWC sensed odors whereas *cnx-1* mutants failed to adapt, when compared with wildtype. These results indicate that CNX-1 and CRT-1 may be involved in adaptation of AWC-mediated chemosensation in different mechanisms. We present several experimental evidences to support that Ca^{2+} is critical for the action of CRT-1 in olfactory adaptation, but not likely for CNX-1.

Proceedings of the UK-Korea Neuroscience Consortium vol. 1, *2011:10*

Peripheral pain pathways

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Pain afflicts a fifth of the population; there is an urgent need for new analgesic drugs with minimal side effects. Mechanistic studies in transgenic mice have transformed our understanding of peripheral pain pathways, but the translation of genetic information into useful drugs has been so far disappointing. Human monogenic disorders of pain perception have focused attention on voltage-gated sodium channels, particularly Nav1.7 as a potential drug target, because loss of function in this channel leads to pain-free people. However, general analgesia is not desirable for the treatment of chronic pain conditions, because of the dangers of accidental self-harm. Dissecting molecular mechanism linked to particular types of pain is a route to modality specific pain treatments. We have provided evidence that distinct sets of sensory neurons are involved in different types of pain sensations (Abrahamsen 2008). More recently we have gained insights into some of the mechanotransducing molecules that may be involved in mechanic al hyperalgesia and allodynia, where innocuous stimuli become painful (Eijkelkamp et al. 2013). Surprisingly, a role for the sympathetic nervous system not only in chronic pain, but even acute thermal pain perception has recently been demonstrated (Minett et al. 2012). By comparing a range of chronic pain conditions, (including cancer pain, the pain caused by cytostatic drugs and nerve injury pain) in mice lacking sodium channels in different sets of sensory and sympathetic neurons, we found that phenotypically identical pain conditions arise through different cellular and molecular mechanisms. These observations are important for the analysis of clinical trials data, because they suggest that the mechanistic stratification of pain patients is essential for a rational approach to treatment. Interestingly, the deletion of Nav1.7 in transgenic mice does not compromise the development of pain in a bone cancer model relevant to breast and prostate cancer metastases, or the development of pain caused by the chemotherapeutic agent oxaliplatin. Thus multiple mechanisms contribute to pain, and whilst human phenotypic stratification is an essential start, further mechanistic insights are a prerequisite for the identification of useful analgesic drugs. (*We thank the Wellcome Trust, the BBSRC and MRC and ARUK for generous support.)*

Proceedings of the UK-Korea Neuroscience Consortium vol. 1, *2011:11*

Function of ERM proteins in migration of neuroblasts following traumatic brain injury

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In rodents, neuroblasts are continuously generated from the subventricular zone and migrate toward the olfactory bulb through the rostral migratory stream throughout life. Upon brain injury, neuroblasts can change their route toward injured regions, triggered by SDF1 released from the damaged site. However, it is yet unknown how SDF1 signals influence the motility and the direction of neuroblast migration. In this study, we found that SDF1 promotes the phosphorylation of ezrin-radixin-moesin (ERM) proteins, which are key molecules in organizing cell membrane and link signals from the extracellular environment to the intracellular actin cytoskeleton. Blockade of ERM activation by overexpressing dominant-negative ERM (DN-ERM) efficiently perturbed the bipolar morphology of migrating neuroblasts, resulting in the failure of efficient migration. These results suggest that ERM activation is an important step in the directional migration of neuroblasts in response to SDF1-CXCR4 signaling following brain injury.

Proceedings of the UK-Korea Neuroscience Consortium vol. 1, *2011:12*

NeuroD, a proneural bHLH transcription factor, relays metabolic signals to nuclei

In-Su Cho, Young-Guk Shin, Seunghwan Jung, Young-Don Lee, Sungsoo Kim and **Haeyoung Suh-Kim***

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Signals initiated by hormones, neurotransmitters, or metabolism are transmitted to the cell where they inversely affect gene expression. CREB is the best known transcription factor that relays cAMP signals to the nuclei and activates CRE-mediated gene expression. Here we report that NeuroD/BETA2, an essential transcription factor for differentiation and survival of neurons and pancreatic β-cells, also couples cAMP-triggered signals to gene expression in pancreatic β-cells. We propose that downregulation of NeuroD is the major pathway leading to β-cell failure occurring in the late phase of type II diabetes. We will also discuss cAMP regulation of NeuroD's activity at the protein level and the physiological relevance of cAMP-dependent phosphorylation in neurons.

Proceedings of the UK-Korea Neuroscience Consortium vol. 1, *2011:13*

The life and death of the synapse: a role for Wnt signalling

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Our laboratory is studying the molecular mechanisms that regulate the formation, growth and function of synapses in the vertebrate nervous system. We found that Wnt secreted proteins promotes the formation of central and peripheral synapses. More recently we have focused our attention the mechanisms by which Wnts promote the formation of dendritic spines and regulate synaptic plasticity in the hippocampus.

Another major focus of the lab is to investigate the role of Wnts in synaptic maintenance in the adult brain and how dysfunction in Wnt signaling contributes to synaptic loss in neurodegenerative diseases. The degeneration and/or dysfunction of synapses in Alzheimer's and Parkinson's diseases are correlated with cognitive decline and motor defects. However, little is known about the mechanisms that lead to synapse loss. We have generated an inducible transgenic mouse line deficient in Wnt signaling. Selective loss of Wnt signalling in the adult brain results in the loss of synapses without neuronal loss, mimicking early stages of neurodegenerative diseases. Our studies demonstrate a novel role for Wnt signalling in the maintenance of adult synapses and identify Dkk1, a Wnt antagonist, as a potential therapeutic target for the treatment of neurodegenerative diseases.

Our work is funded by the MRC, Wellcome Trust, Alzheimer's Research UK, Parkinson's UK and EU F7.

Proceedings of the UK-Korea Neuroscience Consortium vol. 1, *2011:14*

Imaging Pain and Relief in the Human Brain

Irene Tracey

University of Oxford

Irene Tracey is the Nuffield Professor of Anaesthetic Science, Director of the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) and Head of the Nuffield Division of Anaesthetics at the University of Oxford, England. Over the past 12 years her multidisciplinary research team has contributed to a better understanding of pain perception, pain relief and nociceptive processing within the injured and non-injured human CNS using neuroimaging techniques. The FMRIB Centre is recognised as one of the world's leading neuroimaging laboratories that integrates research into key neurological and neuroscientific problems with cutting-edge developments in MR physics and data analysis (http://www.fmrib.ox.ac.uk). The Centre has approximately 100 scientists and clinicians from a range of backgrounds and Professor Tracey has been their Director for the past eight years.

Irene Tracey was born in 1966 and performed her undergraduate and graduate studies in Biochemistry at the University of Oxford where she graduated with First Class Honours, winning the Gibb's Prize for joint top-First. She held a post-doctoral position at Harvard Medical School before returning to the UK in 1996 to help establish the FMRIB Centre. She is an elected Councillor to the International Association for the Study of Pain (IASP) and Chair of the Scientific Program Committee for the Milan 2012 biannual world congress. In 2008, she was awarded the triennial Patrick Wall Medal from the Royal College of Anaesthetists and in 2009 she was made a FRCA for her contributions to the discipline. She is Deputy Chair of the UK's Medical Research Council's Neuroscience and Mental Health Board.

She is married to Professor Myles Allen, a climate physicist, and they have three wonderful yet irrepressible children: a daughter, Colette, and two sons, John and Jim.

Proceedings of the UK-Korea Neuroscience Consortium vol. 1, *2011:15*

Thalamocortical circuits in control of consciousness and cognition

Hee-Sup Shin

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Korea

Professor Hee-Sup Shin is the Director of the Center for Cognition and Sociality at the Institute of Basic Sciences in Daejeon, Korea. Between 2001 and 2012, Professor Shin worked as a principal research scientist at Korea Institute for Science and Technology (KIST) before becoming Director of the Center of Neural Science, KIST in 2005. His time at KIST culminated in becoming the Director-General of the Brain Sciences Institute in 2011. Previous to these appointments, Professor Shin worked as an Associate Professor in the Department of Biology at MIT.

Professor Shin gained a medical degree from SNU in 1977 before completing a PhD in Genetics and Cell Biology at Cornell University in 1983. Following his time in the U.S, he returned to Korea to become a Professor in the Department of Life Sciences at POSTECH.

Moving from the field of cancer to neuroscience, Professor Shin's research now focuses on the derangement of calcium regulation in neuronal cells, the consequences of which include defects in learning and memory and underlying issues in neurological diseases such as epilepsy, stroke, and dementia. Professor Shin's laboratory has pioneered the use of novel transgenic models to study intracellular calcium regulation in an attempt to identify the genes that may be involved in the aberrant calcium dynamics observed in these disorders.

Professor Shin's research has been recognised throughout his career including receiving the Dupont Prize in 2004 as well as the Order of Civil Merit from the President of Korea in the same year. Other honours include an AHF Lectureship award from Calgary University and the Frank Lappin Horsfall Jr. Award from Cornell University.

Proceedings of the UK-Korea Neuroscience Consortium vol. 1, *2011:16*

Cognition in preclinical models of dementia

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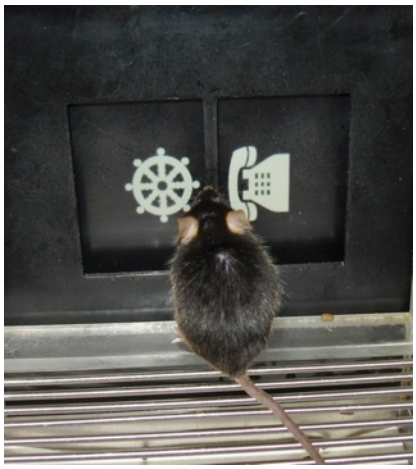
Current methods of cognitive testing in rodents, such as fear conditioning and maze testing, have led to important advancements. However, more recently, we have developed a new method of assessing cognitive behaviour in pre-clinical models, with potentially greater relevance to human disease. This method of testing is much more comparable to test batteries used in humans, such as CANTAB: it uses the same types of stimulus materials (objects and locations on a computer screen), and the same types of responses (responses directly to the stimuli on the screen using a touchscreen apparatus). This new form of assessment has three main advantages when compared with previous models.



First, the tasks are more representative of the tasks used to measure cognitive deficits seen in patients - in many cases, virtually identical paradigms and methodologies can be used. Second, a battery approach can be taken - the tasks are carried out in the same apparatus, using the same type of stimuli, with the same rewards, and requiring the same responses, thereby controlling for many potential confounds. Third, there are a number of practical advantages -- many animals can be tested simultaneously, experimenter contact with animals during testing is minimised, and many behavioural measures are possible. Our current test battery comprises nine tasks, each of which targets different aspects of cognitive functioning and different brain regions (particularly the hippocampus, prefrontal cortex and striatum). In this talk I will focus on how we are using the test battery to phenotype mouse models of Alzheimer's Disease (AD).

Proceedings of the UK-Korea Neuroscience Consortium vol. 1, *2011:17*

Early functional impairments caused by Ca^{2+} dysregulation in dentate granule cells of Tg2576 mice

Kyung-Ran Kim, Sang Hun Lee, Inhee Mook, Suk-Ho Lee and **Won-Kyung Ho***

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Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder characterised by progressive memory impairment, which may be attributable to synaptic dysfunction in the early stages of the disease. Oxidative stress, mitochondrial dysfunction, Ca^{2+} dysregulation, synaptic dysfunction, and abnormal excitability are key factors in the pathogenesis of AD, but the causal relationship between these factors is not clearly understood. We found that in the hippocampus of an AD mouse model (Tg2576) at the age of 1-2 months, mitochondrial Ca^{2+} handling in dentate granule cells (GCs) was impaired, and this Ca^{2+} dysregulation caused an impairment of post-tetanic potentiation in mossy fiber-CA3 synapses. Impairment of mitochondrial Ca^{2+} uptake was associated with increased mitochondrial reactive oxygen species and depolarization of mitochondrial membrane potential. Mitochondrial dysfunctions in GCs and impairment of post-tetanic potentiation in mossy fiber-CA3 synapses were fully restored when brain slices obtained from Tg2576 were pretreated with antioxidants. In addition, we found that intrinsic excitability of GCs is increased in Tg2576, which is also reversed by antioxidant treatment. Reversibility of early dysfunctions by antioxidants at the pre-clinical stage of AD highlights the importance of early diagnosis and antioxidant therapy to delay or prevent the disease processes.

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NGF and BDNF: Their roles in Alzheimer's disease and as therapeutic targets

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Alzheimer's disease is the most common cause of dementia, with loss of ability to form new memories as the earliest symptom. Current treatments for Alzheimer's disease are cholinesterase inhibitors; however the relentless progression of the disease means that treatment only lasts for a limited period. Memory formation is associated with the interaction of the cholinergic basal forebrain neurons with hippocampal glutamate neurons. The cholinergic neurons are reliant on the neurotrophins for maintenance of synaptic connections in adulthood. In particular, the loss of trophic signalling by nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) is thought to be significant in the onset and progression of pathology. We aim to understand more clearly the roles of these neurotrophins and their proforms in the disease and to produce small molecule mimetics/ modulators which stimulate their respective tyrosine kinase receptors, TrkA and TrkB, and mimic trophic functions.

Part of this work has involved using data from the crystal structures of the TrkIg2 domains in complex with neurotrophins, and design of appropriate *in silico* techniques to select small molecule binders to the extracellular domain of TrkA or TrkB. Approximately four hundred compounds were initially selected and tested for ability to bind and activate downstream Trk signalling in culture. Binding sites were then verified using Nuclear Magnetic Resonance HSQC (heteronuclear single quantum coherence). High performance computer-assisted design modification is now underway.

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A role for microRNA-188 in synaptic function: Implications for Alzheimer's disease

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MicroRNAs have emerged as a part of key gene regulation. In the central nervous system, microRNAs have been shown to regulate development, survival, function and plasticity. Previously, we reported that an activity-regulated microRNA, miR-188, controls dendritic plasticity and synaptic transmission by downregulating neuropilin-2 (Nrp-2). Nrp-2 was known to be a negative regulator of dendrtic spine formation and synaptic transmission. In the present study, we investigated the pathological significance of miR-188 in Alzheimer's disease (AD). miR-188 was significantly downregulated in the cerebral cortices (premedial gyrus) and hippocampi of AD patients compared with those from age-matched control subjects. In addition, immunoreactivity against Nrp-2, the molecular target for miR-188, was highly increased in the brains from AD patients, compared with age-matched control subjects. We also demonstrate that treatment with oligomeric amyloid beta peptide$_{1\text{-}42}$ (A$\beta_{1\text{-}42}$) significantly diminished the expression of miR-188 whereas treatment with brain-derived neurotrophic factor significantly upregulated the expression of miR-188 in primary cultured hippocampal neurons. The replenishment of miR-188 in A$\beta_{1\text{-}42}$ treated rat primary cultured hippocampal neurons rescued the reduction in dendritic spine density in the cells. Taken together, the reduction of miR-188 in the brains from AD patients may contribute to the cognitive dysfunctions observed in the disease.

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Synaptic receptor interplay in Aβ-driven pathophysiology in the perirhinal cortex

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Aggregation of Amyloid-β (Aβ), an endogenous protein of unknown precise physiological function, is postulated as being at the centre of AD pathogenesis. Recent studies have suggested that deficits in object recognition memory are found in early stages of AD. The perirhinal cortex is the area of the brain that is thought to be responsible for the processing of recognition memory. This is particularly interesting given how this region is susceptible to AD-mediated pathogenesis.

Synaptic plasticity is a well-characterised cellular phenomenon, expressed as a dynamic change in synaptic strength between neurons, and is thought to underlie learning and memory. In the perirhinal cortex, the long-term depression (LTD) form of synaptic plasticity is now believed to serve as the cellular substrate for recognition memory (Griffiths et al., 2008). It was recently shown using CRND8 transgenic mice, which overexpress Aβ and so serve as an AD model, that dysregulation of recognition memory could be prevented by treatment with memantine, a partial NMDA receptor antagonist (Romberg et al., 2012). Moreover, these findings were mirrored by dysregulation and subsequent restoration of perirhinal cortex synaptic plasticity. In the present study, we have found that Aβ inhibits the induction of mAChR mediated LTD in the perirhinal cortex. In trying to understand a potential mechanism behind this effect, we have considered previous findings outlining both positively-coupled and negatively-coupled relationships between different classes of receptors at the synapse (Jo et al., 2006; Moore et al., 2009). Our findings suggest that Aβ potentiates the function of the metabotropic glutamate receptor 5 subtype (mGluR5), and in doing so impairs mAChR-mediated signalling. Further, we find that activation of mGluR5 in the absence of Aβ similarly dysregulates mAChR-function. Together, these data characterise an underlying mechanism by which Aβ might impair recognition memory, reliant on Aβ-mediating dysregulation of LTD by mGluR5.

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The effects of repeated seizures on ionotropic glutamate receptors

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The imbalance of excitatory (glutamatergic) and inhibitory (GABA-ergic) neurotransmission in the forebrain is a key feature of epilepsy. It is widely accepted that ionotropic glutamate receptors (iGluRs) are involved in the development of various forms of epilepsy. In the present study the effects of repeated 4-aminopyridine (4-AP) induced seizures on the excitability of the entorhinal cortex and changes in iGluRs were investigated. Evoked field excitatory post-synaptic potentials (fEPSPs) were tested to evaluate changes in the basic excitability together with the pharmacological sensitivity to specific AMPA and NMDA receptor antagonists (GYKI 52466 and D-APV, respectively). Kainate-induced Co^{2+}-uptake assay was performed to evaluate changes induced by the repeated 4-AP treatment in the Ca^{2+}-permeability of AMPA and kainate receptors. Alterations in iGluR protein expression levels were analysed by semiquantitative histoblots using selective antibodies to GluA1, GluA2, GluA1-4, GluK5, GluN1 and GluN2 iGluR subunits. While there was a marked decrease in the level of GluA1-4, GluA2 and GluK5 receptor subunits, GluA1 and GluN2A protein levels increased moderately. Our results indicate that repeated brief convulsions can increase entorhinal cortex excitability despite an overall reduction in AMPA/kainate receptor activity, probably through the alteration of NMDA receptor susceptibility.

Reference

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Regulation of homeostatic and experience-dependent synaptic plasticity by MSK1

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The ability of synapses to adapt to constant activity is fundamental to the correct functioning of the mammalian brain. Accordingly, means must exist to limit the extent to which synapses become inexorably stronger or weaker when faced with constant barrages of activity. One such mechanism has been proposed – homeostatic synaptic plasticity – in which synapses uniformly scale synaptic strength up or down, primarily via the trafficking of glutamate AMPA receptors, whilst maintaining the relative weights of synaptic strength across synapses and preserving the information coded therein. We have discovered that the CREB and histone H3 kinase MSK1 is necessary for homeostatic synaptic plasticity in hippocampal neurones. Mice with an inactivating kinase-dead (KD) mutation of MSK1 did not display synaptic up-scaling or down-scaling in response to activity deprivation or enhancement, respectively. This MSK1-dependent process requires activation of BDNF TrkB receptors, the MAPK cascade and induction of Arc/Arg 3.1. Furthermore, MSK1 KD mice did not display an upregulation of hippocampal synaptic transmission following exposure to environmental enrichment. These data suggest that MSK1 is crucial in converting sensory experience and synaptic activity into long-lasting neuronal structural and functional adaptations.

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The role of glutamate autoreceptors in plasticity

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A rise in $[Ca^{2+}]_i$ provides the trigger for neurotransmitter release at neuronal boutons. Measurement of the action potential-evoked $[Ca^{2+}]_i$ in the boutons of Schaffer collaterals reveals that the trial-by-trial amplitude of the evoked Ca^{2+} transient is bimodally distributed. We have found that 'large' Ca^{2+} transients occur when presynaptic NMDA receptors are activated following transmitter release, thus they serve as autoreceptors.

Since autoreceptors 'report' transmitter release on a trial-by-trial basis we have used this to estimate the probability of release, (p_r). We use this novel estimator to show that p_r increases following the induction of LTP.

We have also sought to identify a functional role for presynaptic NMDA autoreceptors. We propose that they form part of a signalling network at the synapse that regulates p_r following the induction of LTP and LTD.

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Spartin Regulates Synaptic Growth and Neuronal Survival by Inhibiting BMP-Mediated Microtubule Stabilization

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Troyer syndrome is a hereditary spastic paraplegia caused by human spartin (SPG20) gene mutations. We have generated a Drosophila disease model showing that Spartin functions presynaptically with the endocytic adaptor Eps15 to regulate synaptic growth and function. Spartin inhibits bone morphogenetic protein (BMP) signaling by promoting endocytic degradation of the BMP receptor Wishful Thinking (Wit). Drosophila fragile X mental retardation protein (dFMRP) and Futsch/MAP1B are major downstream effectors of Spartin and BMP signaling in regulating microtubule stability and synaptic growth. Loss of Spartin or elevation of BMP signaling induces age-dependent progressive defects resembling hereditary spastic paraplegias, including motor dysfunction and brain neurodegeneration. Null spartin phenotypes are prevented by administration of the microtubule-destabilizing drug vinblastine. Together, these results demonstrate that Spartin regulates both synaptic development and neuronal survival by controlling microtubule stability via the BMP-FMRP-Futsch pathway, suggesting that impaired regulation of microtubule stability is a core pathogenic component in Troyer syndrome.

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Genetics and the nature of schizophrenia

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Schizophrenia is highly heritable, and it has long been assumed that the identification of risk genes will provide fundamental insights into pathogenesis upon which disease modification strategies can be built. Recent genomic studies have identified a number of specific risk alleles and begun to reveal the genetic architecture of schizophrenia. Although only a small proportion of the total genetic liability has so far been accounted for, these findings have important implications for our understanding of the classification and pathogenesis of schizophrenia that will impact on future research.

We now have molecular genetic evidence that a very large number of genes, possibly thousands, contain risk alleles for schizophrenia in the population and that genetic susceptibility involves a spectrum of risk alleles, from common to rare, with individual effect sizes ranging from small to large, but with each allele contributing only a small fraction to the total population variance. Genome-wide association studies (GWAS) have so far identified over 70 common, small-effect risk loci at genome-wide levels of significance as well as evidence for a substantial burden of such risk loci. Genomic studies have also implicated at least 11 rare, but recurrent, copy number variants (CNVs) that confer high individual risk of schizophrenia. Further studies over the coming years with larger samples and using new generation sequencing will identify other risk alleles across the spectrum of allele frequencies.

An important finding has been the extent to which risk-associated variation confers susceptibility for mental disorder across current categorical classifications. This is the case for both common variants and more highly penetrant mutations such as CNVs. These findings, together with others, suggest that it is no longer tenable to regard schizophrenia, autism, intellectual disability, epilepsy, ADHD and the major affective disorders as discrete disorders, or sets of disorders, with specific causes, symptoms and consequences. They also imply that a genetically driven neuroscience approach to these disorders should not focus on trying to model specific diagnostic categories but should rather establish the cross-diagnostic biological processes upon which the effects of these mutations converge.

It is incorrect to assume that the identification of small effect risk alleles by GWAS cannot point to import pathogenic mechanisms. However, it is certainly true that it is challenging to use the identification of multiple alleles of small effect to generate testable hypotheses of pathogenesis. Rare alleles associated with higher individual risk are more attractive targets for animal and cellular studies of disease biology, but, with the exception of NRXN1 deletions, many of the schizophrenia-associated CNVs involve multiple genes, and it is usually not immediately clear which are relevant to pathogenesis. Another approach is to identify gene sets representing biological pathways that are over represented among those genes disrupted by pathogenic CNVs. Recent studies of this kind have implicated genes encoding members of the postsynaptic density proteome, specifically those involved in NMDA receptor signaling complexes and synaptic plasticity. Most recently, our exome-sequencing studies have revealed an excess of deleterious mutations in these same synaptic genes, strongly implicating these pathways in the pathogenesis of major mental disorders. These penetrant mutations offer a novel and compelling entry point for the integrated study of biological risk.

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A positive feedback loop between Sox2 and Sox6 inhibits neuronal differentiation in the developing central nervous system

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How a pool of undifferentiated neural progenitor cells is maintained in the developing nervous system is an issue that remains unresolved. One of the key transcription factors for self-renewal is Sox2 whose over-expression has been shown to inhibit neuronal differentiation *in vivo*. In order to dissect the molecular mechanisms of Sox2 activity, we attempted to identify direct target genes of Sox2 using a ChIP-on-chip assay. We report a mechanistic study of one of the proposed targets, Sox6, which like Sox2 belongs to the SRY-related HMG box transcription factor family. We show that Sox2 binds to conserved Sox-binding-elements in the promoter of Sox6 and that Sox2 promotes expression of Sox6 gene in a manner dependent on the identified enhancer elements. *In vivo*, Sox6 is expressed in the ventricular zone of developing CNS with a temporal lag compared to Sox2 consistent with that Sox2 targets Sox6. We demonstrate that Sox2 promotes expression of Sox6 as a transcriptional activator *in vivo* as well. Interestingly, gain- and loss-of-function assays indicate that Sox6 promotes Sox2 expression suggesting that a positive feedback loop, which functions to inhibit premature neuronal differentiation, exists between the two genes.

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To be or not to be (standing), that is the question: neuronal regulation of a dispersal behavior in nematodes

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Behavioral alterations upon environmental changes emerging from neuronal circuits are essential for survival. Many nematode species including the free-living nematode C. elegans exhibit an evolutionarily conserved, developmental stage-specific behavior called nictation: standing and waving in three-dimensional loops on a projection. We demonstrated that nictation is required for transmission of C. elegans to a new niche using flies as carriers, suggesting a role of nictation as a dispersal and survival strategy under harsh conditions. We found that cholinergic transmission in IL2 ciliated head neurons was both necessary and sufficient for the initiation of nictation. Now we have established signaling pathways and genes that are involved in this stage-specific behavior. We are also searching for the environmental stimuli that can activate IL2 neurons and what is (are) the downstream target cell(s) of IL2 neurons in the neural circuit by use of neural imaging.

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A Novel Function of DISC1 related to ER

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Schizophrenia is a mental disease characterized by distorted perception of reality, which is commonly expressed in the form of hallucination, delusion, or paranoia. DISC1(Disrupted-in-schizophrenia-1) has emerged as a convincing schizophrenia susceptibility gene based on multiple human genetics studies, but its mechanistic link to the pathogenesis of schizophrenia is yet to be fully understood. Intracellular calcium, which is heavily dependent on calcium buffering function of endoplasmic reticulum(ER), plays critical roles in regulating fundamental neuronal functions encompassing axonal growth, synaptic plasticity, and neuronal excitability. In this study, we characterize potential roles for DISC1 in the regulation of ER function. DISC1-containing protein complex resides on the surface of ER membrane and appears to be involved in calcium dynamics associated with the calcium buffering function of ER. Further work on its mechanistic aspects is in progress and, we believe that the results will provide novel insight into the molecular basis DISC1 function potentially linked to schizophrenia.

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The amplitude modulation of the HPA code

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Pulsatility is a fundamental characteristic of endogenous glucocorticoid secretion. Although this was previously assumed to be the product of an unknown hypothalamic pulse generator, we show that it is actually a deterministic rhythm which emerges as a consequence of the feedforward:feedback interaction between the pituitary corticotrophs and the adrenal cortex.

This fundamental oscillatory activity would be expected to be matched by appropriate decoding mechanisms both at the level of ACTH activation of the adrenal and corticosteroid signalling in all tissues of the body. We have shown that the adrenal gland does indeed show a much greater response to pulses of ACTH than to constant infusions of the same amount of this hormone. Furthermore, there is an intracellular cycle of glucocorticoid synthesis that is very sensitive to oscillations of ACTH concentration.

We have also shown that both within the brain and the liver, glucocorticoid receptor mediated transcriptional responses are sensitive to hourly fluctuations in corticosterone. This not only results in cyclical translocation of GR to the nucleus, but also DNA binding to the promoters of glucocorticoid regulated genes, the recruitment of the histone acetyltransferases CBP and P300, the binding of RNA polymerase II and the transcription of hnRNA.

Finally, at the whole animal level we can demonstrate that oscillating levels of corticosterone are critical for normal neuroendocrine and behavioural responses to a stressor.

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Role of dopamine D2 receptors in plasticity of stress-induced addictive behaviours

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Dopamine systems are thought to be important modulators of stress-related behaviour. We have investigated the behavioral responses to chronic stress in dopamine D2 receptor knockout ($D2R^{-/-}$) mice and have found that $D2R^{-/-}$ mice manifest increased anxiety-like and depressive behaviors after such stress compared with wild-type (WT) mice. Repeated stress exposure suppressed the expression of cocaine-induced behavioural sensitization as well as cocaine-seeking and relapse behaviours in D2R mutant animals. Cocaine challenge after drug withdrawal in cocaine- experienced WT or $D2R^{-/-}$ mice was associated with inhibition of long-term depression (LTD) in the nucleus accumbens; chronic stress during the withdrawal period prevented this inhibition of LTD after cocaine challenge in cocaine-experienced $D2R^{-/-}$ mice but not in corresponding WT mice. Our results suggest that D2R plays a key role in regulation of synaptic modification triggered by stress and drug addiction, as a key mediator of stress-induced drug-seeking and relapse behaviours.

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Acute stress and synaptic plasticity

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Acute episodes of stress are crucial for survival whereas chronic stress is detrimental. Learning and memory are particularly susceptible to stress and the underlying mechanisms have been extensively studied with respect to chronic stress, which results in cognitive deficits and neurodegeneration. In contrast, little is known about how acute stress is able to enhance cognitive performance. We have therefore examined the effects of acute stress and brief exposure to glucocorticoids on long-term potentiation (LTP) in the hippocampus, a well-established model system for investigating the synaptic basis of learning and memory. Our study has uncovered a novel mechanism whereby acute stress can facilitate synaptic plasticity in the hippocampus. We find that hippocampal slices, either prepared from rats following 30 min restraint stress or directly exposed to glucocorticoids (GCs), exhibits an NMDAR resistant form of LTP that is absent in controls and which results in a larger magnitude of LTP in the stressed group. The stressors activate PKA, increase the phosphorylation of Ser845 on GluA1 subunit of AMPAR and increase the surface expression of the GluA1 subunit. These subunits likely form functional homomeric AMPARs that trigger the stressor-induced LTP (sLTP) since it is completely prevented by IEM-1460, an inhibitor of Ca^{2+}-permeable AMPARs. Although NMDARs are not required for the induction of sLTP they are essential for the sensitisation of the plasticity state, during the exposure to GCs. Thus acute stressors elicit an NMDAR-dependent form of metaplasticity that enhances LTP via the priming of a form of LTP that is independent of, but additive with, NMDAR-dependent LTP.

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Is hippocampal LTP really the basis of long-term spatial memory?

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The crucial role that NMDARs and NMDAR-dependent synaptic plasticity play in learning and memory, and in behaviour more generally, is exemplified by the global behavioural impairment that is seen in genetically modified mice with knockdown of NMDARs across the principal cells of the forebrain. Of course the precise role that NMDARs play depends upon the neural circuitry in which they are embedded. Region-specific and cell type specific NMDAR knockouts have now identified a number of these roles. For example, we have identified roles for NMDARs in both hippocampal and extra-hippocampal principal cells while mice perform spatial memory tasks. Extra-hippocampal NMDARs play an important role in associative long-term spatial memory formation. In contrast, NMDARs in hippocampal principal cells act to resolve conflict or uncertainty, such as when disambiguating between overlapping memories on spatial discrimination tasks, or deciding between competing approach/avoidance response options in ethological, unconditioned tests of anxiety. These results also have important implications for contemporary theories of hippocampal function.

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A novel sleep maintenance pathway composed of myoinhibitory peptide and sex peptide receptor in *Drosophila*

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The invertebrate sex peptide receptor (SPR) is the first peptide G protein-coupled receptor (GPCR) that interacts with evolutionarily unrelated ligands: sex peptide (SP), a seminal peptide, and myoinhibitory peptide (Mip), a brain-gut peptide. *SP* occurs only in related *Drosophila* species and regulates female post-mating behavioural changes. *SPR* and *Mip* are widely conserved in Ecdysozoa and Lophotrochozoa, but the biological function of ancestral Mip-SPR signalling is unknown. We show that SPR promotes sleep by mediating inhibitory Mip actions on the *Drosophila* arousal centre. Mutants lacking *SPR* or *Mip* demonstrated significantly reduced daily sleep, mainly due to shortened sleep-bout duration. SPR sleep function mapped to *pigment dispersing factor (pdf)* neurons, the functional analogue of wakefulness-promoting hypothalamic orexin/hypocretin neurons in vertebrates. During sleep, centrally released Mip modulates intracellular cAMP levels of *pdf* neurons through SPR. Identification of the ancestral function of Mip-SPR signalling is critical to understanding how GPCR and ligands co-evolve functional multiplicity.

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Brain circuits involved in selection of avoidance response under threat

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Avoiding harmful consequences in a variety of threatening situations is an essential ability for survival. Patients with psychiatric disorders, such as depression, tend to adhere to sub-optimal behavioral choices, despite their self-harming nature. Here I introduce two novel protocols developed to investigate defensive response selection in a laboratory using small rodents. In the discriminatory avoidance learning (DIAL), a modified active avoidance conditioning with Go/No-Go response selection, rats are placed in a shuttle box with free access to both compartments and presented with one of the two auditory cues: one signals a Go response (crossing over to the adjoining compartment) and the other No-go response (staying in the current compartment). Response selection was heavily biased toward No-Go response during the early phase of learning. The rate of Go response gradually increased as the training continued. We found that the medial prefrontal cortex (mPFC) is necessary for normal acquisition of successful response selection. The second paradigm is anti-predatory avoidance response in a semi-naturalistic foraging situation. A hungry rat is faced with an artificial predator (fast-approaching robotic agent) when approaching a food pellet. This produced an immediate fleeing and prolonged reduction of approach to the food which was dependent on the perceived distance from the predator in relation to the distance from the food. We found that the amygdala regulates avoidance response in the face of predatory threat. Taken together, our results suggest that investigating the cortico-amygdala interaction is essential for understanding risk-taking and response selection in threat-posing situation.