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The Auditory Laboratory

Deafness and other hearing disorders such as tinnitus are among the most common forms of sensory impairment with profound consequences for the individual and society. Normal hearing depends on the proper function of the many component parts of the inner ear and the brain pathways to which it is connected. Our laboratory seeks an integrated understanding of the normal operation of this sense organ and its associated neural pathways and to describe the mechanisms underlying various hearing pathologies.

PROJECTS

1. Effects of loud sound on gene expression in the cerebellum

(With Dr Jenny Rodger)

Loud sound exposure is known to provoke changes in gene expression in central auditory pathways and these changes are of interest for understanding the molecular and cellular basis of phenomena such as hyperacusis and tinnitus. It has recently been reported that human tinnitus patients have elevated neuronal activity in part of the cerebellum, a structure with multisensory roles but not normally associated with auditory processing. This project will use experimental animals to investigate changes in gene expression in the cerebellum that may be associated with this hyperactivity. Primers for a number of candidate guinea pig genes have already been constructed and qPCR will be used to measure changes in mRNA expression after loud sound exposure. In addition to the molecular skills, students will also acquire skills in small animal handling and minor surgery.

Note: this project would be suitable for a student with level 3 knowledge of molecular biological techniques (either PHYL3300 or PHYL3340 or GENE3300 together with SCIE3325).

2. Electrophysiology of plasticity in the auditory brainstem after partial unilateral deafness

We have now established that after a partial unilateral deafness induced by loud sound exposure, there is a time-dependent rise in the background neuronal firing levels in the contralateral auditory midbrain (the inferior colliculus). This neuronal hyperactivity is of interest because it is a likely neuronal correlate of tinnitus (phantom auditory sensation) that is an increasing problem in today's society. It is of interest to know whether this hyperactivity in the midbrain is generated at a lower level of the auditory pathway, eg the cochlear nucleus. The project will involve recording single neuron activity in anaesthetized guinea pigs. Students will acquire skills in small animal handling, anaesthesia and surgery, single neuron electrophysiology, digital data acquisition and analysis and histological verification of recording sites.

3. Anatomy of plasticity in the auditory brainstem after partial unilateral deafness

We have established that after partial unilateral deafness induced by loud sound exposure, the expression of genes related to inhibitory neurotransmission is decreased in the auditory midbrain. Although this is consistent with observed increases in neuronal excitability, it needs to be established that the relevant protein synthesis is altered. In addition, it is of interest to know precisely where in the midbrain the plastic changes occur. This project will use immunocytochemistry to map and quantify changes in inhibitory transmission proteins. Students will acquire skills in small animal handling, anaesthesia and surgery, immunocytochemistry, digital data acquisition and analysis of histological material.

4. Regulation of inner ear function by ATP receptors

Hearing sensitivity is determined by a number of variables in the peripheral receptor organ. One of these is the voltage in the scala media, the fluid compartment into which the stereocilia of the hair cells project. This large extracellular voltage is a vital element in the total driving force on ions through the hair cell transduction

channels. Disturbances of this voltage could underly a variety of hearing pathologies including tinnitus and hence it is interesting to study the mechanism by which it is regulated. We have consistently found that perfusion of the cochlea with agonists of receptors for ATP (so-called purinergic receptors) causes a marked rise in the voltage in the scala media (endocochlear potential). Three possible hypotheses of the mechanism of this increase are 1) that there is a change in activity in a neural efferent feedback loop regulating the voltage, 2) that there is activation of P2 receptors in the stria vascularis (the transporting epithelium that is responsible for generating the voltage) and 3) that there is a reduction in the current drain on the scala media voltage by closure of ion channels in hair cells and/or supporting cells lining the scala media. These hypotheses will be tested by a series of experiments using intracochlear perfusion, intracochlear electrical measurements and surgical interventions in the brainstem.

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1. Can non-musicians use visual cues to enhance tone detection in noise?

The ability to detect a tone in a noisy background is enhanced if the tone that is to be detected, is preceded by a tone (the cue) of the same frequency. This so-called “attentional filter” could play a role in improving the detection of salient signals such as speech in the presence of competing sounds. We have found that this effect is reduced in subjects with hearing loss, possibly contributing to the reduced speech intelligibility that such individuals experience. We have also found that in musically-trained subjects, including those with perfect pitch, a visual stimulus that conveys frequency-relevant information, can be as effective as an auditory cue in enhancing the detection of a subsequent tone. It would be of great interest to learn if visual cues could also enhance detection for hearing impaired subjects, but before proceeding with this stage of the research we need to know if the visual cuing effect depends on a well-developed pitch sense derived from prior musical training. The project will therefore investigate whether non-musicians can benefit from a visual cue, either immediately, or as a result of prolonged training on the task.

2. Is the effect of an auditory gap on the blink reflex altered in tinnitus sufferers?

Tinnitus is the sensation of a sound being present when there is none. It is a common consequence of inner ear damage and can have serious consequences for a sufferer’s quality of life, mood and cognitive function. Tinnitus quality and severity is commonly evaluated by eliciting conscious behavioural responses from subjects, for example, questionnaires, matching to a real acoustic stimulus, or various forms of ranking measures. Such measures are highly subjective and it would be of considerable use, both clinically and for scientific investigation of underlying tinnitus mechanisms, to have an objective measure of tinnitus quality and severity. Animal studies use a variant of the pre-pulse inhibition of the startle reflex in which a gap in continuous background noise takes the place of the usual pre-pulse acoustic stimulus. In animals with tinnitus, the gap is “filled-in” by the phantom auditory percept, and hence pre-pulse inhibition is reduced. The project will investigate whether a similar effect can be seen in tinnitus sufferers, using the blink reflex, which has been shown to exhibit pre-pulse inhibition.

Primary supervisor

Prof Mathew Martin-Iverson
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Project title Cannabinoid and stress interactions in Schizophrenia

Project description

There is current controversy concerning the relationship between cannabis use and schizophrenia. We are examining this relationship in both people and animal models, using the endophenotype of schizophrenia known as reductions in prepulse inhibition of the startle reflex (PPI). Conflicting reports of the effects of cannabinoid agonists on prepulse inhibition exist, some claiming that cannabinoids increase PPI and some claiming that they decrease PPI (Kedzior and Martin-Iverson 2005; Schneider and Koch 2002; Stanley-Cary et al. 2002). We have evidence that the effects of cannabinoids on PPI depends on the level of activation of glucocorticoid hormone receptors in rats. That is, the effects of cannabis on schizophrenia may alter with stress levels. This honours project will explore this relationship between stress hormone receptors and cannabinoid receptors further.

References

1. Kedzior KK, Martin-Iverson M (2005) Chronic cannabis use is associated with attention-modulated reduction in prepulse inhibition of the startle reflex in healthy humans. *Journal of Psychopharmacology* 0269881105057516
2. Schneider M, Koch M (2002) The cannabinoid agonist WIN 55,212-2 reduces sensorimotor gating and recognition memory in rats. *Behavioural Pharmacology* 13: 29-37
3. Stanley-Cary CC, Harris C, Martin-Iverson MT (2002) Differing effects of the cannabinoid agonist, CP 55,940, in an alcohol or Tween 80 solvent, on prepulse inhibition of the acoustic startle reflex in the rat. *Behavioural Pharmacology* 13: 15-28

Project title: Effects of Dexamphetamine in Humans on Prepulse Inhibition of the Startle Reflex, Time Perception and Hedonia

Much research has shown relationships between the effects of dexamphetamine and schizophrenia. Both have been associated with decreased prepulse inhibition of the startle reflex (PPI) and with changes in time perception and hedonia in rats treated with dexamphetamine and in both people with schizophrenia, and PPI deficits have been observed in certain rodent models of schizophrenia. However, the effects of dexamphetamine in these measures in humans are not presently clear. In this project, all three measures will be taken in people who have been given 0.45 mg/kg of dexamphetamine in a double-blind placebo-controlled cross-over design.

Project title Behavioural analysis of MDMA analogues

3,4-methylenedioxymethamphetamine (MDMA, ecstasy) is a commonly used illicit drug in Australia. With the recent discovery that MDMA may have therapeutic value for conditions as diverse as post-traumatic stress disorder and Parkinson's disease, interest in the development of analogues of MDMA has grown. Dr Matthew Piggott and members of his lab at UWA have synthesised a number of analogues of MDMA, many of which have not been tested. This project seeks to characterise the behavioural effects of some of these analogues and compare them to known psychoactive drugs including MDMA and other amphetamines, such as dexamphetamine. Models used will include the open field and elevated plus maze tests, prepulse inhibition and tests of social behaviour such as social interaction and resident-intruder procedures.

Project title Psychopharmacological analysis of an endocannabinoid drug and a mGluR receptor antagonist

Project description

There is current controversy concerning the relationship between cannabis use and schizophrenia. There is evidence that it may be detrimental to those with schizophrenia, but there is also evidence that it can treat people with schizophrenia. In this series of experiments, we will examine the effects of an inhibitor of Fatty Acid Amide Hydrolase (FAAH), the enzyme responsible for metabolising endogenous cannabinoids such as anandamide and therefore regulates its duration of action, in an animal model of schizophrenia, Prepulse Inhibition of the Startle reflex (PPI). This drug should elevate endogenous cannabinoid in the brain. In addition, an antagonist for the metabotropic Glutamate receptor subtype 5 (mGluR5) will be tested in the same model. The mGluR5 receptor is often localised presynaptically, regulates neurotransmitter release, and has been implicated in schizophrenia. Since the primary action of cannabinoid CB1 receptors is also to regulate neurotransmitter release, especially that of glutamate, these two drugs will be tested individually and together, to determine if the mGluR5 receptor can potentiate the effect of the FAAH inhibitor.

DR LINDY FITZGERALD, PROFESSOR SARAH DUNLOP

Experimental and Regenerative Neurosciences, School of Animal Biology, UWA

Title: First in vivo assessments of nanomaterials for treatment of secondary degeneration following injury to the central nervous system

Nervous tissue can be further damaged following brain and spinal cord injury, when tissue outside the trauma site succumbs to delayed damage known as secondary degeneration. Current delivery of therapeutics to prevent secondary degeneration does not work effectively. We have comprehensively characterised a model of secondary degeneration in the central nervous system, where we partially transect the optic nerve, resulting in clear spatial separation of tissue undergoing secondary degeneration from the initial injury. We are therefore in a good position to assess the potentially beneficial effects of new treatments for secondary degeneration. In collaboration with our colleagues at the Centre for Strategic Nanofabrication at UWA, particularly Dr Iyer Swaminatha, we are developing nanomaterials with real possibilities to alleviate the complex problems of secondary degeneration. However, toxicity of the nanoparticles may preclude use of this exciting treatment tool. Using the visual system we will conduct a first assessment of the toxicity of the nanomaterials with the eventual aim of examining the potential of nanomaterials loaded with therapeutic drugs to prevent secondary degeneration. These studies form part of our ongoing collaborative assessment of nanomaterials in neuroscience, involving our colleagues at the Centre for Strategic Nanofabrication, Prof Alan Harvey at the School of Anatomy and Human Biology and Dr Giles Plant, Director of the Eileen Bond Spinal Research Centre.

The Aims of the current project are to ensure nanomaterials we have developed are not toxic and to ascertain their location in the body following intravitreal administration. Specifically the project aims to:

1. Ensure there is no toxicity or adverse effects on animal health following intravitreal administration of nanomaterials.
2. Ascertain the location of nanomaterials following intravitreal delivery of positively or negatively charged fluorescent polymer nanoparticles.

PROFESSOR SHAUN COLLIN

Eco-Neurophysiology Laboratory School of Animal Biology Honours Projects

The following are a list of potential Hons Projects for 2010/2011 (Feb or mid year intakes). More information can be provided by Professor Shaun P. Collin (WA Premier's Research Fellow) at s.collin@uq.edu.au (at UWA from the 7th December 2009). Senior members of staff (Associate Professor Nathan Hart, n.hart@uq.edu.au and Professor David Hunt, d.hunt@ucl.ac.uk) also listed after each project can also be contacted by email for more information.

1. Spectral sensitivity and tuning of visual pigments in the eyes of marine and estuarine teleost fishes. (Hart, Collin)
2. Inner ears of deep-sea myctophids: Structural adaptations for hearing. (Collin)
3. Visual processing in the eye of birds: Neuronal mosaics and retinal circuitry in the avian retina (Hart, Hunt, Collin)
4. Circadian control of behaviour: the structure and function of the pineal organ in sharks and rays (Collin, Hart)
5. Eye retraction in aquatic vertebrates: vision and eye protection in amphibious fishes (Collin, Hart)
6. The eyes of deep-sea fishes: the structure and function of the eyestalk. (Collin)
7. Sampling of colour space in the eyes of vertebrates: an *in situ* hybridization study of retinal photoreceptors (Hunt, Hart, Collin)
8. A functional connection between olfaction and vision: the behavioural basis of the olfactoretinalis system in fishes (Collin)
9. Magnetoreception in birds: the identification of a signal detector (Hart, Collin)