SYMPOSIA

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SYM-01-01

MOLECULAR PATHWAYS TO DIAGNOSIS, PREVENTION AND TREATMENT OF DEAFNESS.

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Background: At least 120 genetic loci are predicted to encode heritable forms of deafness, but half of these genes are yet to be discovered. Furthermore, very little is known about the genetic variation that predisposes to progressive and acquired forms of hearing impairment. Through better understanding of the genetics and molecular biology of hearing loss it is hoped that we will identify therapeutic targets for prevention and treatment of deafness.

Objectives: To understand the molecular basis of deafness so as to improve diagnosis and to identify drug targets for prevention and treatment of hearing impairment.

Method: A combination of reverse and forward genetic approaches have been used to study deafness in mouse models. Firstly, Ethyl Nitrosourea (ENU) mutagenesis screens are being conducted to identify genes involved in progressive forms of hearing loss. Secondly, a panel of engineered mouse strains harbouring mutations in apoptotic regulators is being assessed for hearing loss, to better understand the role of cell death in the auditory system.

Results: Mutations at particular points of the intrinsic pathway of apoptosis have a profound effect on the auditory system. In addition, genome-wide ENU mutagenesis screens have generated a number of mutant mouse strains with subtle and progressive forms of hearing loss. Several interesting mutations are currently being characterised.

Conclusion: Our work suggests that tightly regulated apoptosis is required for both development and maintenance of hearing. Targeting of apoptotic regulators may prove useful in prevention of cell death and resultant hearing loss in the ear.

(246 words)

SYM-01-02

THE INSIDIOUS NATURE OF NOISE DAMAGE: HOW AUDITORY THRESHOLDS DON'T TELL THE WHOLE STORY

Author: M. Charles Liberman, Ph.D.

Research on acoustic injury has long focused on permanent damage to the sensory hair cells and on the irreversible elevations of response thresholds that this damage produces. Correspondingly, it has long been assumed that noise-induced damage to cochlear sensory neurons only occurs secondarily to loss of hair cells. Our recent work in animal models shows that there can be significant (>50%) degeneration of cochlear neurons after noise exposures even if they cause no hair cell loss and only temporary threshold shifts, as measured by auditory brainstem responses or otoacoustic emissions. There several reasons why this "hidden hearing loss" has remained undiscovered for so long. First, the neural degeneration initially appears as a loss of synaptic connections between cochlear-nerve terminals and hair cells, and these connections are not visible in routine light microscopic examination: their assessment requires serial-section electron microscopy or confocal microscopy after immunostaining for pre- and post-synaptic markers. The death of the spiral ganglion cells (the neuronal structures typically evaluated in histological material) is delayed for months to years. The second reason is that, although the neurons are immediately silenced by the synaptic damage, the noise-induced neuropathy is selective for the subset of cochlear-nerve fibers that normally have high thresholds. These high-threshold neurons are not required for signal detection in quiet (i.e. the pure- tone audiogram), but, almost certainly, are essential for hearing in a noise environment. We will review the evidence that this type of primary neural degeneration is rampant in human populations, that it is exacerbated by noise exposures even when there is no change in the audiogram, and that it is likely a major contributor to the decline in auditory performance in the aging ear.

SYM-01-03

CELLS, CIRCUITS, AND CENTRAL AUDITORY PLASTICITY

Muniak MA

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The systematic and topographic representation of frequency in the mammalian brain commences at the cochlea, and is retained as a first organizing principle throughout much of the central auditory system. Reduced auditory stimulation for prolonged periods, such as deafness or acquired hearing loss, can have definable pathologic effects on the structural and functional organization of synapses, cells, and circuits. The cochlear nucleus (CN) and inferior colliculus (IC) are two key structures in the auditory pathway that lend themselves to the systematic study of changes to intrinsic functional organization. By pairing electrophysiological recordings with targeted injections of neuronal tracers, we have developed quantitative three-dimensional models of frequency representation of these structures in the mouse. These models provide insight regarding normal brain organization, and are powerful tools for analyzing topographic changes to circuits following hearing loss. One pathway under investigation is a “feedback loop” between the CN and IC. Principal projecting cells of the dorsal CN (DCN) provide a major source of ascending input to the contralateral IC. We have shown that these DCN cells also receive bilateral and frequency specific descending projections that originate from the same topographic area of the IC in which their ascending axons terminate. Ultrastructural evidence indicates this descending pathway is excitatory, and thus may be involved in enhancing signal discrimination and/or selective attention. These techniques are now being applied to mouse models of hearing loss to investigate how the specificity of these pathways is influenced by auditory experience.

(242 words)

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SYM-01-04

COCHLEAR IMPLANTS, COGNITION, AND THE CONUNDRUM OF WHICH EAR TO IMPLANT".

Catherine McMahon, Isabelle Boisvert, Bjorn Lyxell, Richard Dowell, Dayse Tavora-Vieira.

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Abstract

Outcomes of cochlear implantation in deaf adults have long been assumed to be related to the history of hearing loss in the implanted ear and surgical events that affect peripheral auditory structures. As such, it is generally accepted that poorer implantation outcomes should be expected in an ear with a long duration of deafness. While this conclusion may be largely true for individuals with symmetric hearing (aided in both ears), it is not the case with asymmetric hearing (aided in only one ear and no hearing in the other ear). Our 4 recent retrospective studies and 1 prospective study indicates that speech recognition outcomes are related more to the hearing *in the better ear*, than to the duration of sound-deprivation in the implanted ear. These observations suggest that the preservation of central function can be achieved with auditory input from only one ear. Currently, it is not clear why this occurs. Either retained auditory input in one ear: (i) limits structural and functional degradation in the bilateral auditory pathway; or (ii) preserves phonological representations known to be affected by auditory deprivation, compensating for the degraded acoustic signal reaching the auditory cortex. Disentangling these give rise to a better understanding of the physiological changes that occur with auditory deprivation and remediation strategies to maximize speech perception outcomes of implantation. The results from our studies, possible mechanisms underpinning these as well as clinical implications will be discussed.

SYM-02-01

HYPOGLYCAEMIA IN DIABETES: RISKS, MANAGEMENT AND PREVENTION

Jones T

University of Western Australia

Prof. Timothy Jones will describe the significance of the blood glucose control in Type 1 diabetes and additional consequences of antecedent hypoglycaemia, such as hypoglycaemia unawareness and hypoglycaemia-associated autonomic failure

SYM-02-02

BULBOSPINAL CIRCUITRY INVOLVED IN THE COUNTER-REGULATORY RESPONSE

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Physiological experiments indicate that adrenaline-synthesizing (C1) neurons in the ventrolateral medulla (VLM) are activated by hypoglycaemia. In the counter-regulatory response, these C1 neurons are thought to excite sympathetic preganglionic neurons (SPN) in the spinal cord, causing adrenaline release from the adrenal medulla. To investigate the bulbospinal circuitry underlying the counter-regulatory response in rats, we used immunohistochemistry, neuroanatomical tracing methods and Fos induced by lowering glucose availability with 2-deoxyglucose (2-DG). Immunostaining for phenylethanolamine N-methyltransferase (PNMT, the adrenaline-synthesizing enzyme) and tyrosine hydroxylase (TH, an enzyme present in all catecholamine neurons) with black and brown peroxidase reaction products, respectively, showed that spinal regions containing sympathoadrenal SPN were innervated by very many PNMT-immunoreactive axons but almost no TH-immunoreactive axons. In the same spinal regions, a dense network of GFP-positive axons occurred in rats with VLM injections of a lentiviral vector that drives GFP expression exclusively in C1 neurons. Treating rats with 2-DG caused Fos expression in PNMT-immunoreactive C1 neurons as well as in SPN identified by immunoreactivity for the acetylcholine-synthesizing enzyme, choline acetyltransferase (ChAT). In 2-DG-treated rats with retrograde tracer (cholera toxin B, CTB) injected into the adrenal medulla, virtually all Fos-positive/ChAT-positive SPN also contained CTB-immunoreactivity. Light microscopy showed PNMT-positive axons forming close appositions on Fos-positive/ChAT-positive SPN. Electron microscopy revealed TH-immunoreactive terminals synapsing on Fos-immunoreactive SPN retrogradely-transported CTB-gold from the adrenal medulla. These results indicate that, in the counter-regulatory response, bulbospinal hypoglycaemia-responsive C1 neurons in the VLM drive adrenaline secretion via synapses on SPN that project to the adrenal medulla. (246 words)

SYM-02-03

ADRENALINE AND THE GLUCOSE COUNTERREGULATORY RESPONSE: AN OREXINERGIC CONNECTION

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The glucose counterregulatory response helps restore normoglycaemia in response to hypoglycaemia or neuroglucoprivation. In diabetes, adrenaline is the major counterregulatory hormone since diabetics also lose the ability to secrete glucagon. It has been assumed that sympathetic control of adrenaline secretion operates similarly to sympathetic vasomotor control. However, we have shown that adrenal presympathetic neurons in the rostral ventrolateral medulla (RVLM) that control adrenaline secretion are not barosensitive and are activated during glucoprivation. We have shown that local neuroglucoprivation in the perifornical hypothalamic area (PeH) activates adrenal sympathetic nerve activity (ASNA) through activation of orexin receptors in the RVLM. In addition, inhibition of PeH neurons with muscimol abolishes the increase in ASNA produced by systemic glucoprivation. These findings suggest that declining brain glucose is sensed by neurons in the PeH, or nearby – and is capable of eliciting counterregulatory responses. Conversely, local glucoprivation in RVLM does not activate ASNA, suggesting that sympathoadrenal premotor neurons are not intrinsically glucose-sensitive. Neuroglucoprivation also activates locus coeruleus (LC) neurons and PeH stimulation activates LC neurons via orexin release. These observations are consistent with the notion that hypoglycaemia/neuroglucoprivation may elicit alerting responses. Finally, electrical stimulation of RVLM evokes an ASNA response that depends on slow and fast conducting spinal pathways. Clonidine sensitivity of the long-latency, pre-ganglionic component suggests the involvement of C1 adrenergic neurons. These findings indicate that orexin inputs to adrenal medullary presympathetic neurons in the RVLM mediate adrenaline release in response to neuroglucoprivation or hypoglycaemia. (240 words)

SYM-02-04

CIRCUITRY AND MECHANISMS OF GLUCOSE HOMEOSTASIS: KEY ROLES FOR HINDBRAIN CATECHOLAMINE NEURONS

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Considerable effort has been devoted to understanding the anatomical substrates and cellular mechanisms that monitor and control glucose availability. Early data strongly implicated central catecholamine neurons in these processes. More recent use of the retrogradely transported immunotoxin conjugate, anti-dopamine beta hydroxylase saporin (DSAP), which selectively targets norepinephrine (NE) and epinephrine (E) neurons, has enabled identification of catecholamine subgroups with distinct glucoregulatory functions. NE and E neurons with projections to the medial hypothalamus are required for feeding, corticosterone and reproductive responses to glucose deficit. Spinally-projecting E neurons are required for the adrenal medullary response. Follow-up studies showed that simultaneous local silencing of co-expressed *Npy* and *Dbh* in the A1/C1 cell groups eliminates glucoprivic feeding, indicating a prominent role for these particular groups in the feeding response. DSAP-induced lesions impair glucoregulatory responses to both systemic hypoglycemia and 2-deoxy-D-glucose. However, recent experiments have shown that glucosamine (a glucokinase inhibitor), phloridzin (an SGLT inhibitor) and 5-thioglucose (5TG, which reduces glucose metabolism in all cells) also require NE/E neurons to stimulate feeding, regardless of whether these agents are injected into the lateral or 4^{th} ventricle. Presently, it is not known whether the different glucosensing mechanisms activated by these various agents are expressed in NE or E neurons themselves or whether they influence NE/E neurons by convergent circuitry. Moreover, only 5TG, but not glucosamine or phloridzin increased blood glucose. Thus, catecholamine neurons control food intake and blood glucose using a variety of glucosensing mechanisms, and these mechanisms may differ for the various glucoregulatory responses. NIH R01-040498 (250 words)

SYM-03-01

GENETIC, NEURAL AND HORMONAL INFLUENCES ON SOCIAL COGNITION

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Underpinning social responsiveness is a set of skills termed 'social cognition'. Successful social interactions require us to observe and monitor other people's behaviour in relation to ourselves, and to respond appropriately. Social understanding, language and imitation are probably learned through neural systems that respond both during our own actions and when we see others behaving in a similar way. The development of social cognition involves the co-action of a network of cortical loci, often known as the 'social brain'. In certain neurodevelopmental disorders, coordination of this multiplicity of neural systems is inefficient. Paradigmatic among such conditions are autism spectrum disorders (ASD): recent research suggests autism is in essence a 'neural connectivity disorder'.

In order to understand the biological basis of social cognition, we need to map the relationship between functionally relevant anatomic areas and neurochemical pathways. In recent years, animal models of social reward have been studied intensively. New evidence is emerging about how and where a range of critical neuropeptides, including oxytocin and vasopressin, interacts with dopaminergic 'reward' circuits in those model systems.

One aspect of this complex neural system, which has been subject to extensive research in human and animal models, underpins social recognition. Most of us find social encounters rewarding but those with ASD seem not to share those feelings to the same extent; they are less able to recognise emotions and remember unfamiliar faces. The inter-relationship between genetic influences on neuropeptide function and dopaminergic-mediated social reward could contribute to individual differences in the social brain's functioning, and hence the neural basis of neurodevelopmental disorders in which social cognition is impaired.

SYM-03-02

AUTISM AND SCHIZOPHRENIA: CONVERGENCES AND DIVERGENCES IN NEURODEVELOPMENTAL DISORDERS.

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Autism and schizophrenia are neurodevelopmental disorders affecting broad areas of social, cognitive and affective function, autism occurring in the first few years of life and schizophrenia typically during adolescence and young adulthood. While considered different disorders, there is accumulating evidence that the two disorders may be associated with overlapping abnormalities in neurodevelopmental pathways. These include recent identification of a striking number of shared genetic risk factors, particularly relating to synaptic development; similar deficits in many core behaviours, particularly in social cognition and communication; and data from multiple sources suggesting that both disorders are associated with perturbed interactions between excitatory and inhibitory neurons.

This presentation will review work regarding the neurodevelopmental trajectories of autism and schizophrenia, with emphasis on how these disorders interact with normal developmental processes in different ways across childhood and adolescence. Imaging and post-mortem studies have demonstrated that the brain has a prolonged developmental trajectory that includes programmatic large scale changes in gene expression across childhood and adolescence. These include changes in the structure and activity of excitatory and inhibitory synapses, which may provide a clue into why related but distinct neurodevelopmental disorders may present at different points in development. The presentation will emphasize data from brain imaging studies across childhood and adolescence in these disorders, how these may relate to genetic and environmental risk factors pertinent to different stages in development, and implications for intervention. (228 words).

SYM-03-03

RISK & RESILIENCE BIOMARKERS IN NEUROPSYCHIATRY: PREDICTING THE RISK FOR AUTISM SPECTRUM DISORDER

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Neuropsychiatric disorders in childhood and adolescence impact the development of social and cognitive functions. However, diagnosis depends on clinical interview, aetiology is unclear, and no biomarkers are available. Further, biomarker research focuses on 'risk' rather than 'resilience' factors.

I first discuss our study investigating SNPs of individuals with autism spectrum disorder (ASD) (Skafidas et al, *Mol Psychiatry*, 2012). Using Autism Genetic Resource Exchange (AGRE), SNPs were mapped to KEGG-pathways to identify affected cellular processes and develop a test of ASD risk. Using AGRE Central European (CEU) cohort we created a genetic classifier of ASD, involving 237 SNPs in 125 genes; these correctly classified ASD in 85.8% of CEU cases. This classifier predicted 84.3% of cases in an ethnically related Tuscan cohort; however, prediction was poor (56.3%) in a HAN Chinese cohort. The classifier correctly predicted ASD cases in independent samples from the Simons Foundation Autism Research Initiative (SFARI) (ASD) and Wellcome Trust 1958 normal birth cohort (WTBC) (controls) (accuracy of 71.7% in CEU individuals).

Prediction accuracy diminished as SNP numbers were decreased. Our classifier identified 'risk' and 'resilience' SNPs for ASD, as well as molecular and cellular pathways that may be disrupted, including metabotropic glutamate receptor 5 (GRM5).

I will discuss further validation work on the classifier, a study examining ASD subgroups, and work examining GRM5 in ASD. Finally, I will consider the importance of considering both risk and resilience neurobiology in the context of emerging mental disorders in adolescence, such as schizophrenia.

SYM-03-04

TRANSCRIPTIONAL NETWORKS IN AUTISM SPECTRUM DISORDERS

Irina Voineagu[1]
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Given that ASD are both phenotypically and genetically heterogeneous, we are interested to investigate whether the wide variety of genetic variants associated with ASD ultimately dysregulate a common set of transcriptional networks. I will discuss our co-expression network data from ASD postmortem brain tissue, as well as integrative analyses investigating the effect of copy number variants (CNV) on gene expression in ASD brain.

SYM-04-01

AUTOANTIBODIES IN AUTOIMMUNE MOVEMENT AND PSYCHIATRIC DISORDERS

Sinmaz N[1], Pathmanandavel K[1], Ramanathan Sudarshini[1], Merheb V[1], Mohammed SS[1], Pillai S[1], Tantsis E[1], Dale RC[1], Brilot F[1]

1. Neuroimmunology Group, Institute for Neuroscience and Muscle Research, The Kids Research Institute at The Children's Hospital at Westmead, University of Sydney.

Recently, autoantibodies have been detected in defined treatable forms of autoimmune movement and psychiatric disorders. Targets of these autoantibodies are neuronal surface receptors or synaptic proteins essential to brain physiology, such as N-Methyl D-Aspartate Receptor (NMDAR), or Dopamine-2 Receptor (D2R). While these autoantibodies usually target extracellular domains and are generally detected in patients benefiting from immunosuppressive therapies, the exact recognized epitope and the pathogenic mechanism in human autoimmune diseases are still unknown. In this symposium, we will use the specific case of anti-D2R autoantibodies and discuss issues related to brain autoantibody detection, epitope recognition, and potential pathogenic mechanisms. The study of autoantibody response may provide valuable insight into the earliest immune mechanisms of CNS autoimmunity. (116 words).

SYM-04-02

MOLECULAR SIGNATURES OF SYSTEMIC AUTOANTIBODIES ASSOCIATED WITH NEUROLOGICAL SYNDROMES

Prof. Tom P. Gordon[1]
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Neurological manifestations of primary Sjögren's syndrome, a classical systemic rheumatic disease, occur in about 20% of patients and include peripheral neuropathies, mononeuritis, gangliopathies, spinal cord lesions and CNS vasculitis. These complications occur chiefly in patients with autoantibodies directed against the Ro52/Ro60 La ribonuclear complex, although the precise pathogenic pathways are poorly understood. Despite antibodies being discovered over a century ago by Behring and Ehrlich, human autoantibody proteomes present in complex human autoimmune sera are just beginning to be unravelled at a molecular level. Remarkably, anti-Ro/La autoantibodies derive from a markedly restricted set of shared (public) clonotypes among unrelated patients: this is difficult to reconcile with the current paradigm of clonal selection on an unbiased B-cell repertoire that predicts a more polyclonal and diverse autoantibody repertoire. The discovery that unrelated patients express identical H/L chain-paired clonotypes is translating to targeted mass spectrometric-based technologies that can potentially measure serum autoantibodies in multiplex one-step assays with high precision and accuracy. Temporal studies of Ro60-specific clonotypes also challenge current orthodoxy by undergoing a relentless turnover of short-lived clonotypic variants, masquerading as long-lived Ro60 humoral autoimmunity.

SYM-04-03

FUNCTIONAL EFFECTS OF AUTOANTIBODIES AGAINST MYELIN PROTEO-LIPID PROTEIN IN MULTIPLE SCLEROSIS.

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Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). Autoimmune T cells are critical for the pathogenesis of MS, but it is also likely that autoantibodies play a role, although this remains to be proven. We have found that a high proportion of MS patients have elevated levels (compared to healthy controls and patients with other neurological diseases) of autoantibodies specific for the second extracellular loop of myelin proteolipid protein (PLP), the most abundant CNS myelin protein. The aim of the current study was to investigate these antibodies further, in order to determine if they could play a functional role in MS. The majority of PLP-specific antibodies from MS patients showed evidence of isotype-switching to IgG and thus of an ongoing active response to PLP in MS patients. In contrast, PLP antibodies detected in healthy controls and patients with other neurological diseases were almost all IgM. Serum from MS patients was found to opsonize human myelin for uptake by macrophages, whereas antibodies from healthy individuals or from patients with other diseases affecting the CNS did not. In 65% of MS sera, pre-adsorption with PLP peptides showed that the opsonising activity involved antibodies specific for PLP. In an animal model of MS, PLP-specific antibody was able to shift the location of lesions within the CNS in a complement-dependent manner. These findings suggest that antibodies directed against extracellular parts of PLP have the potential to induce effects that could be pathogenic in patients with MS. (249 words).

SYM-04-04

ANTIBODIES TO MUSK DISRUPT THE FUNCTIONAL HOMEOSTASIS OF THE MATURE NEUROMUSCULAR SYNAPSE

M. Morsch, R. Cole, N. Ghazanfari, S. Ngo, A. Cheng, K. Toyka, S. REDDEL, W. Phillips,

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Muscle Specific Kinase (MuSK) plays a critical role in establishing the embryonic neuromuscular synapse. Our findings suggest ongoing MuSK signaling is required for maintenance of the adult neuromuscular junction and that the neuromuscular junction undergoes constant remodeling with a balance of competing influences that underlie changes in myasthenia gravis.

About 10% of myasthenia gravis patients have antibodies against MuSK, predominantly IgG4. In vitro, anti-MuSK-positive patient IgG caused internalization of MuSK and tyrosine phosphorylation of both MuSK and the downstream pathway targets, rapsyn and the acetylcholine receptor (AChR) beta-subunit.

In mice, anti-MuSK- IgG passive transfer caused a reduction in postsynaptic MuSK staining intensity, with a progressive decline in postsynaptic AChR over time. This AChR loss correlated with a decline in endplate and miniature endplate potential amplitudes and later electrophysiological endplate failure and clinical weakness.

Neuromuscular synaptogenesis requires an agrin-Lrp4-MuSK signalling pathway that appears to be partially counterbalanced by cholinergic activity. MuSK autoantibodies produced decay in the critical components of the mature synapse despite MuSK autoantibodies producing activation of MuSK and downstream regulated components. Furthermore we show that increasing cholinergic activity in the mouse model accelerates AChR loss and synaptic failure. The results suggest the mature neuromuscular junction is also a dynamic structure determined by ongoing MuSK presence at the endplate surface and MuSK and ACh signalling, that can be disrupted by autoantibodies in the anti-MuSK form of myasthenia gravis.

SYM-05-01

NEURONAL INHIBITION IN MOUSE BRAIN IS ENHANCED BY KCC2

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Hyperpolarizing GABA-mediated synaptic inhibition requires an electrochemical driving force for Cl^- influx. This is enhanced by neuronal Cl^- extrusion by the K+-Cl- cotransporter (KCC2; *SLC12A5*). KCC2 expression is downregulated following brain traumas, including epileptic seizures, resulting in a reduced efficacy of GABA inhibition. To address the consequences of changing KCC2 expression in healthy and injured brain, we generated a conditional transgenic mouse in which a rapid and reversible increase in KCC2 mRNA and protein expression occurs upon withdrawal of doxycycline from the diet. Brain inhibition was assayed by seizure susceptibility in response to systemic injection of pilocarpine (250- 350 mg/kg) or kainic acid (KA, 30-50 mg/kg in 10mg/kg doses). In hemizygous and DOX on control mice (normal KCC2 levels), KA induced status epilepticus in 90% of mice (4/5 hemizygotes, 5/5 DOX on). In contrast there was no status seen in any of the 5 DOX-OFF mice (0%). There was also a significant decrease in the number of seizures in DOX-OFF mice ($p<0.01$ vs DOX-ON). For the heterozygous, DOX-ON and DOX-OFF mice the average (and SD) number of seizures was 15 ± 4, 17±5 and 2±2, respectively. Further, pilot data indicate KCC2 upregulation results in a modest but significant decrease in total movement in open field and elevated plus maze behavioural tests, and a significant increase in relative open arm entries, indicative of reduced anxiety. Our results indicate that enhancing KCC2 expression and Cl transport in healthy brain enhances neuronal inhibition, which is particularly evident during neuronal stress. (247 words)

SYM-05-02

THE ROLE OF THE SODIUM CALCIUM EXCHANGER (NCX) IN RESPONSE TO STROKE/CEREBRAL ISCHAEMIA

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Impaired calcium homeostasis across the plasma membrane is one of the major contributors leading to neuronal cell death and eventual brain damage following stroke or cerebral ischaemia. The sodium calcium exchanger (NCX) is a plasma membrane-bound protein channel that can transport calcium ions either into or out of cells, including neurons. The bidirectional nature of NCX provides a potential target to enable neurons to better manage calcium following stroke. In order to investigate the role of NCX in ischaemic brain injury our laboratory has: 1) used NCX3 knockout mice and cortical neuronal cultures derived from these mice in *in vivo* and *in vitro* stroke models (i.e. permanent middle cerebral artery occlusion and oxygen glucose deprivation, respectively); and 2) assessed the outcome of NCX over-expression on primary cortical neuronal and HEK293 cell viability following *in vitro* ischaemia. In addition, we have used a yeast-two hybrid screen to identify peptides that interact with the XIP binding domain (XBD) located in the NCX regulatory cytoplasmic f-loop. Taken together, this work has confirmed the importance of NCX activity in cell survival under ischaemic conditions, and identified a number of novel lead compounds that may enhance NCX activity and be used in the development of a stroke/cerebral ischaemia therapeutic agent.

SYM-05-03

PROBING THE LOCATION OF THE GLUTAMATE TRANSPORTER CHLORIDE CHANNEL

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The concentration of glutamate within a glutamatergic synapse is tightly regulated by the excitatory amino acid transporters (EAATs). In addition to their primary role of clearing extracellular glutamate, the EAATs also possess a thermodynamically uncoupled chloride (Cl^-) conductance. This Cl^- conductance has been proposed to play roles in regulating ionic homeostasis and glutamate release in the retina and is present in all members of the glutamate transporter family. Several crystal structures of an archaeal homologue of the EAATs, Glt_{Ph}, at different stages of the transport cycle have been solved. In a recent structure, a small cavity located at the interface of the transport and trimerisation domains has been identified and is lined by polarizable residues, several of which have been implicated in Cl^- permeation. We hypothesize that throughout the transport cycle this cavity opens up to form the Cl^- channel.

Residues which line this cavity in EAAT1, including Ser366, Leu369, Phe373, Arg388, Pro392 and Thr396 were mutated to small hydrophobic residues. Wild type and mutant transporters were expressed in *Xenopus leavis* oocytes and two-electrode voltage clamp electrophysiology and radiolabelled substrate uptake were used to investigate function. Significant alterations in substrate-activated Cl^- conductance properties were observed for several mutant transporters while no variations in substrate transport properties were observed. These results support the hypothesis that this aqueous cavity at the interface of the transport and trimerisation domain is a partially formed Cl^- channel which mediates chloride permeation through members of the glutamate transporter family. (243 words)

SYM-05-04

GLUTAMATE TRANSPORTER DYSFUNCTION IN EPISODIC ATAXIA

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Episodic ataxia is a human genetic disease characterized by paroxysmal cerebellar incoordination. There are several genetically and clinically distinct forms of this disease, and one of them, episodic ataxia type 6, is caused by mutations in the gene encoding a glial glutamate transporter, the excitatory amino acid transporter (EAAT) 1. EAAT1 is a dual function protein that mediates secondary-active glutamate transport and also functions as anion channel. We examined the effects of a disease-associated point mutation, P290R, on glutamate transport, anion current as well as on the subcellular distribution of human EAAT1 using heterologous expression in mammalian cells. P290R impairs glutamate transport rates and reduces the number of *h*EAAT1 in the surface membrane. Moreover, P290R results in gain-of-function of *h*EAAT1 anion channels by increasing the channels´ open probability. Voltage clamp fluorometry on the homologous P259R *h*EAAT3 identified modification of a conformation change associated with sodium-binding to mutant transporters as molecular basis of reduced glutamate transport and enhanced anion currents in mutant EAAT. We are currently testing how increased EAAT1 anion currents modify synaptic transmission in the mammalian brain. Episodic ataxia type 6 represents the first human disease found to be associated with altered function of EAAT anion channels and illustrates the pathophysiological impact of the anion channel mode of this class of glutamate transporters. (213 words).

SYM-06-01

ACTIVATION AND PLASTICITY OF AIRWAY VAGAL NOCICEPTORS

Undem BJ

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The majority of airway afferent nerves fit Sherrington's definition of nociceptors and provides the organ with a sense of its own potential injury. Airway nociceptors comprise vagal C-fibers that innervate the entire respiratory tract and a unique Aδ cough receptor that innervates extrapulmonary airways. The vagal C-fibers can be subdivided based on the location of their cell body. The C-fibers arising from neurons in the jugular ganglia (neural crest in origin) innervate extrapulmonary and intrapulmonary structures. The C-fibers arising from the nodose ganglia (placodal in origin) innervate primarily intrapulmonary structures. The Aδ cough receptors have their cell body in nodose ganglia. In guinea pigs bradykinin and activators of TRPV1 and TRPA1 can stimulate all C-fibers, whereas ATP, serotonin, and adenosine stimulate only nodose C-fibers. The Aδ cough receptors, lacking TRPV1 and TRPA1, have a limited activation profile, responding only to light touch and sudden decreases in pH. Viral or allergy mediated inflammation, can lead to phenotypic switches in airway afferent nerves. For example, Aδ fibers can be switched to a C-fiber phenotype in that they begin to express, de novo, sensory neuropeptides as well as TRPV1 and TRPA1 ion channels. These data indicate that an understanding of defensive reflexes will require an appreciation for both placodal (nodose) and neural crest (jugular) C-fibers, and will also require an understanding of how the activity and phenotypes of afferent nerves change in the face of airway inflammation.

SYM-06-02

PONTINE CONTROL OF RESPIRATION IN HEALTH AND DISEASE: AIRFLOW PATTERNING, AIRWAY PROTECTION AND PLASTICITY.

Mathias Dutschmann, Tara Bautista, Sarah Jones, David Farmer, Davor Stanic.

Florey Institute of Neuroscience and Mental Health

Pontine respiratory nuclei such as the Kölliker-Fuse nucleus, lateral crescent nucleus of the lateral parabrachial complex, inter-trigeminal and A5 regions provide synaptic input to medullary rhythmogenic circuits to shape and adapt the motor pattern of breathing. An understanding of this mechanism requires an appreciation of breathing as a dynamic motor behavior, rather than a stereotypic rhythm linked to the vital functions of respiration. The first part of the seminar will be dedicated to synaptic mechanisms underlying the Kölliker-Fuse nucleus mediated inspiratory off-switch (IOS), which produces postinspiratory glottal constriction in response to reflex inputs and descending commands from cortical and/or limbic brain circuits. In the second part we will introduce the concept that synaptic plasticity, including learning and recall of programmed breathing patterns, is required for dynamic and efficient modulation of the expiratory breathing pattern. Such synaptic mechanisms of the Kölliker-Fuse nucleus are critical for controlling a rapid and secure transition from eupneic to adaptive breathing associated with exploratory (foraging, sniffing) and expulsive (vocalizing, coughing, sneezing, retching) behaviors. The final part of the seminar will focus on the pontine pathways of respiratory control, with direct links to disorders of upper airway control (e.g. swallowing, vocalization, sleep apnea) in neurodevelopmental and neurodegenerative disease.

SYM-06-03

MECHANISMS OF SENSORIMOTOR DYSFUNCTION IN PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA

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The human upper airway is comprised of over 25 muscles. Coordinated changes in upper airway muscle activity facilitate speech, swallowing of food, and breathing. However, reliance on muscle activity to control the shape and size of the upper airway also renders it prone to unwanted collapse during sleep when muscle control is altered.

The most extensively studied and largest upper-airway dilator muscle is the genioglossus located at the base of the tongue. In addition to sleep-related changes in activity, genioglossus receives input from respiratory pattern generator neurons and reflex input via negative pharyngeal pressure. Contraction of genioglossus is believed to yield airway opening thus protecting the upper airway from closure.

In patients with obstructive sleep apnoea (OSA), a common condition characterised by repetitive closure of the upper airway during sleep, genioglossus electromyographic activity is increased during wakefulness compared to healthy non-OSA controls. Historically, this increase has been attributed to a neurocompensatory response to an anatomically narrow upper airway via increased reflex activation/drive. However, recent studies investigating genioglossus single motor unit activity suggest that neurogenic processes may also contribute. Indeed, there is mounting evidence for upper airway neurogenic remodelling in OSA although it remains controversial as to whether or not these changes adversely affect upper-airway muscle function and OSA disease progression.

This presentation highlights the complexity of upper airway and its neural control and outlines the various mechanisms whereby upper airway sensorimotor dysfunction may contribute to OSA pathogenesis. (237 words).

SYM-06-04

PLASTICITY OF SENSORIMOTOR RESPONSES ASSOCIATED WITH AIRWAY SENSITIVITY AND PERSISTENT COUGH

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Airway irritation in humans evokes an urge-to-cough, and at low to moderate levels of tussive stimulation the suppression or initiation of coughing is discretionary. Under normal circumstances an urge-to-cough resolves soon after the initiation of coughing. Patients with respiratory disease and idiopathic cases can present with an urge-to-cough that is elicited by normally innocuous airway stimulation and that fails to satiate in response to coughing. These patients can also show a decreased capacity to suppress coughing. The term “cough hypersensitivity syndrome” has recently been developed to encapsulate the attributes of these patients. This presentation will examine the proposition that altered responses in the central nervous system may contribute to patients’ symptoms. The functional neuroanatomy of regional brain responses associated with tussive airway stimulation and the control of coughing will be briefly reviewed before the presentation of functional brain imaging data collected from patients with cough hypersensitivity and healthy controls. The outcomes of the functional brain imaging suggest that cough hypersensitivity is associated with increased activation in pro-nociceptive midbrain regions, and decrements of responses in cortical regions ascribed with a role in cough suppression. (183 words)

SYM-07-01

VISUAL REPRESENTATION IN THE MACAQUE AND HUMAN CORTEX

Schwartz, EL[1,2]

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Building on classical anatomical observations from the early and mid twentieth century, the overall anatomical layout of the representation of the visual field in V1,V2 and V3 has been established, over the past thirty years, based on electro-physiological recording, in-vivo fMRI, ex-vivo high resolution structural MRI. and mathematical modeling. The ex-vivo reconstruction of the entire surface of the stria of Gennari (fovea to periphery) obtained via 10-12 hour scans at 7 Tesla, achieved a spatial sampling of roughly 200 micron voxels, and provided good agreement with, and hence cross-validation of, the in-vivo fMRI imaging data. This work indicated a surprising homogeneity in structure across species (Macaque and Human) and individuals (Human), but this degree of concordance only emerges when careful computational methods (e.g. accurate cortical surface flattening) are applied, and where the observational limitations of spatial resolution in current imaging techniques are understood and respected. Using this successful characterization of the supra-neuronal spatial structure of visual cortex as a starting point, and a constraint, existing theories of visual representation will be briefly outlined. This perspective suggests that much of the contemporary discussion of the representational bases of vision has, at best, minimal explanatory power, and at worst, is inconsistent with current knowledge of spatial and computational representation in visual cortex. (210 words)

SYM-07-02

SUPERIOR VISUAL PERFORMANCE IN NOCTURNAL INSECTS: NEURAL PRINCIPLES AND BIO-INSPIRED TECHNOLOGIES

Warrant, EJ

Department of Biology, University of Lund, Lund, Sweden.

At night, our visual capacities are severely reduced, with a complete loss in our ability to see colour and a dramatic loss in our ability to see fine spatial and temporal details. This is not the case for many nocturnal animals, notably insects. Our recent work – particularly on fast-flying moths and bees and on ball-rolling dung beetles – has shown that nocturnal animals are able to distinguish colours, to detect faint movements, to learn visual landmarks, to orient to the faint pattern of polarised light produced by the moon and to navigate using the stars. These impressive visual abilities are the result of exquisitely adapted eyes and visual systems, the product of millions of years of evolution. Nocturnal animals typically have highly sensitive eye designs and visual neural circuitry that is optimised for extracting reliable information from dim and noisy visual images. Even though we are only at the threshold of understanding the neural mechanisms responsible for reliable nocturnal vision, growing evidence suggests that the neural summation of photons in space and time is critically important: even though vision in dim light becomes necessarily coarser and slower, it also becomes significantly more reliable. In collaboration with Toyota (to develop new types of low-light video technologies) we explored the benefits of spatiotemporal summation by creating a computer algorithm that mimicked nocturnal visual processing strategies. This algorithm dramatically increased the reliability of video collected in dim light – including the preservation of colour – strengthening evidence that summation strategies are essential for nocturnal vision.

SYM-07-03

BIONIC VISION AUSTRALIA PROTOTYPE SUPRACHROIDAL WIDE-VIEW RETINAL IMPLANT STUDY.

Burkitt AN 1,2,3,4 and the Bionic Vision Australia partnership

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Testing of an early prototype retinal prosthesis implanted in the suprachoroidal space has been undertaken with three patients at the Royal Victorian Eye and Ear Hospital in Melbourne. The objective is to demonstrate that the suprachoroidal electrode placement is surgically feasible and mechanically stable, as well as to demonstrate that it is capable of delivering functional vision outcomes for patients with degenerative vision loss caused by conditions such as retinitis pigmentosa. All three implantations were successful, with no breakage of electrode or leadwires in any patient. To date there have been no unexpected device-related serious adverse events. Monitoring of electrode position using OCT imaging for a period of over 12 months post-operatively indicates that the electrode array has not moved horizontally. Electrical stimuli are delivered via a percutaneous connection directly to the implanted electrodes using charge-balanced biphasic pulses of electrical stimulation at levels that have been establish as safe through pre-clinical studies. Results of psychophysical studies show that all three subjects are able to perceive phosphenes of varying intensity and dynamic range within safe charge limits. The results of vision processing studies, in which images are captured on a miniature camera mounted on glasses and then processed to determine appropriate electrical stimuli to be delivered to the implanted electrodes, indicate that patients are able to locate light sources in a dark room and can identify the edges of white objects on a black background. The results provide strong support for the viability of the suprachoroidal electrode placement for retinal prostheses. (250 words)

SYM-07-04

SYNCHRONY AND EVENT-BASED SILICON RETINA VISION SENSORS

Delbruck, T

University of Zurich and ETH Zurich

Machine vision based on conventional image sensors has fundamental drawbacks, including limited dynamic range, limited sampling rate, and expensive post-processing of redundant output. Compare this to the eye: Its output is pushed to the brain as a river of asynchronous digital spike events based on local decisions involving spatio temporal context. This presentation will be about our developments of asynchronous “silicon retina” vision sensors that offer this same form of spike event output. These neuromorphic sensors offer unique advantages in terms of latency, dynamic range, temporal resolution, and post-processing cost. These sensors have machine vision applications right now, and are possible translational neuroscience candidates for neural prosthetics and cortical-style computation based on spike- synchrony. The talk will include demonstrations of the sensor.

link: http://siliconretina.ini.uzh.ch

SYM-08-01

PHENOTYPIC AND FUNCTIONAL HETEROGENEITY AMONGST QUIESCENT PRECURSOR CELLS IN THE ADULT HIPPOCAMPUS: IMPLICATIONS FOR THE TREATMENT OF MOOD DISORDERS

Jhaveri DJ, O'Keeffe I, Newcombe E, Robinson GJ, Zhao Q-Y, Zhang ZH, Nink V, Wray NR, Bartlett PF

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The adult hippocampus contains both quiescent and active neural precursor cells, which proliferate to generate new dentate granule neurons. Accumulating evidence suggests a causal relationship between adult-born immature neurons in enhancing spatial learning and memory as well as in improving mood. However, the precise role of new neurons in regulating such diverse behavioural outcomes is still not clear. It is not known whether all newborn neurons in the adult hippocampus are functionally equivalent or whether there is heterogeneity amongst this pool such that molecularly discrete populations regulate cognitive versus mood-regulating functions. Previous studies from our laboratory have uncovered neuronal depolarisation (high KCl) and norepinephrine (NE) treatment as potent neurogenic stimuli that activate discrete populations of quiescent hippocampal precursor cells. In the present study we have tested the hypothesis that the adult hippocampus contains phenotypically and functionally distinct populations of quiescent precursor cells and investigated their identity, topographical distribution and functional potential. Using transgenic reporter mice, flow cytometry-based purification and neurosphere assay, our findings indicate that NE- and KCl-responsive populations are phenotypically distinct, are segregated along the septo-temporal axis of the hippocampus and exhibit differential sensitivity to stress. Deep sequencing of progeny generated from NE- versus KCl-activated quiescent precursor cells reveal distinct molecular profile suggesting that new neurons may have functionally different properties. Our current efforts are focused on understanding the functional contribution of new neurons arising from these distinct populations as this information will be vital to effectively harness their potential in the treatment of learning versus anxiety/mood disorders.

SYM-08-02

GENETICS OF DEPRESSION: THINKING OUTSIDE THE BOX.

Wray NR

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Genome-wide association studies (GWAS) have been a key tool of complex trait genetics of the last five years and for some diseases results have already led to clinical trials of new drugs (or old drugs for new diseases). International Psychiatric Genomics Consortium has brought together GWAS from around the world to generate the largest experiment in psychiatry. These data present a paradigm shift in our understanding of these disorders and novel analyses have started to reveal the secrets of the genome. The results from the schizophrenia consortium, the flag-ship disorder in psychiatry, have both simultaneously revealed the complexity of the disorder and generated exciting leads on how to progress research into the future. The results to date for MDD are considerably less impressive. I will compare and contrast the results to date from genetic studies of schizophrenia and MDD and explore the multiple reasons why interrogating the genetic etiology of MDD is more difficult than almost any other complex trait. I propose that we need to think “outside the box” to generate resources that would impact many studies of MDD not just genetic studies. (184 words)

SYM-08-03

IMMUNE FUNCTION AND DEPRESSION: A SYSTEMS APPROACH TO THE TRANSLATION OF MENTAL HEALTH NEUROSCIENCE

Baune BT

Discipline of Psychiatry, University of Adelaide, Adelaide, AUSTRALIA Systemic

inflammatory processes have long been related to psychiatric conditions, such as clinical depression since the formulation of the macrophage theory of depression by Smith (1991). Subsequently, brain specific mechanisms of inflammation have been identified and it has been suggested that inflammation and immune cells more broadly may affect neuronal function, molecular mechanisms of learning and memory and neuroplasticity. Clinical research has shown that markers of inflammation may be predictive of onset and course of depression and cognitive dysfunction/cognitive decline. The aim of this presentation is to demonstrate evidence from a variety of animal studies and human molecular studies conducted in this lab showing that immunological markers both as peripheral proteins and genetic variants can assist in predicting depression, antidepressant treatment response and morphological brain changes. In addition, we will demonstrate results of animal studies on signaling pathways of TNF and various chemokines relevant to neuroplasticity, memory and learning and depression- / anxiety-like behavior and neurotrophic signaling in the hippocampus.

In summary, increasing evidence from animal and human studies suggests a functional relationship between serum and genetic markers of the immune system and neuropsychiatric conditions such as depression, treatment response and morphological brain changes. Moreover, in this presentation it is postulated that inflammatory genes may increase the susceptibility towards brain inflammation in young ages possibly increasing the risk of subsequent psychiatric disorders.

SYM-08-04

PHARMACOGENOMICS OF DEPRESSION: TRANSLATING GENOMIC SCIENCE INTO PERSONALIZED THERAPEUTICS

Julio Licinio and Ma-Li Wong

Mind and Brain Theme

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Depression affects over the lifetime at least 15% of Australians. Major depressive disorder is this country's leading cause of non-fatal disease burden. Moreover, suicide, which is in most cases an outcome of depression, is the third cause of fatal disease burden in Australian men. It is therefore imperative to effectively treat this disorder, which is a national health priority. The response to antidepressant medication varies from individual to individual, and can range from 60% for a single trial to up to 85% after multiple drugs are tried. The outcome of pharmacological treatment for depression is that some individuals undergo complete remission and can lead full and productive lives, while others either respond partially or have no response. Moreover some patients experience no adverse drug reactions, while others do. There are currently no biomarkers of antidepressant treatment response that are ready for widespread clinical use. The therapeutics of depression would be much improved if such validated markers existed. While some of the variability in treatment outcome has an environmental component, it is widely accepted now that genetic variations contributes to antidepressant treatment response. The field of pharmacogenomics aims at utilising the sequence of the human genome to identify markers that predict clinical response to antidepressant treatment. Such markers would not only be useful indicators of treatment outcomes, but they can also point to new targets in the biology and pharmacology of depression. This presentation will summarize new findings that confirm and extend what is known in this exciting clinical in which genomic science is of direct clinical relevance. The emerging picture in this field is that any specific variant contributes only in part to treatment outcomes and that a full validation of genomic predictors of treatment outcomes will be achieved by replicated studies that use panels with several variants that can maximally predict outcomes. Large-scale studies are being planned to achieve this goal.

SYM-09-01

THE PHYSIOLOGICAL ROLE OF OREXIN/HYPOCRETIN NEURONS ON SLEEP/WAKEFULNESS REGULATION

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Although we spend 1/3 of our life time to sleep, little is known about its regulatory mechanism so far. Recently developed techniques, such as Optogenetics or DREADD system enable control the activity of specific type of neurons using a whole animal. In this study, we generated transgenic mice which express channelrhodopsin2/archaerhodopsin/DREADDs in orexin neurons. Using these mice we applied optpgenetics to orexin/hypocretin neurons and revealed its role on sleep/wakefulness regulation. Keep on activating of orexin neurons using DREADD system induced long lasting wakefulness with increasing spontaneous locomotor activity, oxygen consumption, and drinking and feeding behavior. On the other hand, inhibition of orexin neurons induced fragmentation of wakefulness in the dark period. To show physiological role of orexin neurons, orexin neurons was ablated using tetracycline gene expression system. Timing controlled ablation of orexin neurons showed that 85% ablation induced fragmentation of sleep/wakefulness and 95% ablation of orexin neurons induced cataplexy-like behavioral arrest. During ablation of orexin neurons, body weight was significantly increased without affecting feeding amount. These results suggest importance role of orexin neurons on the maintenance of arousal and energy homeostasis.

SYM-09-02

THE CONTRIBUTION OF OREXIN SYSTEM TO INTEGRATED ULTRADIAN PHYSIOLOGICAL PATTERN

Ootsuka Y[1,2], Miyata K[2], Ikoma Y[2], Kuwaki T[2], Yamanaka A[3].

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Our resent study reestablished that behavioral activity, bodily metabolism, wakefulness and other physiological parameters including blood pressure, heart rate, body and brain temperatures increase synchronously in episodic manner at every 1-2 hours (ultradian cycle range) in conscious rats under undisturbed stable environmental condition. Importantly, food seeking is integrated in the ultradian pattern and it occurs approximately 15 min not before but after the ultradian episodic increase. We hypothesized the integrated ultradian physiological pattern is coordinated by brain rather than peripheral/external events. Orexin, also known as hypocretine, is a neuropeptide localized in hypothalamus and is known to promotes wakefulness and appetite and modulates autonomic physiological function such as cardiovascular and temperature regulation. The orexin system may contribute to coordinating the ultradian pattern. To investigate this possibility, we assessed the integrated ultradian physiological pattern in orexin-related genetically modified mice; orexin knock out mice (KO) and orexin neuron-ablated mice (DTA) in which timing of degeneration of orexin neurons can be controlled by conditional expression of neurotoxin (diphtheria toxin) after birth. In KO mice, amplitude of ultradian episodic changes was attenuated considerably in body temperature and locomotor activity, but not in heart rate. In DTA mice, amplitude of ultradian episodic changes (cycle range 50-200 min) in carbon dioxide production (index of metabolism) were attenuated (from 2476±162 to 1117±71, n=5, $P<0.01$, wavelet amplitude) with time after degeneration of orexin neurons was initiated. These results suggest that orexin system has a modulatory role in coordinating the ultradian pattern.

SYM-09-03

THE ROLES OF OREXIN1 AND OREXIN2 RECEPTORS IN CONSUMMATORY AND APPETITIVE BEHAVIOUR

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We were the first to demonstrate a role for orexins in both ethanol consumption and cue-induced reinstatement of ethanol-seeking. Fos studies suggested that the prelimbic cortex was a potential locus where ascending orexinergic input could modulate relapse-like behaviour. We therefore tested the role of prefrontal cortical OX1R in cue-induced ethanol-seeking. Immediately prior to cue-induced reinstatement, iP rats were microinjected with either vehicle or SB-334867 (3µg/side; 300nl/side). Antagonism of prelimbic OX1R with SB-334867 significantly attenuated cue-induced reinstatement of ethanol-seeking in an anatomically specific manner, with no effect on sucrose-seeking. While a role for OX1R has been established in both ethanol reinforcement and ethanol-seeking behaviour, the role of orexin2 receptors (OX2R) in these behaviours is less clear. We therefore sought to determine the role of central OX2R in ethanol-taking and ethanol-seeking behaviour. Following icv injection, the selective OX2R antagonist (TCS-OX2-29) reduced self-administration of ethanol, but not sucrose. Despite reducing ethanol self-administration, TCS-OX2-29 had no impact on cue-induced reinstatement of ethanol-seeking. To determine where in the brain OX2R were acting to modulate ethanol self-administration, TCS-OX2-29 was microinjected into either the shell or core of the nucleus accumbens (NAc). Intra-NAc core, but not shell, infusions of TCS-OX2-29 decreased responding for ethanol. OX2R in addition to OX1R may represent a potential therapeutic target for the treatment of alcohol use disorders. However, unlike OX1R, no impact of OX2R antagonism was observed on cue-induced reinstatement, suggesting a more prominent role for OX2R in ethanol self-administration compared to cue-conditioned ethanol-seeking. (242 words)

SYM-09-04

ROLE OF OREXIN AND ITS RECEPTORS IN THE CARDIOVASCULAR RESPONSE TO PSYCHOLOGICAL STRESS

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Orexin plays a critical role in the regulation of arousal, not only to maintain wakefulness but also to drive certain types of motivated behaviours. Orexin act via two receptors, OX1R and OX2R. Blockade of OX1R and OX2R with the dual receptor antagonist Almorexant reduces (~50%) the cardiovascular response to disinhibition of the dorsal hypothalamus, indicating that orexin makes a strong contribution to the sympathetic output of the hypothalamus. Almorexant also reduces (~45%) the cardiovascular response to novelty stress and conditioned fear but not the cardiovascular response to restraint or cold exposure, suggesting that orexin contributes to the cardiovascular response of some stressors, especially psychogenic ones. A comparison of the effect of Almorexant on novelty stress to that of blockade of OX1R or OX2R with selective antagonists (ACT-335827 and EMPA, respectively) indicates that blockade of one receptor alone can cause some reduction, but not as much as Almorexant. Thus both receptors may contribute to the cardiovascular action of orexin. Interestingly, double immunolabelling of the two receptors shows that sympathetic preganglionic neurons are almost exclusively Ox1R immunoreactive whereas orexin neurons themselves harbour both receptors. Finally, recent reports show that Almorexant can reduce blood pressure and heart rate in spontaneously hypertensive rats (SHR), raising the possibility of an overactive orexin system in these animals. Indeed, SHR have 20% more orexin neurons than their normotensive counterparts. Thus, there may be an important link between psychological stress, orexin and hypertension. It could be a clue for the treatment of certain forms of hypertension. (248 words)

SYM-10-01

RECEPTORS, SYNAPSES AND MEMORY

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Neurotransmitter receptors mediate signal transduction at synaptic connections between neurons in the brain. We have been studying the regulation of glutamate receptors, the major excitatory receptors in the central nervous system, and examined the modulation of receptor function by protein phosphorylation and the regulation of subcellular targeting of glutamate receptors to synapses. Studies in our laboratory have found that glutamate receptors are multiply phosphorylated by a variety of protein kinases. Phosphorylation regulates several properties of these receptors including ion channel properties and membrane targeting. Recent studies in our lab have demonstrated that the phosphorylation of glutamate receptors is regulated during cellular models of learning and memory such as long-term potentiation (LTP) and long-term depression (LTD). Moreover, phosphorylation of the glutamate receptor GluA1 subunit is required for the expression of these forms of plasticity, for the retention of spatial memory and also regulates emotional memory formation and fear erasure. We have also identified a variety of proteins, including the PDZ-domain containing proteins GRIP1/2 and PICK1, that directly interact with glutamate receptors and are critical for their proper subcellular trafficking. We have shown that this PDZ-domain based complex is required for cerebellar LTD and is critical for hippocampal LTP and LTD and spatial learning. These studies indicate that the modulation of receptor function is a major mechanism for the regulation of synaptic transmission and is a critical determinant of animal behavior. Importantly, recent evidence has implicated the mis-regulation of glutamate receptors in several neurological and psychiatric disorders including Alzheimer's, schizophrenia, and autism. {250}

SYM-10-02

PROBING THE MICROENVIRONMENTAL FORCES APPLIED TO SECRETORY VESICLES ON THEIR JOURNEY TO THE PLASMA MEMBRANE: MYOSIN VI, A GRABBING CLAW

Meunier FA[1,2], Tomatis VM[1,2]

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Neurosecretory granules (SGs) are storage compartments for neuropeptides and hormones that are released in response to stimulation. The release mechanism called neuroexocytosis relies on a number of key molecules such are Munc18 that prime and dock vesicles and SNAP-25, VAMP2, Syntaxin-1 that form a SNARE complex bringing together the vesicular membrane with the plasma membrane. Prior to fusion with the plasma membrane SGs need to overcome a diffusion barrier imposed by a highly organized F-actin cortical network localised underneath the plasma membrane. The mechanism underpinning the recruitment and mobilisation of SGs to cortical actin is still unknown.

We hypothesized that one or several cytosolic proteins are recruited on to SGs in a Ca^{2+}-dependent manner facilitating their interaction with the cortical actin network. Our laboratory established a pull-down assay, using purified SGs as bait, couple to mass spectrometry to identify cytosolic proteins recruited to SGs in the presence of Ca^{2+}. One of the identified proteins, whose interaction with SGs was myosin VI. I will discuss our latest results on how Myosin VI act to recruit SG at the cortical actin network and what role this key steps play in the overarching neurosecretory process. (192 words).

SYM-10-03

PRESYNAPTIC TRAFFICKING PATHWAYS IN SYNAPTIC VESICLE BIOGENESIS

Robinson PJ, Xue J, Luo L, Quan A, Engholm-Keller K, Graham ME, Yang X and Miller L

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Synaptic vesicles (SVs) are produced by the recycling of their required component proteins and lipids from two distinct sets of endocytic pathways. The first involves multiple modes of rapid synaptic vesicle endocytosis (SVE) involving clathrin-mediated endocytosis (CME, half-life is 45-60s) and rapid F-actin-endophilin-dynamin dependent retrieval (FEDx, half life <5s) which appear to supply the readily releasable pool of SVs. The second is the production (<1s) of bulk endosomes (BE) which slowly (15-30 min) undergo budding in the nerve terminal to produce SVs which specifically supply the SV reserve pool. We will show how these multiple presynaptic trafficking processes are controlled by a large network involving thousands of protein phosphorylation events and unique modes of protein-protein interactions. We are revealing examples of how each trafficking pathway involves both common and unique proteins that appear to be used in different ways within some of the paths. We are also revealing how phosphorylation independently regulates each mode. One new example is the endophilin-dynamin interaction, which we found to be regulated by a novel type of phospho-regulated protein-protein interaction mechanism. A second is the BE mode, which is regulated by dephosphorylation of multiple proteins. A third example involves our observations of major changes in presynaptic protein kinases and phosphatases to mediate SV budding events from BEs. Our observations improve our understanding of the molecular mechanisms of SV biogenesis and provide new insights into synaptic transmission and mechanisms of short-term presynaptic plasticity. (237 words).

SYM-10-04

REGULATION OF AMPA RECEPTOR FUNCTION BY PROTEIN UBIQUITINATION

Anggono V

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AMPA receptors (AMPARs) mediate the majority of fast excitatory synaptic transmission in mammalian central nervous system. Dynamic changes in synaptic strength are thought to underlie information coding and storage during learning and memory. The trafficking of AMPARs into and out of synapses is highly dynamic and is regulated by subunit-specific AMPAR interacting proteins as well as by various post-translational modifications that occur on their carboxy-termini. The past 3 years have seen the emergence of post-translational ubiquitination as one of the mechanisms that regulate AMPAR function. However, the molecular mechanisms underlying this process are poorly understood and remain controversial. Here, I will present data to address questions regarding which AMPAR subunit is ubiquitinated, when and where they get ubiquitinated, what is the site of ubiquitination and what effect ubiquitination has on AMPAR function.

SYM-11-01

MULTIPLE REPRESENTATIONS – BODILY AWARENESS AND SPATIAL PERCEPTION IN HEALTH AND DISEASE.

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Abstract: The sense that we have of our own body, that we know where it is and that it is indeed ours, is something most of us take for granted. Unless we encounter a situation where our bodily awareness is disrupted, or we lose the sense of where a limb is, or that we are so in touch with, for example a musical instrument, that it truly begins to feel 'a part of us'. One common human experience that is fundamentally dependent on the sense we have of our own body is pain. Pain is always felt *somewhere* and it is 42onceptualized in terms of what it tells us about our body – it alerts us to danger and it motivates us to protect the area that hurts. The last few years has seen rapid progress in our understanding of the interactions between pain, bodily awareness, and spatial perception. In this talk I will provide an overview of some of these interactions, recent discoveries and their implications for our understanding of how the brain regulates and protects the body. I will introduce the territory into which the remaining three speakers will speak and I will provide a context in the real world where these issues are becoming important – namely that of clinical rehabilitation.

SYM-11-02

THE MALLEABLE SELF AND THE EXPERIENCE OF SOMATIC CONTAGION

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As a social altruistic species seeing others in pain can be distressing. When we do see another in pain, we not only resonate with their emotional state, but also anticipate the sensory qualities of their pain and if appropriate, express compassion and concern. Many neuroimaging studies have shown that this affective and sensory "empathic" resonance corresponds to activation in the affective and sensory regions of the brain that are involved in personal pain experience. Prior experiences can modulate sensitivity, and neural activation, when viewing noxious procedures. My work has identified that some people are more prone to taking on the burden of another's pain to such a degree that they experience "somatic contagion" with the vicarious experience of non- painful and painful sensations. My research is now beginning to differentiate between at least two unique profiles of somatic contagion: those who have always been prone to it (congenital variant) and those whose somatic contagion begins after a trauma, injury or chronic pain (acquired variant). The congenital variant appears to involve a more malleable sense of self, with heightened vicarious embodiment of a self-attributed injury and heightened trait empathy. Acquired somatic contagion, on the other hand, is characterised by motor cortex facilitation when seeing others in pain, reduced trait empathy, but heightened proneness to personal distress, suggesting that their vicarious pain experience corresponds to a focus on the self rather than others. This talk will present and discuss a multidimensional factors underlying "empathy for pain", somatic contagion, trait empathy and pain experience (250 words).

** Note that this abstract is part of the symposium titled "The Big Bang - A Foray in How Percepts Collide to Give Rise to Embodied Sensory Experience"

SYM-11-03

PERCEPTUAL DISTORTIONS OF THE BODY IN PAIN: THE ROLE OF MULTISENSORY ILLUSIONS

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Unique, dynamic, brain-held representations of our body allow us to precisely monitor and control our body. In chronic pain, the brain's representation of the painful body part is often disrupted. Concomitantly, people often report that the affected body part doesn't feel like it should (ie, patients report that their painful limb feels swollen, although objectively, it is not). People in pain also present with disruptions to their ability to accurately localise information coming from that body part. This reduction in perceptual acuity is correlated to disruptions of the brain-held representation of that body part. Further, imaging studies have shown that pain reduction corresponds with normalised tactile acuity, bodily perception and cortical organisation. Thus there appears a complex relationship between bodily perception and pain. This raises the intriguing possibility that we may be able to target pain by altering one's perception of the affected body part. My research into chronic pain and multisensory illusions suggests that this may be possible. People with long-standing osteoarthritis respond to illusory resizing of the affected body part – illusory stretch/shrink results in ~50% pain reduction. Further, illusions normalise bodily perception; perceptual size ratings become indistinguishable from those made by healthy controls. Whether this altered perception results in updates to brain-based body representations, intervenes in multimodal processing areas or works via more general mechanisms is unknown. I will present data demonstrating the effects of multimodal illusions on pain in clinical painful conditions and will provide a theoretical discussion of the possible mechanism of effect of such illusions.

Word count: 250

SYM-11-04

WHY DO HAPTICS MATTER? A LOOK AT THE 'VISUAL' BODY TOUCH

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Touch is the channel through which humans first start to explore the world and it plays a key role in communication and in emotional interaction. However, touch has another important function: it provides a border between 'the self' and 'the world'. It allows us to know what is part of our body and what is not, a function that is essential for survival. This role of the perceptual sense of touch in contributing to embodiment will be the focus of my talk. I have interrogated this issue of multisensory embodiment by manipulating proprioception, touch and vision and by evaluating the effects of these manipulations on the sense of ownership and location of our limbs. We have found, for example, that, under some conditions, viewing an object instead of viewing an arm can advantage the processing of tactile stimuli delivered on participants' arm. This suggests that viewing an image of a body part might require more attentional resources than viewing an object. This raises an intriguing possibility: can we embody space, without needing to see a body part? Indeed, our results suggest that there is a visual capture of the perceived position of one's own body that seems to be unrelated to visually seeing a body part. In fact, the mere vision of touch (i.e. a finger indicating a point in blank space) seems to be sufficient to shift the touch perceived on one's own arm. Such discoveries underline the importance of the multisensory perception in feeling one's own body. (249 words)

SYM-12-01

A PATHOGENIC MECHANISM FOR CGG REPEAT EXPANSION DISORDERS

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The human exome contains over 200 genes with 6 or more CGG repeats located exclusively in either the 5'UTR or the ORF of the RNA. CGG repeats can undergo expansions, which are associated with neurological and neuromuscular disorders. CGG repeats in one RNA can form duplexes with CGG repeats in other RNAs. TMPyP4 is a membrane-permeant non-toxic porphyrin ring compound that binds to CGG repeat RNAs and disrupts duplex formation. CGG repeat RNAs are localized and translated in RNA granules. Some CGG repeat RNAs encode proteins that regulate granule translation and others encode proteins that regulate calcium transients. Duplex formation between different CGG repeat RNAs in the same granule inhibits granule translation and enhances calcium transients in microinjected neurons and in human fibroblasts from individuals with CGG repeat expansions. TMPyP4 rescues granule translation by blocking duplex formation between CGG repeat RNAs. This represents a potential pathogenic mechanism and potential therapeutic strategy for neurological and neuromuscular disorders caused by CGG repeat expansions.

SYM-12-02

TUMOR OVEREXPRESSED GENE (TOG) PROTEIN IS REQUIRED FOR RNA GRANULE ASSEMBLY AND TRANSLATION IN NEURAL CELLS.

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In dendrites of neurons and in the myelin compartment of oligodendrocytes, specific RNAs are localized and translated in RNA granules. However it is not known what selective advantage granule assembly confers. To address this question we disrupted granule assembly by knocking out tumor overexpressed gene (TOG), a scaffold protein required for granule assembly. TOG contains multiple binding sites for heterogeneous nuclear ribonucleoprotein (hnRNP) A2, another granule component that recognizes *cis*-acting sequences called hnRNP A2 response elements (A2REs). A2REs are present in granule RNAs such as activity-regulated cytoskeleton-associated protein (Arc) mRNA in neurons and myelin basic protein (MBP) mRNA in oligodendrocytes. TOG expression was conditionally knocked out (KO) in either mouse hippocampal neurons or in oligodendrocyes using cre/lox technology with cell specific drivers. When TOG was KO in neurons, granule assembly was disrupted and bursty translation of Arc mRNA was abolished. Synaptic sensitivity and long term potentiation (LTP) measured in brain slices were reduced. These mice also exhibited signs of autism including hyperactivity, perseveration and impaired short term habituation of locomotion and vocalization. When TOG was KO in oligodendrocytes, MBP translation was severely reduced despite a normal amount of transcripts and the TOG KO mice were dysmyelinated, had seizures and shivered. Our data indicate that TOG acts as a scaffold for granule assembly of specific RNAs in neurons and oligodendrocytes, that granule assembly is required for high efficiency translation of the specific granule RNAs in these cells, and that granule translation is required for cellular specific functions of neurons and oligodendrocytes. (250 words).

SYM-12-03

SYNAPTIC PROFILING OF MRNA AND MIRNA IN ALZHEIMER'S DISEASE

Hynd MR[1], Lewohl JM[2], Ho A[1], Chew C[1], Smith R[1], Rothnagel J[1], and Dodd PR[1]

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MicroRNAs (miRNAs) are small non-coding RNA molecule present in virtually all animals and plants. miRNAs are ~20-25 nucleotides long and affect gene expression by interacting with messenger RNAs. In contrast to short-interfering RNA (siRNAs), miRNAs are encoded in the human genome and function as endogenous in vivo regulators of gene expression. To date, over 1,500 miRNAs have been identified to be encoded within the human genome and comprise approximately 2% of all mammalian genes. It has been hypothesized that deregulation of miRNA expression in the brain may be involved in neurological dysfunction and/or neurodegenerative processes.

Recently it has been suggested that AD is primarily a disease of synaptic dysfunction. Mounting evidence suggests that the loss of synapses is the best pathological correlate for the cognitive decline observed in AD. One of the major neuropathological findings in the brains of individuals with AD is the loss of synaptic contacts in areas of the brain known to be affected in AD.

Here we discuss the differential expression of both mRNA's and miRNA's localized to the synaptic terminal and their involvement in the pathogenesis of AD. Whole tissue and synaptosomal fractions were taken from control and AD cases. Transcripts analysed included Neuroligin, Synaptophysin, Setptin 8, Neurexin, Tau, and the Vesicular Glutamate transporter 1. Based on the results from this study, molecular profiling of miRNA's may have potential for the therapeutic amelioration of AD.

This work was enabled by donors to the QLD Brain Bank.

(243 words)

SYM-12-04

ROLES OF hnRNP PARALOGS AS *trans*-ACTING FACTORS DIRECTING *cis*-ELEMENT (A2RE)-DRIVEN TRANSPORT OF CYTOPLASMIC mRNA TRAFFICKING GRANULES.

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mRNA trafficking in transport granules of neural cells is a highly regulated process in which a subset of mRNAs is transported from the nucleus to the distal processes, where translation leads to localized protein expression. Heterogeneous nuclear ribonucleoprotein (hnRNP) A2/B1 was one of the first *trans*-acting factors to be described in neural mRNA trafficking and is necessary for dendritic targeting of various mRNAs that are involved in myelination and synaptic regulation. hnRNP A2/B1 recognizes the hnRNP A2 response element (A2RE), a *cis*-acting signal present in certain trafficked mRNAs, including those encoding myelin basic protein, CaMKIIα and, neurogranin.

There are three hnRNP A/B paralogs: A1, A2/B1 and A3: each is subject to post-translational modifications (PTM) identified by mass spectrometry as methylation of arginine residues within their RGG box domain. This PTM has been ascribed a role by others in partitioning of the hnRNPs between the cytoplasm and nuclei.

We have studied the functional consequences of modification of hnRNPs. Arginine residues in the RGG box domain of hnRNPs A1 and A3 are almost exhaustively, asymmetrically dimethylated whereas hnRNP A2 is dimethylated on a single residue (Arg-254).We also show that transfected cells expressing an $A2^{R254A}$ point mutant exhibit no difference in subcellular localization. Similarly, immunostaining and mass spectrometry of endogenous hnRNP A2 in transformed cells reveals a naturally occurring pool of unmethylated protein with an exclusively nuclear pattern of localization. Our results suggest an alternative role for post- translational arginine methylation of hnRNPs and offer further evidence that the hnRNP A/B paralogs are not functionally redundant.

We postulate that arginine methylation allows discrimination between trafficked and non-trafficked transcripts by hnRNP A2b.

(268 words)

SYM-13-01

A DIFFERENT WAY OF THINKING ABOUT ALZHEIMER DISEASE

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Alzheimer disease (AD) is characterized by neuronal loss, especially in the cortex and hippocampus, accompanied by accumulation in the brain of extracellular neuritic plaques containing β-amyloid (Aβ) and of intracellular neurofibrillary tangles consisting of hyperphosphorylated tau protein. The most widely accepted hypothesis, called the "amyloid cascade," is aimed at explaining plaques and tangles as the proximal cause of the disease. However, it does not explain other features of AD that have received far less attention, including aberrant cholesterol, phospholipid, and calcium homeostasis, and altered mitochondrial function and dynamics.

Another challenge in deducing the molecular mechanisms underlying AD is our lack of an understanding of the precise subcellular localization(s) of presenilin-1 (PS1) and presenilin-2 (PS2), and of γ-secretase activity, which processes the amyloid precursor protein (APP) to produce Aβ.

We recently discovered that PS1 and PS2, and γ-secretase activity itself, are located predominantly in a specialized subcompartment of the endoplasmic reticulum (ER) that is physically and biochemically connected to mitochondria, called mitochondria-associated ER membranes (MAM). MAM is involved in the regulation of cholesterol and phospholipid metabolism, in calcium homeostasis, and in mitochondrial function and dynamics.

We also found that cells from AD patients have massively upregulated MAM activity and increased ER-mitochondrial connectivity, resulting in altered cholesterol, phospholipid and calcium homeostasis, and in aberrant mitochondrial dynamics, which may help explain not only the deposition of Aβ in plaques, but also many of the seemingly unrelated biochemical and morphological features of the disease.

Based on these findings, we propose that ER-mitochondrial hyperconnectivity plays a fundamental role in the pathogenesis of AD (the "MAM hypothesis"), with major implications for both diagnosis and treatment of this devastating disorder.

SYM-13-02

TARGETING ABNORMAL METAL DISTRIBUTION IN ALZHEIMER'S DISEASE

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Both Alzheimer's disease and Parkinson's disease are complicated by a conspicuous redistribution of biological transition metals in the brain. Components of the proteinopathies of these disorders, Aβ, presenilins, APP, and tau, have physiological interactions with transition metals and play roles in metal homeostasis. These functions are perturbed in the diseases. Illustrating the potential consequences of loss of metal homeostasis, primary lesions of metal homeostasis, aceruloplasminemia, Wilson's disease, neuroferritinopathy, and NBIA, cause movement disorders and dementia. With aging there is a slowing down of the trafficking of essential metal ions, and pooling dynamic compartments (metallostasis). This allows elevations of metal ions in one compartment, and deficiencies in another. In AD, zinc pools outside of neurons leading to reaction with soluble Aβ and amyloid formation; copper levels within the cortex are decreased, yet the fraction of exchangeable copper rises due to aberrant intracellular ligand coordination. Correction of these abnormalities with small molecules or biologicals (ionophores, chelators, protein chaperones) has been shown to rescue models of Alzheimer's disease and Parkinson's disease. Such approaches have shown promise in phase 2 clinical trials. Rescue of loss of metal homeostasis with prosthetic molecules may be of therapeutic utility in neurodegeneration.

SYM-13-03

TAU AND ABETA TOXICITY IN ALZHEIMER'S DISEASE

Götz J

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Genetics and histopathology point at two key players in Alzheimer's disease, tau and Abeta. Tau is the principal component of neurofibrillary tangles, and Abeta is the principal component of amyloid plaques. In my presentation I will discuss the relative role Tau and Abeta have in impairing neuronal function and how the two molecules interact. I will present novel strategies we have devised in cell culture and animal models to reduce tau and Abeta pathology and to abrogate the associated memory and motor impairments.

SYM-13-04

THE CHOLINERGIC HYPOTHESIS OF ALZHEIMER'S DISEASE: CAUSE AND EFFECTS OF CHOLINERGIC DEGENERATION IN ALZHEIMER'S DISEASE.

Coulson EJ

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The oldest theory of Alzheimer's disease is the cholinergic hypothesis. It is based on the characteristic loss of cholinergic basal forebrain neurons in post-mortem brains of patients with Alzheimer's disease, and is the basis for the most widely used Alzheimer's disease drugs. Despite the change in focus of Alzheimer's disease research to the amyloid hypothesis 20 years ago, there is strong evidence that basal forebrain cholinergic dysfunction contributes to cognitive decline in Alzheimer's disease, and new evidence suggests its may be a causative factor driving amyloid and tau pathology in sporadic cases. The Coulson lab is testing these ideas in cell culture, animal models and humans. Understanding the mechanisms and regulators of basal forebrain degeneration could lead to a better understanding of the aetiology and pathophysiology of sporadic Alzheimer's disease, and therefore better and potentially earlier treatment strategies.

SYM-13-05

CHRONIC NEUROINFLAMMATION IN ALZHEIMER'S DISEASE – A THERAPEUTIC TARGET FOR ANTI-INFLAMMATORY ANTIOXIDANTS?

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Chronic neuroinflammatory processes in AD are characterized by the activation of microglia and astroglia as well as by pro-inflammatory cytokines and chemokines release. Initial triggers of the inflammatory response might be peripheral, such as inflammation triggered by bacterial or viral infections, or central, activated by aggregates of beta-amyloid (Aß) peptide. Subsequently, interactions between damaged neurons (which might be compromised by lack of oxygen and energy) and overactivated microglia create a vicious self-propagating cycle causing uncontrolled, prolonged inflammation that drives the progression of AD. Among the potential pro-inflammatory signals driving this vicious circle, "damage associated pattern molecules (DAMPs)" have received most attention. DAMPs, also known as alarmins, are released by cells undergoing necrosis and act as endogenous danger signals to promote and exacerbate the inflammatory response via "pattern recognition receptors" such as the "Receptor for glycation endproducts" (RAGE). "Anti-inflammatory antioxidants" are novel anti-inflammatory drugs blocking this pathway, by scavenging intracellular reactive oxygen species (ROS) acting as secondary messengers in inflammation. One of the primary redox-sensitive transcription factors in the RAGE pathway activated by ROS is NF-κB. NF-κB is capable of inducing multiple cytokines, and can also increase expression of iNOS. We propose that modulation of this inflammatory reaction by interrupting the vicious cycle might be a promising disease-modifying therapeutic strategy for AD. (211 words)

Abstract Theme: Convergent and Divergent Theories of Alzheimer's Disease -Beyond the Amyloid Hypothesis

SYM-14-01

STUDYING BIOMARKERS, PATHOPHYSIOLOGICAL MECHANISMS, AND TREATMENTS FOR CONCUSSION IN RODENT MODELS

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Although a single concussion rarely has lasting neurological effects, in recent years evidence has emerged that repeated concussions might result in cumulative and chronic neurological impairments, and have been associated with the onset of neurodegenerative diseases such as chronic traumatic encephalopathy. However, there are numerous limitations associated with these studies and, if chronic impairment and neurodegeneration does occur, little is known regarding the factors and pathophysiological mechanisms that might contribute to these effects. Considering these reasons, the current treatment options for concussions are limited, and there is growing societal and medical debate surrounding the proper clinical management of these injuries. To provide insight into this serious medical problem we have recently developed, characterized, and validated rodent models of concussion, repeated concussion, and chronic traumatic encephalopathy that we are now applying to better understand the consequences, pathophysiological mechanisms, and therapeutic approaches of concussions. Here I will present recent findings regarding neuroimaging and behavioral biomarkers, the pathophysiological roles of hyperphosphorylated tau and neuroinflammation, and the use of pharmacological interventions targeting these mechanisms in the context of these rodent models.

(204 words)

SYM-14-02

MODELLING CHRONIC TRAUMATIC ENCEPHALOPATHY – SMALL AND LARGE ANIMAL APPROACHES

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It has been postulated that repeated exposure to mild traumatic brain injury (mTBI) may result in a neurodegenerative condition known as Chronic Traumatic Encephalopathy (CTE). The condition is characterised by the accumulation of phosphorylated tau, predominantly around cortical blood vessels and at the base of the sulci, and it is claimed that the accumulation of the tau protein may be associated with the development of cognitive and behavioural changes that express themselves later in life. The development and screening of potential pharmacotherapies that might target tau phosphorylation will require the availability of animal models that accurately mimic the human condition. Although a number of studies have attempted to mimic the disease in animal models, few have succeeded. We describe both small and large animal models that have been developed to characterise CTE. These models have successfully replicated tau phosphorylation and accumulation of the protein, as well as persistent cognitive and behavioral deficits in the absence of gross tissue loss or motor deficits. We also propose a mechanism to account both for the initial perivascular accumulation of the tau protein as well as the propensity for the protein accumulation to occur at the base of the sulci in gyrencephalic animals. This mechanism offers the first targeted therapeutic approach to management of CTE. (211 words).

SYM-14-03

SPORT-CONCUSSION SYMPOSIUM – NEUROPSYCHOLOGICAL ASSESSMENT

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Acute and sub-acute sequelae of sport-related concussion may include physical/ somatic complaints, emotional concerns and/or cognitive symptoms. Given that resolution of cognitive and physical symptoms do not always overlap, neuropsychological testing has been demonstrated to contribute clinically-useful information to the process of concussion assessment and return-to-play decision- making. However, it is important to be cognisant, that cognitive testing only forms one aspect of a multifactorial assessment and return-to-play decision-making process.

Neuropsychological testing within the field of sport-related concussion was pioneered by Barth et al. in 1989. Barth and colleagues introduced the baseline – post-injury paradigm with pencil and paper neuropsychological assessment measures. With the increasing development of technology this paradigm has been translated into a computerised format, with numerous test batteries having been development to facilitate the cognitive assessment of athletes. There are advantages and disadvantages to the computerised format, one of the most important of which revolves around the psychometric properties (i.e. normative data, reliability, validity, sensitivity and specificity) of these test batteries.

While cognitive testing is universally accepted as a useful method for assisting with the management of sport-related concussion, a number of limitations have also been raised, particularly regarding the endorsement of the baseline post-injury assessment paradigm. In this aspect of the sport-related concussion symposium, neuropsychological perspectives will be presented as they related to the field of sport-related concussion. (220 words)

SYM-14-04

THE LONG-TERM CLINICAL AND PATHOLOGICAL CONSEQUENCES OF SPORTS-RELATED CONCUSSION

McCrory P.

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Recent publications from Australia, Canada and the US have proposed a unique degenerative tauopathy as a consequence of single or repetitive impact from playing sport and called chronic traumatic encephalopathy (CTE). While animal models have demonstrated tau and amyloid deposition following impact, at this stage the human pathological case series are inconclusive.

To date, approximately 15 human cases have been demonstrated with this tauopathy that has a predominantly fronto-temporal deposition with a predilection for tau deposition at the base of the sulci and in perivascular regions. A larger number of cases have been also proposed with this tauopathy; however these cases share additional and overlapping neuropathological findings including amyloid deposition, Lewy bodies and microvascular disease. The methodology in these studies does not allow determination of risk factors or predictors for this condition.

The clinical phenotype of these cases presents as two overlapping presentations. The most common presentation in two thirds of cases is with mood and neurobehavioural dysfunction whereas the less common presentation with cognitive dysfunction is seen in an older age group. The clinical features are similar to that seen in fronto-temporal dementia, which also shares some of the neuropathological features of CTE.

The published evidence for this condition as well as the current controversy in clinical and neuropathological circles will be discussed. (214 words)

SYM-15-01

THE AUSTRALIAN BRAIN BANK NETWORK AND THE ROLE OF NEUROPATHOLOGIC DIAGNOSIS

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The Australian Brian Bank Network (ABBN) provides human brain tissue (and cerebrospinal fluid), for research, facilitating advances in understanding of neurodegenerative and psychiatric disease. Since 2003, the ABBN has collected 1,942 brains nationally. 121,188 samples have been given to 314 research groups (74% Australian), resulting in 630 research publications. Funding is from multiple sources including the NHMRC. As compared to American and European brain banks the ABBN case numbers and research publication output per grant dollar is extremely cost effective. Researchers can access the ABBN online at www.austbrainbank.org.au and view the cases applicable to their project. Researchers are required to have institutional ethics approval. Subsequent tissue applications are reviewed at the level of State Scientific Review Committees and costings are quoted in line with our National access policy, approved by the NHMRC, to allow for direct research cost provision as directed by the NHMRC from 2012.

Critical to provision of tissue for accurate research in this complex area is the neuropathologic diagnosis for disease and ‘controls’. Neuropathologists use current internationally accepted criteria for diagnosis. Currently there are 112 different disease processes and control tissues available for research. Careful selection of relevant tissue from specific anatomical sites, by highly experienced neuropathologists is also essential to the accuracy of tissue provision for each research project.

The ABBN in its current organisational structure is cost effective and provides relevant, accurately diagnosed, carefully sited tissues primarily to Australian researchers. The ABBN is central to improving our understanding of neurodegenerative and psychiatric diseases. (248)

SYM-15-02

COPPER PATHOLOGY IN THE VULNERABLE SUBSTANTIA NIGRA IN PARKINSON'S DISEASE

K.M. Davies[1,2], S. Bohic[3], R. Ortega[4], V. Cottam[1], D.J. Hare[5], J.P.M. Finberg[6], G. Halliday[1,2], J.F.B. Mercer[7], K.L. Double[8,1,2]

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[7]Centre for Cellular and Molecular Biology, Deakin University, Australia

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The characteristic motor symptoms of Parkinson's disease (PD) result from relatively selective neuron death within the substantia nigra (SN). A growing body of evidence suggests that brain copper levels are disrupted in PD and that this has functional implications for PD pathology and neuronal survival. We used synchrotron X-ray micro- and nano-fluorescence technologies to demonstrate a significant decrease in intraneuronal copper (Cu) levels in surviving neurons in the PD SN ($p=0.004$). Such a reduction suggests changes in copper transport pathways and dysregulation of cuproproteins. We therefore examined the distribution and cellular localisation of Cu transport proteins, and activity of the protective antioxidant, and cuproprotein, superoxide dismutase 1 (SOD1), in post-mortem human brains with a pathological diagnosis of PD ($n=8$), compared with controls ($n=8$), using inductively coupled plasma-mass spectrometry, western blot, and immunofluorescence. We identified a marked reduction in neuronal Cu transport protein 1 (Ctr1) immunoreactivity in the SN in PD. Further, in the PD SN, neuron-associated Ctr1 levels were significantly correlated with Cu levels ($p=0.008$). In these same PD cases, in brain regions displaying α-synuclein pathology, SOD1 specific activity was altered to reflect the pattern of cell loss ($p=0.028$). These data suggest that regions affected by α-synuclein pathology display enhanced vulnerability and cell loss if Cu-dependent protective mechanisms are compromised. Further investigation of cupropathology in PD may identify novel targets for the development of protective therapies for this disorder.

SYM-15-03

FROM BRAINS TO BEDS: LESSONS FROM DONATED PSYCHIATRIC BRAINS.

~~Scarr E~~[1,2].

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It is widely accepted that both genetic and environmental factors are important in the genesis of psychiatric disorders. The brains from people with psychiatric disorders are an optimal resource to investigate the outcomes of such interactions and to provide information regarding the neurochemical changes associated with the disorders.

This presentation will focus on a series of studies spanning seventeen years, using post-mortem brain samples. These data have firmly placed the muscarinic component of the central cholinergic system in the pathophysiologies of psychiatric disorders. The post-mortem studies will be placed in the context of clinical research and the potential consequences of the neurochemical changes discussed with respect to the clinical presentations of the disorders. Finally, the influence of the research outcomes of the post-mortem studies on novel drug discovery projects and the conceptualisation of psychiatric disorders will also be explored. (139 words).

SYM-15-04

DEMENTIA AND THE AGEING BRAIN: LESSONS YOU CAN ONLY LEARN FROM HUMAN BRAIN STUDIES.

Vickers JC

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Investigations on the neurobiology of dementing disorders such as Alzheimer's disease (AD) have become a major area of neuroscience research world-wide. Such studies rely on the use of human brain tissue as well as a variety of *in vivo*, particularly transgenic, and *in vitro* models. Experimental models provide an extremely valuable set of tools with which to determine specific mechanistic features of aspects of neurodegenerative disease processes, as well as to explore potential therapeutic interventions. However, it is likely that there are still vital lessons to be learnt from studies of the human brain, both in terms of the key pathological changes linked to neurodegeneration as well as understanding the potential points of intervention amenable for therapeutic approaches. In this regard, placing experimental models in context relative to the type and stageing of pathology in AD is important. We have determined that many of the transgenic mouse models that express human amyloid precursor genes bearing familial AD mutations demonstrate ageing-related plaque, as well as axonal and synaptic, pathology that is more alike to the earliest stages of AD in the human brain. This potential context exemplifies the value of such animal models for mechanistic studies as well as treating/reducing risk of AD at early time points. Cross-matching and contextualising human brain and experimental model data may therefore assist in the translation of research into productive outcomes. (226 words).

SYM-16-01

PROTECTING GLIA FROM SECONDARY DEGENERATION FOLLOWING NEUROTRAUMA

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Following neurotrauma, tissue adjacent to the primary injury undergoes a cascade of cellular and molecular events termed secondary degeneration, leading to further loss of neurons, glia and function. Mediators of secondary degeneration, including Ca^{2+} and reactive species, diffuse and may spread *via* connections between astrocytes, oligodendrocyte precursor cells (OPCs) and axons. We have demonstrated increases in reactive species, oxidised products and anti-oxidant enzymes in CNS glia vulnerable to secondary degeneration, following partial transection of rat optic nerve. Oxidative stress in oligodendrocytes is associated with alterations in node of Ranvier/paranode complexes, with significant lengthening of the paranodal gap and paranode as well as paranode disorganisation. A high proportion of OPCs proliferate in optic nerve vulnerable to secondary degeneration, and the appearance of shortened myelin internodes at 3 months suggests remyelination. However, OPCs die and numbers remain chronically lower, accompanied by persistent myelin decompaction, axon swelling and functional loss. We have used multiple combinations of Ca^{2+} channel inhibitors to treat secondary degeneration and demonstrated that combinations that include the L-type voltage gated calcium channel inhibitor lomerizine, improve myelin compaction. Treatment with a combination of three inhibitors (lomerizine, INQ and oxATP) prevents lengthening of the paranodal gap and preserves visual function. Strategies to reduce the spread of excess Ca^{2+} and resultant reactive species may protect oligodendrocytes from oxidative stress and thereby preserve function following neurotrauma. (220 words)

SYM-16-02

NUCLEAR FACTOR I TRANSCRIPTION FACTORS IN GLIAL DEVELOPMENT AND DISEASE

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The nuclear factor I (*Nfi*) family of transcription factors play an important role in the normal development of the brain. Similar to human with *NFI* mutations, knockout mouse for either *Nfia* or *Nfib* display a similar brain phenotype, which includes agenesis of the corpus callosum. *Nfi* knockout mice display an elongation and thinning of the cerebral cortex. Although all cortical layers are formed, the ventricular zone is enlarged and the formation of the other cortical layers is delayed.

Our results indicate that NFI proteins regulate radial glial proliferation by controlling the balance of symmetrical versus asymmetrical division. Immunohistochemical staining revealed an increase in radial glia, indicating prolonged symmetric division of these cells. The production of basal progenitors and neurons via asymmetric division is therefore delayed. The total NFI protein level across different family members is important, as the severity of this radial glial phenotype increases with number of *Nfi* alleles simultaneously inactivated. Furthermore, this effect is cell autonomous. Overexpression of NFI via *in utero* electroporation resulted in precocious differentiation of radial glia into mature astroglia, while knockdown via shRNA resulted in decreased neuronal differentiation. Expression profiling in knockout and wildtype cortex revealed that the expression of progenitor fate and differentiation genes rather than cell cycle regulatory components is altered. This suggests NFI signalling does not directly regulate the progression of the cell cycle. Rather, we conclude that NFI signalling is a key regulator of neocortical development by controlling the mode of radial glial proliferation throughout cortical neurogenesis.

(247)

SYM-16-03

GLIAL REMODELING: A NOVEL FORM OF PLASTICITY TO ADAPT TO ENVIRONMENTAL CHALLENGES.

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Glial cells exhibit a remarkable ability to undergo significant structural remodelling in order to engage and connect with other elements within the central nervous system. Efficient remodeling is required for all activities that glia are involved in ranging from monitoring synaptic information flow through to phagocytosis of tissue debris. Despite the fact that morphological remodeling is a pre-requisite many glial activities, relatively little research has been undertaken on the topic. Our research group has been interested in examining how glia transform themselves during development, under physiological conditions in response to changes in neuronal activity, and under pathological circumstances. Specific attention in this talk will be given to exploring a variety of models that have been proposed to account for glial transformation as well as the signals that are known to trigger these transformations.

SYM-16-04

TRANSCRIPTIONAL REGULATION OF TERMINAL OLIGODENDROCYTE DIFFERENTIATION AND CNS MYELINATION

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Oligodendrocyte differentiation and the myelination of axons are crucial steps during vertebrate CNS development, allowing for the rapid saltatory conduction of action potentials. We previously identified a putative transcription factor, Myelin Regulatory Factor (Myrf, also known as MRF and GM98), that is vital for oligodendrocyte differentiation and CNS myelination during development. Myrf is also required for the maintenance of CNS myelin in the adult. It has been controversial, however, whether Myrf directly regulates transcription, with reports of a transmembrane domain and lack of nuclear localization. Here, we investigate the molecular mechanisms by which Myrf promotes CNS myelination. We find that that Myrf is a membrane-associated transcription factor that, like other membrane-associated factors such as Notch and the SREBPs, undergoes an activating proteolytic cleavage event. This cleavage separates the transmembrane domain containing region from the nuclear-targeted N-terminal region. Using ChIP-Seq we show that the N-terminal cleavage product directly binds DNA, with Myrf binding sites strongly clustered around genes required for CNS myelination. Luciferase assays confirm that Myrf strongly promotes transcription from myelin gene enhancers via a newly defined DNA binding consensus sequence. These findings identify Myrf as a transmembrane transcription factor, reconciling previous questions regarding its subcellular localization. Our findings that Myrf directly activates a wide range of myelin genes by directly binding to their enhancer regions also confirm Myrf as a key transcriptional regulator of the CNS myelin process. We are currently investigating the expression and role of Myrf in human demyelinating disease and its animal models. (247 words)

SYM-17-01

DEVELOPMENT AND APPLICATION OF A CLOSED-LOOP NEURAL PROSTHESIS.TO POTENTIATE FUNCTIONAL CONNECTIVITY AND RESTORE FUNCTION AFTER CORTICAL INJURY

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We tested the hypothesis that recovery after brain injury can be facilitated by a neural prosthesis serving as a communication link between distant locations in the cerebral cortex. The primary motor area in the cerebral cortex was injured in a rat model of focal brain injury, disrupting communication between motor and somatosensory areas and resulting in impaired reaching and grasping abilities. After implantation of microelectrodes, a neural prosthesis discriminated action potentials (spikes) in premotor cortex that triggered electrical stimulation in somatosensory cortex continuously over the subsequent weeks. Within one week, while receiving spike-triggered stimulation, rats showed substantially improved reaching and grasping functions that were indistinguishable from pre-lesion levels by two weeks. Post-hoc analysis provides compelling evidence that the neural prosthesis enhanced functional connectivity between the two target areas. Our more recent results now reveal that ADS can potentiate functional connectivity between cortical areas within a single anesthetized recording period. Additionally, ADS-driven facilitation was found to also occur in cells recorded from electrode contacts adjacent to the trigger-cell recording site, suggesting that stimulation may affect the network of cells that are spatially, and likely synaptically, coupled with the trigger-cell. Facilitating connectivity within a short epoch and during anesthetization provides a foundation for rapidly assessing the optimal stimulus parameters for implementing ADS, and may in the future aid directly in facilitation of functional recovery after brain injury. These proof-of-concept studies demonstrate that neural interface systems can be used effectively to bridge damaged neural pathways and promote recovery after brain injury. (248 words).

SYM-17-02

NON-INVASIVE BRAIN STIMULATION TECHNIQUES FOR THE EVALUATION AND MODULATION OF PLASTICITY IN STROKE

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Recently protocols of repetitive transcranial magnetic stimulation (rTMS) of the human brain that resemble experimental models of LTP have been introduced. The paradigm named intermittent theta-burst stimulation (iTBS) produces a prolonged increase of cortical excitability and pharmacological studies have shown that iTBS effects are influenced by drugs that act at the NMDA receptor, supporting the hypothesis that the iTBS after-effects involve LTP like-changes. Intermittent TBS may also induce excitability changes in remote brain sites that are functionally connected to the targeted area: together with facilitation of stimulated hemisphere, iTBS produces a long term depression (LTD) like phenomenon in contralateral hemisphere. The effects of iTBS have been explored both in acute and in chronic stroke patients revealing that the excitability of the lesioned motor cortex can be modulated using this technique and the results of the studies suggest a tight relationship between motor cortex plasticity and recovery after stroke. The knowledge of the mechanisms that might be involved in the process of recovery has led to a fast multiplication of the attempts to interfere with the stroke-induced functional changes of the brain, in order to prompt natural recovery. Even though non-invasive neuromodulation appears very promising, new strategies of brain stimulation should be developed based on a diagnostic multimodal approach and a new model that takes into consideration several characteristics such as the functional and structural reserve spared by the lesion in each single patient and also the possibility to promote recovery via complex mechanisms such as the phenomenon of “homeostatic” plasticity. [number of words 250]

SYM-17-03

HARNESSING BRAIN PLASTICITY FOR REHABILITATION IN THE INTACT NERVOUS SYSTEM – A CLINICAL PERSPECTIVE

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People in pain move differently. Although obvious, the mechanisms that underpin the potential for the nervous system to change in pain are only beginning to be understood. Recent work highlights extensive neuroplastic change at multiple sites in the nervous system from the sensory and motor regions of the cortex to spinal cord circuitry. The mechanisms that underpin these changes and the potential role of sensorimotor changes in the perpetuation and recurrence of pain have been studied extensively. This presents a host of opportunities to understand behaviors in people with pain and new avenues for potentially more effective treatments. Rewiring of the brain and nervous system (neuroplasticity) can underpin both negative and positive changes in motor and sensory aspects of movement in association with the pain experience. Interventions that can harness and optimize plasticity to promote change in motor control range from exercise targeted to motor control and motor learning and treatments that aim to “prime” the nervous system to change. Clinical trials show that training interventions can modify motor cortex organization towards that observed in painfree individuals; that interventions that aim to prime the nervous system (e.g. non0invasive brain stimulation) can induce positive change; that changes in the nervous system are related to motor behaviours; and these changes are associated with clinical improvements in pain and disability. The mechanisms for efficacy are beginning to be understood. These effects require consideration in planning optimal treatments.

(234 words)

SYM-17-04

THE WAY AHEAD – DO NON-INVASIVE BRAIN STIMULATION (NIBS) TECHNIQUES OFFER REAL THERAPEUTIC POTENTIAL?

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A wealth of evidence shows that NIBS can interact with and cause lasting effects on CNS circuits that have observable effects on behaviour. As such they are ideal candidates for potential new therapeutic interventions in a variety of CNS disorders. However, a crucial problem needs to be addressed before any real progress can be made: all published methods have a very high inter- individual variability in their effects. When tested in the usual model of the primary motor cortex, often only 30-50% individuals respond in the “expected” way. There are two potential solutions to this problem. First, it may be possible to predict which individuals are likely to respond to a given NIBS protocol, and exclude from a trial “non-responders”. Second, it may be possible to refine NIBS methodologies to increase responsiveness in a larger proportion of participants. I will present recent work exploring each of these options, using MEP onset latencies to predict the response to theta burst protocols, or short interval intracortical inhibition to predict the response to paired associative stimulation protocols; and using a new controllable transcranial magnetic stimulator to improve targeting of neural populations in cortex.

SYM-18-01

MOLECULAR MECHANISMS OF PAR SIGNALING TO TRPV4

Grace, MS[1], Darby,W[1], Lieu TM[2], Veldhuis, NV[2], Poole, D[2] , Bunnett NW[2] and McIntyre P[1]

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The mechanism by which inflammatory proteases activate protease activate receptors (PARs) such as PAR_2 are well understood but the signaling pathways and mechanism by which PAR_2 causes inflammatory pain is not well understood. We are studying the possibility that TRPV4 is a receptor operated ion channel that is important in PAR-dependent signaling in excitable cells including neurons.

TRPV4 is widely expressed in epithelial, endothelial, neuronal and glial cells. Quite a lot is known about TRPV4's structure however, little is known about how it is activated by physiological mechanisms. We have found that in some cell types, including HEK293 cell lines, TRPV4 is activated (opened) as a result of activation of PAR_2–dependent intracellular signaling pathways. In HEK cells, activation of TRPV4 depends on tyrosine 110 phosphorylation and various kinase inhibitors, including some tyrosine kinase inhibitors, can block this. Signaling is not inhibited by depletion of intracellular stores with thapsigargin, which prevents the PAR_2 tethered ligand mimetic peptide, SLIGRL-NH_2 from mobilizing intracellular calcium stores. Nor does the Gq inhibitor, UBO-QIC, which also prevents calcium mobilization by SLIGRL-HN2, inhibit TRPV4 activation. A tyrosine kinase inhibitor that prevents PAR_2 activation from opening TRPV4 in HEK293 cells also inhibits SLIGRL-induced pain behavior in mice when given orally 30 minutes before injection of the PAR_2 activating peptide into the paw. Thus we may have discovered a novel therapeutic approach to treating inflammatory pain involving PAR_2 activation. (231 words)

Oral Presentation Preferred

SYM-18-02

SPECIFIC CONTRIBUTIONS OF SELECT TRP CHANNELS TO ACUTE AND CHRONIC VISCERAL HYPERSENSITIVITY

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Chronic Visceral Pain (CVP) derives from our internal organs, is debilitating and one of the most common reasons for seeing a GP. Irritable Bowel Syndrome (IBS) is one of the leading forms of CVP, affecting up to 15% of Western populations. One of the underlying causes of IBS is a preceding bout of gastroenteritis, which can trigger long-term neuroplasticity, resulting in chronic visceral hypersensitivity (CVH) and CVP. In order to identify therapies for CVP we have identified the fundamental properties of sensory afferents innervating the gastrointestinal tract, the molecular basis of their transduction and how this changes during inflammatory hypersensitivity and CVH.

We have shown distinct TRP channel family members are key contributors to visceral nociception. In health TRPV4 and TRPA1 contribute to mechanical nociception, whilst TRPV1 contributes to chemical nociception. Endogenous mediators such as 5,6-EET sensitize TRPV4, whilst bradykinin and TNF-α sensitize TRPA1 to induce mechanical hypersensitivity. However, fundamental changes in the expression and function of these channels are evident during inflammatory hypersensitivity and CVH. During inflammation TRPA1 and TRPV4 expression and function are increased, which contributes to inflammation-induced mechanical hypersensitivity. However, TRPV1 expression and function are decreased at the same time point. During CVH increased TRPA1 expression and function are maintained, with additional novel TRP channels also contributing to neuroplasticity.

These findings identify key mechanisms that underlie the neuroplasticity of colonic sensory pathways during inflammatory hypersensitivity and CVH. They also identify several channel and receptor interactions, which may hold promise for the pharmacological treatment of CVP.

(250 words): ** Please note that this abstract is for a selected talk as part of the “TRP channels in health and disease” Symposium **

SYM-18-03

THE BILE ACID RECEPTOR TGR5 SENSITIZES THE TRPA1 CHANNEL TO INDUCE ITCH

Tinamarie Lieu[1], Gihan Jayawerra[1], Peishen Zhao[1], Daniel P. Poole[1], Dane Jensen[1], Megan Grace[2], Romke Bron[3], Peter McIntyre[2] and Nigel W. Bunnett[1,4]

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Patients with cholestatic disease have elevated systemic concentrations of bile acids (BAs) and exhibit profound pruritus. The BA receptor TGR5 is expressed by nociceptive neurons of dorsal root ganglia (DRG), where activation induces hyperexcitability and scratching behavior in mice by unknown mechanisms[1]. We evaluated the contribution of transient receptor potential ankyrin 1 (TRPA1) to BA-evoked, TGR5-dependent pruritus. Using retrograde tracing, single cell RT-PCR, immunofluorescence and *in situ* hybridization, we detected TGR5 in a subpopulation of DRG neurons innervating the mouse skin. TGR5 and TRPA1 were coexpressed in retrogradely-labeled small diameter neurons. In HEK cell lines expressing TGR5 and TRPA1, and in mouse DRG neurons in culture, pre-incubation with the BAs deoxycholic acid (DCA) and taurolithocholic acid (TLCA) magnified TRPA1-dependent Ca^{2+} signals, indicating channel sensitization. TRPA1 antagonism or deletion or inhibition of protein kinase A all prevented sensitization. Intradermal injection of DCA or TLCA induced scratching behavior in mice. TRPA1 antagonism or deletion prevented BA-evoked scratching, whereas antagonism of TRPV1 had no effect. TGR5 transgenic mice demonstrated enhanced spontaneous scratching that was attenuated by feeding the BA sequestrant colestipol and is thus dependent on endogenous BAs. Antagonism of TRPA1 also suppressed spontaneous scratching in TGR5 transgenic mice. Thus, TGR5 is coexpressed with TRPA1 by a subpopulation of DRG neurons that innervate the skin. TGR5 causes protein kinase A-dependent sensitization of TRPA1, which is required for the pruritogenic actions of exogenous and endogenous BAs. This mechanism may contribute to cholestatic pruritus in patients with elevated systemic concentrations of BAs.

1. J Clin Invest, 123: 1513-1530, 2013.

SYM-18-04

QUANTIFICATION AND FUNCTIONS OF ENDOGENOUS AGONISTS OF TRANSIENT RECEPTOR POTENTIAL CHANNELS IN IRRITABLE BOWEL SYNDROME

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The presence of potential endogenous activators of transient receptor potential channels (TRPs) in the intestine as well as their possible role in the context of Irritable Bowel Syndrome (IBS) has never been investigated. TRP channels can be activated or inhibited *in vitro* by different polyunsaturated fatty acid (PUFA) metabolites. We dosed those metabolites in tissues harvested from IBS patients. Whereas TRPV1 and TRPA1 agonists were unchanged, the quantity of TRPV4 endogenous agonist (5,6-EET) was increased in biopsies of IBS patients compared to controls. Intracolonic administration in mice of supernatants from colonic biopsies of IBS patients, but not controls, caused hypersensitivity in response to colorectal distension. This hypersensitivity was inhibited by TRPV4-targeted SiRNA. In hypersensitive mice, TRPV4 and TRPV1 endogenous agonists were increased in colonic tissues, compared to normo-sensitive mice. PUFA metabolites extracted from IBS biopsies or hypersensitive mice colon signaled to sensory neurons through TRPV4 activation. Exposure of sensory neurons to supernatants from IBS patient biopsies provoked the production of the TRPV4 agonist 5,6-EET through protease-activated receptor-2 and cytochrome epoxygenase activation. Our study establishes that specific PUFA metabolites are increased in IBS and that they can directly stimulate sensory neurons and generate hypersensitivity symptoms through the activation of TRPV4. (199 words)

SYM-19-01

MECHANISM AND THERAPY FOR ERRORS IN RNA BINDING PROTEINS IN ALS AND FTD

Don W. Cleveland[1,2,3], Michael Baughn[2], Shuying Sun[1,3], Shuo-Chien Ling[1,2], Sandrine Da Cruz[1,2], Jie Jiang[1,2], Qiang Zhu[1,2], Dara Ditsworth[1,3], Frank Rigo[4], Sebastian Markmiller[3], Andy Watt[4], Eveline Sun Arnold[1,3], Stephanie Huelga[3], Ying Sun[1], Jinsong Qiu[3], Hai-Ri Li[3], Yuan Xue[3], Magdalini Polymenidou[1,2], Kevin Clutario[1, 2], Anthony Q Vu[4], Patrick Liu[4], Xiang-Dong Fu[3], Gene W Yeo[3], C. Frank Bennett[4], John Ravits[2], and Clotilde Lagier-Tourenne[1,2]

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Identification of genes, whose mutation is causative of Amyotrophic Lateral Sclerosis (ALS) and frontal temporal degeneration (FTD) have revealed an unexpected convergence in disease mechanisms that includes errors in RNA binding proteins and RNA metabolism. Two of these genes encode the widely expressed RNA binding proteins, TDP-43 and FUS/TLS. These two proteins have been demonstrated to act in mechanistically divergent roles in RNA pre-maturation, but their functions intersect in 45 RNAs that require the action of either TDP-43 or FUS/TLS, including the RNAs with the longest introns and which encode proteins related to synaptic function. Analysis of transgenic mice has demonstrated that age-dependent, mutant TDP-43- or FUS/TLS- dependent degeneration of lower motor neurons occurs with both loss of function and gain of toxicity, without loss of either protein from the corresponding nuclei or accumulation of aggregates.

The most frequent genetic cause of ALS and FTD is hexanucleotide expansion in a non- coding region of the *C9orf72* gene. Sense and antisense strand repeat-containing RNAs have been found to accumulate in distinct nuclear RNA foci, the hallmark feature of repeat expansion RNA-mediated toxicity. Antisense oligonucleotides (ASOs) have been developed that selectively target sense strand repeat-containing RNAs and reduce sense-oriented foci without affecting overall C9orf72 expression. Importantly, reducing *C9orf72* expression does not cause behavioral or pathological changes in mice, and induces only few genome-wide mRNA alterations. These findings establish ASO- mediated degradation of repeat-containing RNAs as an attractive therapeutic approach.

SYM-19-02

RNA PATHOGENESIS VIA TOLL-LIKE RECEPTOR-ACTIVATED INFLAMMATION IN EXPANDED REPEAT NEURODEGENERATIVE DISEASES

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Previously, we hypothesized that an RNA-based pathogenic pathway has a causal role in the dominantly inherited unstable expanded repeat neurodegenerative diseases. In support of this hypothesis we, and others, have characterized rCAG.rCUG100 repeat double-strand RNA (dsRNA) as a previously unidentified agent capable of causing pathogenesis in a Drosophila model of neurodegenerative disease. Dicer, Toll, and autophagy pathways have distinct roles in this Drosophila dsRNA pathology. Dicer dependence is accompanied by cleavage of rCAG.rCUG100 repeat dsRNA down to r(CAG)7 21-mers. Among the “molecular hallmarks” of this pathway that have been identified in Drosophila, some [i.e., r(CAG)7 and elevated tumor necrosis factor] correlate with observations in affected people (e.g., Huntington’s disease and amyotrophic lateral sclerosis) or in related animal models (i.e., autophagy).TheTollpathwayisactivatedinthepresenceofrepeat-containingdsRNAand toxicity is also dependent on this pathway. How might the endogenously expressed dsRNA mediate Toll - dependent toxicity in neuronal cells? Endogenous RNAs are normally shielded from Toll pathway activation as part of the mechanism to distinguish “self” from “non-self” RNAs. This typically involves post-transcriptional modification of the RNA. Therefore, it is likely that rCAG.rCUG100 repeat dsRNA has a characteristic property that interferes with or evades this normal mechanism of shielding. We predict that repeat expansion leads to an alteration in RNA structure and/or form that perturbs RNA modification, causing the unshielded repeat RNA (in the form of its Dicer-cleaved products) to be recognized by Toll-like receptors (TLRs), with consequent activation of the Toll pathway leading to loss of cell function and then ultimately cell death. We hypothesize that the proximal cause of expanded repeat neurodegenerative diseases is theTLR recognition (and resultant innate inflammatory response) of repeat RNA as “non-self” due to their paucity of “self” modification.

SYM-19-03

GROWING EVIDENCE FOR DEFECTIVE RNA METABOLISM IN ALS.

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The familial forms of neurodegenerative disorders offer a unique opportunity to identify molecular defects that are relevant to both familial and sporadic disease. Amyotrophic lateral sclerosis (ALS) is a late-onset fatal disorder characterised by the progressive degeneration of upper and lower motor neurons. Approximately 10% of ALS cases have a positive family history and appear clinically indistinguishable from sporadic ALS cases. To date, the only proven causes of ALS are gene mutations that lead to the death of motor neurons. Known mutations account for approximately two-thirds of familial ALS and 5% of sporadic ALS cases. Other ALS families are not linked to known loci and the cause of most sporadic ALS also remains unknown. Around 20% of ALS patients are also diagnosed with frontotemporal dementia (FTD). The goal of our research is to investigate known ALS molecules, as well as identify and investigate new molecules that play a role in ALS and FTD among international cohorts. We are using traditional genetic techniques coupled with next- generation sequencing (NGS) strategies. The chromosomal regions implicated from our genome-wide linkage scans do not overlap previously identified loci, implicating substantial genetic heterogeneity. Linkage analysis in combination with exome sequencing provides the best opportunity yet to identify novel ALS genes. Our recent ALS gene discoveries have implicated common disease mechanisms including RNA metabolism and protein degradation pathways. The identification of novel ALS genes provides insight into the biological basis of motor neuron degeneration, development of new disease models, and new targets for diagnostic and therapeutic development. (250 words).

SYM-19-04

IDENTIFICATION OF RNAs REGULATED BY TDP-43 SUGGEST A ROLE IN THE MAINTENANCE OF NEUROMUSCULAR JUNCTIONS.

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Abnormal TDP-43 protein aggregates are a characteristic of several neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Mutations within TDP-43 have been found in both ALS and FTD. However, the precise function of TDP-43 in the nervous system remains unknown and its role in pathogenesis is unclear. TDP-43 is an RNA binding protein involved in RNA splicing and transport, implying that abnormal RNA processing is involved in neurodegeneration. Our preliminary analysis of TDP-43 RNA binding partners has identified a large number of genes related to synaptic transmission, and in particular, synaptic vesicle recycling. The role of TDP-43 in transport of synaptic vesicle-RNA for local translation is further supported by our findings that TDP-43 is localised to presynaptic regions of motor neuron terminals at the neuromuscular junction in mice. We subsequently generated a *C. elegans* model for TDP-43 pathology by expressing wild-type TDP-43 or mutant TDP-43 specifically in GABAergic motor neurons. We found that mutant TDP-43 disrupted presynaptic loci and produced clear axonal degeneration defects. Both these phenomena were adult onset and progressive in nature. To investigate TDP-43 localization in *C. elegans* we generated transgenic strains in which TDP-43 is tagged with GFP and expressed in the same GABAergic motor neurons. We observed for both wild type and mutant alleles that TDP-43 is localized predominantly in the nucleus with some expression in the cytoplasm and in puncta consistent with synaptic loci. This resembles the subcellular localization observed in mice, with TDP-43 shuttled between the nucleus and the synapses. (250 words)