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SYMPOSIUM 1 – TRANSLATIONAL NEUROSCIENCE SYMPOSIUM

A Special Symposium of the ANS 2013 Local Organising Committee

Sponsored by Vice Chancellor's Fund, Monash University

SYM-01-01

TRANSLATIONAL RESEARCH IN PARKINSON'S DISEASE (PD)

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Purpose: To review the translation of basic science into clinical practice for patients with PD. Methods: Critical assessment of literature. Results: Observations in the late 1800s and early 1900s identified midbrain lesions in the substantia nigra as important and Lewy first described the pathological cellular inclusions in 1912, findings that still underpin the definitive diagnosis of PD. In the 1950s the discovery of the dopaminergic nature of nigrostriatal neurons led Carlsson to discover the neuromediatory role of dopamine, a finding at the origin of the mainstay L-dopa therapy for PD, and Hassler identified that surviving dopamine neurons contained Lewy bodies. Subsequent basic science studies have identified that the degree of dopamine neuron loss correlates with the disabling motor symptoms of PD, stimulating research into cell replacement therapies. In 1997 the first dominant familial mutation associated with PD was identified in the α-synuclein gene, and the protein was shown to be the main constituent of Lewy bodies. In 2003 Braak hypothesized that inclusion pathology spread from caudal to rostral through the brain, confirming the work of others that α-synuclein inclusions affected more than just the dopamine system. More genes have been found to cause familial PD than for Alzheimer's disease, and a number of important risk factors for PD have been identified. Clinical work has confirmed that more symptoms are associated with PD and have begun to plot their evolution over the disease course, identifying a number of subtypes including a preclinical phase. Conclusion: Basic science discoveries have recently led to new concepts on the aetiology and pathogenesis of PD with preventative strategies and novel therapeutics now under active research development.

SYM-01-02

THE TRANSLATION OF BIONICS INTO CLINICAL TOOLS

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Advances in materials sciences and computers, combined with the success of early generation devices such as the bionic ear and thalamic stimulation for Parkinson's disease, are responsible for increasing interest in bionic therapies for a number of chronic - mainly neurological - conditions. Optimisation of stimulation strategies, electrode characteristics, and long-term management of the devices remain major problems, together with regulatory issues. Our work with counter stimulation techniques for the treatment of epilepsy will be described, and our work with a first-in-human implanted device for the prediction of seizures. More recent studies demonstrating how the devices could be used for the anticipation of therapeutic agents will also be discussed. Benefits and potential disadvantages of these devices in the clinical setting will be outlined in the context of this work.

SYM-01-03

THE TRANSLATION OF POTENTIAL NEW DRUGS AFFECTING ENDOCYTOSIS

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The protein dynamin plays a crucial role as the final step of SV endocytosis (SVE). Dynamin has the ability to bind and fragment lipid and the ability to self-assemble into rings and helices around the necks of budding vesicles. Dynamin I was originally identified as a nerve terminal phosphoprotein. Stimulus-dependent dephosphorylation rapidly activates dynamin (<1s) and is mediated by the phosphatase calcineurin. Calcineurin has a specific docking site on the tail of one dynamin I isoform to target the complex for rapid dephosphorylation. After the stimulus terminates, dynamin is rephosphorylated by cooperative action of two protein kinases - cyclin-dependent kinase 5 and glycogen synthase kinase 3. Dynamin-dependent endocytosis is a rate-limiting step for synaptic transmission because it controls the supply of SVs. Blocking dynamin function causes a rundown of glutamate release, which might have clinical implications for treating neurological disorders such as epilepsy. Epilepsy is a disease of synaptic transmission affecting up to 1% of the population. Seizures may be managed by anti-epileptic drugs, but over 30% of people do not respond to any drugs. Dynamin I is an attractive candidate for a novel anti-epileptic drug as reducing its function would not affect synaptic transmission at lower frequency, but would reduce synaptic transmission during excessive brain activity. We have developed a range of compounds that inhibit dynamin by multiple distinct mechanisms. The compounds reversibly inhibit SVE and cause an activity-dependent run-down in synaptic transmission. One of the allosteric regulators blocks the neurotoxic action of botulinum neurotoxin. Two of the GTP-targeted compounds show anti-convulsant activity in two animal models of epilepsy. Therefore understanding the molecular mechanisms of synaptic transmission may lead to new therapeutic approaches for treatment of disorders of synaptic transmission.

SYM-01-04

ATTENTIONAL ASYMMETRY AS A PREDICTOR OF STIMULANT RESPONSE IN ADHD

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An intriguing aspect of the attentional profile of individuals with ADHD is a subtle bias, or asymmetry, of directed attention away from the left side of space. Put simply children and adults with ADHD have been reported to be slower and less accurate when detecting visual targets presented in left space compared to comparable targets on the right. This asymmetry of attention is qualitatively similar to that seen following acquired lesions to the right cerebral hemisphere where "neglect" of left space is dramatic. This similarity has led to the hypothesis that ADHD might represent a developmental form of neglect. The observation that attentional asymmetry in ADHD can be modulated by psychostimulants suggests a catecholamine origin for this phenomenon. In this talk I will review our genetic and pharmacogenetic work that has shown that (i) common DNA variation in the dopamine transporter gene (DAT1) accounts for significant individual differences in attentional asymmetry in children with ADHD as well as non-clinical children and adults; (ii) attentional asymmetry is related to symptom severity in children with ADHD; (iii) attentional asymmetry is a significant predictor of stimulant response with this relationship moderated by DAT1 genotype. Further, I will discuss data from a recent fMRI study which has attempted to isolate the neural substrate of attentional asymmetry and its modulation by psychostimulants in children with ADHD.

SYM-02-01

HUMAN STUDIES DEFINING THE CELLULAR AND TISSUE RESPONSES TO ALZHEIMER PROTEINS

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Purpose: Abnormal accumulations of amyloid-beta (Aβ) and hyperphosphorylated tau (phospho-tau) constitute the major neuropathological hallmarks of Alzheimer's disease (AD). Significant inflammation and neuronal death also accompany the disease process. Aβ is thought to exert its neurotoxic influence through formation of insoluble fibrils and/or oligomers, although the precise neurotoxic species (Aβ40 or 42) is still debated. Methods and Results: Our studies examining human tissue responses to Aβ40, Aβ42 and phopho-tau have shown significant deposition of Aβ42 in the absence of inflammation or neuronal loss with only Aβ40 and phospho-tau being associated with significant astrocyte and microglia upregulation (84-97%). To identify the type of Aβ involved, cell culture experiments were performed demonstrating a neurotoxic (cell death and tau hyperphosphorylation) role for oligomeric ($p=0.037$), but not fibrillar Aβ40. In deciphering the major factors mediating this response, we identified significant increases in interleukin-6 (IL6), IL8 and CCL2 in sporadic and familial AD ($p=<0.0029$), with cell culture work suggesting IL8 is involved acutely ($p=0.037$). Early increases in CCL2 appear to sustain and drive the inflammatory process in AD ($r = 0.483$, $p < 0.001$), with levels of CCL2 correlating with both phospho-tau protein levels ($p=0.01$) and neurofibrillary tangle number ($r = 0.52$, $p < 0.01$). Importantly CCL2 levels were not correlated with Aβ protein levels or plaque pathology. Furthermore, these increases in CCL2 were closely associated with neuronal death ($r = -0.61$, $p = 0.01$), suggesting a dominant and highly neurotoxic role in the disease process. Conclusion: Our data demonstrate that Aβ42 does not evoke a significant inflammatory response in human brain tissue, rather deposition of Aβ40 and significant tau changes are required to initiate the inflammatory tissue changes associated with AD specific cell death.

SYM-02-02

TAM RECEPTOR SIGNALLING, NEUROINFLAMMATION AND DEMYELINATION

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The TAM family of receptor tyrosine kinases is comprised of three members Axl, Tyro3 and Mertk. Recent studies have shown that TAM receptor signalling is an important modulator of both oligodendrocyte survival and immune cell phenotype both in vivo and in vitro. We have previously shown, that administration of the TAM ligand Gas6 to microglia isolated from the CNS leads to increased Axl and Mertk expression together with decreased cytotoxic TNFα production, demonstrating the immunomodulatory function of TAM signalling. We have also investigated the role of these receptors in two mouse models of Multiple Sclerosis (MS). In the cuprizone model of central demyelination, Tyro3 expression is decreased during demyelination, correlating with the loss of oligodendrocytes, whilst Axl, Mertk and Gas6 expression is increased on microglial cells. Further, in the absence of Gas6 during cuprizone-induced demyelination, we observed increased demyelination, concomittant with increased numbers of microglia, and delayed remyelination during recovery. Gas6 deficiency also leads to worsened clinical outcome in experimental autoimmune encephalomyelitis (EAE), an inflammatory model of demyelination. Analysis of expression levels of TAM receptors in $CD11b^+$ monocytes and $CD11c^+$ dendritic cells of the peripheral immune system during EAE demonstrates that there is disparity between disease-associated TAM levels in the periphery compared to levels of expression in the CNS. Genetic association studies have also identified MERTK as a risk gene for MS, and preliminary data in human monocytes shows risk-genotype dependent differences in MERTK expression. Together, these results highlight the role of this family in neuroinflammation, and identify them as potential therapeutic targets for diseases such as MS.

SYM-02-03

LOW NITRIC OXIDE BIOAVAILABILITY IS A CENTRAL MEDIATOR OF CEREBRAL MALARIA PATHOGENESIS

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Disruption of the blood brain barrier by a combination of inflammation and endothelial dysfunction leading to vascular leak is a hallmark of cerebral malaria. Low nitric oxide bioavailability during experimental cerebral malaria is due to (i) release of free hemoglobin as a consequence of the asexual cycle of the malarial parasite, (ii) high levels of reactive oxygen species during cerebral malaria, and (iii) low levels of circulating arginine. Both free hemoglobin and reactive oxygen species scavenge nitric oxide. Due to the "arginine paradox", nitric oxide production is impaired in endothelial cells if plasma levels of arginine are low because endothelial nitric oxide synthase is coupled to the arginine transporter. Restoring nitric oxide bioavailability protects against the development of cerebral malaria by decreasing cell adhesion, vascular leak, and haemorrhage in the brain. Mechanisms that restore nitric oxide bioavailability significantly ($P<0.05$) protect recipients from the genesis of experimental cerebral malaria. However, the difficulty of administering nitric oxide gas in malaria endemic areas is a logistical hurdle. We investigated whether citrulline is an alternative adjunctive therapy for cerebral malaria. Citrulline is converted by Kidney to arginine and represents a mechanism for restoring arginine levels without activating arginases in the liver. Citrulline administered throughout the course of experimental malaria significantly ($P<0.05$) protected from development of mortality and rapidly restored arginine levels to normal. Arginine ingestion in drinking water is also effective in protecting mice from experimental cerebral malaria, but i.p. injections resulted in toxicity in the peritoneal cavity; we did not observe any toxicity with citrulline injections. We propose that citrulline be investigated as a potential adjunctive therapy for cerebral malaria.

SYM-02-04

CONNEXON ROLES IN NEUROINFLAMMATION AND VASCULAR LEAK

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Gap junctions allow direct communication and the passage of small molecules between cells, for example enabling astrocytes in the brain to form a functional syncytium. Gap junction channels consist of two connexons (or hemichannels), one contributed by each of the abutting cells, with each connexon made up of six connexin proteins. The most ubiquitous of these is connexin43, a 43kD molecule and one of 21 isoforms in the human genome. Increased connexin43 expression occurs following injury in many tissues including the CNS, leading to secondary damage with spreading waves of depression triggering cell death in neighboring uninjured tissues. In addition, the opening of unopposed hemichannels causes cellular oedema and mediates release of molecules that propagate cellular death messages such as ATP, NAD(+) or glutamate. It is possible to significantly reduce the spread of damage after injury by transiently suppressing the induction of connexin proteins that form hemichannels, or by preventing hemichannel opening. We have demonstrated further that connexin43 is upregulated in vascular endothelial cells following retinal ischemia, causing endothelial cell oedema and breach of the blood-brain barrier. Localised inflammation (astrocytosis) results with subsequent neuronal (retinal ganglion cell) loss. Systemic delivery of connexin mimetic peptides that block hemichannels reduced vascular leak, and so inflammation, to give almost total neuronal sparing. Vascular dropout (or die back) is also a feature of chronic inflammatory diseases including Parkinson's and Alzheimer's diseases and macular degeneration. This seminar will discuss the role of gap junction mediated vascular degeneration in the neuroinflammatory process in both acute and chronic CNS injury. Regulation of hemichannels to reduce endothelial leak and inflammation provides a basis for functional recovery that may have application in the management of neurodegenerative diseases.

SYM-03-01

USING IPS CELLS TO STUDY AUTISM SPECTRUM DISORDERS

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Over the last decade, many genetic defects associated with autism spectrum disorders (ASDs) have been identified. However, the mechanism by which these mutations alter human neuronal development and lead to ASDs is not understood. We have used induced pluripotent stem cells (iPSCs) and genetically engineered mouse models to explore the effects of ASD-associated mutations on the function and development of the brain. We have initially focused our studies on individuals with mutations in the L-type calcium channel CaV1.2 and in the synaptic scaffolding protein, Shank-3. Mutations in CaV1.2 cause Timothy Syndrome (TS), a neurodevelopmental disorder associated with autism, and are also associated with bipolar disorder. We have found that iPSCs from TS patients have defects in calcium signaling, neuronal differentiation and dendritic arborization. Some but not all of these defects can also be observed in a mouse model of TS providing validation for the use of iPS cells to study autism and validating the mouse model of TS. We have also uncovered cardiac defects in iPSC-derived cardiomyocytes from TS patients and used these to identify a lead compound that can reverse both the cardiomycocyte and neuronal defects in TS. Mutations in Shank-3 are the main cause of neurodevelopmental defects in Phelan McDermid Syndrome (PMS) and are also associated with psychosis and schizophrenia. We have found that neurons from PMS patients have defects in synapse formation and synaptic transmission. We have also identified a treatment that can reverse these defects in-vitro. These studies are helping us to identify the cellular and molecular basis of syndromic autism and set the stage for using iPSCs to study idiopathic forms of autism and for identifying treatments for these disorders.

SYM-03-02

A CELLULAR MODEL FOR SPORADIC ALS USING PATIENT-DERIVED INDUCED PLURIPOTENT STEM CELLS

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iPierian Inc.

Amyotrophic lateral sclerosis (ALS) is an adult-onset genetically complex neurodegenerative disease marked by degeneration of upper and lower motor neurons. About 10% of cases are familial (fALS) and 90% are sporadic (sALS) with largely unknown genetic etiology. The most dominant form of pathology present across sALS patients includes TAR DNA-binding protein 43 (TDP-43, TARDBP) inclusions, aggregates, and cleavage in motor neurons yet the underlying mechanisms remain unknown. While numerous disease models have been developed for a form of familial ALS caused by mutations in the SOD1 gene, no models of sALS exist and no effective treatments that can extend the lives of patients beyond a few months are available. Reprogramming of sALS patients' fibroblasts into induced pluripotent stem cells (iPSC) and differentiation into affected neurons that show a disease phenotype could provide a cellular model for disease mechanism studies, target identification, and drug discovery for sporadic ALS. We report the reprogramming to pluripotency of fibroblasts from a large cohort of both healthy and ALS patients and their differentiation into motor neurons. We demonstrate that upper and lower motor neurons derived from multiple sALS patients show de novo TDP-43 pathology in the form of phosphorylated, intranuclear aggregates and that the aggregates preferentially occur in motor neurons. Importantly we show for the first time, that the phenotype observed in iPSC-derived neurons recapitulate pathology in postmortem tissue from one of the same patients the iPSC were derived from. Furthermore, we configured a high-content chemical screen using the TDP-43 aggregate endpoint and identified small molecule modulators. Taken together, these findings demonstrate the feasibility of patient-derived iPSC-based disease modeling and its application to drug screening for an adult onset, genetically complex sporadic disease such as ALS.

SYM-03-03

CHALLENGES FOR STEM CELLS TO FUNCTIONALLY REPAIR THE DEAF COCHLEA

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Purpose: The aim of our research is to determine whether stem cells can provide replacement neurons to the deaf cochlea after hearing loss. Replacing these dying neurons could lead to enhanced benefits with a cochlear implant for severely-to-profoundly deaf individuals. Methods: These studies are aimed at addressing several major challenges including differentiation of stem cells into functional auditory neurons in vitro, examining if these stem cell-derived neurons are electrophysiologically active and can make synapses on appropriate tissues in vitro, and whether neural function can be improved when stem cells are combined with electrical stimulation from a cochlear implant in vivo. Results: We have recently demonstrated that stem cells can be induced to differentiate into sensory neurons in vitro, using both embryonic and induced-pluripotent stem cell lines. Both stem cell types produce cells which express auditory neural proteins (n=42) and are electrically active (n=34). Furthermore, embryonic stem cell-derived neurons make synaptic contacts on peripheral (hair cells n=22) and central (cochear nucleus, n=8) tissues when co-cultured for two weeks. Our recent data show that human stem cell transplants are well tolerated in the deaf mammalian cochlea and survive and differentiate for periods of at least 8 weeks (n=7). Conclusion: The described studies use a well characterised system for proof-of-concept experiments to test the functional integration of human stem cell-derived neurons. This addresses a critical step in the development of a stem cell therapy for neural replacement, by determining whether neurons derived from stem cells can make functional connections with tissues of the peripheral and central nervous system.

SYM-03-04

CHALLENGES TOWARDS STEM CELL THERAPY FOR PARKINSON'S DISEASE

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Considering cell therapy with embryonic stem cells (ESCs) for Parkinson's disease (PD) into clinical application, formation of a graft cell-derived tumor is a major concern about safety of the therapy. We and others have reported transplantation of monkey ESC-derived neural cells or human neural progenitor cells into the brain of monkey PD models, but tumor formation in primates has never been studied. Thus, it is important to determine whether human ESCs are able to form tumors in the primate brain, and to examine the characteristics of the tumors. To answer this question, we compared the growth of cells with different stages of pre-differentiation: neural cell preparations, with or without undifferentiated ESCs. We induced neural progenitor cells from human ESC lines (KhES-1, -2) by the modified SDIA (stromal cell-derived inducing activity) method for 14 to 42 days. Then, the cells were transplanted into the bilateral striatum of monkey models of PD. In this talk, we will show that residual undifferentiated cells expressing ESC markers can proliferate as long as nine months and form tumors in the monkey brain. No signs of malignancy were found, and the tumors mainly consisted of immature neural cells with no teratomatous components. In contrast, cell preparations with sufficient maturation for 42 days did not form tumors, and survived as dopaminergic (DA) neurons proved by immunofluorescence and PET studies. In addition, the monkeys showed behavioral improvement from 3 to 12 months. We also generated DA neurons from human induced pluripotent stem cells (iPSCs) without feeder cells, and confirmed that these cells could survive as long as 6 months in the monkey brain. These results support the idea that human ESCs/iPSCs, after appropriate differentiation towards DA neurons, can be used as a source for cell replacement therapy of PD.

SYM-04-01

MOTOR NEURON DEGENERATION IN SPINAL MUSCULAR ATROPHY

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Spinal muscular atrophy (SMA) is one of the most important neurological causes of childhood death and disability. Recessively inherited inactivating mutations in the survival motor neuron 1 (SMN1) gene lead to loss of lower motor neurons in the spinal cord. The central conundrum of SMA biology is how loss of function of a protein with basic functions in RNA biology, specifically the assembly of the splicing machinery, leads to specific motor neuron degeneration. Evidence from mouse and fly models suggests that SMN may have specific functions in the neuromuscular system, distinct from its canonical function in ribonucleoprotein maturation, and that disruption of mRNA splicing is not a primary pathogenic mechanism. Furthermore, gene therapy experiments in mouse models demonstrate that SMN has its predominant action on the neuromuscular system in early postnatal life, during a discrete phase of development, suggesting that the timing of therapy to increase SMN levels might be crucial. The extent to which SMN is required for the maintenance of motor neurons in later life and whether augmenting its levels could treat degenerative motor neuron diseases, such as amyotrophic sclerosis, is an important area for further research as clinical trials of molecular and genetic therapies which increase SMN levels are now underway.

SYM-04-02

NEWLY IDENTIFIED FAMILIAL ALS GENES PROVIDE FRESH INSIGHTS INTO PATHOGENIC MECHANISMS

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Many neurodegenerative diseases include familial and sporadic forms. The familial forms offer a unique opportunity to identify molecular defects that are relevant to both familial and sporadic disease. Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder that is caused by the progressive degeneration of motor neurons. Familial ALS accounts for approximately 10% of ALS cases with the remainder occurring as apparently sporadic disease. To date, the only proven causes of ALS are gene mutations that lead to the death of motor neurons. ALS is genetically heterogeneous. Recent ALS gene discoveries have implicated common disease mechanisms including RNA metabolism and protein degradation pathways such as the ubiquitin-proteasome system and autophagy. Despite these discoveries, our genetic data suggest that many ALS genes remain to be identified. The goal of our research is to investigate known ALS genes as well as identify new ALS genes in large cohorts of Australian ALS families and apparently sporadic cases. This is being performed using a combination of traditional genetic linkage and sequencing coupled with next-generation sequencing (NGS) strategies. We are also implementing user-friendly bioinformatics pipelines for analysis of large-scale exome sequencing data for unravelling the genetic basis of ALS. 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 capture and sequencing provides the best opportunity yet to identify novel ALS genes. The identification of these novel ALS genes will give insights into the biological basis of both familial and sporadic motor neuron degeneration, allow development of new disease models and provide new targets for therapeutic development.

SYM-04-03

A CENTRAL AND EARLY ROLE FOR DISRUPTION OF COPII-MEDIATED ER-GOLGI TRAFFICKING IN AMYOTROPHIC LATERAL SCLEROSIS

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Cu/Zn-superoxide dismutase (SOD1) is misfolded in familial and sporadic Amyotrophic Lateral Sclerosis (ALS), but its pathobiology remains unclear. Nonetheless, endoplasmic reticulum (ER) stress is a key pathogenic process, but it remains unclear how ER stress is triggered or linked to other disease mechanisms. Here we show that SOD1 is not present in the ER in neuronal cells expressing ALS-SOD1 mutants (mSOD1), revealing that ER stress is triggered from the cytoplasm. Instead, mSOD1 binds to coat protein-II complex (COPII), which mediates vesicular budding from the ER. This in turn blocks ER-Golgi trafficking, leading to ER stress, Golgi fragmentation, aggregation and apoptosis. COPII co-localized with inclusions in motor neurons from SOD1G93A mice and ALS patients, suggesting disruption to COPII machinery and aberrant interaction at ER exit sites. Elevated expression of COPII protected against transport inhibition, ER stress, inclusions and apoptosis, strongly linking COPII-vesicular transport to pathology. We conclude that mSOD1 disrupts ER-Golgi transport by inhibiting COPII-vesicular traffic from the ER, thus triggering ER stress. These findings link several ALS pathologies into a single mechanism occurring early in disease. Hence, dysfunction to basic cellular functions combines with unique characteristics of motor neurons, rendering them vulnerable to ALS pathophysiology.

SYM-04-04

ENDOSOME-LYSOSOME SYSTEM DYSREGULATION IN AMYOTROPHIC LATERAL SCLEROSIS

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Purpose: Cytoplasmic accumulation and aggregation of misfolded proteins, notably SOD1, TDP-43 and FUS, is associated with selective killing of motor neurons in amyotrophic lateral sclerosis (ALS). Cellular responses to protein misfolding including endoplasmic reticulum stress and autophagy occur early in ALS pathophysiology, however the molecular mechanisms triggering these stress pathways remain elusive. We previously showed aberrant secretion of misfolded SOD1 and secretory pathway defects in ALS. Here, we characterise the primary cellular mechanism of secretion of ALS-linked proteins and related endosome-lysosome system (ELS) pathway abnormalities in ALS. Methods: Secretory vesicles were purified from conditioned medium of motor neuronal NSC-34 cells and rat cerebrospinal fluid using ultracentrifugation and characterised by Western blotting, protease protection assay and immuno-electron microscopy. Expression and localisation of ELS markers was examined in normal or mutant SOD1, TDP-43 or FUS stably transfected NSC-34 cells, transgenic $SOD1^{G93A}$ mice and sporadic ALS patients using Western blotting and immunohistochemistry. ELS transport was measured using EGF uptake assay in transfected NSC-34 cells. Results: We demonstrated that SOD1 and TDP-43 are normally secreted by exosomes into neuronal culture medium and cerebrospinal fluid. ALS-linked SOD1 and TDP-43 mutants were significantly depleted from exosomes, corresponding with accumulation of endocytic small Rab GTPases (Rab5, Rab7 and Rab11) and abnormally enlarged early endosomes in transfected NSC-34 cells. These enlarged endosomes were defective for endocytic transport as shown by reduced uptake of EGF. Accumulation of endocytic Rab proteins and enlarged early endosomes occurred in spinal motor neurons, but not astrocytes or microglia, of presymptomatic transgenic mutant $SOD1^{G93A}$ mice and spinal cords of sporadic ALS patients. Conclusions: We propose that failure to secrete mutant SOD1 and TDP-43 may underlie their cytoplasmic accumulation in motor neurons in ALS and that associated slowing of endosome transport may explain other pathogenic mechanisms implicated in ALS such as lysosomal activation and autophagy.

SYMPOSIUM 5 – FAONS SYMPOSIUM I: STRESS AND DRUG ADDICTION

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SYM-05-01

DISSECTING THE CENTRAL STRESS RESPONSE USING SITE-SPECIFIC GENETIC MANIPULATION IN ADULT MICE

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The biological response to stress is concerned with the maintenance of homeostasis in the presence of real or perceived challenges. This process requires numerous adaptive responses involving changes in the central nervous and neuroendocrine systems. When a situation is perceived as stressful, the brain activates many neuronal circuits linking centers involved in sensory, motor, autonomic, neuroendocrine, cognitive, and emotional functions in order to adapt to the demand. However, the details of the pathways by which the brain translates stressful stimuli into the final, integrated biological response are presently incompletely understood. Nevertheless, it is clear that dysregulation of these physiological responses to stress can have severe psychological and physiological consequences, and there is much evidence to suggest that inappropriate regulation, disproportional intensity, or irreversible activation of the stress response is linked to the etiology and pathophysiology of anxiety disorders and depression. Understanding the neurobiology of stress by focusing on the brain circuits and genes, which are associated with, or altered by, the stress response will provide important insights into the brain mechanisms by which stress affects psychological and physiological disorders. The CRF/Urocortin system is fundamental in orchestrating the organisms stress response. In addition to its hypophysiotropic action, CRF integrates the behavioral responses to stress within the CNS. This lecture will present an integrated multidisciplinary approch from gene to behavior using mouse genetics and animal models aim in elucidating the contribution of different members of the CRF/Urocortin family of peptides and receptors to the central stress respone. Defining the contributions of known and novel gene products to the maintenance of stress-linked homeostasis may improve our ability to design therapeutic interventions for, and thus manage, stress-related disorders.

SYM-05-02

HYPOTHALAMIC MECHANISMS PROMOTING AND PREVENTING DRUG SEEKING

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The hypothalamus,in particular the tuberal hypothalamus, serves an important role in regulating the reinstatement of drug seeking in animal models. Here I will discuss experiments showing that lateral portions of the tuberal hypothalamus are important for promoting reinstatement and relapse to drug seeking, an action linked to hypocretin/orexin neurons. In contrast, medial portions of the tuberal hypothalamus are important for promoting extinction of drug seeking, an action linked to prodynorphin neurons. These hypothalamic mechanisms interface with both ventral striatal circuits for appetitive motivation and stress-responsive midline and intralaminar thalamic regions. They suggest a complex interplay between central 'stress' circuits and those that promote relapse to drug seeking.

SYM-05-03

BEHAVIORAL MANIPULATION OF US SPECIFIC RECONSOLIDATION TO ERASE EMOTION MEMORY

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Previous studies have shown that exposure to a conditioned stimulus (CS) initiates CS-specific reconsolidation of learned fear. During the reconsolidation window, the learned fear memory can be updated with extinction training. However, the procedure is specific to the reactivated memories. Various CSs may be associated with an aversive event in daily life. Here, we introduce a new procedure that targets all CSs associated with fear memory. Using fear conditioning, we found that presentation of a lower-intensity unconditioned stimulus (US) alone rendered all CS associations with that US susceptible to disruption by extinction training during reconsolidation in both rats and humans. Moreover, extinction training for one of the CSs 10 min after reactivation of the US disrupted the fear response to all of the CSs. Furthermore, to investigate whether US-triggered reconsolidation is a selective process or whether exposure to a US-eliciting fear renders any aversive memory labile, we paired two distinct USs (i.e., electric shock and noise) with two distinct CSs (CSelectric shock and CSnoise), respectively. Either USelectric shock or USnoise exposure was followed by extinction training 24 h later, and the fear response to the CSelectric shock and CSnoise was tested. We found that disrupted fear responding only occurred in response to the CS associated with the specific US, leaving the fear response to the CS that had been paired with the other US intact. Thus, the disruption of reconsolidation was selective to the activated US. These findings suggest that this modified extinction strategy may lead to new therapeutic approaches for anxiety disorders. Key Words: unconditioned stimulus; reconsolidation; extinction, retrieval, memory.

SYM-05-04

STRESS, CULTURE, AND ALCOHOLISM

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It is well known that stress leads to an increase in eating and drinking behaviors. Many Korean people under stress try to relief the stress by eating spicy (hot) food, which is very popular, and they enjoy it even though it causes pain. Furthermore, it is thought that spicy foods have an addictive tendency. Based on these assumptions, we found that subcutaneous administration of capsaicin significantly increased pro-opiomelanocortin mRNA expression in the rat brain (n=10) and concluded that spicy food could increase activity of the central opioid system. (p=0.001) On the other hand, many previous studies have found that alcohol drinking increases neuronal opioid activity in the brain. Therefore, we investigated whether drinking behavior is associated with a preference for spicy food. Our results showed that subcutaneous administration of capsaicin in C57BL/6 mice (n=5 vs 6) decreased alcohol intake significantly in an animal study (p=0.026). In addition, we found that those who had dependence on alcohol (n=135) preferred spicy food more than that of normal control subjects (n=97) in a human study (p=0.018), and found that naltrexone significantly decreased the stimulative effect from acute alcohol drinking in a group of social drinkers with preference for spicy food (n=13) (p=0.001) but not in a group with no preference for spicy food (n=13) in another human study. Therefore, it is assumed that preference for spicy food affects not only alcohol drinking behavior but also the treatment response when treating alcoholism. It is suggested that the central opioid neuronal systems are involved in these relationships.

SYM-06-01

INHIBITION, SPIKE THRESHOLD, AND STIMULUS SELECTIVITY IN PRIMARY VISUAL CORTEX

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In most sensory areas of the brain, the local circuit transforms its input to generate a novel representation of the external world. The sensory receptive fields that are produced represent the visible result of a neuronal computation. Orientation selectivity in the primary visual cortex (V1) is a receptive field property that is at once simple enough to make it amenable to experimental and theoretical approaches, and yet complex enough to represent a significant transformation in the representation of the visual image. As a result, V1 has become an area of choice for studying cortical computation and its underlying mechanisms. Simple cells in layer 4 of V1, unlike their thalamic inputs, are sensitive to contour length, direction of motion, size, depth, and most famously, orientation (Hubel and Wiesel, 1962). As striking as the cortical transformation is, the resulting changes in the visual representation can be measured experimentally in quantitative detail and described with mathematical precision. Few areas outside V1 have been described so comprehensively and on so many levels, from basic neuronal response properties, to anatomical connectivity, to functional architecture. Since the cerebral cortex is thought to be the primary locus of high-level processes such as perception and cognition, V1 has become the most widely-studied proxy for cortical computation. Not only does it lend itself to questions of how its sensory transformation contributes to visual perception; the emergence of orientation selectivity is the model system for studying how cortical circuitry performs a neuronal computation. Here I will consider how the receptive field properties of the simple cells in the cat V1 likely arise. I will demonstrate that almost every receptive field property of V1 simple cells fall directly out of Hubel and Wiesel's feedforward model when the model incorporates realistic neuronal and synaptic mechanisms, including threshold, synaptic depression, response variability, and the membrane time constant.

SYM-06-02

ORIENTATION AND DIRECTION SPECIFICITY IN THE CAT VISUAL CORTEX - DISSECTING THE INTRACORTICAL NETWORK

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Based on the hypotheses of Hubel & Wiesel (1962) that explained the origin of orientation and direction specificity in the visual cortex and following the suggestion of Sillito (1975) that inhibitory mechanisms might be significantly involved we were interested in the specific contributions of intracortical excitatory and inhibitory processing. Cortical inactivation was microiontophoretically induced with GABA in functionally identified sites at determined distances from single cells recorded in the cat visual cortex. During focal inactivation of identified small regions of the cortical network we observed significant changes in orientation and direction specificity of the recorded cells. In studies carried out over more than 15 years we elucidated the contributions of intracortical horizontal processing to orientation and direction selectivity in cat areas 17 and 18 and found strong evidence that in both areas intracortical excitatory and inhibitory interactions play a crucial role in the generation of both properties. It appears most probable that cortical orientation selectivity derives not solely from thalamocortical feedforward inputs but from intracortical sharpening due to excitatory and inhibitory signal processing. Cortical direction selectivity appears largely dependent on short-range lateral excitatory and inhibitory interactions occurring within a single receptive field subregion. In addition, the receptive field specificities in area 18 are not merely dependent on input from area 17 but reflect de novo computations in the intrinsic circuitry of area 18. Our inactivation studies provide evidence for the involvement of the following intracortical processes in the generation of orientation and direction specificity: - suppression of non-optimal orientations and directions as a result of intracortical cross-orientation and iso-orientation inhibition, respectively; - amplification of responses to optimal stimuli by iso-orientation excitation; - control of cortical amplification via iso-orientation inhibition. The work was supported by the German Research Fondation (DFG) and performed together with John M. Crook and Zoltán F. Kisvárday.

SYM-06-03

MULTIPLE MECHANISMS – SUBCORTICAL AND CORTICAL – IN THE GENERATION OF STRIATE CORTICAL ORIENTATION SELECTIVITY

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In the classical model proposed by Hubel & Wiesel, a striate cortical simple cell derives its orientation selectivity from the excitatory convergence of a number of geniculate afferents with circular receptive fields (RFs). However, a number of studies have now shown that responses of most cells in the retina and dorsal lateral geniculate nucleus (LGN) of a number of species exhibit some degree of orientation sensitivity. Drawing an analogy with human colour vision, where just three broadly tuned cone pigments with different peak sensitivities code for the narrowly tuned spectral sensitivities and a broad range of chromatic preferences seen cortically, it is proposed that orientation is coded in the periphery in the activity of cells that are only broadly tuned for orientation, but form the basis for cortical orientation selectivity. In support of this, we find the following in experiments done on anaesthetised and paralysed cats: (1) Non-specific inhibition acting on an LGN cell with responses that show an orientation bias can markedly increase the orientation selectivity to nearly match the selectivity of typical cortical cells. (2) LGN cells and striate cells with overlapping RFs show a higher degree of coherence in their spike trains if their orientation preferences are matched. (3) Single geniculate afferents in striate layer 4 show orientation preferences matching that of the orientation domain that they terminate in. (4) A model that assumes non-specific intracortical inhibition acting on a geniculate input biased for a stimulus orientation can explain not only the typical narrow tuning for orientation seen in target striate cells, but also their other response properties, such as the selectivity for spatial frequency and length of stimuli.

SYM-06-04

Abstract unavailable at time of printing

SYM-07-01

ABOLISHMENT OF BURST-FIRING-MEDIATED EXCITABILITY IN THALAMIC NEURONS AND ABSENCE SEIZURES BY A NOVEL T-TYPE CALCIUM CHANNEL BLOCKER

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The pharmaceutical therapies available for the treatment of epilepsy are few and are often associated with pharmaco-resistance and significant side-effects. The Genetic Absence Epilepsy Rats from Strasbourg (GAERS) absence epilepsy model displays a functional missense mutation in the Cacna1h (Cav3.2) T-type calcium channel gene. The R1584P mutation correlates with seizure expression and increases both CaV3.2 rate of recovery from inactivation and charge transference during bursting in a splice-variant specific manner (Powell et al., 2009, J Neurosci 29:371). Examining acute thalamic brain slices from epileptic animals we have identified two distinct burst-firing alterations in the GAERS model compared to non-epileptic controls. GAERS reticular thalamic nucleus (RTN) neurons display an enhanced oscillatory burst-firing in a frequency-dependent manner as a result of Cav3.2 channel activity. Further, GAERS ventrobasal thalamic (VB) neurons require a greater magnitude hyperpolarizing current injection stimulus in order to generate rebound bursts as the result of an enhanced basal Ih current. We hypothesize that sustained burst activity from the RTN drives overactive rebound bursting in VB neurons leading to a compensatory increase in Ih as a mechanism of suppressing VB burst-firing and stabilizing thalamocortical excitability. Z944, a novel small organic, high affinity T-type calcium channels blocker (EC50 ~ 100 nM), completely suppresses pro-epileptic burst-firing in the RTN. Furthermore, oral administration of Z944 to GAERS attenuates absence seizures and also reduces the duration of seizures. While its effects in other brain areas are not yet known, we predict that the potent efficacy of Z944 occurs as a result of its ability to attenuate T-type calcium channel-mediated burst-firing in the thalamus.

SYM-07-02

REDUCED PYRAMIDAL NEURON DENDRITIC ABORIZATION UNDERLIES ENHANCED EXCITABILITY IN A NAVβ1 MODEL OF SEVERE EPILEPSY IS SENSITIVE TO DISEASE MECHANISM BASED THERAPY

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Early-onset epileptic encephalopathy (EOEE) is a severe form of epilepsy with developmental regression that is frequently treatment resistant. We develop a mouse model of the disease based on a human mutation in the β1 sodium channel accessory subunit. The mouse shares behavioural phenotypes and pharmacosensitivity with humans and other genetic rodent models of the disease. Analysis revealed an increase in pyramidal neuron action potential firing due to an increase in electrical resistance. A reduction in dendritic arborization of mutant neurons is likely to underlie the change in electrical properties. The antiepileptic drug, retigabine, was used to target the cellular electrical deficit and was effective in reducing action potential firing and the threshold at which thermogenic seizures occurred in the mouse model. These results suggest a novel mechanism of disease genesis in genetic epilepsy and demonstrate that disease mechanism based therapies may be a useful treatment strategy.

SYM-07-03

ENVIRONMENTAL STIMULATION MITIGATES EPILEPSY PROGRESSION: A NOVEL THERAPEUTIC STRATEGY

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Purpose: Increasing evidence implicates environmental influences as modulators of epileptogenesis. Environmental enrichment (EE), whereby laboratory animals are housed with running wheels, tunnels, and other stimulating objects, is neuroprotective in several models of neurological disorders. We assessed whether EE affected epileptogenesis using the kindling model of acquired epilepsy, and the Genetic Absence Epilepsy Rats from Strasbourg (GAERS) model of generalized epilepsy. Methods: Beginning at 3 weeks of age, male Wistar rats or GAERS were housed in environmentally enriched (EE) or impoverished housing (IH) conditions. For the kindling study, rats were implanted with a stimulating electrode into the amygdala, and were kindled twice daily. Seizure severity and duration were measured for each seizure during kindling and compared between EE and IH. For GAERS, at 8 weeks of age, rats were implanted with EEG recording electrodes, and underwent 24 hour weekly recordings thereafter. Seizure frequency was assessed and compared over time between groups. Results: In both models, EE induced anti-epileptogenic effects. For kindling, EE increased the number of stimulations required to reach the different stages of kindling ($p=0.05$), and also reduced mossy fibre sprouting. In GAERS, EE delayed the onset of epilepsy: at 9 weeks of age, only 3 out of 8 rats had developed seizures, whereas in the IH group, all rats had seizures. As time progressed, the number of seizures experienced was less in the EE group, and at the end of the study (20 weeks) EE rats were having 50% less seizures than IH ($p<0.001$). Conclusion: Environmental stimulation, in the form of enrichment, retards the development of both acquired and genetic forms of epilepsy. The fact that contrasting types of epilepsy are similarly influenced by enrichment may indicate that the mechanisms underlying this neuroprotection are common effects of the environment.

SYM-07-04

TARGETING TAU PHOSPHORYLATION WITH SODIUM SELENATE TO IMPACT ON EPILEPSY

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Purpose: Common pathological processes may be involved in the development of neurodegeneration and epilepsy. One of the pathological hallmarks of neurodegeneration are neurofibrillary tangles composed of hyperphosphorylated tau protein, which have also been identified in epileptogenic pathologies. PP2A is the major phosphatase in the brain that removes phosphate residues from tau, thereby stopping its ability to self-assemble into tangles. We had previously discovered that sodium selenate is a specific activator of PP2Aand therefore hypothesized that it might have efficacy in inhibiting seizures. Methods: We tested the effects of sodium selenate in multiple models of acquired epilepsy, including 6 Hz stimulation induced seizures (n=6, group), Amygdala kindling rat models of acquired TLE (n=6), and epileptogeneis models using amygdala kindling rats (n>12).Results: Sodium selenate treatment resulted in a dose dependent protection against 6 Hz stimulation induced seizures, with increasing protection over time following dosing and significantly reduced the total number and duration of seizures following PTZ injection. Treated Amygdala kindled rats had significantly reduced seizure duration compared with controls. Utilizing amygdala kindling rats as a model of epileptogensis, we found that PP2A activity was significantly decreased and phosphorylation of tau, were increased in brains of kindling rats compared with controls. Treatment induced significantly slower progression of the behavioural class of seizures during kindling, and the total and primary electrographic seizure durations, compared with controls. Conclusion: Sodium selenate suppresses seizures in a variety of rodent models via boosting PP2A activity and reducing Tau phosphorylation. This potentially represents a novel approach to epilepsy treatment.

SYM-08-01

NEURAL CORRELATES OF COGNITIVE TRAINING IN OLDER ADULTS

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Cognitive training for older adults has received increasing recognition for its potential to slow and/or delay cognitive decline leading to dementia. To-date, however, little is known about the neural correlates of cognitive training. For example, are brain changes suggestive of brain neuroplasticity? Do associated brain changes suggest compensatory or restorative mechanisms and are brain changes likely to be influenced by pre-existing cognitive, clinical and demographic variables? This symposia talk will examine the existing literature pertaining to neuroimaging outcomes in association with cognitive training in healthy older adults, those 'at risk' of dementia, and those with established dementia. It will also present some preliminary MRI data pertaining to a healthy brain ageing cognitive training trial.

SYM-08-02

TRAINING THE MULTITASKING BRAIN

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Despite the immense processing power of the human brain severe 'bottlenecks' of information processing are revealed when individuals attempt to perform two, even simple, tasks at once - multitask. Under such conditions, performance of one or both tasks is impaired relative to when the tasks are performed in isolation (Pashler, 1994) and performance on the second task improves as the time between the tasks increases. Such dual-task limitations/costs can be observed at both perceptual (e.g., attentional blink, AB) and decision-making (e.g., psychological refractory period, PRP) stages of information processing. It has previously been shown that some dual-task costs can be virtually eliminated after extensive training (e.g. Schumacher at al., 2001). However, the neural basis for these training effects has not been elucidated. In addition, whether training benefits all types of dual-task limitations and the extent to which training transfers between distinct stages of processing is still hotly debated. Here I will present time-resolved functional magnetic resonance imaging data which shows that a network of frontal regions including posterior lateral prefrontal cortex, superior medial frontal cortex, and bilateral insula, is associated with the capacity-limits of perceptual encoding and decision-making. Further to this I will argue that training reduces multitasking costs by increasing the processing efficiency of the posterior lateral prefrontal cortex rather than by funnelling information away from this bottleneck region. Finally, I will demonstrate that training has distinct influences on multitasking limitations at different stages of processing with training transfer only being observed for perceptual encoding.

SYM-08-03

EFFECTS AND CORRELATES OF MEMORY TRAINING IN THE ADULT BRAIN

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Neuronal mechanisms underlying the well-documented behavioral effects of cognitive training are mostly unknown. We studied effects of 2-months memory training on short-term brain structure changes in older adults (mean age = 61) by means of magnetic resonance brain imaging. There were two training groups, a healthy community sample and a memory clinic outpatient sample with subjective memory impairment, and a control group. Brain structure changes following intervention were evaluated using three different longitudinal multi-modal MR-imaging suites: FreeSurfer, FSL, and Quarc. Results: We found increases in cerebral cortical thickness and white matter integrity in healthy elderly undergoing memory training, compared with controls. The healthy training group also showed longitudinal increases in hippocampal volume compared with controls. Finally, we found increases in cortical grey matter volumes in the patient sample. The training-related grey matter changes were comparable in magnitude and extent compared to healthy subjects groups, and stood in contrast to cortical decreases in passive controls. Greater pre-training hippocampal volumes predicted benefit from intervention in the patient training group, but we found no apparent training effect on hippocampal volume change. Conclusion: Structural magnetic resonance imaging can be used to assess effects of cognitive training in the adult human brain. MR-volumetry pre-intervention might also predict treatment outcomes. Training-related brain changes may not be restricted to healthy aging; increases in cortical volume were found in a memory clinic sample undergoing workup for cognitive impairment. The stability and duration of the reported effects needs further investigation.

SYM-08-04

TIMECOURSE OF COGNITIVE, STRUCTURAL AND FUNCTIONAL RESPONSES TO COGNITIVE BRAIN TRAINING IN AT-RISK ELDERLY

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Purpose: Growing evidence suggests that Cognitive Brain Training may help to augment, support and optimize cognitive function in later life. However, the specific mechanisms that underlie successful transfer from training to cognitive gains remain unclear. Specifically, we do not know: 1) the dose-responsiveness of training-induced cognitive gains, 2) the durability of cognitive gains and the rate by which specific gains may wane after cessation of training, and 3) training-induced neurobiological adaptations. Methods: In a randomised, double-blind, longitudinal, active-controlled trial, 80 cognitively-intact older adults (mean age 71.8 years) underwent 36 hours of either a computerised multidomain cognitive training program or an active control intervention. Cognitive performance was assessed at five time points: baseline, after 3 weeks and 3 months of training, as well as 3 weeks and 3 months after cessation of training. In addition, a subsample underwent multimodal MRI scans at the first three time points. Results: Compared to the active control group, subjects in the cognitive training group showed significant improvement in visual and verbal memory, response inhibition and processing speed. Cognitive gains were largely maintained 3 months after training cessation. The timecourse of training-induced changes differed by cognitive domains. Similarly, changes to resting-state brain networks were more sensitive to training than structural brain changes. Conclusions: Cognitive training may assist in the maintenance of cognitive function in the aged, but community-based implementation will need to consider how different cognitive domains follow different timecourses. Use of booster sessions and personalisation of training may be required. Neuroimaging is starting to reveal some of the underlying neuroplastic changes.

SYM-09-01

NOVEL MULTI TARGET NEURORESTORATIVE ANTI ALZHEIMER DRUGS WITH CELL CYCLE ACTIVITY

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The role of iron in Alzheimer's Disease (AD) lead us to develop non-toxic, lipophilic propargylamine, brain permeable multifunctional compounds with iron chelation, cholinesterase and monoamine oxidase inhibitory moieties properties for AD. We investigated the neuroprotective effects of M30 in transgenic APP/PS1 aggregation and plaqueβ(Tg) mice model of AD, including its regulatory on A areas, holo-APP expression levels and APP-processing mechanisms and cognitive abilities, since the 5' untranslated region of APP mRNA has a functional iron-responsive element. Comprehensive behavioral batteries determined at 10 month of age revealed that transgenic APPswe/PS1 mice given M30 during that period were protected from cognitive impairments in a verity of tasks of spatial learning and memory retention, working memory, learning abilities, anxiety level, and memory for the novel food and nesting behavior. Non treated transgenic mice remained impaired in all of these cognitive tasks/ domains. M30 markedly reduced the levels of holo- APP and β-CTF in the frontal cortex, hippocampus and parietal cortex of APP/PS1 treated mice compared to non-treated animals. Coordinately, the levels of cerebral amyloidogenic Aβ peptide in soluble and insoluble fractions and the number of Aβ plaques and dimeric Aβ contents in the frontal cortex, hippocampus and parietal cortex were decreased in M30-Tg mice as compared to non-treated animals. Regarding aspects of cell signaling pathways associated with Alzheimer's disease (AD) pathology, M30 activated HIF,enhanced the levels of phospho-AKT and phospho- glycogen synthase and attenuated Tau phosphorylation. The neurorestorativeβkinase (GSK)-3 activity of these drugs has been identified as being associated with neurogenesis and activation of HIF (hypoxia inducing factor), which regulates a whole battery of neurotrophins including GDNF, BDNF, VEGF, erythropoeitin and induces cell cycle arrests Go/G1, resulting in neuronal differentiation. This is complimented by their ability to covert human embryonic stem cells into neurons in cellcutlres.Our findings provide support for long-term M30 or its derivatives therapy, as primary strategy for treatment of AD.

SYM-09-02

NOVEL THERAPEUTIC APPROACHES FOR THE NEURODEGENERATIVE DISEASES

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A common feature of the neurodegenerative diseases is the deposition of insoluble misfolded proteins. In Alzheimer's disease (AD) the amyloid-β peptide (Aβ) is the principle constituent of amyloid plaques while α-synuclein is the major component of Lewy bodies the pathological hallmark of Parkinson's disease (PD). While large aggregated protein deposits are the most obvious pathological feature of these diseases, recent interest has focused on smaller soluble oligomeric forms of these proteins as the likely cause of neurodegeneration. In many instances it is co-factors or post-translational modifications that drive the formation of oligomeric species. Aβ will react with metal ions to form toxic aggregates, while α-synuclein will react with peroxynitrite to form toxic oligomers. We have developed therapeutic strategies to inhibit these reactions. These include the MPAC technology designed to inhibit Aβ metal interactions, with the lead compound (PBT2) progressing into clinical development. Mechanistic studies show that in addition to inhibiting Aβ/metal interactions PBT2 is able to chaperone the metal into cells thereby activating protective signaling cascades. This discovery prompted us to investigate the potential of metal based therapeutic agents for the neurodegenerative diseases. We identified the metal bis(thiosemicarbazonato) complexes as ideal scaffolds whose structures can be manipulated to fundamentally change the properties these compounds possess. With some forms of these complexes acting as metal delivery agents initiating neuroprotective signaling pathways, while other complexes deactivate reactive nitrogen species and show beneficial therapeutic activity in multiple animal models of PD and amyotrophic lateral sclerosis.

SYM-09-03

STRUCTURAL CHARACTERIZATION FOR THE DESIGN OF ALZHEIMERS DISEASE DIAGNOSTICS AND THERAPEUTICS

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Purpose: Alzheimer's disease (AD) is the most common form of dementia in humans and is related to the accumulation of the amyloid-β peptide and its interaction with metals (Cu, Fe and Zn) in the brain. The aggregation of Aβ is deemed the major culprit in AD and although the amyloid plaque is the main pathological hallmark of AD, small molecular weight oligomers of Aβ are also thought to exert the neurotoxic effects. The Aβ peptide and in particular the disaggregation of Aβ oligomers, is therefore a valid therapeutic target in the treatment and prevention of AD. Methods: Structural information on the Aβ peptide required to facilitate the development of therapeutics is limited however due to the propensity of Aβ to aggregate and form a distribution of oligomeric states. Here we partially resolve this bottleneck by utilizing the Im7 immunity protein and a shark IgNAR single variable domain antibody as efficient scaffolds for the stabilization of Aβ in combination with complex formation using the Aβ specific WO2 Fab. Results: This protein engineering approach allows us to report the atomic resolution crystal structures of Aβ metal binding region (1) and a tightly-associated Aβ dimer, with paired dimers forming a tetramer in the crystal structure (2). Conclusion: Our structures correlate with independently observed features of small non-fibrillar Aβ oligomers and Aβ-metal complexes, reveal conserved elements consistent with residues and motifs predicted as critical in Aβ folding and oligomerization, thus potentially providing a model system for the design of AD diagnostics and therapeutics. 1. Nisbet, R.M. et al (2012) Acta Crystallographica D, under revision. 2. Streltsov, V.A. et al (2011) J Neurosci 31, 1419.

SYM-09-04

Abstract unavailable at time of printing

SYMPOSIUM 10 – FAONS SYMPOSIUM II: DEVELOPMENT OF CORTICAL CIRCUITS

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SYM-10-01

GLOBAL AND CROSSMODAL EFFECTS OF EARLY ENVIRONMENTAL STIMULATION ON NEURAL CIRCUIT FORMATION IN THE SENSORY CORTICES

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Sensory experience has long-lasting effects on the developing nervous system. In rodents, whisker trimming during development leads to alterations in the function of the cortical barrel circuit and to behavioral deficits later in life. To study the earliest effects of whisker deprivation on cortical development, we investigated the electrophysiological properties of glutamatergic and GABAergic synapses in mice whisker deprivation (WD) from birth. Recording from layer 2/3 pyramidal neurons of the primary barrel and visual cortices in acute brain slices prepared from control and WD mice at P14, we observed that WD from birth reduced the frequency of miniature excitatory postsynaptic currents (mEPSCs) in both barrel and visual cortices without significant effects on inhibition. The cross-modality of the effect of WD on the visual cortex prompted us to explore the effects of other sensory deprivation paradigms that have been demonstrated to affect cortical circuitry during development, such as dark rearing (DR). We found that in mice dark reared from birth, the frequency of the mEPSCs and spontaneous firing rates in both visual and barrel cortices were significantly reduced at P14. In ongoing work, we are exploring the molecular and circuit mechanism underlying this global and crossmodal change in the sensory cortices. Enriched environment (EE) rearing is a well-established paradigm for increasing neural activity in vivo through natural sensory stimulation. Previous work from our laboratory showed that EE-rearing from birth increased the level of glutamatergic and GABAergic synaptic proteins in the mouse forebrain (He et al., J. Neurosci., 2010). Consistently, EE-rearing increased the frequency of both miniature excitatory and inhibitory postsynaptic currents in barrel and visual cortices during the second post-natal week. Importantly, environmental enrichment rescued the reduction of mEPSC frequency induced by WD or DR. These results underscore the importance of neonatal natural stimulation on neural circuit development.

SYM-10-02

MOLECULAR MECHANISMS INVOLVED IN REGULATION OF NEURONAL MIGRATION, CELL AUTONOMOUS AND NON-CELL AUTONOMOUS

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Proper laminar organization of the cerebral cortex requires the orchestrated motility of neurons from their place of birth to their final destination. During brain development, excitatory neurons are born in the ventricular and subventricular zones and migrate along radial glia to form defined layers in the cerebral cortex. On the other hand, inhibitory neurons originate from a different area, as they are born in the ganglionic eminences, and migrate tangentially to the cerebral cortex. Once they arrive there, they then move to the proper laminar position via the radial route and in this position the neurons integrate into the circuitry and form proper connections. Purpose: Our research is aimed to identify genetic pathways involved in the cell autonomous and non-cell autonomous regulation of neuronal migration. Methods: We have identified candidate molecules involved in regulation of cell autonomous mechanisms using an educated guess approach, non-cell autonomous molecules were identified using a non-biased expression. We have examined the roles of these molecules in migration of pyramidal neurons using in utero electroporation. Results: Our results indicate the role of novel molecules in regulation of neuronal migration. Conclusions: Improper neuronal migration may result in a wide range of diseases, including brain malformations, mental retardation, Schizophrenia, and autism. Our results demonstrate that our knowledge in regard to these processes is as of yet, still limited.

SYM-10-03

MOLECULAR MECHANISMS OF BARREL CORTEX DEVELOPMENT

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Purpose: In the mouse primary somatosensory cortex (barrel cortex), thalamocortical axons (TCAs) from individual thalamic barrelloids are almost entirely confined to single barrel clusters, followed by arrangement of cortical layer IV neurons into barrel hollows and septa during early postnatal stage. Furthermore, spiny stellate neurons in barrel hollows form unidirectional dendrite toward barrel TCAs during first postnatal week for efficient synapse formation. However, the molecular mechanism of unique dendrite development is not known. Methods: We first searched for genes expressed in the barrel cortex using Allen Brain Atlas. As a consequence, we identified Btbd3, BTB/POZ domain containing 3, is expressed exclusively in barrel hollow. BTB/POZ domain mediates homomeric/heteromeric dimerisation and its family member, Abrupt, controls dendrite formation in Drosophila. Therefore, we tested Btbd3 function in spiny stellate dendrite using in utero electroporation and shRNA construct. Results: Suppression of Btbd3 is efficient to generate more numbers of primary dendrite. We also revealed that initial expression of Btbd3 is induced by TCA innervation that suggests correct synapse formation control gene expression in postsynaptic neuron. We further tested whether this induction of Btbd3 expression is controlled by neuronal activity. However, no difference of Btbd3 expression was observed in neuronal activity suppressed somatosensory cortex. We next performed microarray analysis from neuronal activity suppressed barrel cortex and isolated molecule, which has BTB/POZ domain in its internal sequence. Conclusion: These results suggest that dendrite formation of spiny stellate cells is controlled by dimerization of both molecules induced by neuronal activity independent Btbd3 expression and neuronal activity dependent gene expression. Taken together, our results provide molecular framework of activity dependent/independent circuit development.

SYM-10-04

EARLY STRESS EVOKES AGE-DEPENDENT BIPHASIC CHANGES IN HIPPOCAMPAL NEUROGENESIS, EPIGENETIC REGULATION OF THE BDNF GENE, AND COGNITIVE BEHAVIOR

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Early stress experience evokes persistent maladaptive changes, however it remains poorly understood whether it results in any potentially adaptive consequences. We show that the early stress of maternal separation elicits a continuum of responses ranging from transiently adaptive effects observed soon after early stress, with a transition into maladaptive consequences in middle-aged life. Early stress animals exhibit enhanced hippocampal neurogenesis, decreased repressive histone methylation at the Bdnf IV promoter along with enhanced Bdnf expression, and improved performance on the stress-associated Morris Water Maze task during postnatal life and in young adulthood. Strikingly, opposing changes in these very same measures of structural plasticity, epigenetic regulation of Bdnf IV expression, concomitant with significant impairments on both stress-associated and non-emotive learning tasks were observed in middle-aged ES animals. Furthermore, early stress animals show distinct changes in the hippocampal transcriptome in young adulthood and middle-aged life. Long duration, adult-onset treatment with the antidepressant amitriptyline attenuated the maladaptive neurogenic and cognitive changes observed in middle-aged life in early stress animals. Our study provides novel insights into the short and long-term consequences of early stress, demonstrating biphasic, as well as unique, age-dependent changes at the molecular, epigenetic, neurogenic and behavioral level. These results indicate that early stress experience endows animals with a transient adaptive advantage in stressful environments, but across a life-span is associated with long-term deleterious effects. This raises the possibility that the trade-off for short-term adaptive effects may be the hastening of an age-dependent compromise of hippocampal plasticity and cognitive function.

SYM-11-01

CRE-DEPENDENT PSEUDORABIES VIRAL APPROACHES FOR EXAMINING POLYSYNAPTIC CONNECTIONS

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Neurotropic viruses, such as pseudorabies virus (PRV), have been used to map connectivity of neural circuits. Following injection of such a virus into a specific site, the virus spreads in a temporally specific manner through the neural circuits connected to that region. For example, injecting PRV into a kidney in rats and then examining the location of PRV-infected neurons at various times (e.g., 2-5 days) post-injection, it is possible to map the hierarchical organization of neurons connected to that kidney. One limitation of this general approach is that the pathway by which higher-order neurons become infected is often unclear. A way around that issue is to utilize a recombinant strain of PRV in which one reporter gene is replaced by another in a Cre-dependent manner in combination with localized expression of Cre produced via delivery with a viral vector. Furthermore, by using gene promoters selective for different populations of neurons in a heterogeneous brain region, it is possible to delineate the circuits involving specific subgroups of neurons. The use of this versatile approach to describe the neural circuitry involving the C1 neurons in the ventrolateral brainstem involved in autonomic regulation will be presented.

SYM-11-02

MAPPING THE CONNECTOME OF FUNCTIONALLY-IDENTIFIED NEURONS

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One of the central tenets of neuroscience is that the structure of the brain underpins its function: physical connections between neurons, in the form of synapses, are responsible for the functional coupling that underlies neural computation. In order to understand the factors that determine, firstly, the behaviours of networks of neurons that subserve discrete functions and, ultimately, the behaviour of the whole brain, we must first develop tools that will enable us to create maps of neuronal connectivity: the connectome. A number of recently developed anatomical and molecular techniques have provided researchers with a first generation of tools that can be used to probe the connectome. Of particular interest to our laboratory is the development of genetically modified neurotropic viruses that selectively spread in anterograde or retrograde directions across networks of synaptically linked neurons. Although still in its infancy, this approach has already provided other investigators with novel insights into the architecture of local, regional and brain-wide neural networks. However, to date, these techniques have been restricted to populations of neurons defined by anatomical or phenotypic criteria. Although there is correlation between phenotype and function in many brain regions, expression of a distinct phenotype is rarely exclusive to any functional class of neuron. This prevents current connectomic circuit-tracing techniques from reaching their potential to bridge the gap between form and function. In the current paper I will describe ongoing experiments that combine electrophysiological recordings with the delivery of macromolecule and genetic payloads to functionally identified cells in deep brain structures. Our strategy, in combination with genetically engineered virus variants developed elsewhere, will enable researchers to identify and manipulate the pre- or post-synaptic targets of single neurons functionally identified in vivo.

SYM-11-03

CELL-SELECTIVE LENTIVIRUSES ENABLE MAPPING OF THE PROJECTIONS OF SPECIFIC NEURONAL CELL GROUPS THROUGHOUT THE CNS

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Development of techniques using lentiviral vectors for phenotype-specific neuronal transfection in vivo have enabled functional and anatomical experimentation on select populations of neurons. The data presented here detail the projections of C3 adrenergic neurons induced to express green fluorescent protein behind a promoter selective to Phox2 expressing cells. This technique has enabled the tracing of C3 efferent fibres throughout the rat central nervous system (CNS). Combining this technique with immunohistochemistry also allows for identification of vesicular transporters at release sites, and the phenotype of target nuclei. C3 neurons, located in the dorsomedial medulla, constitute one of three known adrenergic nuclei in the rat CNS. C3 terminal fields were observed in over forty different CNS nuclei, spanning all levels of the spinal cord, and various medullary, mesencephalic, hypothalamic, thalamic, and telencephalic nuclei. The highest densities of C3 axon varicosities were observed in Lamina X and the intermediolateral cell column of the thoracic spinal cord, the dorsomedial medulla, ventrolateral periaqueductal gray, dorsal parabrachial nucleus, periventricular and rhomboid thalamic nuclei, and paraventricular and periventricular hypothalamic nuclei. Moderate or sparse projections were observed in many catecholaminergic and serotonergic nuclei, the area anterior and ventral to the third ventricle, Lamina X of the cervical, lumbar and sacral spinal cord, and various hypothalamic and telencephalic nuclei. The anatomical map of C3 projections detailed in this survey takes the first steps towards developing a functional framework for this nucleus.

SYM-11-04

IN VIVO FUNCTIONAL CONNECTOMICS USING FMRI

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Functional magnetic resonance imaging (fMRI) has become the method of choice for studying functional interactions within and between large-scale brain networks in living humans. These interactions are typically quantified as a statistical dependence between regional activity measures. This dependence, broadly referred to as functional connectivity, occurs in either spontaneous or stimulus-evoked dynamics, and can be studied within specific functional circuits, spatially extended ensembles of brain regions, or at the level of whole-brain networks. This talk will overview some of the major approaches used in the field and highlight recent findings demonstrating that fMRI-based functional connectomics can provide novel insights into brain disorders, the genetic basis of brain organization, and the neural basis of individual differences in cognitive abilities. Limitations of current methodologies and challenges for the field will also be discussed.

SYM-12-01

THE DEVELOPING BRAIN: PATHWAYS THROUGH ADOLESCENCE

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Magnetic resonance imaging (MRI) has made it possible to trace the normal trajectory of brain development in children and adolescents. The Child Psychiatry Branch of the U.S. National Institutes of Health has acquired over 1500 MRI scans in a longitudinal study of typically developing children and adolescents. Key findings from this study that will be discussed included demonstration of an inverted U-shaped trajectory of brain growth. Gray matter peaks in early adolescence, an important period in the development of many major psychiatric disorders such as schizophrenia, while white matter continues to increase into the early twenties. Brain volumes peak earlier in females. Findings using structural equation modeling in a subset of 600 MRI scans obtained from twins, siblings, and singletons showed that relative contributions of genetic and environmental factors to variance in cortical thickness changes over development, with late-maturing areas becoming more heritable with age. Brain regions which have functional interactions show greater structural correlation over development and increased connectivity as described with graph theory, consistent with findings from functional studies. These findings provide a basis for understanding how developmental trajectories may be affected in neurodevelopmental disorders.

SYM-12-02

DRUGS, STRESS AND INFLAMMATION: EXPLAINING PROGRESSIVE BRAIN CHANGES IN SCHIZOPHRENIA

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In schizophrenia the view since the 1980's was that brain pathology begins during foetal development and is static. This suggested that identification of abnormalities in patients with established disorder would provide markers for early identification of at-risk individuals. However, the available neuroimaging evidence does not support such a notion. Rather, the evidence indicates that there is neuroprogression in psychotic disorders (Pantelis et al, Schizophr Bull, 2005). Such progressive change is also consistent with the clinical picture of psychosis. While progressive brain changes over the initial phase of illness are consistent with the observed clinical deterioration, there is a continuing debate about their validity, and the nature of the underlying neuropathology. Criticism has been leveled at the methods, possibility of artefact, impact of therapeutic as well as illicit drugs, diagnostic heterogeneity, and effects of factors like stress and HPA-axis function. Methods: In a series of cross-sectional and longitudinal imaging studies involving over 500 subjects at all stages of psychosis, across the stages of illness from pre-psychosis onset, we have examined some of these potential confounds. Results: We have demonstrated that progressive brain changes in psychosis occur particularly in temporal lobe (STG, medial temporal), insula, and prefrontal cortex, starting from before illness onset and over the first 4 years of illness. I will consider the influence of potential confounds that may explain these changes (esp. cannabis, stress and the effects of medication). Conclusions: Progressive brain changes begin from before illness onset and are most apparent over the first few years of illness. Factors such as drug use, the impact of stress and medication need to be taken into account in understanding these changes. The role of neuroinflammation will be considered.

SYM-12-03

EARLY INTERVENTION IN PSYCHOSIS: WHAT CAN BE LEARNED FROM ANIMAL MODELS

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Schizophrenia (SCZ) originates in early neurodevelopment yet manifests symptomatically after puberty, raising the possibility that early intervention can be effective in preventing /delaying symptom onset. Studies in high risk individuals have been encouraging but given their diagnostic, ethical, clinical and methodological limitations, remains a challenge. Animal neurodevelopmental models of SCZ are invaluable for investigating this question. Purpose: To demonstrate prevention of SCZ-like brain structural and behavioral abnormalities using the prenatal immune stimulation model that is based on the known association of prenatal infection and increased risk for SCZ. Methods: Pregnant rats were injected on gestational day 15 with the viral mimic polyriboinosinic-polyribocytidylic acid (poly-I:C) or saline. Longitudinal in-vivo structural imaging and behavioral testing were conducted on the male and female offspring between early adolescence (PND35) and adulthood. In other experiments, offspring of polyI:C- and saline-treated dams received the atypical antipsychotic drugs (APD; clozapine (7.5mg/kg) or risperidone (0.045mg/kg) in different developmental windows and underwent behavioral testing and imaging at adulthood. Results: Prenatal polyI:C exposure led to aberrant postnatal brain development as manifested in structural abnormalities in the hippocampus, the striatum, the prefrontal cortex and lateral ventricles, as seen in SCZ. The specific developmental trajectories were region-, age- and sex-specific, with females having delayed onset of pathology. Brain pathology was accompanied by development of behavioral abnormalities phenotypic of SCZ with same sex difference. APD treatment at different developmental windows prevented brain structural and behavioral abnormalities most effectively if given during the behaviorally asymptomatic period of adolescence (PND 35-47). Conclusion: prenatal insult leads to progressive postnatal brain pathology, which gradually gives rise to "symptoms"; atypical APDs can prevent both brain and behavioral pathology; earlier intervention is more effective.

SYM-12-04

INDICATED PREVENTION IN PATIENTS AT INCIPIENT RISK OF DEVELOPING PSYCHOSIS

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While universal or selective prevention would be the ideal approach for preventive strategies in psychotic disorders, indicated prevention is the current focus that has the best prospects of success. Indicated prevention means intervention at a point when symptoms have appeared but these symptoms, while they may provoke help-seeking and produce functional impairment, have not yet technically allowed the person in need of care to cross the diagnostic threshold for the traditional psychiatric diagnoses of schizophrenia and other related psychotic disorders. It has been well recognised that the need for care long precedes the capacity to assign one of the major psychiatric diagnoses. Conversely fear of over diagnosis and treatment has stimulated controversy in this frontier area of psychiatric reform and progress. Much of this relates to the equation of treatment with drug therapy - a non -sequitur. Most of these patients need psychosocial care as a first line therapy and in any case there is a need for RCT's to guide the evidence based treatment of people in this stage of illness. A clinical staging approach is a potential framework to guide this research and clinical strategy. The full set of RCT's will be reviewed and an evidence-based approach will be presented.

SYM-13-01

SEROTONERGIC REGULATION OF ENTERIC NERVOUS SYSTEM DEVELOPMENT/PLASTICITY

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Neuroplasticity in the enteric nervous system (ENS) is critical during early postnatal life. Although the ENS must be operative at birth to enable the bowel to support oral feeding, enteric neurons continue to be born and integrated into an already functioning ENS. Because enteric neurons are generated in a phenotype-dependent order, early-born neurons coexist with neuronal precursors. The neurotransmitters of neurons generated first may thus affect the fates of later-generated neurons. Serotonergic neurons are among the earliest born in the ENS. In mice, the last enteric serotonergic neurons are born before the birthdays of CGRP-expressing or dopaminergic neurons commence. In vitro, 5-HT promotes development of total, CGRP-expressing, and dopaminergic neurons. In vivo, the total number of enteric neurons as well as dopaminergic and CGRP-expressing neuronal subsets are deficient in mice that lack tryptophan hydroxylase 2 (TPH2; TPH2KO mice), which and thus are unable to synthesize neuronal 5-HT. Similar defects are found in the ENS of mice that express an autism-associated mutant form of the serotonin transporter (SERT.G56A) that is overly active and prematurely terminates actions of released 5-HT. In contrast, these ENS deficiencies are not found in TPH1KO mice, which lack mucosal 5-HT. Gastrointestinal transit is slow in TPH2KO and SERT. G56A-expressing mice; however, their abnormal motility may be due to their reduced numbers of total and/or specific phenotypes of enteric neuron or to deficient serotonergic neurotransmission. Through 5-HT4 receptors, 5-HT is able to induce neurogenesis, even in the adult ENS. Given that environmental stimuli, including psychosocial and infectious events, can affect serotonergic neuronal activity, serotonergic regulation of neuronal development/plasticity may mediate long-lasting changes in the properties of the ENS. Such effects could contribute to the pathophysiology of GI disorders experienced later in life, such as irritable bowel syndrome and inflammatory bowel disease.

SYM-13-02

MECHANISMS UNDERLYING NEURONAL CELL DEATH IN COLITIS

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Inflammatory bowel diseases (IBD) are chronic relapsing and remitting conditions that cause alterations in gut function, even when inflammation has been controlled. Structural and functional changes the enteric nervous system are thought to be responsible for the abnormalities in secretion and motility associated with IBD, particularly those that persist. The mechanisms underlying inflammation-induced enteric neuron death are not well understood. Neuronal apoptosis has been described early in inflammation, but the events triggering this or leading to cell death were not known. Using in vivo models of experimental colitis in mice that cause loss of enteric neurons, we investigated the mechanisms responsible. Neurons were lost in vivo and in vitro by activating enteric neuronal purinergic P2X7 receptors, which cause the release of ATP. These receptors are in a signaling complex with pannexin-1 (Panx1) channels, Asc and caspase(s). Inhibiting P2X7 receptors, Panx1, Asc or caspase activity prevents enteric neuronal cell death. Inflammation-induced impairments in inhibitory enteric neuromuscular transmission in the colon may contribute to the long-term alterations in colonic motility that persist following the resolution of inflammation. We found a 35% reduction in neuronal nitric oxide synthase neurons during experimental colitis in mice. Decreased nitrergic innervation in experimental colitis was associated with a persistent decrease in electrical field stimulation-evoked colonic relaxations and enhanced EFS-stimulated contractions. Panx1-mediated neuroprotection during colitis maintained normal colonic relaxations and contractions following colitis, suggesting that inhibiting Panx1-mediated neuronal death during colitis could be therapeutically useful, by preserving functional innervation and the control of colonic motility. In conclusion, P2X7 receptor activation of neuronal Panx1 underlies enteric neuron death and subsequent development of the abnormal gut motility in experimental colitis.

SYM-13-03

ROLE OF TRP CHANNELS IN THE MECHANICAL HYPERSENSITIVITY OF EXTRINSIC SENSORY NEURONS THAT PROJECT TO THE GUT

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Pain and discomfort originating from the gastrointestinal tract are common and often debilitating complaints of patients with functional gastrointestinal disorders. In patients with Irritable Bowel Syndrome (IBS), a preceding bout of gastrointestinal inflammation or infection can trigger long term neuronal hypersensitivity, resulting in chronic pain and discomfort. In order to understand how these symptoms are generated in the gut and transmitted to the central nervous system we need to understand the fundamentals of extrinsic sensory afferent nerve function. First, what types of sensory afferents are involved and what do they signal? Secondly, what is the molecular basis of their sensory transduction? Thirdly, how does this change in disease? In particular this talk will focus on the role of Transient Receptor Potential (TRP) channels in the gastrointestinal tract, how they contribute to specific afferent subtype function and how this changes in acute and chronic visceral pain. We have shown that distinct members of the TRP channel family, including TRPA1, TRPV4 and TRPV1 are key contributors to visceral nociception. It is clear from these studies that TRP channel expression varies between different subtypes of afferent neuron, depending on their reputed function. This is underlined by their contribution to chemosensory and mechanosensory signalling and their ability to interact with numerous inflammatory and immune mediators. However, these channels contribute differently to inflammatory pain and chronic visceral pain. Indeed, the same channel can contribute via different mechanisms to alter afferent function at different time-points. Understanding the mechanisms underlying the neuroplasticity displayed by afferents, the channels/receptors underlying their function and the interaction of these channels/receptors with inflammatory and immune mediators holds promise for future treatments of visceral pain.

SYM-13-04

ENTERIC NERVOUS SYSTEM AS A THERAPEUTIC TARGET

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Inflammatory bowel disease (IBD) patients suffer from chronic diarrhoea, intestinal bleeding and abdominal pain affecting the quality of life. Although considerable progress has been made in the understanding of the pathophysiology of IBD in recent years, treatment still concentrates on suppression of symptoms rather than an effective cure. Thus, investigation of novel therapies for the treatment of IBD is crucial. Gastrointestinal functions are controlled by the enteric nervous system embedded into the gut wall. Biopsies from IBD patients, and samples of intestine from animal models, have provided evidence of enteric neuronal death and axonal damage of enteric neurons in intestinal inflammation. Previous studies in the animal models of IBD demonstrated that axonal damage and neuronal death occurring during the acute stage of inflammation in the ileum and colon contribute to triggering mechanisms of persistent neuronal hyperexcitability. Invasion of the immune cells into the enteric nervous system innervating the gut wall is predictive of IBD recurrence. Thus, structural changes in the enteric nervous system are prognostic of disease progression and may play a role in IBD recurrence. This suggests that enteric neurons may be viable targets to decrease disease severity. Therapeutic potential of novel anti-inflammatory, neuroprotective and cell-based therapies for the treatment of enteric neuropathy associated with Inflammatory Bowel Disease will be discussed.

SYM-14-01

PHYSIOLOGY AND DYNAMICS OF THE MICROTUBULE-ASSOCIATED PROTEIN TAU DURING NEURONAL DEVELOPMENT AND MAINTENANCE

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The microtubule-associated tau proteins are enriched in the axon and are thought to play an important role in regulating microtubule dynamics during neuronal development and maintenance. Dysfunction of tau is associated with a class of diseases collectively called tauopathies, which include Alzheimer's disease as the most frequent neurodegenerative condition of the elderly. In addition to its binding to microtubules, tau has been implicated in mediating interactions with other cellular components and contributing to signal transduction mechanisms, which all appear to be important in maintaining neuronal plasticity. We show using quantitative live cell imaging of photoactivatable constructs that tau dynamically interacts with microtubules and reduces microtubule dynamics in neurons. We demonstrate that tau's aminoterminal projection domain binds to the neuronal membrane cortex, which causes trapping of tau at the distal neurite (Brandt et al., 1995, Weissmann et al., 2009). Recently we identified the calcium-regulated plasma membrane associated protein Annexin A2 (AnxA2) as an interaction partner of tau and show that a disease-associated tau mutation (R406W) abolishes the AnxA2-tau interaction. Loss of binding is associated with decreased trapping at the tip of neurites and increased length fluctuations during process growth (Gauthier-Kemper et al., 2011). We propose that tau acts as a membrane cytoskeleton linker and functions in morphing neurons during health and disease. Pathological effects of tau mutations can be caused by impaired membrane binding, which involves a functional interaction with AnxA2 as a membrane-cytoskeleton linker, or by effects on regulating microtubule dynamics. References: Brandt R et al. (1995) Interaction of tau with the neural plasma membrane mediated by tau's amino-terminal projection domain. J. Cell Biol. 131:1327-1340. Weissmann C et al. (2009) Microtubule binding and trapping at the tip of neurites regulate tau motion in living neurons. Traffic 10:1655-1668. Gauthier-Kemper A et al. (2011) The frontotemporal dementia mutation R406W blocks tau's interaction with the membrane in an annexin A2-dependent manner. J. Cell Biol. 192:647-661.

SYM-14-02

GSK3 REGULATES VESICULAR TRAFFICKING VIA THE LIPID KINASE PI4K2A: IMPLICATIONS FOR MOOD DISORDERS

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GSK3 is an important regulator of healthy brain development and function, with defects in GSK3 regulation contributing to mood disorders and schizophrenia. In order to identify pathways downstream of GSK3 vital for maintaining healthy brain function, we performed a bioinformatic search for novel GSK3 substrates using an updated GSK3 phosphorylation consensus sequence. This identified 147 candidates known to be phosphorylated in vivo, including a surprisingly high number of proteins associated with vesicular trafficking. Several of these were confirmed as bona fide GSK3 substrates using a combination of phosphoproteomics, in vitro kinase assays and phosphospecific antibodies. We have focused on one of these substrates, the lipid kinase PI4K2A. GSK3 targets 2 sites within the N-terminal region of PI4K2A, which can be inhibited by the mood stabilizer lithium. Phosphorylation of PI4K2A promotes binding to the AP-3 complex for trafficking to the lysosome where it is degraded. Blocking phosphorylation by mutagenesis or pharmacological inhibitors of GSK3 decreases AP-3 binding and trafficking to the lysosome, thus stabilizing PI4K2A levels. Importantly, the abundance of cargo proteins, such as transferrin receptor, is also increased in cells expressing non-phosphorylatable mutants of PI4K2A by reducing their degradation by the lysosome. Accordingly, the rate of transferrin trafficking is increased in cells expressing the non-phosphomutant of PI4K2A, but decreased in cells expressing a phosphomimetic form. We are currently investigating the effect GSK3-mediated phosphorylation of PI4K2A has on the stabilization and surface expression of neurotransmitter receptors in neurons and its subsequent affect on neurotransmission. Meanwhile, RNAi-mediated knockdown of PI4K2A levels in Drosophila neurons impairs their circadian rhythm and activity levels, consistent with elevated GSK3 activity and homeostatic symptoms experienced by human mood disorder patients. Together, these observations suggest that deregulated signaling between GSK3 and PI4K2A could contribute to defects in vesicular trafficking and neurotransmission in mood disorders.

SYM-14-03

AXON DEGENERATION IN TRAUMA AND DISEASE: A CRITICAL ROLE FOR THE NEUROFILAMENTS

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Purpose: The axonal cytoskeleton plays an important role in the neural response to injury and neurodegenerative disease, with typical pathologies including the loss, misprocessing, accumulation or compaction of certain cytoskeletal components. We are particularly interested in the role of the neurofilament triplet proteins, comprised of light (NF-L), medium (NF-M) and heavy (NF-H) chains which are part of the type IV intermediate filament family. Using in vitro models we have investigated the role of neurofilament proteins in traumatic brain injury and site-specific excitotoxicity. Method: Cortical neurons were cultured from C57/Bl6 or mice with a knockout of the neurofilament-L gene (NFL-KO) and grown on glass coverslips or in compartmented microfluidic chambers. Complete axonal transection was carried out using a goniotomy knife (15 DIV, four injuries per coverslip). Cultures were fixed and examined at 24hrs post injury. For excitotoxicity studies neurons at 10DIV were exposed to 100μM kainic acid (18hrs) in the soma compartment. Axonal fragmentation was determined from phase contrast images of axons and MAP2 immunocytochemistry (N=5). Results: Following localised axotomy, NF-L KO neurons demonstrated reduced APP accumulation in damaged neurites as well as a significant reduction in the number of axons regenerating (4.79+/-0.58 sprouts) compared to controls (10.47+/-1.11 sprouts) ($p<0.05$). Interestingly, however, axon degeneration after somal excitotoxicty was significantly reduced in cultured cortical neurons derived from NFL-KO mice (15.3%+/-2.1 SEM) compared to controls (41.3%+/-8.5 SEM) ($p<0.05$). Conclusion: These studies demonstrate that whilst the family of type IV intermediate filaments may be capable of compensating for the absence of NF-L with the axon, this core triplet protein is required for axonal regeneration. These studies also indicate a differential role for neurofilament proteins in mediating responses to trauma and mechanisms implicated in neurodegenerative disease.

SYM-14-04

TROPOMYOSINS ARE KEY REGULATORS OF DIFFERENT ACTIN FILAMENT POPULATIONS THAT CONTROL NEURONAL MORPHOGENESIS AND FUNCTION

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Changes in the cellular architecture of eukaryotic cells are driven by the dynamics of the underlying actin cytoskeleton. The dynamic properties of actin filaments are determined by tropomyosins, a family of actin-associated proteins. In neuronal cells, products from three tropomyosin genes (TPM1, 3 and 4) are found. We investigated the tropomyosin isoform-specific role of TPM1 (TmBr1, TmBr2, TmBr3) TPM3 (Tm5NM1) and TPM4 (Tm4) gene products in developing neurons as well as the impact of Tm5NM1 overexpression in the adult mouse brain. Our work has identified distinct actin filament populations in neuronal growth cones and dendritic spines that are defined by the association of different tropomyosin isoforms. The overexpression of different tropomyosins in B35 neuroblastoma cells and primary cortical neurons results in altered neuritogenesis. While overexpression of products from any of the TPM genes induces the formation of neurites in B35 neuroblastoma cells, tropomyosins differentially impact on the extension and branching of neurites. Tm5NM1 and TmBr2 are the only products to promote neurite extension whereas TmBr3 and Tm4 selectively lead to a pronounced increase in neurite branching. The increase of branching in TmBr3 and Tm4 overexpressing B35 cells is associated with an increase in growth cone size and number of filopodia along these neurites, and increased expression of the actin filament-bundling protein fascin and the neuronal marker microtubule-associated protein MAP2c. Overexpression of Tm5NM1 in the adult mice, which localises to the postsynaptic compartment of central nervous system neurons, results in excitotoxicity and increased sensitivity to the seizure inducing drug pentylenetetrazole. Our data suggest a fundamental role for different actin filament populations in regulating neurite outgrowth and synaptic function.

SYM-15-01

NEUROBIOLOGY OF X-CHROMOSOME LINKED INTELLECTUAL DISABILITY, EXTREME GENETIC HETEROGENEITY, UNEXPECTED MUTATION PLEIOTROPY AND SEX (MALE AND FEMALE) BIAS

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Human X-chromosome represents about 5% of the human genome and ~3% of the human exome. It contains ~836 protein-coding genes (of ~1187 known genes, excluding pseudogenes). Over the past 20 years a significant effort has been put into the identification of X-chromosome disease-causing DNA sequence variation, making the X one of the best studied human chromosomes. Of the protein-coding genes 13% (~113) genes have been implicated (published and unpublished data) in various forms of syndromic and non-sydromic intellectual disability (ID). Mutations on the X chromosome are estimated to address about 15% of genetically determined ID and as such at least partly explaining the ~30-60% excess of males with ID. In addition to coding mutations we also investigate non-coding and regulatory region involvement in ID. I will present an up-to-date overview of the X-chromosome sequence variation in intellectual disabilities and how this summarised data is helping us to identify additional X-chromosome regions likely to be implicated (or not) in intellectual disability as well as redefining the role of some known X-linked ID (XLID) loci. I will also discus examples of how XLID gene identification is informing us about the underlying (molecular and cellular) biology of learning and memory and touch on some examples of XLID in males as well as XLID limited to heterozygous mutant females (with hemizygous mutant males being unaffected carriers, i.e. PCDH19 spectrum disorder). I will point to the remaining challenges of ID gene (estimated to be > 1-2 000 genome-wide) identification as well as to the genome-wide relevance of the X-chromosome experience.

SYM-15-02

FGF8 SIGNALLING REGULATES TELENCEPHALIC MIDLINE DEVELOPMENT AND FORMATION OF THE CORPUS CALLOSUM

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The corpus callosum is the principal telencephalic commissure and forms the largest axonal tract in the brain of all placental mammals. During its initial formation, the corpus callosum grows bilaterally through a structure known as the telencephalic midline, which has become highly evolved to facilitate the correct navigation of callosal axons into the opposite hemisphere. Human mutations in Fibroblast growth factor receptor (FGFR)1 and FGFR2 genes have been implicated in developmental absence (or agenesis) of the corpus callosum and midline defects, however, the precise role of FGF signalling in callosal and telencephalic midline development is poorly understood. To address this, we characterised the expression profile of murine Fgf signalling molecules in this system, and used in vivo gene knockdown and overexpression paradigms to probe their function. In particular, these analyses show that the secreted ligand Fgf8 and its downstream signalling effectors regulate a sequence of events that are critical for telencephalic midline and corpus callosum development. Initially, Fgf8 signalling is required for tissue patterning of the telencephalic midline, whereby early perturbation of Fgf8 signalling in the telencephalon leads to a gross loss of midline tissue and holoprosencephaly. Then following initial patterning of this region, Fgf8 signalling is further required for the specification of a population of primordial astrocytes, known as the midline zipper glia. Disruption of Fgf8 and its downstream signalling targets in this cell population results in a critical failure of the telencephalic hemispheres to fuse, leading to callosal agenesis. Importantly, this is the first functional description of the phenomenon of interhemispheric fusion and how it relates to subsequent corpus callosum development and its pathologies.

SYM-15-03

THE TUBULIN GENE FAMILY AND NEURODEVELOPMENTAL DISEASE

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Tubulins are a large family of a proteins that make up components of the microtubule cytoskeleton. Microtubules plays a key role in a myriad of cellular processes during brain development, including the generation, migration and differentiation of neurons. Individual tubulin genes were first implicated in neurodevelopmental disease following the positional cloning of an ENU induced mutation in Tuba1a (S140G) in the mouse mutant Jenna. This mouse presented with disruptions in the laminar architecture of the hippocampus and cortex, accompanied by deficits in hippocampal dependent behaviour. The phenotypic similarity of this mouse mutant with existing models of neurodevelopmental disease (Dcx, Lis1), led to the discovery that de novo mutations in TUBA1A cause lissencephaly in humans. Since this finding additional genetic studies have shown that mutations in the β-tubulin gene TUBB2B causes asymmetric polymicrogyria and that mutations in TUBB3 cause an ocular motility disorder. Most recently TUBA1A and TUBB2B have also been implicated in autism spectrum disorders. Here we report that mutations in an overlooked tubulin gene, TUBB5, cause microcephaly with structural brain abnormalities. We show that Tubb5 is expressed in neurogenic progenitors in the mouse and that its depletion in vivo peturbs the cell cycle and alters the position of migrating neurons. We report the occurrence of three microcephalic patients with de novo mutations in TUBB5 (M299V, V353I and E401K). These mutant proteins, which affect the chaperone-dependent assembly of tubulin heterodimers in different ways, disrupt neurogenic division and/or migration in vivo. These results provide novel insight into the functional repertoire of the tubulin gene family, and expands the spectrum of the tubulinopathies to include TUBB5.

SYM-15-04

A NOVEL BASIS FOR THE DEVELOPMENT OF INTELLECTUAL DISABILITY IN DOWN SYNDROME

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Down Syndrome (DS) is a human genetic disorder which results from an extra copy of human chromosome 21, and this condition is detected in 1 in 700 live births. All patients diagnosed with DS suffer some form of intellectual disability, and current studies indicate that the altered expression of genes within the triplicated chromosome can negatively impact on brain development. We have identified a previously understudied gene, known as eurl, to be expressed during brain development, and our functional studies indicate that eurl controls the production and maturation of neurons during mouse brain development. Strikingly, we also find that eurl can influence the ability for neurons to form dendritic spines (membranous protrusions which constitute their contact points with other neurons, and which are the morphological correlates for memory and learning). Taken together, these studies demonstrate the validity of our approach to identify eurl as a gene that controls brain development, and provides a novel perspective on the contribution of a previously uncharacterised gene to the neurological deficits observed in patients suffering Down Syndrome.

SYM-16-01

MODULATING EFFECT OF 'CALMING' ODOURS ON STRESS, AGGRESSIVE BEHAVIOUR, AND GENE EXPRESSION IN INSECT BRAINS

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Purpose: Stressful situations trigger aggressive behaviour in all animals, including honeybees, where aggression is directed towards potential predators and is triggered by the alarm pheromone iso-amyl-acetate (IAA). This study aimed to investigate modulatory effects of odours on stress-related aggressive behaviour in bees, using the odour Praescent™, a mixture of hexanol, hexenal, and alpha-pinene. Methods and Results: A Petri-dish assay (n=12) using two bees and a dummy treated with IAA showed that short-term (5 min) exposure to Praescent significantly reduces aggression towards the dummy. When bees were kept in cages for 48 hours with IAA, Praescent or IAA+Praescent present (n=3 per treatment), the long-term exposure to Praescent also reduced aggressive behaviour. Furthermore, the brains of the long-term exposed bees showed significant changes in expression of candidate genes involved in regulating aggressive behavior, including DOPA-decarboxylase, Octopamine receptor, and Neurexin. qRT-PCR analysis showed that 48 hour exposure to IAA resulted in down-regulation of these genes, while exposure to Praescent resulted in up-regulation. Interestingly, exposure to lavender, another calming odour known to reduce aggression and stress, did not cause any changes in gene expression, highlighting the unique properties of Praescent odour. Conclusion: Our findings suggest that Praescent acts as calming agent reducing aggressive behaviour and stress in honeybees. Exposure to Praescent appears to modify molecular mechanisms in the brain that may be linked to the control of aggressive behavior, possibly via modulation or inhibition of IAA processing in the olfactory circuits.

SYM-16-02

STRESS AND VOCAL LEARNING IN SONGBIRDS: THE EFFECTS OF GENOTYPE AND ENVIRONMENT

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Purpose: The development of the songbird brain and consequent song production is known to exhibit considerable plasticity in relation to environmental conditions. Whilst stimulation enables neural development and complex cognitive abilities to develop, environmental challenges cause stunting during periods of neural growth and reduce the capacity of animals to perform complex cognitive tasks. Vocal learning in birds offers a unique chance to test the mechanisms underlying these effects, as the neural substrates controlling song production are well defined. Methods: Here, we have tested the contribution of shared environment and genetic background to the ability to withstand the effects of environmental stress. Using a partial cross fostering experiment with breeding pairs of zebra finches in combination with a food restriction regime we quantify the effects on song production and the volumes of the key nuclei in the brain associated with song production. Pairs produced broods under control (N = 56 broods) or food stress (N = 51 broods) conditions. Results: Our results demonstrate that whilst overall brain mass is heritable, the volumes of brain nuclei associated with song production are determined by environmental conditions. For the first time we quantify the independent effects of rearing environment and genotype on the development of the brain nuclei associated with vocal learning, showing low heritability of the HVC, the key brain nucleus associated with the production of complex song repertoires. Conclusion: As a result, we suggest that exposure and response to early developmental stress may have long term consequences for lifetime fitness.

SYM-16-03

THE ROLE OF MICROGLIA IN COGNITIVE DISTURBANCE: A NEW FRONTIER IN THE NEUROBIOLOGY OF STRESS

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Our research group has determined that chronic uncontrollable psychological stress affects microglial activity within the prefrontal cortex (PFC) and, that these alterations are meaningfully related to corresponding changes in PFC regulated cognitive function. Specifically, we have observed that chronic stress induced microglial alterations are positively correlated with increases in long-term neuronal activation. We have also determined that chronic stress impairs spatial working memory, a PFC dependent function, and that the putative anti-microglial activation drug minocycline improves this impairment. Chronic stress is unlikely to provoke changes in microglia via a classical inflammatory pathway as we could find no compelling evidence of increased pro-inflammatory cytokine release (IL-1β) antigen presentation (MHC-II) or apoptosis (activated caspase-3). In exploring other potential neurobiological mechanisms, we have identified, using high resolution three dimensional reconstructions, that chronic stress provokes a unique form of microglial remodelling. Specifically, we have found that stress produces a substantial increase in microglial processes, without influencing the area occupied by the cell, a modification that effectively increases the efficiency with which the cell can make contact with its micro-environment. We have confirmed also that these changes are driven by stress induced disturbances in microglia-extracellular matrix interactions. Collectively, these results confirm that microglia play a significant role in mediating the effects of stress on the PFC and highlight a completely unexplored neurobiological mechanism through which they may accomplish this.

SYM-16-04

THE EFFECTS OF STRESS ON THE MORPHOLOGY AND FUNCTION OF THE AVIAN SONGBIRD BRAIN

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Testosterone and its estrogenic metabolites are involved in both, the developmental and seasonal acquisition of bird song. Singing of songbirds, such as the canary and the zebra finch, is controlled by brain areas interconnected in the song control system. A" key" song area is the HVC (letter based name) that controls the sequential appearance of song motor units. The canonical idea is that the hormone induced singing correlates with hormone induced plasticity of the song system, in particular of the morphology and neuron numbers of HVC. In relation, HVC neurons express androgen and estrogen receptors, ligand-activated transcription factors that mediate hormone-induced changes in the transcriptome of HVC. Next to these gonadal steroid receptors, the HVC expresses occasionally glucocorticoid and mineralocorticoid receptors. Thus, besides the gonadal steroids, stress steroid hormones might have a direct effect on the development and functionality of the song control system and the singing. Here we review such effects and compare them to those of androgens and estrogens.

SYM-17-01

BRAIN INJURY IN THE PRETERM INFANT: CAN WE IMPROVE OUTCOMES?

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Prematurity is a major cause of both morbidity and mortality, with risk being inversely related to gestational age and birth weight. VON and ELGAN studies show 20% of babies 24-0/7 to 27-6/7 weeks admitted to the NICU die before discharge; 20% have severe neurodevelopmental impairment (NDI) and an additional 20% experience moderate NDI. Major morbidities are present in 50% of school aged survivors. Poor neurodevelopmental outcomes may result from an interruption of normal development, or injury to existing tissues. The hematopoietic cytokine erythropoietin (Epo) has neuroprotective and neuroregenerative effects in the brain. Mechanisms of Epo neuroprotection include receptor-mediated, cell specific effects that occur both early and late in the healing process, and non-specific effects that also modulate the response to injury. Epo has anti-inflammatory, anti-excitotoxic, anti-oxidant, and anti-apoptotic effects on neurons and oligodendrocytes, and promotes neurogenesis and angiogenesis, which are essential for injury repair and normal neurodevelopment. Epo effects are dose-dependent, and multiple doses are more effective than single doses. In adults, complications of prolonged Epo treatment include polycythemia, seizures, hypertension, stroke, myocardial infarction, congestive heart failure, tumor progression, and shortened time to death. None of these adverse effects have been reported in Epo-treated neonates. No prospective studies of neonatal Epo treatment have reported group differences in the incidence of neonatal morbidities, including bronchopulmonary dysplasia, intracranial hemorrhage, white matter injury, retinopathy of prematurity (ROP), necrotizing enterocolitis, patent ductus arteriosus, or sepsis, but a Cochrane review found an increased risk of ROP with early treatment. This risk requires confirmation. Randomized controlled clinical trials are now underway to test the safety and efficacy of high dose Epo therapy to prevent or treat brain injury in preterm infants, still others are being planned.

SYM-17-02

GABA, HI INJURY AND SEIZURES IN THE NEWBORN BRAIN

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Hypoxic-ischemic (HI) brain injury in the neonate remains a major clinical problem worldwide. It is the most common underlying cause of neonatal seizures and there is evidence in both humans and animal models that seizures contribute to worsening brain injury. Given that over 50% of seizures in neonates are 'silent' this may be of major consequence; the dependence on clinical seizure signs in the neonatal intensive care unit (NICU) means that there is enormous risk for 'silent' seizures to go undetected and untreated in more than half of term HI babies. Despite widespread clinical use, currently used antiepileptic drugs (AEDs) do not effectively suppress neonatal seizures. Recent data suggests this may be due to the changing role of the $GABA_A$ receptor (an AED target) during normal neurodevelopment. Of greater concern however is that AEDs may cause further harm to the injured HI brain during critical periods of brain development in which GABA functions to excite neurons rather than inhibit. The lifelong consequences of HI brain injury inflict substantial burdens on families and society and urgent studies are required to develop therapies specific for the newborn brain. An understanding of normal brain development as well as the pathways involved in HI brain injury and neonatal seizures will enable more appropriate neuroprotective therapies to be implemented. Furthermore development of synergistic neuroprotective strategies in combination with therapeutic hypothermia (now part of standard clinical care in NICUs worldwide) is key to reducing brain injury and disability providing better neurodevelopmental outcomes for HI neonates.

SYM-17-03

ANTENATAL GLUCOCORTICOIDS, WHAT WE KNOW AND WHAT WE SHOULD KNOW

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Purpose: Preterm fetuses are routinely exposed to synthetic glucocorticoids and their use is associated with reduced acute neonatal morbidity and mortality. However, glucocorticoids are associated with impaired brain development and surprisingly little is known about potential synergistic interactions with adaptations to common adverse events such as hypoxia. The aim of our study was to evaluate the effects of glucocorticoids on the fetal responses to asphyxia. Methods: Preterm fetal sheep (0.7 gestation) were exposed to either sham asphyxia or asphyxia induced by 25 min of umbilical cord occlusion (UCO). 15 min post-UCO ewes received an intramuscular injection of either saline (saline+sham n=8, saline+UCO, n=8) or 12mg of dexamethasone (DEX+Sham, n=7, DEX+UCO, n=10) Fetuses were studied for a further 7 days and then euthanased for tissue collection. Results: No neural injury was observed in the DEX+sham fetuses, but seizure-like events were observed starting around 3 h, maximal around 12 h. Subcortical neural injury was observed in saline+UCO fetuses, and this was made significantly worse after DEX exposure ($p<0.005$). DEX+UCO fetuses had a 25% greater fall in cerebral blood flow (CBF) during early recovery ($p<0.001$), not associated with reduced brain activity. Seizure-like events occurred as described for DEX+sham fetuses, but there was delayed onset of UCO related stereotypic evolving seizures. Conclusion: Sympathetic mediation of post-UCO cerebral hypoperfusion appears to be exacerbated by glucocorticoids, not accompanied by further reduced brain activity. These data suggest that a potential mechanism of injury may be uncoupling of CBF and cerebral metabolism and associated hypoxia. Our data demonstrate that further research is needed to establish when and how glucocorticoids may cause injury when administered in the presence of common adverse events in utero.

SYM-17-04

PROTECTING THE NEWBORN BRAIN WITH MELATONIN

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The developing fetal brain is exquisitely sensitive to changes in oxygen availability. Reduced oxygen supply to the fetus, whether a severe acute hypoxic episode at the time of birth, so-called birth asphyxia, or chronic fetal hypoxia, as occurs secondary to placental insufficiency and intrauterine growth restriction (IUGR), are both strongly associated with perinatal brain injury and subsequent neurocognitive impairment. It is recognized that hypoxia, whether chronic or acute, induces fetal oxidative stress. Thus, we proposed that targeting oxidative imbalance during pregnancy or birth may reduce brain injury and improve newborn wellbeing after hypoxia. Melatonin was our antioxidant of choice; it directly scavengers oxygen free radicals and indirectly stimulates production of further endogenous antioxidants. Melatonin readily crosses the placenta and blood brain barrier and has no known harmful effects in the fetus or newborn. Here, we have investigated the antioxidant and neuroprotective actions of melatonin under 2 different perinatal compromise situations; i) after inducing placental insufficiency and IUGR in the 0.7 gestation fetus, we administered melatonin chronically to pregnant sheep for ~30 days, and lambs were delivered naturally at term after which we assessed newborn wellbeing over 24 h, prior to collection of the brain for histology; and ii) birth asphyxia was induced in term lambs at caesarean delivery and melatonin was administered to lambs at 2-hourly intervals for 24 h, then at 72 h we undertook magnetic resonance imaging and spectroscopy on the brains after which the brains were collected. We demonstrate that melatonin is an efficient antioxidant, reducing lipid peroxidation within the newborn brain following chronic hypoxia or birth asphyxia. Melatonin improved the wellbeing of newborn lambs and reduced brain cell death after chronic or acute hypoxia.

SYM-18-01

INVOLVEMENT OF IMMUNE RESPONSES IN PERIPHERAL NEUROPATHIES

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Peripheral neuropathies due to traumatic peripheral nerve lesion or disease are often associated with disabling neuropathic pain. Although neuro-immune communication often serves to promote recovery following nervous system insult, aberrant inflammation can contribute to the debilitating symptoms of chronic neuropathic pain. Here I will describe recent findings from my laboratory, which identify an important role for immune cells and their mediators in chronic pain following peripheral nerve injury and experimental autoimmune neuritis (EAN). In these animal models, significant T-cell infiltration is observed in the injured nerve and the dorsal root ganglia (DRG) with T-cell-deficient animals displaying reduced pain hypersensitivity. However, the precise roles of the different T-cell subsets in neuropathic pain are poorly understood. In nerve-injured rats, injection of a type 1 T-cell population producing proinflammatory cytokines reversed the decreased pain sensitivity of T-cell-deficient animals, whereas injection of a type 2 T-cell population producing anti-inflammatory cytokines attenuated pain sensitivity of immune-competent animals. Knockout mice that lack the proinflammatory cytokine interleukin (IL)-17, which is produced by a specific T-cell population, displayed significantly decreased mechanical pain hypersensitivity as compared to wild-type mice. This was associated with a reduced neuroinflammation in the injured sciatic nerves, the lumbar DRG and the dorsal and ventral horns of the spinal cord. In addition, several immunomodulatory approaches, which divert the pro-inflammatory to anti-inflammatory response, including: expansion of immunosuppressive regulatory T-cells, an active immunisation with a non-encephalitogenic myelin-derived altered peptide ligand, and transgene delivery of a naked plasmid deoxyribonucleic acid encoding the inhibitory cytokine IL-35, were found to inhibit pain hypersensitivity in nerve-injured and EAN animals. Therefore, understanding the neuro-immune crosstalk in painful neuropathies may help the development of new neuropathic pain therapeutics.

SYM-18-02

THE TOLL OF CENTRAL IMMUNE SIGNALLING: IMPLICATIONS FOR PAIN AND ITS TREATMENT

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Chronic pain is reaching epidemic proportions worldwide. Current neuronally targeted pain medications are effective in managing pain in a proportion of sufferers, but a “pain cure” remains elusive. This pain predicament warrants a significant rethink of the mechanisms underpinning the “pain generators” as there is now substantial preclinical and clinical evidence that neuronal targeted pharmacotherapies are missing a crucial foundational process - Proinflammatory Central Immune Signalling. Over nearly 3 decades an appreciation of central immune cell involvement in chronic pain initiation and propagation has accrued. Significant discoveries in the last 2 years have identified key receptor mechanisms via which this central proinflammatory response is triggered. However, a great deal of this attention has been directed towards glial contributions. It is now apparent that whilst proinflammatory glial responses are key, a myriad of other sources of inflammatory signals within the central nervous system can contribute to the pain pathology. This presentation will introduce some of the latest discoveries of the role of innate pattern recognition receptors in the pain process, discuss the complexity of the pain associated central immune signalling system, and highlight the exciting opportunities that an understanding of these proinflammatory central immune signalling “pain generators” has for the future avoidance, management and potential cures for chronic pain pathologies.

SYM-18-03

ROLES OF PROFESSIONAL AND NON-PROFESSIONAL PHAGOCYTES IN BRAIN MAINTENANCE

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An important focus of the Kipnis Lab is phagocytosis in the CNS in both health and disease. With respect to healthy function, we recently showed dependence of normal neurogenesis on proper phagocytosis. Using a liposome target-based approach to explore the identity of the dominant phagocytes in the neurogenic niches, we were surprised to find that immature doublecortin-positive neuronal precursors were active phagocytes. In vivo, ELMO1-/- knockout mice demonstrated accumulation of apoptotic corpses and poor differentiation of precursors towards neuronal fate in both neurogenic niches, demonstrating a deficit in doublecortin-specific eating while sparing phagocytosis by other cells. In summary, this work provides evidence of the significance of phagocytosis by neuronal precursors as important to healthy adult neurogenesis. Phagocytosis is emerging as a possible mediator in CNS pathology as well. Rett syndrome is a devastating neurodevelopmental disorder, characterized by severe neurological symptoms including apneas, loss of ambulation and seizures. Most cases are caused by the mutation of the gene Mecp2. Although Mecp2 is expressed in many cell types, pathology was historically attributed solely to neurons. However, astrocytes were recently shown to play a major role in pathology. Here, we demonstrate the surprising arrest of disease in Mecp2-null mice by targeting microglia, the resident mononuclear phagocytes of the brain. This is achieved by independent approaches: expression of wild type Mecp2 in mononuclear phagocytes, and by bone marrow transplantation. Both strategies in Mecp2-null mice markedly improved disease sequelae: lifespan was increased, apneas reduced, locomotor performance improved. When brains of transplanted mice were examined, robust engraftment of microglia-like cells was seen. Interestingly, Mecp-null microglia displayed significant impairment in phagocytic ability. When phagocytosis was blocked, phenotypic rescue was abolished. These data suggest the importance of phagocytosis in CNS health and pathology, as well as possible new clinical implications for the treatment of Rett syndrome by targeting immune function.

SYM-18-04

IMMUNE REACTIVITY AND INFLUENCE UPON NEURONAL PATHOLOGY FOLLOWING OLIGODENDROCYTE APOPTOSIS

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Recent studies of newly forming multiple sclerosis (MS) lesions have demonstrated that oligodendrocyte (OL) apoptosis and microglial activation could play crucial roles in MS pathogenesis. To investigate the functional consequences of oligodendrocyte loss, we generated a transgenic mouse model of conditional oligodendrocyte ablation. In this model, oligodendrocytes are rendered selectively sensitive to exogenously administered diphtheria toxin (DT) by targeted expression of the DT receptor in oligodendrocytes. Administration of DT resulted in severe neurological dysfunction with an ascending spastic paralysis within three weeks of DT challenge accompanied by a loss of approximately 26% of oligodendrocyte cell bodies throughout the CNS. Oligodendrocyte cell body loss was associated with moderate microglial activation, but no widespread myelin degradation or lymphocyte infiltration, correlating with upregulation of the interleukin - 4 and interleukin - 10 genes. These changes were accompanied by acute axonal injury and dysfunction as characterized by alterations at nodes of Ranvier and reduced somatosensory evoked potentials, independent of demyelination. We further investigated whether microglial activation following OL apoptosis contributed to axonal pathology and clinical disease using the immune modulating drug, minocycline. Minocycline treatment inhibited the increase in microglial cell density, attenuated axonal pathology and prevented the lengthening of ankyrin G-immunolabelled nodes. In addition, minocycline attenuated the development of early motor deficits and transiently delayed the progression of clinical symptoms in DT-challenged transgenic mice relative to vehicle-treated controls. These results demonstrate that microglial activation following OL apoptosis likely contributes to axonal damage but that there are complex dynamics between the nervous and immune systems at play during neurodegeneration.

SYM-19-01

REGULATION OF THE ACTIN BINDING PROTEIN DREBRIN BY THE PTEN TUMOUR SUPPRESSOR AT THE CNS SYNAPSE

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The PTEN tumour suppressor acts as a lipid and dual-specific protein phosphatase, which has been shown to regulate various cellular functions in the developing and mature central nervous system. For example, PTEN controls neuronal migration and overall neuronal morphology as well as neuronal cell size, predominantly through its lipid phosphatase activity antagonizing the activity of PI3K. However, there is accumulating evidence that PTEN may mediate PI3K independent mechanisms, potentially involving compartmentalization through interaction with proteins and/or involving the PTEN protein phosphatase activity. In this study we identify and characterise the interaction of PTEN with Drebrin (DBN), an actin-binding protein highly enriched in dendritic spines. Our presented results demonstrate that the PTEN-DBN association is direct and results in the dephosphorylation of a major phosphorylation site present in the DBN C-terminus. By generating a p-DBN specific antibody, we further demonstrate that PTEN and p-DBN segregate, at least partially, into distinct and complimentary neuronal compartments, which supports the idea that PTEN may negatively regulate phosphorylation of DBN. Synaptic activity, on the other hand, induces a dissociation of the PTEN-DBN complex and leads to an increase in phosphorylation of DBN- in neurons. To examine the physiological relevance of the PTEN-DBN interaction at the synapse further we generated a DBN mutant version in which we mutated the phosphorylation site. By recording the postsynaptic currents from AMPAR elicited by uncaging 'caged glutamate' we identify that the level of phosphorylation of DBN directly controls AMPA-mediated currents. Our summarised findings identify PTEN as a direct interactor of DBN in the regulation of cell-surface AMPARs, providing new molecular insights into how PTEN may control synaptic transmission independently of PI3K signalling.

SYM-19-02

HOW PTEN KEEPS NEURONS ALIVE AFTER INJURY

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How does the brain defend itself from cell death following injury? Are there intrinsic mechanisms that protect neurons during critical periods of ischemic and metabolic stress? If yes, what are these mechanisms and why are they inefficient? In this presentation, I will outline key discoveries from our laboratory demonstrating that Ndfip1-mediated regulation of PTEN is a powerful and intrinsic mechanism for increasing neuron survival following injury. I will explain how a cancer cell-survival pathway can be borrowed by neurons to defend against cell death in times of stress. New data will also be presented to demonstrate how this new knowledge can be harnessed for therapeutic purposes.

SYM-19-03

LONG ANTISENSE NON-CODING RNAS; EPIGENETIC REGULATORS OF GENE TRANSCRIPTION IN HUMAN CELLS

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Observations over the past eight years have demonstrated that exogenously introduced small antisense RNAs (asRNAs) can transcriptionally modulate gene expression in human cells by targeting silent state epigenetic marks to targeted loci. The mechanism involved in small asRNA directed transcriptional gene silencing (TGS) appears to involve DNA methyltransferase 3a (DNMT3a). However, an endogenous RNA trigger, which actively directs epigenetic regulatory proteins to targeted genomic loci in human cells, has remained unidentified. We present evidence here suggesting that long non-coding RNAs (ncRNAs) which are antisense to particular protein-coding genes function in human cells as effector molecules driving endogenous TGS. These ncRNAs, in many cases emanating from pseudogenes, function in trans to guide epigenetic remodeling complexes consisting of Enhancer of Zeste (Ezh2) and DNMT3a to target loci. When these regulatory ncRNAs are degraded using RNAi the result can be a concomitant activation of their protein-coding counter part. We also find that some of these asRNAs emanate from bidirectional promoters and form higher ordered RNA:RNA paired structures with their respective sense counterpart. Interestingly, this higher ordered RNA:RNA pairing appears operative in differentially regulating the protein-coding genes expression in a bimodal translational and transcriptional manner. Taken together the data presented here offers a distinctly different picture for ncRNA based epigenetic regulation in human cells and suggests that this RNA based transcriptional regulatory mechanism can be taken advantage of to either transcriptionally silence a genes expression in a long-term manner or activate a genes transcription by the targeted degradation of the regulatory long antisense non-coding RNAs. Grant acknowledgments (NIH-HLB R01 HL83473, NIAID R01AI084406, NCI R01 CA151574, NIH R01 CA153124).

SYM-19-04

ROLE OF INOSITOL POLYPHOSPHATE 5-PHOSPHATASES IN NEURONAL FUNCTION

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Phosphoinositide signalling molecules interact with a plethora of effector proteins to regulate cell proliferation and survival, vesicular trafficking, metabolism, actin dynamics, and many other cellular functions including neuronal cell migration. The generation of specific phosphoinositide species is achieved by the activity of both phosphoinositide kinases and phosphatases, which phosphorylate and dephosphorylate, respectively the inositol headgroup of phosphoinositide molecules. Phosphoinositide 3-kinase (PI3K) generates the signaling molecule $PI(3,4,5)P_3$ which can be dephosphorylated by the inositol polyphosphate 5-phosphatases (5-ptases) to generate $PI(3,4)P_2$. There are ten mammalian 5-phosphatases and recently several of these enzymes have been implicated in neuronal function. Synaptojanin 2 is implicated in the regulation of inner hair cell function and thereby deafness, and synaptojanin 1 regulates post-synaptic vesicle recycling. Genetic mutations in the 5-phosphatase, INPP5E are causative of the ciliopathy syndromes of Joubert and MORM, which are associated with mental retardation, polycystic kidneys, and other developmental defects. Mice with gene-targeted deletion of Inpp5e exhibit open neural tube, exencephaly, polydactyly and polycystic kidneys. The molecular mechanisms by which Inpp5e regulates neuronal signaling and thereby function will be explored.