

## Neuropharmacology Laboratory

### Group Head

Dr Richard Loiacono

BSc(Hons) PhD

Tel: +61 3 9905 4859

Fax: +61 3 9905 5851

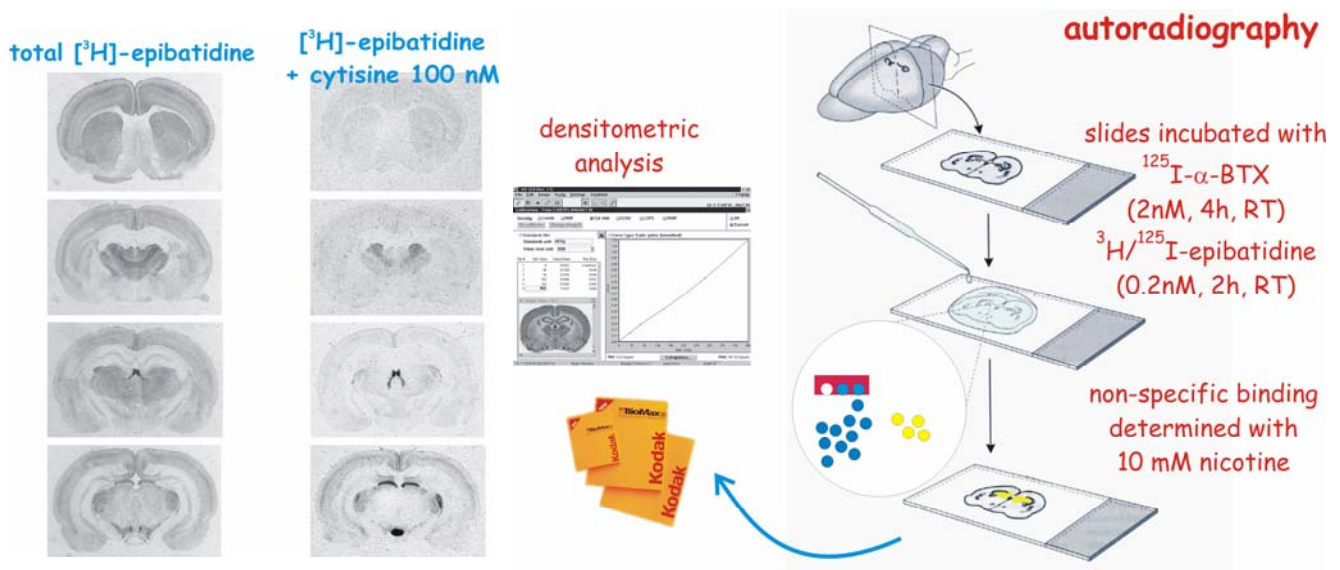
### Specific Interests

My laboratory is interested in investigating the role of ionotropic receptor families (eg: glutamate, GABA and nicotinic receptors) in neurological disorders such as Parkinson's Disease, Alzheimer's Disease and Schizophrenia, as well in the neurodegenerative / neuroadaptive processes that may be associated with these diseases.

### Current projects

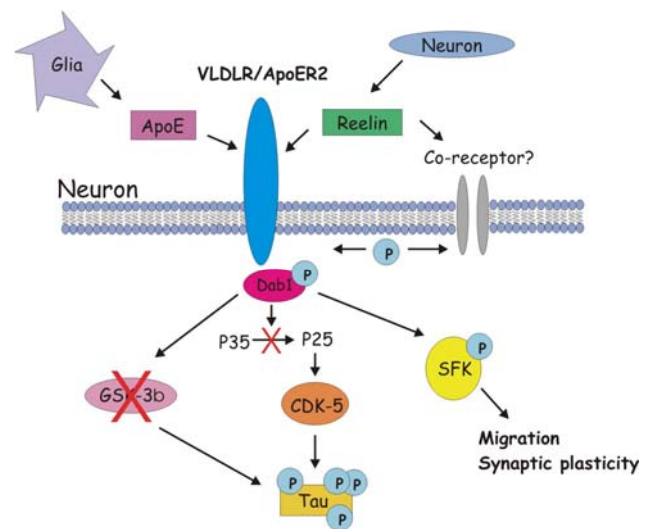
#### Nicotinic Receptors, Dopaminergic and Serotonergic Neurotransmission and Schizophrenia:-

Schizophrenia is a common and complex disorder with a range of symptoms including auditory hallucinations, delusions and flattened affect. A substantial component of schizophrenic symptomatology appears to arise from deficiencies in an ability to automatically filter or "gate" irrelevant thoughts and sensory stimuli from intruding into conscious awareness. In schizophrenic patients, there is a higher than normal prevalence of tobacco smoking (90%). Several studies have since demonstrated that nicotine, administered either through smoking or gum, transiently normalizes some of the symptoms of schizophrenia, including several sensory gating deficits. Conversely, worsening of symptoms occurs following smoking cessation. We believe the most interesting finding to date is that schizophrenic smokers show a significantly greater clinical response to the atypical antipsychotic clozapine than do schizophrenic non-smokers. The aim of this project is to understand why nicotine potentiates the beneficial actions of atypical antipsychotics such as clozapine.



### ApoE, statins cholesterol and Alzheimer's Disease

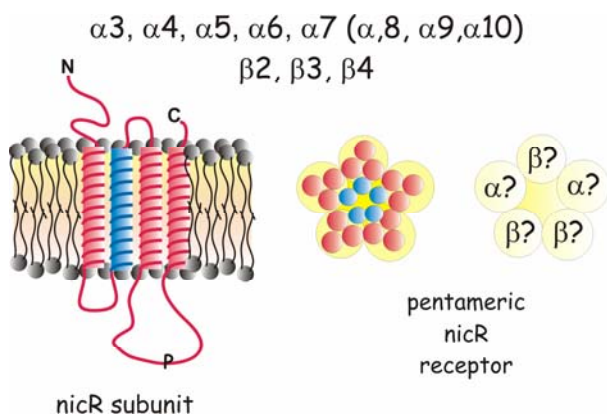
The pathophysiology of Alzheimer's disease is thought to be due to the accumulation of beta-amyloid in the brain. beta-amyloid is derived from APP (amyloid precursor protein). Through different enzymic pathways (alpha, beta and gamma secretases) APP can give rise to APPs $\gamma$  which is neuroprotective and has trophic effects or beta-amyloid; which is neurotoxic and neurodegenerative. There is evidence to suggest an important link exists between beta-amyloid, cholesterol and Alzheimer's disease; the prevalence of Alzheimer's disease is reduced in people taking cholesterol-lowering agents (HMG-CoA reductase inhibitors / statins such as simvastatin). There is now some evidence suggesting that statins reduce beta-amyloid production both in vitro and in vivo; and that this might be due to the shunting of APP towards the increased production of APPs $\gamma$  and decreased production of beta-amyloid. ApoE exists in three major forms, ApoE $\epsilon$ 2, ApoE $\epsilon$ 3, and ApoE $\epsilon$ 4, of which ApoE $\epsilon$ 3 is the most common form, with the ApoE $\epsilon$ 4 form being much weaker in biological function. ApoE has several functions in the body; it is important in cholesterol transport and clearance. Some disease states are associated with the disruption of normal ApoE function. For example, the presence of ApoE $\epsilon$ 4 form reduces the efficacy in transport and regulation of cholesterol levels, and the presence of this form in humans is a high risk factor for the development of Alzheimer's disease (AD). There is increasing evidence that ApoE has roles in synaptic remodelling, repair, and regeneration after brain injury that are independent of its role in cholesterol transport. Studies have suggested that ApoE may be increased in brain responses to neuronal injury or disease, and its presence has been shown to improve the outcome after brain injury. Mice which are deficient in ApoE, or mice which have ApoE $\epsilon$ 4 form have been shown to respond poorly to brain injury. The mechanism by which ApoE protects or modifies the outcome of brain injury and the impact of this on ongoing neurodegenerative diseases is not yet understood.



### Inflammatory Processes in Parkinson's Disease

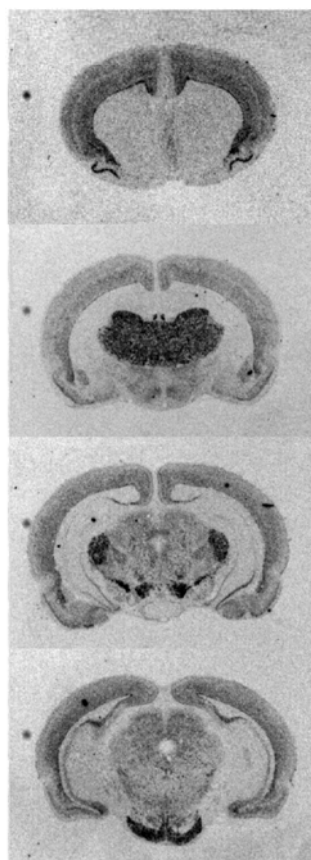
Parkinson's disease (PD) is a multifactorial disease and is characterised by a loss of the transmitter dopamine and most animal models try to mimic this loss by the selective destruction of the neurones that contain this transmitter. Recent evidence however suggests that the part of the process of neurodegeneration involves the activation of inflammatory mechanisms. In order to target therapy for PD, the underlying cause for its incidence and progression must be better understood. It is likely that the inflammatory process accompanies the loss of dopamine in PD, but how inflammation effectively kills neurones is unclear. This project uses a model of PD that involves inflammatory processes and examines the role and production of reactive oxygen species (ROS) as part of the process that leads to dopaminergic cell death and the development of PD. Specific aspects of the project examine the role of NADPH oxidase (and its isoforms) in the generation of ROS.

## Nicotinic Receptors in Parkinson's Disease

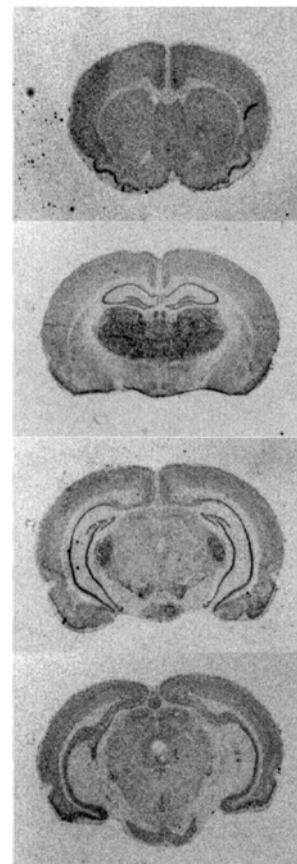


There are 2 main types of nicotinic receptor present in brain, the alpha4 and the alpha7 type, although many additional types also exist. Nicotinic receptors are largely localized to basal ganglia structures; and thus are of direct relevance to the fine control of movement. Interestingly, in Parkinson's disease there is a loss of nicotinic receptors in these regions. Our studies have focused on whether nicotinic receptor activation can slow the neurodegeneration seen in Parkinson's disease. We have already shown that the activation alpha4 type nicotinic receptor is important in preventing neurodegeneration in animal models of Parkinson's disease. What we don't know is whether these are the only types of nicotinic receptors involved

Nicotinic  $\alpha 4$  subunit mRNA expression



Nicotinic  $\beta 2$  subunit mRNA expression



## Endocannabinoids in Neuroprotection

The endocannabinoid system comprises the endogenous lipids anandamide and 2-arachidonoylglycerol (2-AG), the proteins responsible for their biosynthesis, uptake and inactivation, and the receptors through which their responses are mediated; the cannabinoid receptors (CB1 and CB2). This system is proposed to be involved in various neurodegenerative diseases such as Parkinson's and Huntington's diseases as well as Multiple Sclerosis. It has been demonstrated that the endocannabinoid system can protect neurons against some forms of neuronal damage.

## Members of Laboratory

Ms Nicola Ingram (PhD Student)  
Ms Fiona Kennon (PhD Student)  
Mr Leigh Brown (PhD Student)  
Ms Stephanie Robinson (PhD Student)  
Mrs Maha El Batsh (PhD student)  
Ms Sarah Brooker (BNS Hons Student)  
Mr Josh Laing (BMS hons Student)  
Mr Aaron Mentha (BMS hons Student)

## Funding

National Health & Medical Research Council  
Brain Foundation Australia

## Recent selected publications

1. Ingram, N., Martin, S., Wang, JH., van der Laan, S., Loiacono, R., & van den Buuse M. Interaction of corticosterone and nicotine in regulation of prepulse inhibition in mice *Neuropharmacol.* 48, 80-92 (2005)

2. Wickramaratna JC, Fry BG, Loiacono RE, Aguilar MI, Alewood PF, Hodgson WC. Isolation and characterization of cholinergic nicotinic receptors of a neurotoxin from the venom of the *Acanthopis* sp. Seram death adder. *Biochem Pharmacol.* 68 383-94 (2004)
3. Henderson DJ, Eberl S, Thomson S, Smith A, Allan RD, Fulham MJ, Loiacono R, Kassiou M. 3-Pyridyl ethers as SPECT radioligands for imaging nicotinic acetylcholine receptors. *Appl Radiat Isot.* 60669-76 (2004)
4. Hemedah, M. Loiacono, R.E. Coupar, I.M and Mitchelson, F.J. (2001) Lack of evidence for histamine H3 receptor function in rat ileum and human colon. *Naunyn Schmeideberg's Arch Pharmacol* 363 133-8 (2001)
5. Ryan, R.E., Ross, S., Drago, J. and Loiacono, R.E. Dose Related Neuroprotective Effects of Nicotine in 6-hydroxydopamine treated rats and  $\alpha 4$  nicotinic receptor knockout mice. *Brit J Pharmacol* 132 1650-6 (2001)
6. Ryan R.E and Loiacono, R.E. Upregulation in  $\alpha 7$  nicotinic receptor subunit mRNA in rat - Role in addiction to nicotine. nicotinic receptors in a rat model of Alzheimer-type neurodegeneration. *Neuroreport* 12 569-72 (2001).
7. Ryan, R. and Loiacono, R.E. Nicotinic receptor mRNA expression in rat thalamus – Relevance to human schizophrenia. *Neuroreport* 11 3693-8 (2000)
8. Ryan, M.C., Loiacono, R.E. & Gundlach, A.L Galanin messenger RNA during postnatal development of the rat brain: expression patterns in purkinje cells differentiate anterior and posterior lobes of cerebellum. *Neuroscience* 78 1113-1127 (1997)