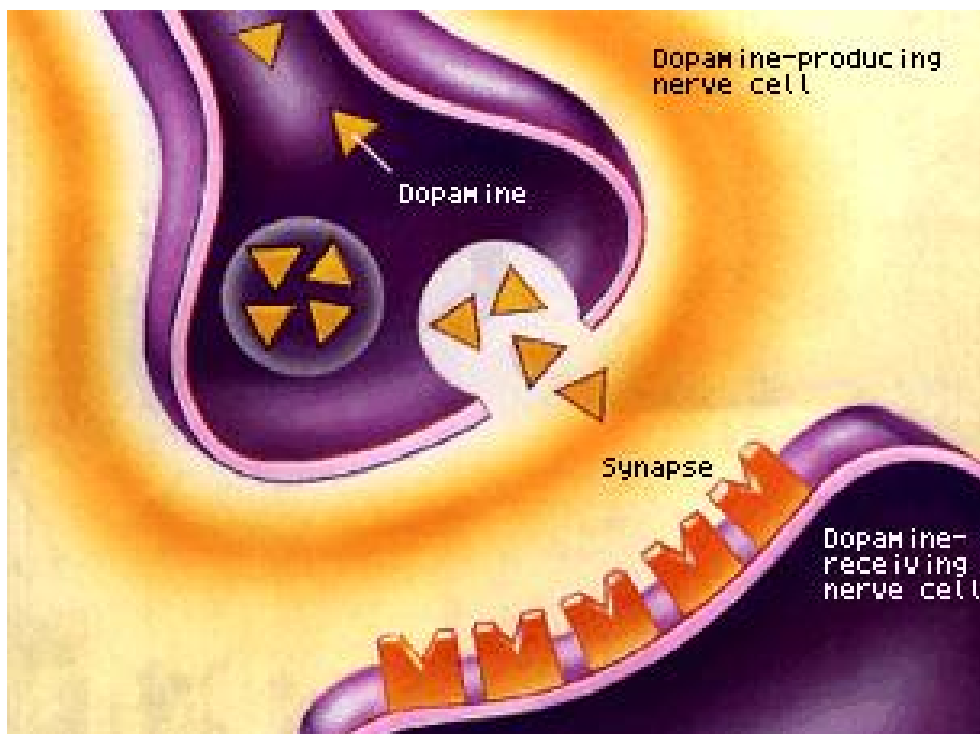


School of Medical Sciences Discipline of Pharmacology

Honours Projects Available in 2009



COMPARATIVE SEDATIVE EFFECTS OF METHADONE AND BUPRENORPHINE*

Supervisor:

Prof Jason White

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Buprenorphine is a partial agonist used as an analgesic and in the treatment of opioid dependence. There is some evidence suggesting that buprenorphine may have less pronounced sedative effects than morphine and this is consistent with the self-report of patients who indicate that they feel more alert than normal when maintained on buprenorphine. However, there are no experimental data that provide objective evidence of this difference. Most measures of sedation rely on performance of psychological tests or subjective report. However, the measurement of saccadic eye movement provides an objective indicator of sedation. The current study will utilise this test together with self-reported and psychological measures of sedative effects to determine whether there is a difference between patients maintained on methadone and buprenorphine.

Students will be expected participate in the development of the design of the study and the ethics application. They will learn to conduct human research to the standard for clinical trials and to prepare the appropriate materials. They gain experience in human experimental research in a controlled environment and also interaction with a variety of clinical staff.

EFFECTS OF CAFFEINE ON OPIOID-INDUCED RESPIRATORY DEPRESSION*

Supervisors: Prof Jason White, Dr Paul Williamson

Opioid-induced opioid respiratory depression is the major cause of death from prescription drugs. In patients maintained on methadone for treatment of opioid dependence, it has been demonstrated that the highest risk occurs in the first two weeks of treatment. We have shown in a number of studies that even amongst tolerant patients, there is a decreased respiratory rate and oxygen saturation that occurs as methadone concentration increases following oral dosing. Methylxanthines are used clinically for treatment of sleep apnoea. There is also limited evidence from animal studies that caffeine may reverse the respiratory depression induced by morphine. In this study we will examine the hypothesis that caffeine is able to reduce opioid-induced respiratory depression in patients maintained on methadone.

The project will be conducted as per the standards of a clinical trial and students will learn the methodology involved in such trials. They will also be expected to assist in the preparation of the ethics proposal and therefore the detailed design of the study. They will learn the practicalities of human research and interaction with clinical staff in conducting this research.

EFFECTS OF APREPITANT ON OPIOID-INDUCED HYPERALGESIA*

Supervisors: Dr Abdallah Salem, Assoc Prof Rod Irvine, Prof Jason White

Opioid-induced hyperalgesia has been demonstrated in animal models, including a model developed in our laboratory. These models can be used to examine strategies to prevent and reduce the hyperalgesia following repeated opioid administration. There is some evidence that the NK1 antagonist aprepitant may be effective in preventing opioid-induced hyperalgesia, but this is yet to be tested experimentally. The present study will use our established animal model to test whether co-administration with morphine or methadone will prevent the hyperalgesia that develops with prolonged administration of the opioid.

DO ENANTIOMERS OF METHADONE HAVE POTENTIAL AS ANTI-LEUKAEMIA AGENTS?

Supervisors: Prof Jason White, Dr Ian Musgrave

The therapeutic opioid methadone, used to treat cancer pain and opioid addiction, is also a potent inducer of apoptosis in cancer cells, thereby inhibiting their growth. Methadone is also able to reverse chemoresistance, rendering drug resistant cancer lines susceptible to drug therapy once more. Unfortunately, the levels of methadone required to kill leukaemia cells would produce respiratory arrest in humans. Currently, all experiments have used racemic methadone. However, methadone enantiomers have different affinities and efficacies at opioid receptors, so a more therapeutic concentration of methadone may be achieved using enantiometrically pure drugs. This project will examine testing the role of opioid receptors in leukaemia cells using S-methadone and naloxone blockade as well as a range of opioids with different μ -receptor potencies. Methods include tissue culture, cell viability assays and molecular biology.

PHARMACOGENOMICS AND METHADONE MAINTENANCE THERAPY*

Supervisors:

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Opioid dependence is a major national and international problem costing hundreds of millions of dollars in Australia alone. Both nationally and internationally the most common treatment of dependence is that of substitution therapy such as methadone maintenance therapy.

There is wide inter-individual variability in the pharmacokinetics and pharmacodynamics of methadone that influences the success of treatment. This variability may be partly explained by differences in the metabolism, mediated by the CYP3A and 2B6 enzymes, whose expression is influenced by genetic polymorphisms. This project will investigate the impact of the genetic variability of the drug metabolising enzymes CYP3A5 and 2B6 on the variability in methadone metabolism determined *in vitro* using human liver microsomes. The student will learn basic molecular biology, *in vitro* drug metabolism and drug analysis (HPLC) techniques.

PHARMACOGENOMICS OF OPIOID ADDICTION*

Supervisors: Dr Janet Coller, Dr Mark Hutchinson, Prof Andrew Somogyi

Opioid addiction and dependence is a major national and international problem costing hundreds of millions of dollars in Australia alone. Many factors, both environmental and genetic, have been associated with the development of dependence and impact on the successful treatment with opioid substitution programmes such as methadone maintenance treatment. In particular the immune cells of the brain (glia) may play a role as they are activated to release pro-inflammatory cytokines when opioids are present. We have recently shown that lack of genetic variability in a gene encoding for pro-inflammatory cytokine is associated with the risk of developing dependence, most probably as a result of altered response of glia to opioid. Consequently, differences in the genetic variability of the complex network of genes involved in the regulation of pro-inflammatory cytokines and immune signalling pathways in general may also be associated with the development of opioid dependence. Two projects will be offered to retrospectively investigate the impact of the genetic variability of two genes, interferon-gamma and MCP-1, on the occurrence of opioid dependence. The student will learn basic molecular biology techniques used routinely for genotyping.

NEUROIMMUNOPHARMACOLOGY OF NEUROPATHIC PAIN AND OPIOIDS

ACTION*

Supervisors:

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Over the past 15 years there has been a growing recognition that the immune cells of the brain and spinal cord contribute significantly to neuropathic pain states. Over the past 5 years these same immunocompetent cells have been implicated in opposing the analgesic actions of opioids & contribute to the negative/unwanted pharmacology associated with opioid use, ie opioid tolerance, reward & dependence. As such pharmacological targeting opioid-induced & neuropathy-induced glial changes is a novel & untargeted mechanism of action for the treatment of neuropathic pain & improvement of opioid analgesic actions. In collaboration with my colleagues at the University of Colorado at Boulder I have demonstrated glial modulatory capacity of several existing pharmacotherapies with differing chemistries and indications. As such the beneficial action of these agents in reversing animal models of neuropathic pain & potentiating opioid analgesia will be examined. Up to 3 projects will be offered to investigate the action of novel glial modulatory pharmacotherapies in neuropathic pain & opioid analgesia.

The research proposed will incorporate training in several intricate surgical techniques (intrathecal catheterisation, spinal cord & nerve surgeries), in addition to extensive animal handling, behavioural testing & molecular quantification techniques. Since these projects

involve the use of challenging experimental techniques, only students who can demonstrate strong commitment to this type of research will be considered. An interview process will be used to determine appropriateness of interested students to the research projects.

COLLABORATIVE PHARMACOGENOMIC STUDIES

Supervisor: Prof Andrew Somogyi

Several pharmacogenomic studies are likely to be offered for 2009 in collaboration with Prof Chris Sweeney (Cancer Therapy) investigating the role of polymorphisms in several CYP enzyme genes in the response, both efficacy and toxicity to drugs used in cancer treatment. Please contact Prof Somogyi for more details.

CLINICAL AND LABORATORY STUDIES OF METFORMIN IN PREGNANCY

Supervisors: Prof Andrew Somogyi, Dr Bill Hague, Dr Matt Doogue

Metformin is a drug that has been used for many years in the management of patients with diabetes. It improves insulin sensitivity, probably by activating AMP kinase, and is not associated with weight gain or hypoglycaemia. Its use in pregnancy has, however, remained controversial until a recent large randomised trial (the MiG study) showed it to be as effective as insulin in reducing the neonatal complications of gestational diabetes. There was less severe neonatal hypoglycaemia in the offspring of women taking metformin, while control of maternal blood glucose was achieved more quickly with metformin compared with insulin. About 2% of women in the metformin arm were not able to tolerate metformin at all without developing severe side effects, while 9% could only tolerate a limited dose. Experience of the use of metformin in pregnant women outside the trial has shown that some women are able to tolerate higher than average maximum doses compared with non-pregnant persons, perhaps due to the increased renal clearance of the drug in pregnancy. Some of this variation in tolerance to metformin may be due to different genotypes of the various metformin transporters. This project investigate the role of genetic variability in OCT-1 and OCT-2 in the response (efficacy/side effects) to metformin by genotyping subjects for OCT-1 and OCT-2 and relating the genotype to their responses. It will also explore the responses of subjects both to the timing of metformin administration and to different formulations of metformin in respect of their glucose and insulin profiles.

ASSESSMENT OF THE ENDOGENOUS OPIOID SYSTEM IN THE ELDERLY BY PLACEBO ANALGESIA*

Supervisors: Prof Paul Rolan, Dr John Maddison

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Placebo analgesia is a well studied phenomenon and a significant component is due to activation of the endogenous opioid system, as it is largely blockable by the opioid antagonist naloxone.

The cold pain model, commonly used pain test, is highly sensitive to exogenous opioids and might be an indicator of the activity of the endogenous opioid system. Large surveys have found that elderly people have a lower cold pain tolerance time than others. We hypothesise that this may be due to reduced activity of the endogenous opioid system. We propose to investigate this by comparing placebo analgesia in elderly and younger participants. The project will be a clinical study based at the Pain and Anaesthesia Research Clinic at the Royal Adelaide Hospital. Students will learn the principles of undertaking clinical trials to the standards of Good Clinical Practice which includes protocol design, ethics committee submission, data capture and management.

INFLUENCE OF AMBIENT TEMPERATURE ON NEURONAL DEGENERATION FOLLOWING ACUTE AND REPEATED MDMA (ECSTASY) ADMINISTRATIONS IN RATS*

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The main 3,4-methylenedioxymethamphetamine (MDMA)-induced adverse effect is disruption of normal thermoregulation leading to life threatening hyperthermia. MDMA-induced 5-HT release has been suggested as the main neurotransmitter involved in mediating acute changes in thermoregulation. We have recently investigated influence of ambient temperature on MDMA-induced hyperthermia and striatal 5-HT release in fully conscious rats. Although our results demonstrated a greater risk of hyperthermia when MDMA is administered at elevated ambient temperatures, the functional significance of this effect is not clear. In addition, the role of the main MDMA metabolite, 3,4-methylenedioxyamphetamine (MDA), in MDMA-induced hyperthermia is yet to be determined. This project will investigate influence of ambient temperature on neuronal degeneration following acute and repeated administration of MDMA and MDA. Brain regions known to play a central role in MDMA-induced thermoregulation disruption and rewarding effects will be investigated. The aim of this project is to use an established and reliable marker of neuronal degeneration to compare MDMA and MDA-induced neurotoxicity following acute and repeated administrations of the drug at normal ambient temperature (22°C) and elevated ambient temperature (30°C).

CANNABINOID PHARMACOLOGY AND BIOCHEMISTRY IN THE HUMAN GASTROINTESTINAL TRACT

Supervisor:

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The discovery of specific membrane-bound cannabinoid (CB) receptors in the early 1990s led to the subsequent discovery of endogenous ligands for the cannabinoid receptors. The

pharmacological effects of all CB ligands are mediated through two G protein-coupled receptors termed CB1 and CB2; CB1 receptors are found predominantly in central and peripheral neurons (including enteric neurons in the gut plexus). Cannabinoids suppress motility and secretion in the gut and as such, may be promising pharmacotherapies in the treatment certain gastrointestinal disorders. They do this in much the same way as opioids, by inhibiting the release of contractile neurotransmitters like acetylcholine. Recently however, we found that endogenous cannabinoids do not share the same functional properties of exogenous, synthetic cannabinoids in modulating enteric nerve transmission.

This project aims to discern why there is a distinct difference between endogenous (endo) cannabinoids and synthetic cannabinoids on gastrointestinal inflammation, which may centre on endocannabinoids also being substrates for inflammatory reactions via COX-2. This specific project will use human gastrointestinal tissue taken from patients undergoing surgical procedures at local hospitals. This tissue will be used in conventional organ bath experiments to determine the role of endocannabinoids on functional indices, such as neurogenic contractility. Additionally, binding studies may be carried out to determine whether endogenous cannabinoids, such as anandamide and 2-AG, may be acting as allosteric modulators of the muscarinic receptor. Other interesting pharmacological or immunohistochemical studies may be performed on the tissue. This includes culturing mucosal explants with cytokines to induce inflammatory changes, with pharmacological interventions in cannabinoid, COX-2 and prostamide pathways to test their effects on the development of inflammation.

Students will be liaising with pathology and nursing staff, collecting biopsies and performing organ bath and binding studies. This project may suit someone who is interested in the hospital and surgical environment generally. Students will present their findings from this project at the national pharmacology conference (ASCEPT) in late 2009.

CHARACTERISING THE BIOACTIVE PROPERTIES OF RED WINE

Supervisors: Dr Scott Smid, Dr Ian Musgrave

Since the identification of the health benefits of moderate red wine consumption, intensive research has been focused on profiling the extent of its bioactivity and the isolation of bioactive components from red wine that may confer such health benefits. The research has been systems-based, centred predominantly on cardiovascular health, but has also investigated effects on neurodegeneration, cancer development and inflammation. The scientific basis underlying the beneficial effects of red wine on cardiovascular health has focused on the effects of red wine polyphenols (RWPs) on blood vessel (vascular) function. RWPs promote endothelial-dependent relaxation primarily via an action on nitric oxide/EDHF production. A significant component of this response is attributable to red wine polyphenols, which influence such cardiovascular biomarkers to a degree more than can be contributed by other components, such as alcohol alone. One component that has received much attention is the phytoalexin resveratrol, a non-flavonoid stilbene produced

by the grape as a defense mechanism to fungal attack. However, it is generally agreed the flavonoid components confer additional bioactivity, as the concentration of resveratrol in wines is typically low and the bioavailability poor.

Studies last year in our laboratories demonstrated that grape skin extracts were able to stimulate proliferation of neuronal cell lines in culture, as was resveratrol. The aims of this project are to extend these findings to characterize the mechanisms of proliferation and possibly the pharmacological basis behind such effects. The project will centre on neuronal cell culture and tissue bioassays to profile any functional effects of such bioactive compounds on nitric oxide pathways. This will include gastrointestinal and possibly also vascular assays using blood vessel rings. Further chemical synthesis may be possible to generate compounds and their bioactivity compared to resveratrol, or extraction of bioactive fractions from grape skin extracts. Students will present their findings from this project at the national pharmacology conference (ASCEPT) in late 2009.

DRUG INTERACTIONS BETWEEN ECSTASY (MDMA) AND CANNABINOIDS*

Supervisors: Dr Scott Smid, Dr Abdallah Salem, Assoc. Prof Rod Irvine

3, 4-Methylenedioxymethamphetamine (MDMA, 'Ecstasy') is a widely used illicit drug. The possible adverse effects of MDMA use are of concern. In laboratory animals, MDMA causes 5-HT nerve degeneration with a reduction in brain 5-HT content. Human MDMA users also exhibit effects consistent with 5-HT depletion. The drug most commonly taken with MDMA in human users is cannabis. It is estimated that more than 90% of ecstasy users take cannabis regularly. Cannabis is frequently used to relieve the MDMA 'comedown' effect, but is also commonly used before and during dance parties at which MDMA is taken.

There is very little understanding of how these two drugs interact when taken together. Some studies suggest that cannabinoid drugs can actually mitigate the neurotoxicity associated with MDMA use. It is not known whether this is an effect related to a distinct pharmacological mode of action of cannabinoids, or whether aspects related to temperature regulation or even purported antioxidant properties of cannabinoid molecules play a role.

In this project, the Honours student will be investigating how cannabinoid-receptor specific ligands influence neurodegeneration associated with MDMA exposure in laboratory rats. Indices of body temperature, behavioural and locomotor activity will be measured in vivo. Measures of brain neuronal morphology, 5HT levels and possibly other neurochemical markers will then be measured via HPLC to correlate with in vivo endpoints. Students will present their findings from this project at the national pharmacology conference (ASCEPT) in late 2009.

MANAGEMENT OF CANNABIS WITHDRAWAL WITH ORAL CANNABINOID PREPARATION*

Supervisor(s): Dr Scott Smid, Dr Linda Gowing, Assoc. Prof Robert Ali

Cannabis is the most commonly used illicit drug. While the prevalence of cannabis use has been declining in South Australia, there is a trend of increasing demand for treatment of cannabis use, particularly for the subpopulation of heavy daily users of cannabis. It is now generally accepted that a cannabis withdrawal syndrome exists, and that the severity of this syndrome is similar to that of nicotine withdrawal. The cannabis withdrawal syndrome remains to be fully characterised but it is clear that withdrawal contributes to the inability of cannabis users to quit. Very few studies have been undertaken to investigate pharmacotherapies to ameliorate cannabis withdrawal.

Bupropion and divalproex have been found to worsen rather than improve symptoms, while nefazodone had only limited effectiveness. On the other hand, oral THC has been found to reduce withdrawal with no adverse effects. The use of cannabinoid preparations to manage cannabis withdrawal would be equivalent to the use of nicotine replacement therapy for smoking cessation, or the use of tapered methadone or buprenorphine to manage opioid withdrawal. This project will investigate the capacity of a cannabinoid preparation (either Sativex® Oromucosal Spray, or Dronabinol oral THC) to ameliorate cannabis withdrawal symptoms, and to validate the use of the Cannabis Withdrawal Scale to assess withdrawal severity, determine the need for medication, and to assess response to medication. Participants for this study will be recruited from clients admitted to the Drug and Alcohol Services SA inpatient unit for detoxification from cannabis. Please contact Dr Smid to confirm availability of this project for 2009.

DEVELOPMENTAL NEUROTOXICITY OF THE DRINKING WATER CONTAMINANT SAXITOXIN

Supervisors:

Dr Ian Musgrave; Dr Andrew Humpage

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Saxitoxin is the most potent of a group of structurally related alkaloid neurotoxins most commonly known as a paralytic shellfish toxins. When concentrated in the flesh of shellfish, these toxins can kill people on acute exposure by neuromuscular paralysis due to blockade of voltage-gated sodium channels. These toxins are also produced by freshwater cyanobacteria and can be present in water used for drinking by humans and livestock. Here the exposure pattern is chronic or episodic low dose exposure. The toxicological consequences of this pattern of exposure are unknown. It is known that interference with neuronal activity, such as that which can occur with low level neuronal sodium channel

blocking, can prevent proper neuronal development. This indicates that one consequence of chronic saxitoxin exposure may be developmental abnormalities of the nervous systems.

In collaboration with Dr Andrew Humpage (Senior Biochemist, Applied Chemistry Research Group, South Australian Water Corporation) and myself, the student will investigate the link between various patterns and levels of saxitoxin exposure and neuronal development using an established model of neurite development. We will also investigate the effects of different structural analogues both individually and in mixtures (the real-life scenario). Neurite extension, arborisation and connectivity will be examined using methods developed in my laboratory.

PROJECTS AT THE QUEEN ELIZABETH HOSPITAL

INTERACTIONS BETWEEN IMMUNOSUPPRESSANTS USED TO PREVENT REJECTION FOLLOWING RENAL TRANSPLANTATION

Supervisors:

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Renal transplantation is the only cure for end-stage renal disease. To prevent rejection of the newly transplanted organ patients receive triple immunosuppressant therapy consisting of a calcineurin inhibitor (cyclosporin or tacrolimus), mycophenolic acid and prednisolone. Most of these drugs have narrow therapeutic indices, and therapeutic drug monitoring is necessary to individualise dosage so as to both avoid rejection and minimise the risk of drug related toxicities. The pharmacokinetics of mycophenolic acid are significantly affected by the type of calcineurin inhibitor used, with patients receiving cyclosporin requiring higher doses of mycophenolic acid compared to those receiving tacrolimus. It is unclear whether cyclosporin affects the metabolism of mycophenolic acid by UDP-glucuronosyltransferases. Using rat liver microsomes, we have recently shown that one of the metabolites of cyclosporin (AM1) significantly enhances the glucuronidation of mycophenolic acid. This project will determine whether a similar metabolic interaction also occurs in human liver microsomes, and whether this may partly explain the interaction observed in transplant patients.

* Projects supervised by members of Centre for Pain, Addiction and Anaesthetic research (CPAAR). Honours scholarships are available for students who enrol in honours pharmacology and projects supervised by members of CPAAR. The annual value of the scholarship is \$3000. CPAAR will also cover travel expenses to national meetings if students are presenting material. Please contact the honours coordinator for more information about these scholarships.