SYMPOSIA

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SYMPOSIUM 01 – HUMAN NEURODEGENERATIVE DISEASES

Sponsored by Neurological Foundation of New Zealand

SYM-01-01

NEURODEGENERATION AND THERAPEUTIC STRATEGIES IN PARKINSON'S DISEASE

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Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by the loss of dopamine neurons in the substantia nigra pars compacta of the brainstem. The typical symptoms of PD are tremor, bradykinesia, rigidity and disturbed postural reflexes. Early in the disease, the symptoms are relatively responsive to dopamine agonists but with time disabling side effects such as dyskinesias develop. The cause of dyskinesias is not known although a variety of theories abound. We sought to understand the underlying mechanism by examining gene and protein expression in a rodent model of levodopa-induced dyskinesias. **Methods:** Rats were made parkinsonian with 6-hydroxydopamine and then treated either with vehicle or levodopa for 21 days. **Results:** Animals developed progressive dyskinesias and were examined for gene and protein expression. Three proteins were found to be dysregulated in concert with the development of dyskinesias and these were CalDAG-GEF1, CalDAG-GEF11 and thyrotropin releasing hormone (TRH). The proteins were all found to be altered in striatum ipsilateral but not contralateral to the dopamine lesion and no changes in these proteins were seen in control animals treated with levodopa. The changes were thus specific to those animals that had dyskinesias. **Conclusions:** Each of these proteins are potential targets for therapies for dyskinesias. In the past thyroid dysfunction has been related to other forms of dyskinesia but the mechanism is unknown. It may be that TRH plays a wider role in basal ganglia function than previously recognized.

SYM-01-02

NEURODEGENERATION IN ALZHEIMERS AND RELATED DEMENTIA

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Purpose: To review and discuss the neurodegenerative features in Alzheimer's disease (AD) and related dementias. **Discussion:** The vast majority of patients with AD survive to old age prior to disease onset, and for those with late-life AD there are a variety of underlying neuropathologies.[1] These cellular pathologies occur years before the onset of dementia and include Aβ plaques, neurofibrillary tau deposits (NFT) and small vessel cerebrovascular disease. In population based studies, 70% of people over the age of 70 have these pathologies but only 30% have cognitive impairment sufficient for a diagnosis of clinical AD.[1] While very mild and relatively stable atrophy is associated with abnormal protein deposition, large focal tissue loss in medial temporal cortex measurable 1-3 years before a clinical diagnosis of AD parallels cognitive decline.[2] The significant dichotomy between the temporally-related large loss of brain tissue and, for many, the unrelated abnormal deposition of proteins in the brain requires further examination. The large loss of brain tissue has been shown to directly relate to microglial activation[3] with changes in inflammatory markers predictive of AD.[4] Only a limited amount of neurons die through a slow NFT process and many studies over a number of years have found significant DNA abnormalities in a proportion of AD neurons, with the loss of microRNA expression a recent finding. Although still controversial, hyperploid neurons occur preclinically and are selectively vulnerable to all types of cell death, possibly through neurotrophin p75 receptor mediated pathways.[5] [1] Neuropathology Group, Medical Research Council Cognitive Function and Aging Study. Lancet 2001;357:169-75. [2] Jack et al; Alzheimer's Disease Neuroimaging Initiative. Brain 2009;132:1355-65. [3] Edison et al. Neurobiol Dis. 2008;32:412-9. [4] Jefferson et al. Neurology. 2007;68:1032-8 & Sokolova et al. Brain Pathol. 2009;19:392-8. [5] Arendt et al. Am J Pathol. 2010 Jul;177(1):15-20 & Frade & López-Sánchez. Cell Cycle 2010;9;in press.

SYM-01-03

Abstract not available at time of printing

SYM-01-04

ADULT HUMAN BRAIN CELL CULTURES FOR DRUG DISCOVERY IN NEURODEGENERATIVE DISEASE

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Neurodegenerative diseases are a huge individual, family and societal burden. No highly effective disease modifying treatments have so far been developed to prevent neurodegeneration or promote brain repair in any of these disorders, despite a huge world-wide effort. In the present talk I will describe the development of a neurodegenerative drug discovery and testing platform based around adult human brain cell cultures. I will describe the use of this platform for compound testing and in particular highlight species differences in drug action that show the importance of testing treatments on human brain cells. Finally, I will describe the development of human brain tissue microarrays that combined with high content analysis, provide opportunities for drug target discovery and validation. Together these platforms provide a rational basis for developing and testing human effective disease-modifying medications to treat neurodegenerative disorders.

SYM-02-01

TOWARDS AN UNDERSTANDING OF THE BRAIN MECHANISMS UNDERPINNING PSYCHOSTIMULANT ADDICTION

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PURPOSE: The molecular mechanisms underpinning psychostimulant addiction are poorly understood. This is a likely obstacle to the development of effective pharmacotherapies for addiction. To identify putative brain mechanisms responsible for the development of addiction-like behaviours, we combined a novel behavioural approach that recapitulates several human addiction traits in rats with genome-wide expression and pathway analysis tools. **METHODS**: Rats (n=52) were trained to self-administer cocaine and phenotyped as addiction and relapse vulnerable or resilient. Gene set enrichment analysis (GSEA) was then performed on genome-wide expression data obtained from macrodissections of the ventral (VS) and dorsal striatum (DS). Follow-up analyses were then performed using quantitative PCR. **RESULTS**: GSEA identified differential expression of core genes within the mammalian target of rapamycin (mTOR) and long-term depression gene sets in the striatum of vulnerable v.s. resilient rats. Using qPCR we confirmed significant transcript down-regulation of a number of synaptic plasticity-related genes in the VS and DS of vulnerable animals. This included reduced expression of genes encoding proteins implicated in the dendritic translation of synaptic plasticity-related transcripts, the regulation and trafficking of ionotropic glutamate receptors, along with neuronal surface receptors that initiate downstream signaling pathways associated with synaptic plasticity. **CONCLUSION**S: We identified differences in genes encoding synaptic plasticity-associated signaling molecules within the VS and DS of addiction-vulnerable compared to resilient animals. Importantly, brain differences between groups were unrelated to levels of drug exposure, as both groups of animals consumed equivalent amounts of cocaine. These data are consistent with functional reports of impairments in the ability to evoke synaptic plasticity in addiction-vulnerable but not -resilient animals.

SYM-02-02

MODELING ADOLESCENT INHALANT ABUSE IN RODENTS: THE EFFECTS OF TOLUENE EXPOSURE ON THE DEVELOPING BRAIN

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Purpose: The purposeful abuse of inhaled vapours to produce self-intoxication and/or altered mental state is a significant public health concern, especially in adolescent and indigenous populations. Inhalants are typically one of the first drugs that young people abuse as they are cheap, legal, accessible and provide a rapid 'high'. Thus, the onset of experimentation with inhalants often coincides with the maturation of crucial cognitive and emotional brain structures. Furthermore adolescent exposure is thought to potentially predispose individuals towards drug-seeking behaviours later in life. However despite long-standing awareness of the significant morbidity and mortality associated with inhalant abuse, fundamental neurobiological research has been comparatively sparse. **Methods:** Utilising a newly established rodent model of chronic intermittent toluene exposure (CIT, 3000ppm for 3 x 1hr sessions for 4-8 weeks) via inhalation during adolescence, with a paradigm relevant to human use patterns, we characterized the behavioural and neuropathological consequences of inhalation abuse. **Results:** We have shown that CIT exposure during adolescence can increase anxiety behaviour, even in the absence of overt brain pathology at the histological level. **Conclusions:** The results from these studies will increase our knowledge of the long-term neurological affects of inhalant abuse on the developing brain and have the potential for clinical applications to increase public awareness towards the detriment of inhalant abuse. Future investigations with this model will also provide information regarding the structural, neurochemical and behavioural consequences of adolescent inhalant exposure and highlight key sites susceptible to this challenge.

SYM-02-03

THE ROLE OF NON-NICOTINE TOBACCO PRODUCTS IN ANIMAL MODELS OF TOBACCO ADDICTION

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Purpose: Nicotine has been considered to have a low reinforcing efficacy in animal models of drug addiction, a finding that is at odds with the high rates of dependence in humans. This has lead to the suggestion that non-nicotine components of tobacco smoke may be important in facilitating and prolonging tobacco dependence. Methods: Recent studies have investigated the role of minor tobacco alkaloids (mTAs) and monoamine oxidase inhibitors (MAOIs) present in tobacco smoke in modifying the reinforcing efficacy of nicotine in rodents. Results: The addition of mTAs to nicotine during intravenous self-administration increases the rewarding efficacy of nicotine and motivation to obtain nicotine. Pre-treatment with MAOIs facilitates the acquisition of nicotine self-administration, increases motivation to obtain nicotine and prolongs the aversive state of withdrawal. However, MAOIs pre-treatment has no effect on nicotine intake under conditions of extended access whereby an escalation of nicotine intake was not evident. Conclusion: The influence of non-nicotine components of tobacco in increasing the rewarding efficacy of nicotine will be discussed with respect to the development of a more complete and valid animal model of human nicotine addiction.

SYM-02-04

BRAIN MECHANISMS FOR EXTINCTION OF DRUG AND REWARD SEEKING

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Effective extinction of craving and drug seeking is essential to achieving long-term abstience from drug taking. The neural mechanisms for the extinction of drug seeking are poorly understood. Here I will describe the results of experiments from my laboratory which identify an important role for cortical-hypothalamic-thalamic and amygdala-striatal pathways in the extinction of alcohol seeking in an animal model. The actions of the neuropeptides CART and dynorphin are central to the cortical-hypothalamic-thalamic extinction pathway and glutamatergic signalling via AMPA receptors in nucleus accumbens shell are central to the amygdala-striatal extinction pathway. This research identifes nucleus accumbens shell and paraventricular thalamus as two points of convergence between the neural circuits controlling reinstatement of drug seeking (i.e. relapse) and the neural circuits controlling extinction of drug seeking (abstinence). The implications of these findings for understanding long term abstinence from drug taking in humans will be discussed.

SYMPOSIUM 03 – FUNCTIONAL, AND FUNCTION OF, NEUROGENESIS IN THE ADULT BRAIN

Sponsored by Neurological Foundation of New Zealand

SYM-03-01

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SYM-03-02

SYNAPTIC INTEGRATION OF NEWLY GENERATED NEURONS IN HIPPOCAMPAL CULTURES

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In the dentate gyrus of the hippocampus new neurons are born from precursor cells throughout development and into adulthood. These newborn neurons hold significant potential for self-repair of brain damage caused by neurodegenerative disease. However, how newborn neurons integrate into the brain is far from understood due to a lack of knowledge of the molecular and functional characteristics of the synapses formed by newborn neurons. Here we describe how dissociated hippocampal cultures continue to produce new neurons in vitro. A subpopulation of these newborn neurons fully integrate into the mature hippocampal culture and take on neuronal structural and functional characteristics. The synapses formed by newborn neurons mature via the sequential recruitment of postsynaptic receptors. The metabotropic subtypes of glutamate receptors play an important role in the initial integration of newborn neurons, with the ionotropic receptors localising to synapses later on in newborn neuron maturation. We also observe a sequential recruitment of postsynaptic but not presynaptic scaffold proteins. GABAergic synapses were also found to mature faster than glutamatergic synapses. These data reveal the unique developmental profile of synapses of newly generated neurons, enabling us to determine how the function of newborn neuron synapses could contribute to restoring damaged neuronal networks.

SYM-03-03

STIMULATION OF LATENT, NEUROGENIC PRECURSORS IN THE ADULT HIPPOCAMPUS BY NOREPINEPHRINE: IMPLICATIONS FOR THE TREATMENT OF DEPRESSION

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The production of new neurons from the endogenous pool of neural stem and precursor cells in the hippocampus is thought to underpin aspects of learning and memory. Therefore, defining how neurogenesis is regulated is essential for the future development of neurogenic-based therapeutics aimed at ameliorating cognitive loss commonly observed in psychiatric disorders including depression. Previous work from our laboratory has uncovered the existence of a latent pool of stem and precursors in the hippocampus that can be activated by synaptic activity. Recently, we have shown that norepinephrine, a key monoaminergic neurotransmitter implicated in the pathophysiology and treatment of depression, directly activates self-renewing and multipotent population of stem and precursor cells. Using selective pharmacological blockers of adrenergic receptors, we provide evidence that β3 adrenergic receptors, which are preferentially expressed on a stem/precursor population in the hippocampus, mediate this norepinephrine-dependent activation. Moreover, we have shown that in vivo administration of a selective β3 adrenergic receptor agonist in mice significantly increases the number of proliferating cells in the subgranular zone, suggesting that the activation of neurogenic precursors via β3 adrenergic receptors could be a potent mechanism to increase neuronal production. Furthermore, we demonstrate that blocking α2 adrenergic receptors also activates the latent precursor cell population and accelerates the behavioural effects of antidepressants. Thus, we have now begun to understand the functional role of various adrenergic receptors that mediate the neurogenic and antidepressant effects of norepinephrine, opening up the possibility of developing faster acting and more effective treatments for mood disorders.

SYM-03-04

VOCAL LEARNING AND NEW NEURONS

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I will contrast vocal learning and adult neurogenesis in two songbirds, the canary *(Serinus canaria)* and zebra finch *(Taeniopygia guttata)*. Both have complex developmental programs that lead to the mastery of vocal imitation, but while canaries can change their song every year, zebra finches cannot. The brain pathways underlying the acquisition and production of learned song are very similar in both species and both put key parts of this system together at the very time song is first acquired. Both, too, continue to produce in adulthood the very type of neuron thought to encode the program of learned song. However, while in canaries these new neurons replace periodically other, older ones of the same kind, perhaps thus enabling new opportunities to imitate new sounds, in zebra finches the new neurons are added to the existing ones, so that the number of these cells doubles after sexual maturity even as the learned song persists, by and large, unchanged. These observations seem paradoxical. Arguments linking new learning to new neurons in one species (canary), cannot easily be extended, in adulthood, to the other. This leaves us with a paradox and scientists recognize that paradoxes are often seminal moments that precede new insights. This lecture is meant to inform, intrigue and stimulate and to make us all look with new wonder at our feathered kin. There is hardly a better model system to get at the evolutionary origins, ontogeny and significance of vocal learning and there are few traits that have so much to tell us about how brains do their work, about their limits and their potential for self repair. The topic of this lecture, at the interface between natural history, ethology and biomedical research, may have a bright future.

SYM-04-01

ENTERIC SECRETOMOTOR NEURONS AND DIARRHOEA: A NEW MODEL FOR CHOLERA

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Purpose: Diarrhoea remains a major health problem throughout the world. Secretory diarrhoea is often caused by the action of a bacterially released exotoxin, the prototype of which is the toxin of Vibrio cholera, cholera toxin (CT). Although it acts directly on the mucosa, the pathogenic effects of CT involve hyperactivity of enteric secretomotor pathways. This work has investigated how these pathways become hyperexcitable. Methods: Our studies involved intracellular recording from submucosal secretomotor neurons identified immunohistochemically, recordings from myenteric intrinsic sensory neurons and video recording of intestinal motor patterns. We incubated isolated segments of guinea-pig jejuna with CT and various antagonists in the lumen. Results: Preincubation with CT causes a long lasting in the excitability of both cholinergic and noncholinergic secretomotor neurons that persists for several hours after the CT is removed from the system. This effect depends on proximity to intact mucosa. Preliminary experiments indicate that the excitability of intrinsic sensory neurons is also enhanced under these conditions. CT acutely increases propulsive motility patterns via a mechanism that is pharmacologically distinct from that responsible for the hypersecretion or the increased excitability produced by this toxin. In contrast, CT suppresses the segmentation produced by luminal incubation with decanoic acid, a fatty acid. Conclusion: Our data indicate that the conventional model of CT action – that it causes an irreversible and long-lasting increase in the mucosal release of serotonin, thereby overexciting secretomotor pathways – is inadequate. Rather CT appears to act though at least three distinct pathways to increase excitability of the output neurons of the secretomotor pathways, to increase propulsive motility and suppress segmentation and perhaps to increase excitability of intrinsic sensory neurons.

SYM-04-02

ABNORMALITIES OF THE ENTERIC NERVOUS SYSTEM AND GAP JUNCTION PROTEINS IN THE COLON OF PATIENTS WITH SLOW TRANSIT CONSTIPATION

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Idiopathic slow transit constipation (STC) represents an extreme colonic dysmotility that predominantly affects women. The pathophysiological basis of STC is poorly understood. To date, studies concerning STC have focused on the enteric nervous system and interstitial cells of Cajal (ICCs). Reduced cell volume or number of ICCs in STC has been reported in some studies, but others failed to detect any abnormalities in ICCs, despite the selection of highly symptomatic individuals. Our recently published studies have demonstrated an aberrant contractile pattern of STC colonic circular muscle in response to electric field nerve stimulation, indicating malfunction of the enteric nervous system in STC. However, these alterations do not seem to fully explain the extreme severity of dysmotility and delayed colonic transit in these patients. Reduced communication between cells may result in defects in synchronous, coordinated gut movements. In this respect, connexins (gap junction proteins) play a critical role in the cell-to-cell signalling of the gastrointestinal tract. Therefore, in recent experiments we addressed the hypothesis that connexins (Cx) are implicated in the pathophysiology of STC. Using real-time PCR, we found a marked down-regulation of genes encoding Cx43 and Cx45, as well as the neuronal marker synaptophysin, in the colonic mucosa of patients with STC compared to control, but the expression of these genes remained unaltered in STC smooth muscle. Western blot showed that Cx43 and Cx45 protein levels were also significantly reduced in STC mucosa. Subsequent immunohistochemical studies demonstrated that the reduction of Cx43 and Cx45 was confined to the mucosal crypts, and there appeared to be fewer Cx45-positive submucosal neurons in STC. Our study raises an important question whether the impairment of gap intercellular communication within the colonic mucosa plays a critical role in the pathophysiology of STC.

SYM-04-03

MECHANISM UNDERLYING DISTENSION-EVOKED PERISTALSIS IN GUINEA-PIG DISTAL COLON: IS THERE A ROLE FOR ENTEROCHROMAFFIN (EC) CELLS ?

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Purpose: To understand how inflammatory bowel disease induces changes in motor activity of the colon and changes in serotonergic signaling, we first need to understand the role of endogenous 5-HT in the initiation of complex motor patterns, such as peristalsis. It has been proposed that the initiation of colonic peristalsis, following distension, is due to release of 5-hydroxytryptamine (5-HT) from enterochromaffin (EC) cells in the mucosa. However, direct evidence to support this hypothesis is lacking because real time recordings of 5-HT release have not been made during colonic peristalsis. The aim of this study was to determine whether 5-HT release from EC cells was required for distension-evoked colonic peristalsis in isolated guinea-pig distal colon. Methods: Real time amperometric recordings of 5-HT release combined with video imaging were made during peristalsis evoked by fluid infusion and by fecal pellets. Results: Amperometric recordings revealed a basal release of 5-HT from EC cells of 22μM (n=7). Prior to the initiation of peristalsis and during peristalsis, evoked by natural fecal pellets a basal and transient release of 5-HT was detected. However, removal of the mucosa and submucosal plexus abolished all release of 5-HT, but did not inhibit the initiation of peristalsis, nor prevent the propagation of fecal pellets along the colon. Maintained distension by pellets generated cyclical peristaltic waves, which also persisted following removal of the mucosa and submucosal plexus, but at reduced pacemaker frequency. The frequency or peristaltic waves evoked by maintained distension, or constant fluid infusion were unaffected by removal of the mucosa and cessation of all 5-HT release. Although the propagation velocities of peristaltic waves was slower. Conclusion: The sensory neurons and mechanoreceptors which initiate peristalsis lie in the myenteric plexus and/or muscularis externa, and do not require any release of 5-HT from EC cells, the submucosal plexus, or activation of sensory nerve endings in mucosa, as previously hypothesized.

SYM-04-04

ENTERIC GLIAL CELLS, NEURONS AND IMMUNE SYSTEM IN THE DEVELOPMENT OF MEGACOLON IN CHRONIC CHAGAS DISEASE

Reis D.D.'A.[1], Nascimento R.D.[1] and Da Silveira A.B.M.[2]
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Enteric glial cells, neurons and immune system in the development of megacolon in chronic Chagas disease Reis, D.d'A.; Nascimento, R.D.; da Silveira, A.B. Institute of Biological Sciences, Federal University of Minas Gerais, Brazil. Chagas disease is caused by the infection with the protozoa named Trypanosoma cruzi. Perhaps one of the most intriguing aspects of human Chagas disease is the complex network of events that under¬lie the generation of protective versus pathogenic immune responses during the chronic phase of the disease. While most individuals do not develop chronic disease, a large percentage may develop cardiac and/or digestive severe forms that eventually lead to death. Although many efforts have been devoted to deciphering the mechanisms that lead to the chronic disease, there is still much to be learned. Concerning the digestive disease that is characterized by megaesophagus and/or megacolon, it is clear that the local immune response associated with destruction of neurons, is decisive in this process. More recently, the denervation process in chagasic megacolon has been further analyzed by immunopheno¬typing the enteric neurons in the colon. Since the en¬teric nervous system contains between 10-100 million neurons with a great variety of neurotransmitters and/or neuropeptides, destruction of certain selective neuronal classes in Chagas disease could easily affect the peristalsis and vascular tonus, favoring the development of pathology. Another important co-factor in cell-mediated pathol¬ogy of megaoesophagus and megacolon is the enteric glial cell (EGC). These cells are activated by inflammatory ac¬tivity and may contribute actively to inflammatory pa¬thology via antigen presentation and cytokine synthesis. We will present some data, from our group, on the immunophenotyping of neurons, EGC and inflammatory cells in Chagas patients, and discuss the possible involvement of such neuroimmune network in the development of the digestive disease. Financial support: FAPEMIG.

SYM-05-01

FUNCTIONAL CIRCUITS IN THE DEVELOPING SPINAL CORD CONTROLLING LOCOMOTION

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Keywords: *Neural circuits, spinal cord, locomotion, interneurons, genetics behaviour.* The spinal cord plays a central role in generating both the simple and complex patterns of motor activity needed for locomotion. It also processes and relays sensory information from the body to spinal motor centres and other CNS structures involved in somatosensation. Recent developmental studies have provided an outline of the key pathways that control the specification, organization and functional properties of the neurons that contribute to sensory-motor circuits in the spinal cord. Using a comprehensive approach that combines genetics, neuroanatomical, electrophysiological and behavioural analyses we have begun to assess the contribution that molecularly identified neuronal cell types make to the control of movement in mammals. We have characterized various populations of the spinal interneurons including dI6, V0, V1, V2b and V3 interneurons. Our studies show that each interneuron class controls a distinct facet of walking, thereby revealing that spinal locomotor circuits are organized in a modular fashion. V0 interneurons control left-right stepping. Excitatory V3 commissural interneurons are required for the generation of robust and balanced motor rhythm. V1 interneurons, which generate inhibitory neuron cell types, control the cadence of the step cycle. Together with V2b inteneurons, they control movements of the limbs, and are therefore critical for limbed locomotion. Since both cell types are present in the spinal cords of aquatic vertebrates, we posit that these interneurons were hijacked and reconfigured to control primitive fin/limb movements.

SYM-05-02

DEVELOPMENT AND FUNCTION OF HINDBRAIN COMMISSURES

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Coordination of the left and right sides of the body requires the action of neurons whose axons cross the nervous system midline. The precise contributions of "commissural" neurons to sensory and motor functions remain poorly understood. To probe these crossing circuits, we took advantage of the recent finding that the Robo3 axon guidance receptor is required for midline crossing by axons at most axial levels. A Robo3 conditional knockout mouse line was generated, allowing Robo3 to be deleted in selective neuronal populations. This led to disruption of specific commissures in the sensory, motor, sensorimotor and respiratory systems, and resulted in severe but specific functional deficits. Surprisingly, although rerouted axons do not cross the midline, they still project to their appropriate neuronal targets, suggesting that midline crossing is not required to complete the axonal guidance program of those neurons. We further showed that the ipsilateral rewiring of the projections from the brainstem which convey sensory information to the thalamus, has profound effect on the development of the barrel field. These mouse lines represent good models for human syndromes, including horizontal gaze palsy with progressive scoliosis (HGPPS), which is characterized by deficits in coordinated eye movements. This study links defects in commissural axon guidance with specific and dramatic behavioral phenotypes. We have also generated mice that lack all Robo receptors or all Slit ligands which are being used to interfere with axon guidance and neuronal migration but also to study the function of these molecules in the adult brain.

SYM-05-03

AXONAL GUIDANCE MECHANISMS IN THE DEVELOPMENT OF THE CORPUS CALLOSUM

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Axonal connections between the two sides of the brain occur through three major commissural projections; the anterior commissure, the hippocampal commissure and the corpus callosum. The ability of these axons to cross the midline depends on the formation of a substrate called the commissural plate, the guidance of commissural axons by midline glial populations, and the expression of specific axon guidance molecules. Both the correct patterning and formation of the commissural plate, and the secretion of guidance cues from this region, are essential for the development of all forebrain commissures. A number of mouse mutants exist where the development of specific commissures is impaired. Understanding the patterning and development of the commissural plate has allowed us to examine the molecular mechanisms that regulate all forebrain commissures and to compare these to commissural malformation defects in humans. As commissural axons arrive at the midline they navigate through an environment of both positive and negative molecular axon guidance cues. Callosal axons utilize multiple guidance cues simultaneously such as Netrin-DCC and Slit-Robo by integrating the information to modulate their growth and guidance. Such cues are expressed by midline glial populations and are critical for callosal axon guidance, but little is know about how these glia develop. Recent data demonstrates that a family of transcription factors called the Nuclear Factor One (Nfi) genes regulate commissure formation indirectly by regulating the formation of midline glial populations. Given that there are over 60 genes associated with commissural defects in mouse, these results demonstrate that a number of critical mechanisms are required for commissure formation in the brain, each of which may be regulated by separate molecular mechanisms.

SYM-05-04

THE SPECTRUM AND CAUSES OF CORTICAL MALFORMATIONS IN HUMANS

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Purpose: Malformations of cortical development are increasingly diagnosed in patients presenting with congenital neurological deficits, developmental and intellectual disabilities and epilepsy. The study of these disorders in humans has led to improvements in our understanding of the mechanisms of normal cortical development. The purpose of this presentation will be to review the spectrum and known causes of cortical malformations in humans, highlighting the translational link between clinical research and developmental neuroscience. **Methods:** The clinical, imaging and genetic features of the most common malformations of cortical development will be reviewed, including lissencephaly, grey matter heterotopia, polymicrogyria and cortical dysplasia. **Results:** Elucidation of the genetic and molecular basis of malformations of cortical development through the study of human patients has led to direct advances in our understanding of normal cortical development mechanisms including the modeling of such malformations in functional studies including animal models. **Conclusions:** Significant advances in our understanding of the causes and mechanisms of human cortical malformations have been made over the past 15 years. This is a direct consequence of improvements in imaging techniques (MRI) and gene identification techniques. However, a number of common human cortical malformations remain poorly understood, providing fertile ground for ongoing clinical and basic science research in this growing field of neuroscience.

SYMPOSIUM 06 – NEUROMODULATORS, PLASTICITY AND BEHAVIOUR: DOPAMINE MADE ME DO IT

Sponsored by Neurological Foundation of New Zealand

SYM-06-01

OPIOID MODULATION OF STRIATAL DOPAMINE ACTIVITY IN ACTION SELECTION

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The amygdala and ventral striatum play complex roles in regulating the learning processes involved in simple evaluative conditioning, the conditioning of consummatory responses, preparatory responses, and more complex actions associated with food seeking. In this latter context these structures and the limbic-striatal network generally appears to be involved in two forms of motivational process, one that encodes experienced reward values and a second associated with the use of predictive cues to formulate expected rewards. In recent research investigating these distinct learning and motivational processes we have found evidence that (i) dissociable regions of amygdala and ventral striatum are involved in these motivational effects; that distinct opioid and dopaminergic processes are involved in their modulation; and (iii) that, whereas the amygdala encodes specific reward values, the ventral striatum brings these values to bear on performance, in line with its description as a component of the limbic–motor interface.

SYM-06-02

COCAINE EXPERIENCE DURING ADOLESCENCE SELECTIVELY ARRESTS THE MATURATION OF PARVALBUMIN POSITIVE/GABAERGIC FAST-SPIKING INTERNEURONS IN THE PREFRONTAL CORTEX

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Experience to a drug of abuse during adolescence significantly increases the risk for addiction. However, the mechanisms underlying the increased susceptibility to drug addiction during the periadolescent transition period remain elusive. Our recent study in rodents showed that repeated non-contingent cocaine experience elicited differential changes in prefrontal cortical metabolic activity, an effect that is age dependent. Whereas activity in the prefrontal cortex increased following 3 weeks withdrawal from cocaine injection during adolescence (PD35-40), an overall frontal cortical metabolic inhibition was observed in the adult (PD75-80) group. We therefore hypothesized that such a distinctive age-dependent prefrontal neuroadaptation observed following cocaine exposure could be due to a developmental interference of local/cortical interneuronal maturation/function that typically take place during the periadolescent transition period. Among cortical GABAergic interneurons, the parvalbumin (PV)/fast-spiking cell type is of particular interest due to its role in prefrontal functioning. In the present study, we assessed the impact of repeated cocaine injection and asked whether the age at which the drug exposure takes place plays a role in altering interneuron function in the prefrontal cortex. PV interneurons function was assessed by means of immunohistochemical measures. PV is a calcium binding protein used by fast-spiking interneurons and its immunoreactivity is positively correlated to neuronal activity. We observed that PV-immunoreactivity in the normal prefrontal cortex follows a distinctive developmental trajectory with the lowest activity in juveniles and maximal activity in adulthood. In the cocaine group, we found that such a developmental enhancement of prefrontal PV-immunoreactivity was lacking when repeated cocaine experience occurs during adolescence. Interestingly, cocaine exposure did not affect prefrontal cortical PV staining in the adult group. Our results indicate that exposure to cocaine during adolescence prevents the normal developmental facilitation of fast-spiking interneuron function in the prefrontal cortex. Correlation analyses further indicate that such a developmental dysregulation of prefrontal interneuronal circuits could trigger and sustain a disinhibited prefrontal cortex, a prefrontal state that may contribute to the increased risk for drug abuse in adolescence. *Supported by Rosalind Franklin University and National Institute of Health Grants DA004093 and MH086507.*.

SYM-06-03

DOPAMINE MADE ME DO IT, BUT WHAT DID I LEARN?

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In the neuroscience community there is general agreement that the basal ganglia (one of the brain's ancient and fundamental processing units) play an important role in behavioural selection and reinforcement learning. It is also agreed that within the basal ganglia, the sensory response of midbrain dopaminergic neurones to biologically salient stimuli, acts as a reinforcement signal. From this point there is less agreement. The majority view is that the dopamine neurones signal a reward prediction error that is used to reinforce the maximisation of future reward acquisition. For various reasons, which will be covered in the talk, our view is that reinforcement learning can be split into independent processes that have been recognised by biological evolution, and separate mechanisms have been developed accordingly: (i) A mechanism to determine agency (events in the world for which the agent is responsible), only partially related to any detailed assessment of value. A subsidiary process of agency determination is the development of novel actions; i.e. identification of the causal aspects of behavioural output by means of trial and error. It appears the basal ganglia and the phasic dopamine reinforcement signal are ideally configured to perform this function, which is intrinsically motivated. (ii) A mechanism to bias future action selections based on outcome value. Detailed determinations of outcome value are used to maximise future reward acquisition via a mechanism that applies selective bias to the looped inputs of the basal ganglia. This enables behavioural outcomes associated with high value to have the competitive edge.

SYM-06-04

TARGETING SOLUBLE GUANYLYL CYCLASE IN EXPERIMENTAL PARKINSONISM

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Purpose: The soluble guanylyl cyclase (sGC)-cGMP signaling cascade is an important, yet understudied, pathway involved in the regulation of corticostriatal transmission. Neuroadaptations in cGMP synthesis and metabolism occur in the dopamine (DA)-depleted striatum, but it is unclear how these enduring changes impact on neuronal excitability and locomotor activity observed in parkinsonian animals. **Methods:** This study examined the utility of systemic administration of the selective sGC inhibitor [1H-[1,2,4] oxadiazolo-[4,3-a] quinoxalin-1-one] (ODQ) for reversing electrophysiological, histochemical, and behavioral correlates of experimental parkinsonism induced in 6-hydroxydopamine (6-OHDA)-lesioned rats. Outcomes from behavioral studies were also confirmed in chronic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice. **Results:** Consistent with previous studies, striatal single-units recorded in 6-OHDA-lesioned rats exhibited increased spontaneous firing and burst activity compared to neurons recorded in sham-operated controls (n=13-15 cells per group). ODQ treatment reversed the pathological elevations in spontaneous firing of striatal neurons observed in DA-depleted rats and strongly suppressed striatal spike trains (n=5-7 cells/rats). Systemic administration and intrastriatal infusion of ODQ also reversed increases in cytochrome oxidase staining observed in the subthalamic nucleus (STN) of 6-OHDA-lesioned rats (n=5-11 rats per group). The ODQ-mediated reversal of overactivity observed in the striatum and STN of DA-depleted rats was found to be behaviorally relevant as the same treatment transiently attenuated the reduction in forelimb use observed in DA-depleted rats (n=8 rats per group) and mice (n=5-7 mice per group). **Conclusions:** Taken together, these observations indicate that cGMP signaling contributes in an important manner to the overactive excitatory transmission observed in striatopallidal neurons in the DA-depleted striatum. Therefore, down-regulation of the NO-sGC-cGMP pathway may represent an effective therapeutic strategy for restoring motor deficits observed in Parkinson's disease.

SYM-07-01

THE NEUROCHEMISTRY OF INTELLIGENCE AND CREATIVITY (AND PERSONALITY); INITIAL FINDINGS IN A COMPLEX FIELD

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Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) has been used widely by neuroscientists to assess biochemical abnormalities associated with neurological and psychiatric disease. More recently, this imaging technique has been applied to assess structure-function relationships in the normal human brain. Here we report results in a large (N=60) unified sample of relatively young (18-32), neurologically healthy adults who were administered standardized measures of intelligence, creativity, and personality, and imaged at 1.5 Tesla (^{1}H-MRSI; superventricular slab; TE=135). Intelligence: lower NAA within the right cingulate region predicted higher Verbal Intelligence Quotient (p=0.04), while higher NAA within the right cingulate region predicted better Performance Intelligence Quotient (p=0.03). Creativity: higher left cingulate NAA predicted the Composite Creativity Index (p=0.004). Personality: higher levels of Creatine within the posterior cingulate region predicted lower levels of Neuroticism (p=0.032). Higher Creatine within the right parietal white matter also predicted lower Extraversion (p=0.021), and lower Agreeableness (p=0.006). ^{1}H-MRS appears to be a sensitive marker of biochemical processes associated with higher cognitive functioning. NAA appears to be well related to cognitive measures, including intelligence and creativity, while Creatine was associated with measures of normal personality functioning. Regional biochemical-function relationships also were evident, with notably high associations being observed within the posterior cingulate.

SYM-07-02

HOW DOES BLOOD FLOW RELATE TO BRAIN ACTIVITY? THE BIG BOLD HEADACHE

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Brain blood flow and oxygen metabolism are vital for normal function in the mammalian nervous system, and provides the basis for functional neuroimaging. The presentation will focus on recent progress in our understanding of how neuronal signalling, and in turn information processing, impacts vascular regulation and oxygen metabolism in rat and mice primary somatosensory cortex and cerebellum. Evoked activity induces brief and local changes in blood flow and oxygen metabolism which may be controlled by different mechanisms in pre- and postsynaptic cellular elements, and astrocytes. The high level of energy consumption and blood flow in the resting state is incompletely understood, but non-signalling house-keeping activities play a more important role than hitherto believed. Our results suggest that all types of nerve cell activities use energy, and that there is clear correlation between synaptic activity and oxygen consumption in most networks. Neurovascular and neurometabolic coupling vary between networks due to activation of different cell types by different sunaptic inputs. This is likely to be reflected in the response amplitude and phase of the evoked BOLD signal.

SYM-07-03

NEUROCHEMISTRY OF SLEEP: HYPOTHALAMIC REGULATION OF CIRCADIAN SLEEP CYCLES

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The 24-hour pattern of sleep and wake is driven by circadian pacemaker neurons in the suprachiasmatic nucleus (SCN) in the anterior hypothalamus. In humans, exposure to the solar cycle normally insures that a consolidated bout of sleep is achieved at night. Daily exposure to light resets the phase of clock neurons in the SCN which, in turn, send multi-synaptic projections to arousal- and sleep-promoting brain regions to determine the timing of wake and sleep. In the first part of my talk, I will discuss the neurochemical basis for circadian control of sleep cycles, with emphasis on how the SCN drives rhythmic excitation and inhibition of the monoaminergic arousal system. In the second part of my talk, I will argue that in humans exposure to light in the late evening engages multiple arousal systems and may disrupt nighttime sleep by shifting the natural sleep cycle to a later hour. I will present evidence that exposure to ordinary room light in the late evening results in strong suppression of the sleep-promoting hormone melatonin in about 99% of individuals and shortens the duration of melatonin secretion by 90 minutes. Moreover, dim light, similar to that provided by LCD monitors, is sufficient to delay the circadian clock and could contribute to the high prevalence of delayed sleep phase disorder. These findings suggest that chronically exposing oneself to electrical lighting near bedtime could potentially disrupt sleep.

SYM-07-04

NEUROCHEMISTRY OF ADDICTION

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Purpose: Addiction can be regarded as a chronic disorder, typified with periodic relapse to drug-seeking following bouts of abstinence. Various theories have attempted to unravel the transition from casual to habitual drug use and recent studies suggest dysregulation of corticostriatal glutamatergic signalling is implicated in addiction. We set out to develop a rodent model to assess the enduring propensity of drug-seeking and to examine the likely brain nuclei behind this behaviour. An additional component of the study examined the involvement of orexins in drug-seeking. Methods: Alcohol-preferring rats (iP) were trained to self-administer ethanol (10%v/v) under operant conditions. Alcohol availability was signalled with a discrete cue (S+) and alcohol delivery was paired with a conditioned stimulus light (CS+). After 35 days of stable alcohol responding, rats were subject to extinction training and divided into two groups; immediate (reinstated immediately following extinction), and delayed (extinguished and then housed for five months before reinstatement). Prior to reinstatement rats were treated with vehicle (immediate n=11, delayed n=11) or SB-334867 (20mg/kg i.p.; immediate n=6, delayed n=11). Fos expression was compared between each group and to animals that underwent extinction only. Results: SB-334867 significantly attenuated cue-induced reinstatement in both groups. Immediate reinstatement increased cortical Fos expression in the infra- (IL), pre-limbic (PrL), orbitofrontal (OFC) and piriform cortices. Following delayed reinstatement, Fos expression was further elevated in cortical structures. Concurrent with preventing reinstatement, SB-334867 decreased Fos in NAc core, PrL and OFC following immediate reinstatement. Following protracted abstinence, SB-334867 treatment decreased reinstatement-induced Fos in cortical structures only. Conclusion: Cue-induced alcohol seeking can be triggered following protracted abstinence in rats and cortical structures appear to be implicated.

SYM-08-01

THE ROLE OF CHROMATIN MODIFYING ENZYMES IN LONG-TERM MEMORY PROCESSES

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Gene expression is dynamically regulated by chromatin modifications on histone tails, such as acetylation. In general, histone acetylation promotes transcription, whereas histone deacetylation negatively regulates transcription. The interplay between histone acetyltranserases (HATs) and histone deacetylases (HDACs) is pivotal for the regulation of gene expression required for long-term memory processes. Currently, very little is known about the role of individual HDACs in learning and memory. We examined the role of HDAC3 in long-term memory using a combined genetic and pharmacologic approach. We used HDAC3-FLOX genetically modified mice in combination with AAV expressing Cre recombinase to generate focal homozygous deletions of Hdac3 in area CA1 of the dorsal hippocampus. To complement this approach, we also used a selective inhibitor of HDAC3, RGFP136. Immunohistochemistry showed that focal deletion or intrahippocampal delivery of RGFP136 resulted in increased histone acetylation. Both the focal deletion of HDAC3 as well as HDAC3 inhibition via RGFP136 significantly enhanced long-term memory in a persistent manner. Next we examined expression of genes implicated in long-term memory from dorsal hippocampal punches using qRT-PCR. Expression of nuclear receptor subfamily 4 group A, member 2 (Nr4a2) and c-Fos was significantly increased in the hippocampus of HDAC3-FLOX mice as compared to wildtype controls. Memory enhancements observed in HDAC3-FLOX mice were abolished by intrahippocampal delivery of Nr4a2 siRNA, suggesting a mechanism by which HDAC3 negatively regulates memory formation. Together, these findings demonstrate a critical role for HDAC3 in the molecular mechanisms underlying long-term memory formation.

SYM-08-02

GENE-ENVIRONMENT INTERACTIONS AND EXPERIENCE-DEPENDENT MODULATION OF COGNITIVE FUNCTION IN MICE

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There has been enormous progress in recent years in understanding genetic factors contributing to brain development, function and dysfunction. However, great challenges remain in understanding how genetic and environmental factors combine in the healthy and diseased brain. We have been examining how genes and environment can combine to mediate cellular plasticity, and modulate cognitive and affective endophenotypes, in various mouse models. Huntington's disease (HD) is caused by a CAG trinucleotide repeat expansion encoding a polyglutamine tract in the huntingtin protein. HD patients exhibit cognitive deficits (culminating in dementia), psychiatric symptoms (the most common of which is depression) and motor abnormalities. In a transgenic mouse model of HD we have correlated early deficits of cellular plasticity with onset of cognitive (e.g. impaired spatial memory) and affective abnormalities (including sexually dimorphic depression-related behaviours), and identified potential molecular mechanisms. We have also demonstrated that enhanced sensory, cognitive and motor stimulation can significantly delay disease onset and slow progression in HD mice. A more specific component of environmental enrichment, voluntary physical exercise, was found to delay the onset of cognitive and affective endophenotypes. We have found that environmental enrichment, versus physical exercise alone, has differential effects on expression of specific genes. These findings have been extended to other mouse models. In addition to investigating the positive effects of enhanced mental and physical activity we are also exploring how negative environmental factors, such as chronic stress, can combine with genetic factors to modulate cognition and behavior. Our data indicates that the modulatory effects of various environmental stimuli on cognitive and affective function in wild-type and mutant mice involve experience-dependent changes in gene expression.

SYM-08-03

HISTONE MODIFICATIONS, DNA METHYLATION, AND MICRORNAS: THREE LAYERS OF EPIGENETIC COMPLEXITY INVOLVED IN MEMORY PROCESSING

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Broadly speaking, epigenetic mechanisms function to establish and maintain different gene expression programs in specific cell types, leading to phenotypically different tissues despite each cell sharing the same genetic information. Once considered important only during cellular differentiation early in development, these mechanisms of cellular memory are now known to be active across the lifespan. They orchestrate gene expression patterns in the adult brain, and recent evidence confirms that the epigenome serves as an important point of convergence between environmental signals, activation and repression of genomic responses, and persistent behaviour. Recently, we, and others, demonstrated that epigenetic regulatory proteins contribute to behavioural phenotypes in models of fear learning. Histone modification, DNA methylation and correlated gene expression patterns occur in brain regions that support fear-related memory, which may be associated with the development of psychiatric disorders such as phobia or post-traumatic stress disorder. We now have evidence suggesting that transient increases in the expression of small non-coding RNAs are also required for the establishment of fear-related memories. These findings represent a major conceptual shift in the way we think about genomics, toward one aligned with multi-layered epigenetic regulation of gene function in response to environmental cues, the importance of which for long-term memory and psychiatric disease is only beginning to be appreciated.

SYM-08-04

PLASTICITY-RELATED GENE NETWORKS

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The consolidation of long-term potentiation (LTP), a cellular mechanism of memory, is strongly dependent on *de novo* gene transcription; however, little is known about the gene networks and controlling elements that serve this function *in vivo*. **Purpose:** To identify gene networks and microRNA associated with LTP persistence. **Methods:** LTP-related gene expression was profiled using Affymetrix RAT230.2 microarrays 20 min, 5 h and 24 h (n=4) post-LTP induction at perforant path synapses in the dentate gyrus of awake, adult rats. The functional relationships of the differentially expressed genes, within and across each time-point, were explored using Ingenuity Pathway Analysis. LTP-related microRNA expression was investigated using Affymetrix GeneChip microRNA arrays 20 min post-LTP (n=4). **Results:** Our data show temporally specific gene responses, beginning with a rapid upregulation of gene expression that is accompanied by a downregulation of microRNA. At 20 min post-LTP the transcription factor, NFκB, extracellular signal-related kinase (ERK) and RNA Pol II form central hubs in the top three gene networks. At 5 h post-LTP, NFκB and ERK remain as hubs, but the structures of the networks change and canonical pathway analysis predicts a significant involvement of cAMP and G-protein coupled receptors. By 24 h post-LTP many genes are downregulated and microRNA now form significant hubs. **Conclusion:** Our data suggest that regulation of microRNA levels contributes both to the LTP-induced upregulation of gene expression as well as the subsequent homeostatic response marked by a downregulation of gene expression. Together this programme of genomic responses is likely to be critical to the consolidation of LTP *in vivo*.

SYM-09-01

STRUCTURE-FUNCTION STUDIES OF CYS-LOOP RECEPTORS

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Cys-loop receptors are key determinants of the delicate balance between cellular excitation and inhibition in the central nervous system. Their importance is illustrated by the myriad of diseases (e.g. anxiety, epilepsy, schizophrenia) and drugs (e.g. alcohol, tobacco, sedatives, anaesthetics, anxiolytics, anti-epileptics) that directly target them. Members of the Cys-loop receptor superfamily, which includes nicotinic acetylcholine (nAChR), 5-hydroxytryptamine type 3 (5-HT_3R), γ-aminobutyric acid type A/C ($GABA_{A/C}$R) and glycine (GlyR) receptors, are located in cell membranes and convert the chemical messages conveyed by neurotransmitters into excitatory or inhibitory electrical signals via the selective conduction of ions. Our work focuses on understanding how the structure of Cys-loop receptors influences their overall function. Each receptor is formed by five protein subunits, arranged around a central ion pore. Each subunit consists of four membrane spanning domains (M1-M4), with the second domain (M2) forming the majority of the ion channel wall. The amino- (N) and carboxy- (C) termini of the subunits lie on the extracellular side of the membrane, with the N-terminal providing ligand-binding sites, while a large intracellular loop extends between the M3 and M4 domains. We have employed site-directed mutagenesis and electrophysiology to identify residues that are critical to receptor function, demonstrating that single mutations have a dramatic effect on receptor function.

SYM-09-02

ELECTRICAL COUPLING AND A NON LINEAR RELATIONSHIP BETWEEN HYPERPOLARISATION AND VASODILATION COORDINATE VASODILATOR RESPONSES OVER DISTANCE

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Purpose: Spillover of acetylcholine from the neuromuscular junction induces dilation of microvessels that rapidly propagates upstream serving to match blood flow to tissue demand. Conduction depends on the rapid spread of hyperpolarisation through gap junctions, inducing synchronous closure of voltage-gated calcium channels (VGCCs) to coordinate vasodilation over distance. It is not understood how dilation can spread without attenuation if it relies on electrotonic propagation. We hypothesised that dilation could spread unattenuated despite passive decay of the electrical signal if the relationship between hyperpolarisation and relaxation was nonlinear. **Methods:** Spreading responses were recorded simultaneously using intracellular microelectrodes (140-180MΩ) and intravital microscopy in mouse cremaster muscle arterioles *in vivo*. **Results:** Focal acetylcholine application induced local hyperpolarisations that decayed with distance (local: -19±1mV; 1.5mm: -7±1mV), while spread of dilation was unimpaired (local: 32±5%; 1.5mm: 30±7% of maximum dilation). Reduction of the stimulus duration induced a decaying dilation (local: 30±5%;1.5mm: 14±4% of maximum dilation). Dilation also decayed in mice with impaired longitudinal coupling (connexin40 deficient, Cx40ko: local: 52±8%, 1mm: 32±7%). Dilations decayed after reaching a threshold membrane potential, which was shifted from -35mV to -45mV in endothelium dysfunctional Cx40ko. Pharmacological experiments indicated an increased contribution of T-type versus L-type VGCCs under basal conditions in Cx40ko. Computational modelling accurately predicted spread after application of voltage thresholds. **Conclusion:** We propose that the mechanism underlying unimpaired spread of dilation depends on a nonlinear component of electromechanical coupling. Dilation remains unattenuated if the hyperpolarisation is greater than the threshold but decays linearly with hyperpolarisation once the threshold potential is reached.

SYM-09-03

WHAT HAVE MICROGLIA GOT TO DO WITH IT? NEW DIRECTIONS IN THE NEUROBIOLOGY OF DEPRESSION

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Unipolar depression, otherwise known as major depressive disorder, is characterised by severe disturbance of mood, cognitive impairment, lethargy, disrupted sleep, a sense of despair and, very often, social withdrawal. At a neurobiological level, the disorder has long considered to be the result of reduced synaptic levels of serotonin and noradrenalin (i.e. the monoamine hypothesis of depression). This theory has, in a significant way, supported the widespread use of a variety of pharmacological agents that act to boost the synaptic levels of these monoamines. Indeed, in the last year alone, over 20 million prescriptions for antidepressants were filled in Australia. Somewhat perplexingly, however, there is relatively little evidence to show that monoamines are actually reduced in depression. At the same time there is increasing evidence that the efficacy of many antidepressants, particularly the more commonly prescribed selective serotonin re-uptake inhibitors, is significantly more modest than many have assumed. Together, these facts have led to a careful re-evaluation of what we know about the neurobiological basis of depression. This re-evaluation has led to the acceptance that depression is intimately linked with enhanced levels of inflammation (i.e. the neuroinflammatory hypothesis of depression). Using pre-clinical animal models, our research group has been investigating the cellular basis of these inflammatory events, and how they might be manipulated to reduce depression-like symptoms. Our findings are consistent with the view that region-specific populations of CNS microglia, which possess macrophage-like properties, play a critical role in the regulation of mood state. The aim of this presentation will be to provide an overview of our findings within the context of the existing literature, and then highlight possible research directions that may hold promise for the development of improved treatments for depression.

SYM-09-04

EXCITING THE BRAIN AIDS IN POST-STROKE FUNCTIONAL RECOVERY

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Post-stroke neural repair and rehabilitation processes continue for weeks to months after the initial insult. However, no pharmacological therapy is currently available for promoting recovery. Brain regions adjacent to stroke damage, the peri-infarct zone, are critical for rehabilitation, as they exhibit heightened neuroplasticity. This allows sensorimotor functions to re-map from damaged areas and involves, motor learning, dendritic remodeling, axonal sprouting, and cortical reorganization. Post-stroke these processes are in part mediated by activity dependent physiological changes and share similar molecular and cellular properties with learning and memory. We have recently shown that enhancing neuronal excitability by either dampening tonic GABA or activating AMPA receptor (AMPARs) currents aids in functional recovery. After a photothrombotic stroke in mice tonic neuronal inhibition is increased in the peri-infarct zone. This increased tonic inhibition is mediated by extrasynaptic GABAA receptors (GABAARs) and is caused by impaired GABA transporter-3/4 function. To counteract the heightened inhibition, we administered in vivo a benzodiazepine inverse agonist, L655,708, specific for the α5-subunit-containing extrasynaptic GABAARs from 3-42-days after stroke. This treatment produced an early and sustained recovery of motor function in both young (3-month) and aged (24-month) mice. Conversely, positive allosteric modulators of AMPARs enhance recovery of limb control over time when administered from 5-42-days after stroke. The contributions of AMPARs to recovery are mediated by release of Brain-Derived Neurotrophic Factor (BDNF) in peri-infarct cortex, as blocking local BDNF function in peri-infarct cortex blocks AMPAR-mediated recovery and prevents the normal pattern of motor recovery. Together, our results identify new pharmacological targets and provide the rationale for a novel strategy to promote recovery by enhancing neuronal excitability at a delay after stroke.

SYM-10-01

Abstract not available at time of printing

SYM-10-02

THE ROLE OF GLUTAMATERGIC SIGNALLING IN CNS MYELINATION

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Neuregulin expressed by axons can regulate myelination by signalling to ErbB receptors on myelinating cells. Furthermore, in CNS grey matter, neuregulin increases the expression of NMDA receptors. Oligodendrocytes at all developmental stages in the white matter exhibit NMDA evoked currents, mediated by receptors which show very weak magnesium block and are expressed in the myelin (Karadottir et al., 2005, 2008), indicating that they might play a role in myelination. We now use an assay in which cortical oligodendrocytes ensheath dorsal root ganglion cells (Wang et. al., 2006) to show that neuregulin and NMDA receptors interact to regulate myelination. Without neuregulin, blocking NMDA receptors had no effect on myelination. Adding neuregulin (in the form of the extracellular domain of NRG1-β1, 10ng/ml) increased myelination by 60%, and led to the majority of myelination being dependent on activation of NMDA receptors: NMDA receptor block decreased myelination by 80%. Blocking action potentials with TTX also had no effect in the absence of neuregulin, but greatly reduced myelination in the presence of neuregulin. Neuregulin's effect was associated with a 4-fold increase in NMDA receptor current in oligodendrocyte lineage cells. Thus, neuregulin apparently switches myelination from a default programme, that is independent of neuronal activity, to a mechanism that is regulated by glutamate released from active axons. These data reveal a function for oligodendrocyte NMDA receptors, and could provide a novel white matter explanation for how the linkage of neuregulin to schizophrenia can be reconciled with schizophrenia involving a malfunction of NMDA receptors. The absence of neuregulin in multiple sclerosis lesions, and enhanced remyelination by added neuregulin, suggest a role for neuregulin/NMDA receptor dependent remyelination after pathology.

SYM-10-03

TRANSCRIPTIONAL CONTROL OF CNS MYELINATION

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The regulation of oligodendrocyte specification and differentiation is a highly complex process requiring the coordinated action of a large number of transcription factors, including Nkx, Sox and Olig family members. Although the transcriptional regulation of the early specification and differentiation steps has been relatively well established, less is known about the transcriptional control of the later myelination phase. We have recently identified a novel transcriptional regulator, Myelin-gene Regulatory Factor (MRF) that is expressed specifically by postmitotic oligodendrocytes within the CNS. MRF is a nuclear protein containing an evolutionarily conserved DNA binding domain homologous to a yeast transcription factor. Knockdown of MRF in cultured oligodendrocytes prevents expression of most CNS myelin genes; conversely, forced expression of MRF within cultured oligodendrocyte progenitors or the developing chick spinal cord induces the precocious expression of myelin genes. In conditional knockout mice lacking MRF within the oligodendrocyte lineage, OPCs and postmitotic oligodendrocytes are generated but display severe deficits in myelin gene expression and fail to myelinate. These mice display an essentially complete absence of CNS myelin and do not survive beyond the third postnatal week. Moreover, deletion of MRF within mature oligodendrocytes in the adult CNS results in a severe demyelination, demonstrating an ongoing requirement for MRF in the maintenance of myelin integrity. These findings establish MRF as a critical transcriptional regulator essential for CNS myelination.

SYM-10-04

CNS MYELINATION: A GLIAL SPIN ON BDNF

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Generation of the insulating myelin sheath is crucial for the development and function of the central nervous system (CNS). However, little is known about the nature of the signals that control CNS myelination or how these signals are regulated. Brain-Derived Neurotrophic Factor (BDNF) has been implicated in promoting CNS myelination, however whether this results from a primary defect in myelination or is secondary to an indirect mechanism remains unclear. To understand the influence that BDNF exerts in this context, we investigated myelin development in BDNF heterozygous mice. We found delayed CNS myelination, accompanied by a reduction in the number of mature oligodendrocytes and an increase in oligodendrocyte progenitor cells during postnatal development, suggesting that BDNF plays a direct role in potentiating CNS myelination. To investigate the molecular mechanism that BDNF enhances myelination, we utilized co-cultures of dorsal root ganglia neurons and oligodendrocyte precursor cells, and found that exogenous BDNF significantly enhanced myelin formation in these cultures via a direct effect on myelinating oligodendroglial cells. Importantly, we found that BDNF retains its capacity to enhance myelination by oligodendrocytes derived from p75NTR knockout mice, indicating the expression of oligodendroglial p75NTR is not necessary for BDNF-induced myelination. Conversely, we observed that inhibiting TrkB signalling blocked the promyelinating effect of BDNF. The preliminary analysis of transgenic mice with conditional deletion of TrkB in oligodendrocytes (TrkBfl/flMBPcre) suggest that these mice exhibit a reduction of myelin protein expression, accompanied by an increase in oligodendrocyte progenitor cells in the CNS, indicating an innate precursor response. Together, our data reveal a previously unknown role for BDNF in potentiating the normal development of CNS myelination via signalling directly to TrkB-FL receptors expressed by oligodendrocytes.

SYM-11-01

ENDOCYTIC PATHWAYS IN NERVE TERMINALS: KEY TO INITIATION OF LOCAL AND RETROGRADE TRAFFICKING

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Purpose: Botulinum neurotoxins heavy chain (BoNT-Hc) and cholera toxins B subunit (CTB) are highly lethal proteins that have been used as tracer for local and retrograde trafficking pathway respectively. Clostridial botulinum bacteria produce seven serotypes (BoNT/A-G), which specifically intoxicate motor nerve terminals locally to produce flaccid paralysis. CTB has been used as a retrograde tracer in neuroanatomy but how CTB is internalised and packaged to be retrogradely transported is currently unknown. This study aimed to characterise the internalisation and trafficking pathways of BoNT/A. Methods: We used the recombinant binding domain of BoNT/A heavy chain (BoNT/A-Hc) and CTB to characterise the internalisation pathway using fluorescence and electron microscopy in purified hippocampal neurons. We then carried out endocytosis inhibition studies using hippocampal neurons, and motor nerve terminals. Results: BoNT/A-Hc binds to synaptic regions and is taken up in an activity-dependent manner in synaptic vesicles and clathrin-coated vesicles, before also entering endosomal structures and multivesicular bodies. CTB was also internalised in hippocampal neurons and in motor nerve terminals but in areas non-overlapping with that of BoNT/A-Hc. The effect of newly designed endocytosis inhibitors on BoNT/A-Hc and CTB uptake is discussed in this study. Conclusion: This study suggests that retrograde carriers are generated in specialised area of nerve terminals.

SYM-11-02

BRAIN CHOLESTEROL REDUCTION IN HIPPOCAMPAL SYNAPSES OF AGED MICE: CONTRIBUTION TO SURVIVAL AND PERFORMANCE

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Cholesterol plays structural and functional roles in cellular membranes. Among the latter, essential is its role in the generation and maintenance of signalling platforms -rafts-. In neurons, age comes with changes in cholesterol homeostasis:, decreased synthesis and increased hydroxylation (excretion). These changes ought to have strong implications in the lipid composition of the plasma membrane and, on the face of it, in the strength of raft-dependent signalling cascades. In agreement, 83% of hippocampal neurons in vitro (n=6 independent experiments) show increased TrkB activity with age, independently from the increase in the receptor's natural ligands (BDNF and/or NT4) and dependent on an age-paralleling mild (15%, n=6) and progressive cholesterol reduction. The same was observed in the hippocampus of wild-type mice (n=6) and in hippocampal neurons from BDNF knockout mice. In turn, we observed that cholesterol reduction is due to the twofold increase in expression of the cholesterol hydroxylating enzyme Cyp46. Cyp46 up-regulation during aging is the consequence of a transcriptional activation by oxidative metabolism by-products and by an increased mobilization of enzyme from intracellular pools. I will present unpublished data on the consequences of cholesterol loss/Cyp46 activation in synaptic transmission and survival during normative aging.

SYM-11-03

MODULATION OF AMYLOID PRECURSOR PROTEIN TRANSPORT- DELINEATING FUNCTIONAL DOMAINS

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The Alzheimer's disease amyloid precursor protein (APP) is the source of the neurotoxic amyloid beta peptide (Abeta). APP has a large extracellular ectodomain composed of distinct structural domains. We have investigated which regions of APP affect its metabolism and function. We have identified the N-terminal copper binding domain (CuBD), the D6a/E2 domain and the GXXXG motif (which modulates protein dimerisation and is present three times in the APP transmembrane region) as regulators of APP metabolism and/or neuritogenesis. Using the structure of the CuBD site we mutated the proposed Cu binding residues and expressed the mutant APP in cell lines. Mutating the histidines significantly impaired APP maturation and processing, and caused APP retention in the ER. The D6a domain binds to sorLA, a sorting receptor that regulates the transport/processing of APP in neurons. Using the D6a structure we tested the surface hydrophobic and charged regions of D6a as potential sorLA binding sites. Purified recombinant mutant D6a proteins were tested for binding to sorLA using surface plasmon resonance. This identified V364G and R424A as having altered binding to sorLA. APP constructs containing V364G or R424A are being transfected in mammalian cells for effects on APP processing and transport. Mutagenesis of the glycine residues in the APP GXXXG motifs causes a destabilisation of APP transmembrane dimerisation and this leads to increased production of secreted APP ectodomain but also increases secretion of a truncated N-terminal fragment (sNTF) in transfected SY5Y neuroblastoma cells. Stabilisation of the APP dimer via the incorporation of a cysteine near the C-terminus of the ectodomain causes a decrease in secreted APP and sNTF. Interestingly the cysteine mutant severely abrogates neuritogenesis following retinoic acid induced differentiation.

SYM-11-04

DISRUPTION OF PROTEIN TRAFFICKING IN ALZHEIMER'S DISEASE: APP, Aβ AND AMPA RECEPTORS

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The build-up of aggregated β-amyloid protein (Aβ) in the brain is considered to be a key event in the pathogenesis of Alzheimer's disease (AD). Targeting the production of Aβ or the neurotoxic effects of Aβ are a major strategy for therapeutic intervention in AD. Aβ is produced via two proteolytic cleavage events. The β-secretase (BACE1) cleaves the β-amyloid precursor protein (APP) to yield a 99-residue C-terminal fragment (C99) which is further cleaved by γ-secretase to yield Aβ. Our studies have shown that β-secretase cleavage of APP may be regulated by glycosaminoglycans (GAGs) such as heparin. We have identified a putative GAG-binding site in a loop domain of pro-BACE1 which regulates activity of the pro-enzyme. To examine the possibility that exogenous GAGs may influence APP metabolism and Aβ production, we have tested the effect of the heparin and enoxaparin (a low molecular weight form of heparin) on APP metabolism and Aβ production in cortical neurons in culture. Our studies show that heparin and enoxaparin lower Aβ production. Surprisingly, this effect is not mediated by an action on BACE1 processing. Instead, GAGs were found to stimulate a novel APP processing pathway that decreases the availability of APP for BACE1 cleavage. The 39-kDa receptor-associated protein was also able to influence APP processing. Transfection of APP-expressing CHO cells with a RAP cDNA resulted in a shift in APP processing away from the amyloidogenic β-secretase pathway towards the non-amyloidogenic α-secretase pathway. Finally, we have examined the effect of Aβ on AMPA receptor recycling on the surface of hippocampal neurons in culture. These studies have shown that secreted Aβ can decrease the level of cell-surface AMPA receptor by stimulating phosphorylation of serine-880 on the GluR2 subunit. Thus our studies suggest several mechanisms by which Aβ production or toxicity can be regulated and they suggest potential therapeutic targets for the treatment of AD.

SYM-12-01

THE CENTRAL ROLE OF KISSPEPTIN IN SEX STEROID REGULATION OF THE REPRODUCTIVE AXIS AND METABOLIC HOMEOSTASIS

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The reproductive system is driven by the pulsatile secretion of gonadotropin releasing hormone (GnRH) from the hypothalamus. GnRH stimulates synthesis and secretion of gonadotropins from the pituitary gland which, in turn, stimulates steroid production from the gonads. Feedback effects of sex steroids on the brain regulate the secretion of GnRH. Since the GnRH cells do not possess sex steroid receptors, feedback is via interneurons that do express the relevant receptors. Various types of hypothalamic cell express estrogen, progesterone and/or androgen receptors at varying levels, but a plausible model of the feedback loop from the gonads to GnRH cells was not formulated until appreciation of the important role of kisspeptin cells that are found in the arcuate nucleus and the preoptic region of the brain. A high level of expression of sex steroid receptors is a hallmark of kisspeptin cells and neuronal tracing studies link these cells to GnRH cells. Kisspeptin is a potent stimulator of GnRH secretion and the function of kisspeptin cells varies in relation to stage of cycle in the female. In addition, reduced kisspeptin activity in the anestrous period of seasonally breeding mammals further suggests a master role for this peptide in the control of reproduction. Metabolic status is an important determinant of reproductive function, with loss of fertility in conditions of low or high adiposity. Kisspeptin cells possess leptin and insulin receptors and may read peripheral metabolic status. Thus, reduced expression of the kisspeptin gene is seen during undernutrition and this is partially restored by leptin treatment. Neuronal tracing studies show inter-connectivity between appetite-regulating cells and kisspeptin cells, allowing for reciprocal dialogue with in the brain. Sex steroid effects on appetite may be relayed via kisspeptin cells. These studies clearly indicate that kisspeptin cells are the conduit for sex steroid feedback on the reproductive axis and also form a component of the network that links metabolic function and reproduction.

SYM-12-02

SIGNALLING CONVERGENCE: ESTROGEN RECEPTOR ALPHA MEETS RECEPTOR TYROSINE KINASES IN THE REGULATION OF GENE TRANSCRIPTION WITH IMPLICATIONS FOR NEURODEGENERATIVE AND MENTAL DISORDERS

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Purpose: Evidence suggests that altered estrogen/estrogen receptor alpha (ERα) signalling and reduced levels of brain-derived neurotrophic factor (BDNF)/full-length TrkB (TrkB-TK+) receptor in the molecular neuropathology of several neurodegenerative and mental disorders. Considering that ERα and TrkB-TK+ are capable of signalling through overlapping cellular cascades, we tested whether ligands for ERα were able to activate TrkB-TK+ and vice versa. Methods: Neuronal and non-neuronal cell-lines were co-transfected with a 3x estrogen response element (ERE) luciferase reporter construct, TrkB-TK+, and ERα; and changes in ERE-mediated transcription were measured by luciferase reporter assay in triplicate. Immunoprecipitation and western blotting were conducted to determine if TrkB-TK+ and ERα directly interact. Confocal microscopy was used to determine TrkB-TK+ intracellular localization. Results: Overexpression of TrkB-TK+ increased transcription at EREs without exogenous estrogen treatment (t=15.1, df=4, p=0.0001). In the presence of estrogen, TrkB-TK+ further potentiated ERα-mediated transcription (t=2.80, df=4, p=0.05). This synergistic effect was found to occur through cytoplasmic signalling of TrkB-TK+ via the MAPK/ERK pathway to phosphorylate ERα, leading to an induction in ERα-mediated transcription. Interestingly, PI3K/AKT activity constitutively inhibited baseline ERα-mediated transcription and TrkB-TK+-dependent transcriptional potentiation at EREs. Discussion: Our findings suggest that TrkB-TK+-linked second messenger signalling pathways can reciprocally regulate ERα-mediated transcription at EREs and that dysfunction in TrkB-TK+ signalling may occur upstream of, or in conjunction with a dysfunction in ERα. Moreover, transcriptional regulation by ERα may be decreased by reductions in TrkB-TK+.

SYM-12-03

UNDERSTANDING THE IMPACT OF ESTROGEN RECEPTOR BETA ACTIVATION IN THE BRAIN

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Estrogens have long been implicated in influencing cognitive processes, yet the molecular mechanisms underlying these effects and the relative roles of the estrogen receptors alpha (ERα) and beta (ERβ) remain unclear. Utilizing pharmacological, biochemical and behavioral techniques, we demonstrate for the first time that the effects of estrogen on hippocampal synaptic plasticity and agonists increased memory in rodents are mediated through ERβ. Selective ERβ levels of key synaptic proteins in vivo including PSD-95, synaptophysin and the knockout mice. In AMPA-receptor subunit GluR1. These effects were absent in ERβ hippocampal slices ERβ activation enhanced long-term potentiation (LTP), an activation inducedβeffect that was absent in slices from ERβ knockout mice. ER morphological changes in hippocampal neurons in vivo including increased dendritic branching and density of mushroom-type spines. An ERβ agonist, but not an ERα agonist, also improved performance in a variety of hippocampal-dependent memory tasks. Recent studies revealed that a new mechanism by which ERβ activation regulates synaptic plasticity, specifically through regulating protein translation. These findings elucidate an ERβ-mediated mechanism by which estrogen may influence synaptic plasticity in the hippocampus and ultimately learning and memory. Activation of this pathway may confer some of the CNS-mediated benefits of estrogen without the feminizing side effects, and offer a new therapeutic approach for diseases with cognitive deficits such as Alzheimer's disease and schizophrenia.

SYM-12-04

EFFECT OF ESTROGEN IN ANIMAL MODELS OF SCHIZOPHRENIA

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Purpose: Estrogen may be an effective adjunctive treatment in schizophrenia (Kulkarni *et al.*, Arch Gen Psychiatry 2008). At least part of this effect may be through modulation of sensory gating. We have shown in healthy volunteers that estrogen inhibits disruptions of prepulse inhibition (PPI) (Gogos *et al.*, Neuropsychopharmacology 2006) and loudness-dependence of auditory evoked potentials (LDAEP) (Guille *et al.*, J Psychopharmacology, in press), two measures of sensory gating. We have used pharmacological and receptor binding approaches in rats and mice to investigate the neurochemical mechanisms involved in these effects. **Methods:** Female rats (n=8-12 per group) were ovariectomized (OVX) and chronically treated with estrogen. PPI was assessed with automated startle boxes. Receptor binding was done with radioligand autoradiography. **Results:** Estrogen treatment prevented disruptions of PPI by both the dopamine receptor agonist, apomorphine, the serotonin-1A receptor agonist, 8-OH-DPAT (Gogos *et al.*, J Pharmacol Exp Ther 2010), and the NMDA receptor antagonist, MK-801 (unpublished). An extensive series of experiments with dopamine and serotonin receptor antagonist pretreatments suggested that this effect of estrogen was mediated by modulating dopaminergic mechanisms in the brain. Receptor binding experiments confirmed this model. Compared to OVX controls, estrogen treatment significantly increased dopamine transporter (DAT) levels and decreased D2 receptor density in the nucleus accumbens without effects on D1 receptors, serotonin transporters, or serotonin-1A and -2A receptor densities (Chavez *et al.*, Brain Res 2010). **Conclusions:** These results suggest that estrogen modulates sensory gating through an action on dopaminergic activity in rats. These data, as well as additional behavioural and neurochemical studies in control and aromatase knockout mice (Chavez *et al.*, Psychopharmacology 2009), confirm that estrogen could play a role in schizophrenia.