Considering an Honours Degree in Physiology?

The Department of Physiology offers Honours programs for Bachelor of Science, Biomedical Science, Behavioural Neuroscience and Bachelor of Medical Science students. As a Department we take enormous pride in the quality of our Honours program and our Honours students.

The Honours year is a highly challenging and equally rewarding one where you will take the first steps towards a career in scientific research. There are a few important steps you need to take to apply for Honours and this book is designed to take you through them.

Probably the first question you need answered is ………

What is an Honours Degree in Physiology?

The objectives of an Honours degree in Physiology are to:

- Develop high-level skills in the design, implementation and analysis of rigorous scientific research, and problem solving strategies applicable to scientific method.
- Enhance acquisition of transferable skills in scientific communication (written and oral), critical thinking, independent organisation, time and resource management, and collaborative team working.
- Enhance the competitiveness of our graduates in their future chosen career pursuits.

OK, I like the sound of that, but……..

What do I actually do in Honours?

The Physiology BSc Honours course comprises two units:

**PHY4100 (36 points):** The major focus of this unit is the research project that you will carry out under the guidance of your supervisor. The assessment tasks are the thesis that you submit at the end of the year and two seminars that you will present during the year.

**PHY4200 (12 points):** The emphasis of this unit is to provide you with skills essential for good scientific practice, including critical thinking, scientific writing and presentation skills and statistical analysis. The assessment tasks include a written literature review that forms
the background to your project, statistics assignment and exam, and a test of your ability to critically evaluate scientific work.

Bachelor of Biomedical Science (BMS) Honours students do BMS4100 (which is identical to PHY4100) and BMS4200. BMS4200 is similar to PHY4200 but is administered through the School of Biomedical Sciences. For further information go to:


Information on other honours programs run through the faculty of Medicine, Nursing and Health Sciences is available at:


Mmmmmmm, sounds good but……..

Can anyone do Honours?

No. As the name implies the Honours degree is a prestigious course for students who’ve proven their capabilities by doing well in third year.

For entry to BSc Honours in Physiology you need: to have completed a Bachelor of Science or equivalent (e.g. Bachelor of Biomedical Science) with at least a distinction grade (70%) average in 24 points (or equivalent) of level-three studies in physiology (i.e. PHY units). Applicants may include a relevant unit from another department of the School of Biomedical Sciences if they have only completed three PHY units. For further information go to:


For entry to BMS Honours in Physiology you need: to have completed the requirements for a Bachelor of Biomedical Science at Monash University, or a comparable qualification in biomedical science. You will need to have achieved an average of 70% or greater in at least 24 points at third-year level (including at least 12 points in biomedical science core units). There is no pre-requisite in terms of level 3 PHY units, but the Physiology Honours Convenors will need to be satisfied that you have the grounding in physiology to undertake your chosen project. For further information go to:

http://www.monash.edu.au/study/coursefinder/course/3418/

OK, I think I’m on target to achieve these scores and I’m still interested in doing Honours in Physiology……..
What do I do next?

You need to find a research project and supervisor to take you into their lab.

The Department of Physiology is a large research department covering all aspects of Physiology from the level of the cell through to tissue and whole animal physiology. Further we offer projects covering a large range of research fields. These research fields have been listed on Pages 5-8 with a short explanation of the area. We suggest you read through these explanations first and pick the area(s) you are interested in. Then go to the section in the book that lists the projects on offer for that section. We have endeavoured to provide you with photos wherever possible to help you identify the researchers of interest.

Once you’ve found a few projects you like, contact the potential supervisors by email or phone and arrange a visit to find out more about the projects on offer, visit the lab and get an idea of the type of work you would be doing, and talk to other students and research staff from the lab that you would be working with. Remember this is an important year so make sure you are comfortable with all these aspects.

It is important to note that the ability of a supervisor to sign you on to a project will depend on that project still being available, and the limit to how many students a supervisor can take on. So start talking to potential supervisors now. You will also be required to have an alternate choice in case circumstances change and a supervisor is no longer able to take you on, or a project is no longer available.

Great, I’ve picked my project and supervisor………………

How do I formally apply to do Honours in Physiology?

1. **Formal Application to Faculty:** You will need to refer to the application forms on the websites of the specific faculty you are from (e.g. Faculty of Science Website for BSc students). These forms must be signed by one of the Honours Convenors of the Physiology Department (A/Prof Ramesh Rajan, A/Prof Roger Evans or Dr Marianne Tare) and submitted to the Faculty by 12th NOVEMBER (internal students) or 26th NOVEMBER (external applicants only).

2. **Department Project Allocation:** This form will be available on the blackboard sites of all 3rd year Physiology units and needs to be filled in by both you and your potential supervisor. This form must be submitted to the Student Administration Officer by 19th NOVEMBER.

Sounds simple enough but……….
I have a few questions. Who should I ask?

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RESEARCH FIELDS

**Cardiovascular & Renal Physiology**

Cardiovascular disease is the leading cause of death and disability in developed nations such as Australia. In Australia alone, cardiovascular disease affects 3.5 million people, and is responsible for one death every 10 minutes. It is well recognised that high blood pressure, heart failure and kidney disease are major risk factors for the development of cardiovascular disease. However, the mechanisms underlying the development and progression of these diseases are not clearly understood. Our group aims to determine the mechanisms that regulate blood pressure during healthy states as well in disease states such as heart failure and kidney disease. We also aim to determine new ways to treat and prevent high blood pressure, heart disease and kidney disease.

Our group utilises techniques ranging from whole animal physiology and synchrotron based imaging modalities through to the tissue and molecular based techniques. Our multi faceted research approach allows for detailed investigation of complex research questions. Our global aim is to determine the mechanisms underlying high blood pressure, heart failure and kidney disease development and progression and thus provide novel therapeutic targets to cardiovascular disease.

**Cell Systems Physiology**

The focus of our research is to understand the processes involved in the important physiological functions of secretion, contraction and cellular communication. Disturbances of these functions underpin a great many diseases. Projects involve enhancing the understanding of the processes mediating (1) vascular endothelial dysfunction in diabetes and pregnancy-induced hypertension, and as a result of hypoxic insult in the developing fetus, (2) control of untimely smooth muscle contraction, namely, when pre-term labour threatens, during failure to progress in labour and inappropriate contractions of the bladder, ureter and prostate in adults, and large bowel in children (3) intra- and inter-cellular signalling involving neurons and astrocytes, and how failure of these processes gives rise to epilepsy, dementia and Alzheimer’s disease.

**Immune & Respiratory Systems in Infection & Disease**

The groups comprising the Airway Pathobiology Laboratory and Biotechnology Research Laboratory investigate aspects of the immune system, which is central to most disease processes, including tissues of the lung. In its positive form, the immune system protects us from infections by viruses, microbes and parasites and also plays an important role in the suppression of tumour formation. In its negative form, the immune system can mistakenly react against our own body cells, causing autoimmune diseases, or can overreact against foreign antigens causing immunopathology and allergies. Projects are designed to (1) gain a better understanding of how the immune system works to fight infection and how we can use this knowledge to make more effective vaccines, and (2) to gain a better understanding of mechanisms causing allergies and asthma and how we can translate this knowledge into better preventative and therapeutic treatments.
METABOLIC NEUROSCIENCES & LIPID METABOLISM

This group has a primary focus on central neural and peripheral mechanisms involved in the regulation of metabolism. As shown by the diversity of ongoing research projects, our scientific interests span across disciplines including the Neurosciences, Endocrinology, Pharmacology, Electrophysiology, Immunology and Neurodegeneration. We are trying to understand:

• how peripheral signals of energy state are integrated in specific brain centres
• how these signals from the body lose the ability to regulate body weight when the individual is obese or very lean
• how the body escapes the brain’s normal homeostatic regulation of body weight and gives way to obesity
• how changes in metabolic state i.e. obese vs. very lean affect neural function and influence the process of degeneration
• how adipose tissue produces and secretes protein that can then circulate and affect metabolic processes in other peripheral tissues including skin and liver

Projects will also utilise telemetric and calorimetric devices in conscious experimental animals to measure multiple aspects of metabolism, immunocytochemistry, in situ hybridisation, intracerebral injection of specific antagonists, real time PCR, imaging including PET and MRI, mouse mutagenesis models, mouse knock out models, and regulation of genes in cell culture to study cell signalling.

MUSCLE & EXERCISE PHYSIOLOGY

The Muscle and Exercise Research Group is interested in how humans respond to exercise, with a primary focus on skeletal muscle. The areas we are currently investigating include the effect of stretching on muscle passive tension, the effect of muscle fatigue on limb position sense, and physiological stress in motor sport participants. Our laboratory has equipment for measuring muscle force, electromyogram (EMG), limb position and movement, core body temperature, and aerobic capacity. We also have collaborative links with Monash Sport, which will allow us to develop more applied exercise research projects. Our research has potential implications for muscle injury prevention, rehabilitation, optimising performance in sport and reducing fall-relating injuries in the elderly.

NEUROCHEMISTRY AND NEUROPHYSIOLOGY

Metallo-peptidases cleave amino acids from either the N- and C-termini of peptide substrates to either generate or degrade biologically active peptides and the activity and their activities are dependent on the presence of zinc in the catalytic sites. These enzymes play important roles in the body and alterations in their activities can impact on a diverse range of physiological processes in both healthy and diseased states. Research in the team has focussed on the metallopeptidases involved in the processing of angiotensin peptides. Our findings have revealed previously unsuspected and more widespread roles for these enzymes, particularly their involvement in memory processing, glucose homeostasis, cardiovascular function and water and electrolyte balance. We have a drug development program targeting one of these enzymes (IRAP) and have
identified two families of lead compounds that await development into a new class of clinically effective cognitive enhancers useful in treating dementia (patents filed).

**NEUROENDOCRINOLOGY**  

The research groups in the field of Neuroendocrinology study the interactions between the central nervous system and hormonal systems. We have three main research fields focusing on reproduction, stress and aging, each offering a number of projects boasting a wide range of laboratory techniques. Regarding reproduction, we focus on the roles of various neuropeptide systems, such as kisspeptin, RFRP-3 and the melanocortins, as well as oestrogen signalling in the control of sexual behaviour and fertility and their possible impact on infertility. We are also interested in the impact of stress on physiological systems, particularly reproduction and the propensity to become obese, as well as the mechanisms by which stress responses are suppressed or enhanced during these phases of life. In the field of aging, we are interested in the regulation of adult neural stem cells by stress and stress hormones (glucocorticoids) and the implications for brain repair.

**NEUROIMMUNOPHYSIOLOGY**  

The field of neuroimmunophysiology seeks to understand the interactions between the immune system and the neural systems of the brain that regulate physiological functions. This field of research spans multiple research disciplines, thus the projects described are interdisciplinary in nature and involve a range of techniques. The 2 primary research focuses include: 1) Metabolic Neurosciences; understanding the interactions between inflammation and neuropeptides in the brain that regulate energy intake and expenditure, e.g. metabolism. 2) Neonatal Physiology and Neurodevelopment; understanding the role of immune cells and inflammatory factors in the developing brain after neonatal trauma, e.g. infection, ischemia, stress.

**SYSTEMS NEUROSCIENCE**  

The laboratories that form the Systems Neuroscience group investigate the structure and function of the nervous system. Lines of investigation include the central and peripheral mechanisms of sensation, the control of voluntary movement, neuroendocrine interactions, and the cellular mechanisms of neuronal genesis and death. While the work of different laboratories is focused on different parts of the nervous system, and on different research questions, they are united by a common question, "what is the relationship between brain activity and behaviour"? In summary, what makes us feel, act, think, and change, across the lifetime? With 10 full-time staff investigating different aspects of brain function, the Department of Physiology at Monash University is the home of one of the strongest Systems Neuroscience groups in Australia.
**METABOLIC & VASCULAR PHYSIOLOGY: BAKER IDI & DIABETES INSTITUTE**

The Metabolic and Vascular Physiology Laboratory takes a multidisciplinary approach to discovery and translation of novel molecular mechanisms to clinical application with a focus in the following areas:

- Vascular function including mechanical and endothelium properties and their relationship to cardiovascular risk
- Identification of novel predictors of unstable coronary heart disease
- The role of HDL cholesterol in modulation of glucose and fat metabolism
- Exercise mimetics
- Mechanisms for increasing energy expenditure in obese humans

Laboratory members and key collaborators have a broad collective skill base and range from molecular biologists through to endocrinologists and interventional cardiologists. These skills are integrated to investigate novel diagnostics and therapeutic approaches to the disease continuum linking obesity, type 2 diabetes and cardiovascular disease.

**STEROID RECEPTOR BIOLOGY GROUP: PRINCE HENRY’S INSTITUTE**

Research from our group is focused on understanding how steroid hormones control blood pressure and cause heart disease. Steroid hormones play a fundamental role in the physiology of development, metabolism, inflammation and homeostasis. Their effects are mediated through specific nuclear receptors. Our group is focused on the physiological and molecular regulation of the receptors for the adrenal steroids aldosterone and cortisol, particularly their role in heart disease.
Does the renin-angiotensin system determine the severity of cardiovascular outcomes with obesity?

Key words: obesity, renin-angiotensin system, transgenic mice

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Obesity is a major risk factor for cardiovascular disease and is closely associated with hypertension. However, mechanisms or pathways by which an increased fat mass leads to hypertension are not fully understood. The renin angiotensin system plays a major role in regulating blood pressure and has been shown to be an important link between obesity and hypertension. In this project we will study the role of different components of the renin angiotensin system and how they impact on the severity of obesity and hypertension. In this project we will be using a model of dietary induced obesity (i.e. high fat diet) to examine the cardiovascular effects in transgenic mice. The project combines different techniques for whole animal monitoring, surgical techniques and state-of-the-art radiotelemetry to monitor conscious blood pressure.

Postnatal maturation of the kidney: impact of in utero and environmental factors

Key words: fetal programming, kidney maturation, adult cardiovascular risk

Supervisors: A/Prof Kate Denton (Rm F266), Dr Russell Brown (Rm F259), Dr Javed Iqbal
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The kidneys control how much fluid is in the body. Disturbances in kidney function have an enormous impact on blood pressure and cardiovascular disease. The kidneys are immature at birth and they grow and develop throughout childhood. Our studies investigate how the kidney matures and if the course of that maturation can be altered for better or worse by maternal and
environmental factors. These studies will determine if the course of kidney maturation can be altered to protect against future cardiovascular disease.

**New pathways in the renin-angiotensin system: sex-differences in vasodilator / vasoconstrictor balance of the renin-angiotensin system**

*Key words:* arterial pressure, kidney function, knockout mice, radio-telemetry, pregnancy

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The renin-angiotensin system plays a dominant role in regulating arterial pressure and thus cardiovascular disease. In recent years, interest in this system has been re-invigorated by the identification of new receptors and enzymes that form a vasodilator arm of the renin-angiotensin system. The enzyme ACE2 promotes the formation of Ang(1-7), a vasodilator peptide. The two main angiotensin receptors, AT1R and AT2R, exert opposing effects on the cardiovascular system. All of the classical excitatory effects evoked by angiotensin II (vasoconstriction and sodium reabsorption) result from AT1R stimulation, whereas AT2R stimulation causes vasodilatation and natriuresis. Ang(1-7) acts at the AT2R. Our studies demonstrate that this vasodilator arm of the renin-angiotensin system is enhanced in females. Ongoing projects examine the role of this vasodilator arm in the regulation of arterial pressure, kidney function, pregnancy and in aged animals in both males and females.

**Factors regulating kidney oxygenation**

*Key words:* kidney disease, integrative physiology, oxygen, kidney physiology

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There is now very strong evidence that tissue hypoxia (low levels of oxygen) is a final common pathway in kidney disease. But the causes and consequences of kidney hypoxia mostly remain a mystery. We have a range of projects investigating how oxygen levels are normally regulated in a healthy kidney, how the kidney becomes hypoxic in disease, and how tissue hypoxia contributes to the development and progression of kidney diseases. Students can choose from studies of the vascular structure of the kidney, experiments in anaesthetized animals, experiments in conscious unrestrained animals, studies of the signalling pathways induced by tissue hypoxia (using immunohistochemistry, PCR and western blots), studies of oxygen metabolism in kidney tissues in vitro, and mathematical modelling studies. Most projects also involve collaboration with colleagues in other departments at Monash, with colleagues at other universities, or with industry.

**Long-term consequences of alterations to nephron number: are fewer bad? Are more better?**

*Key words:* kidney, salt intake, obesity, hypertension, kidney disease

*Supervisors:* Dr Michelle Kett (Rm F206), A/Prof Kate Denton

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We now know that the intrauterine environment, in particular maternal nutrition, and our genetic makeup controls the number of nephrons we are born with. Studies in humans and animals suggest
that being born with fewer nephrons increases your likelihood of developing high blood pressure (hypertension) and/or kidney disease in adulthood. However this is not always the case. In the following projects we will examine if obesity affects your chance of developing hypertension or kidney disease if you are born with fewer nephrons. Also we will be examining whether having extra nephrons in your kidney protects you from the deleterious effects of obesity. Each project involves using the latest techniques to measure conscious 24hr blood pressure (using radiotelemetry) and renal function in mouse models of nephron deficit. The projects also involve small amounts of histology and molecular biology (PCR).

We will examine the impact of obesity in two different projects where the number of nephrons has been altered by genetics (using knockout models):

1. GDNF Heterozygous mice. With this genetic defect, these mice are born with 2 small kidneys or just a single kidney with 30-65% fewer nephrons.

2. TGFβ2 Heterozygous mice. With this genetic defect, these mice are born with 60% more nephrons.

**Investigating circulatory control in diabetes and heart failure with synchrotron microangiography**

*Key words:* diabetes, coronary dysfunction, lipotoxicity, endothelial function, x-ray imaging

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Control of blood flow and its distribution within the body is a physiological imperative. The heart is critical to the maintenance of a normal arterial blood pressure and the supply of blood to all other organ systems. Many disease states, including diabetes and myocardial infarction, evoke progressive impairment of coronary blood flow, leading to contractile dysfunction and eventual heart failure. In order to understand the causes of this coronary dysfunction in these disease states it is important to visualise the microvessels of the heart. Synchrotron imaging techniques are now developed to achieve this goal and we expect these approaches to lead to breakthroughs in our understanding of diabetes, ischaemia and chronic inflammation in the heart.

**Investigating the mechanisms regulating contractile function in healthy and diseased hearts using synchrotron x-ray radiation**

*Key words:* cross-bridge cycling, muscle contraction physiology, regional cardiac dysfunction

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We have developed a unique experimental approach for investigating the function of muscle fibres in the beating heart wall using a combination cardiac monitoring and physics diffraction techniques. This enables us to examine how any region of the heart wall contributes to the overall pumping ability. We are currently applying this x-ray technique to study 1) how regional muscle performance is affected by diabetes, ischaemic disease and hypertrophy and 2) how new therapies influence long term recovery of contractile function. This is important to our understanding of some of the most common causes of mortality in the world. Projects in either area would provide students with unique multidisciplinary skills that will benefit anybody interested in future careers in biomedicine.
L-arginine transport in obesity induced hypertension: a new therapeutic target

Key words: hypertension, obesity, nitric oxide, L-arginine

Supervisors: Dr Niwanthi Rajapakse (F259), A/Prof Roger Evans (Rm F274), Prof Geoff Head (Baker Institute), Prof David Kaye (Baker Institute)

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Obesity induced hypertension is a growing health issue both in Australia and worldwide. However, mechanisms of obesity induced hypertension remain poorly understood. There is now strong evidence that low nitric oxide (NO) levels contribute to the development and maintenance of this form of hypertension.

In this project we aim to determine whether increasing NO levels by administering L-arginine, (the substrate for NO formation) can reduce obesity induced hypertension, and related kidney damage. Currently, the efficacy of L-arginine in reducing hypertension remains limited as arginine transport is impaired in hypertension. To overcome this issue, we will use a transgenic mouse model with increased L-arginine transport in this study. The findings of this project will aid not only in developing novel treatments for hypertension but also in developing strategies aimed at preventing the development of this debilitating disease.

The project involves molecular biology techniques (PCR, westerns, biochemical assays) as well as measurements of blood pressure in conscious mice with the use of radiotelemetry.

Role of brain pathways in chronic stress

Key words: hypertension, stress, central nervous system

Supervisors: Prof Geoff Head (Baker IDI), Dr Pamela Davern (Baker IDI), A/Prof Roger Evans (Rm F274)

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There is now strong evidence to suggest that the sympathetic nervous system (SNS) makes a significant contribution to certain forms of hypertension. One of the suggested mechanisms through which the SNS may be “activated” in hypertension is through the renin-angiotensin system. We have recently demonstrated that a very low “subpressor” dose of angiotensin given for several months to rabbits can produce a very modest increase in blood pressure but appears to amplify the effects of chronic stress. Using immuno-histochemistry, we have found that specific areas of the brain are activated by infusing angiotensin, an action which is mediated through areas of the brain that do not have a blood brain barrier. These central pathways appear to be “sensitised”, reflecting a type of positive feed forward CNS plasticity. We now wish to determine which areas of the brain and in particular, which areas of the hypothalamus, may be responsible for this effect on chronic stress. The project will involve some animal surgery, experiments to measure blood pressure before and during a relatively mild air jet stress and then perfusion fixation of the brain to process it for immunohistochemistry. The use of specific antibodies and fluorescence and confocal imaging will then be used to identify brain regions and specific neurochemicals involved in the responses to acute and chronic stress.
Role of brain angiotensin in hypertension

Key words: hypertension, angiotensin, stress, central nervous system

Supervisors: Prof Geoff Head (Baker IDI), A/Prof Andrew Allen (Melbourne University), Dr Pamela Davern (Baker IDI), A/Prof Roger Evans (Rm F274)

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Our studies of the spontaneously hypertensive mouse, using radio-telemetry for measurement of blood pressure, have shown that the hypertension can be blocked by central administration of an angiotensin receptor blocker. Further, mice without any angiotensin receptors have low blood pressure. We have now developed the technique of using viral vectors to replace angiotensin receptors in the brain using microinjections. This technique helps us understand which part of the brain is responsible for generating the angiotensin hypertension. The current project will examine the blood pressure in mice after injection of the virus into the nucleus of the solitary tract which is the region receiving baroreceptor afferent information. The project therefore will systematically investigate the cardiovascular effects of angiotensin receptor expression in this brain region by recording blood pressure (using the radio-transmitters) with the mice in their home cage. We will also perform a series of short stress tests to look at how expression of angiotensin receptors in the nucleus tractus solitarius affects the blood pressure and heart rate responses to stress. At the end we will fix the brain for histology. The project involves surgery, animal handling, computerised monitoring and analysis using special software and immunohistochemistry. The experimental work for the project will be carried out at the Baker Institute in Prahran.

Vascular health in rural India

Key words: hypertension, stroke, heart disease, epidemiology, developing nation

Supervisors: A/Prof Amanda Thrift (Baker IDI), A/Prof Roger Evans (Rm F274)

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We now know a lot about the causes of vascular disease such as heart attacks and stroke in developed countries such as Australia. But the major burden of these diseases, in global terms, arises from developing nations such as India. In this project we are studying the health of a rural population of about 30,000 villagers in rural south India. We predict that the causes of cardiovascular diseases in this rural population will differ markedly from those that have been established in developed nations. By showing the causes of cardiovascular diseases we will be able to devise strategies for improving cardiovascular health in this and other rural populations in India. The student(s) undertaking this project would have the opportunity to analyse some initial pilot data and help shape the direction of this project.
Factors determining regional susceptibility to vascular complications of diabetes

**Key words:** diabetes, arteries, vascular disease, endothelium

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Vascular complications are the leading cause of sickness and death associated with diabetes mellitus. Dysfunction of the inner lining cells of blood vessels, known as the endothelium, has an early and key role in the development of diabetic vascular disease. Intensive research on large arteries has resulted in beneficial surgical and therapeutic interventions. However, disease in smaller arteries is a major component of the vascular complications of diabetes, is less well studied and is relatively resistant to current therapeutics. Thus, there is a major medical need for improved understanding of mechanisms that regulate small vessel function in diabetes. Our recent studies have revealed that the susceptibility of the endothelium to dysfunction in diabetes varies across the circulation. These differences relate to the functional relationship between endothelial cells and the underlying smooth muscle, nature of the vasodilators released from the endothelium, potassium channel activity and local differences in oxidative stress. This project will determine the key pathways important in determining regional susceptibility to diabetic vascular disease. Arteries from different regions of the circulation will be studied using a combination of techniques including arterial myography (to record smooth muscle contraction and relaxation), intracellular electrophysiology to record membrane potential, calcium imaging, real time PCR and immunohistochemistry to assess potassium channel expression and localisation.
Fetal hypoxia and heart function

**Key words:** fetus, heart, intrauterine growth restriction

**Supervisors:** A/Prof Helena Parkington (Rm F133), Dr Marianne Tare (Rm F131), Prof Euan Wallace, Dr Suzie Miller

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Placental insufficiency can give rise to a small fetus (intra-uterine growth restriction, IUGR) and developmental abnormalities. Several conditions associated with IUGR (e.g. pre-eclampsia) can demand premature delivery of the fetus. This necessitates rapid development of the lungs if the preterm neonate is to survive. Lung failure sets the limit on the gestational age at which a fetus survived until, in 1972, Liggins and colleagues from Auckland first described a beneficial effect of maternal glucocorticoid administration on lung development and survival in human neonates. Since then, mothers in Western countries about to give birth to a premature baby, especially before 34 weeks of pregnancy, are given an agent such as betamethasone, to ensure or maximize survival of her newborn. This occurs, not only in relation to IUGR fetuses, or with intrauterine infection, but also when premature labour threatens the intrauterine sojourn of a healthy fetus.

It is becoming increasingly apparent that elevated glucocorticoid administration in late gestation may have effects on other systems in the body. Undesirable effects on the brain may occur, and if premature labour subsides and the pregnancy continues, there is an increased risk of sudden intrauterine death following glucocorticoid administration. Thus, if elevated intrauterine glucocorticoids are deleterious, why continue with their use? Without glucocorticoid, the very premature neonate has little chance of survival. We must find another way around this dilemma.

One answer is, determine exactly what is going on in systems other than the lung, and see if ways can be found to offset or alleviate the problems. Our present study focuses on the heart. We are studying the effects of IUGR, with and without maternal betamethasone treatment, on cardiac contractility, responses to stress and ischemia/reperfusion, and coronary flow in sheep. Our next study will embark on a detailed study of the effects of betamethasone on cerebral and coronary arteries. Furthermore, we will move from the fetus to the newborn to broaden the scope of understanding of this important and vulnerable period.

Role of interstitial cells of Cajal (ICC) cells in intercellular communication

**Key words:** cellular communication, pacemaker cells, urinary tract, uterus

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ICC-like cells have been demonstrated in a number of urogenital and non-urogenital smooth muscle organs (corporal tissue of the penis, vas deferens, uterus, fallopian tube, lymphatics, arteries and veins) on the basis of their specific immuno-reactivity to antibodies raised against c-Kit, a receptor tyrosine kinase. A complete understanding of smooth muscle autorhythmicity urgently requires an elucidation of the pacemaker mechanisms used by various c-Kit-positive/negative ICC-like cells in particular smooth muscle organs. It is likely that different pacemaker mechanisms evoking different ion channel conductances are being evoked in individual smooth muscle organs. We are interested in understanding the mechanisms of pacemaking in the uterus, urinary tract and prostate. We have a number of projects to examine the distribution and interconnectivity of ICC-like cells in these tissues as well as to establish their mechanisms of pacemaking.

Upper Urinary Tract: Changes in ICC-like cell distribution and function in normal and diseased states will be probed in the urinary tract. Elucidation of the pacemaker mechanisms could well lead to the development of tissue specific pharmacological interventions to aid or restore normal function. For
example urinary tracts diseases such as kidney stones, infection and ureteric reflux can all lead to pyeloureteric obstruction, swelling of the kidney (hydronephrosis) and permanent kidney disease. Elucidation of the pacemaker mechanisms in the urinary tract is crucial in the development of pharmacological interventions independent of available surgical treatments to reduce the incidence, severity and re-occurrence of pyeloureteric obstruction.

Uterus: During most of pregnancy the uterus is quiet, not contracting, and then it must rapidly develop strong contractions that increase in frequency if normal vaginal delivery is to occur. The events that bring about this dramatic transformation are still unknown! We hypothesize that ICCs are pivotally involved in setting the contraction “clock” in the uterus at the time of labour and we are pursuing this experimentally. We characterize individual cells in terms of ion channels and then perform single-cell PCR to molecularly identify these cells by their mRNA.

Effects of obstruction on ureteric peristalsis

Key words: remodelling, peristalsis, kidney

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Obstruction of the upper urinary tract (UUT) is the most frequently diagnosed cause of hydronephrosis in infants at birth while in adults, hydronephrosis can arise from acute or chronic ureteral obstruction (kidney stones or pregnancy, endometriosis, cysts of the uterus or ovaries) or during bladder infections. Severe conditions of hydronephrosis in infants and adults require surgical intervention, which generally involves either endoscopic internal trans-section of the obstructed region or its removal and reattachment of the renal pelvis to the ureter. Although kidney swelling reduces partially with time after clinical intervention, the kidney never returns to normal and patients have an increased risk of developing stones, hypertension or infection throughout their lives. Non-surgical treatments to alleviate the consequences of ureteric obstruction have not yet been developed due to the lack of an understanding of the basic physiology underlying healthy UUT peristalsis, let alone the consequences of muscle wall remodelling after pyeloureteric obstruction/surgery.

We will investigate remodelling of the UUT and ureteric peristalsis in terms of the relative expression and activity of ICC and the smooth muscle cells in the ureteric wall after unilateral ureteral obstruction.

Role of TRP channels in upper urinary tract (UUT) pacemaking?

Key words: channels, patch clamp, calcium imaging, urinary tract

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There is increasing evidence that transient receptor potential (TRP) channels are involved in ICC pacemaking. Classical or canonical (TRPC1-7), vanilloid (TRPV1-6) and melastatin (TRPM1-7) channels are three subclasses of TRP channels first cloned in Drosophila which encode a diverse group of Ca$^{2+}$-permeable channels that participate in diverse cell functions such as receptor- and store-operated Ca$^{2+}$ entry, Ca$^{2+}$ transport, temperature and osmolality sensation and proliferation. Human ureteric ICC-like cells are immuno-positive for both c-Kit and TRPV2, the genetic transcripts of TRPC4 and TRP6 are present in ICCs, the pacemakers of the gut. TRPM7-specific RNA interference treatment of cultured mouse intestinal ICC blocks pacemaking activity. The cationic selective
channels formed by TRPC4 channel constructs cloned from canine intestinal muscle mimic in many
details the properties of the cationic channels in intestinal ICC. We already have preliminary
evidence that spontaneous electrical activity in UUT ICC-like cells have a pharmacological profile
different from intestinal ICC.

We will establish:

(i) which channels are indeed present in the UUT using immunohistochemistry and the confocal
microscope

(ii) which blockers or activators of TRP channels modify the time course of spontaneous inward
currents and Ca signals recorded in individual UUT ICC and the spontaneous transient
potentials/intermediate action potentials recorded in the intact UUT with intracellular
microelectrodes.

**Effects of age on the spontaneous activity and innervation of the isolated prostate
gland**

*Key words:* electrophysiology, nerves, prostate, organ bath

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The prostate gland commonly enlarges in ageing males resulting in a condition known as benign
prostatic hyperplasia (BPH) that is poorly understood. Because of the strategic position of the
prostate, its enlargement impacts on the urinary system, causing inconvenient and distressing
symptoms such as difficulty and hesitancy in urination, which often require surgical or medical
intervention. Indeed, patients diagnosed with BPH are often treated with pharmacological agents
that reduce the size of the prostate or relax the smooth muscle of the prostate and bladder, thus
relieving some of the symptoms.

In this project the spontaneous activity of the isolated prostate gland, in young and old animals, will
be investigated using video imaging, organ bath or electrophysiological techniques. Furthermore,
the effects of nerves and agents that affect neurotransmission (suramin, guanethidine, muscarinic
antagonists) or the mechanisms underlying the spontaneous activity (nifedipine, caffeine,
neomycin, cyclopiazonic acid) will also be studied.

**Consequences of insult in the fetus on brain function in adulthood – can we rescue
it?**

*Key words:* synaptic plasticity, LTP, electrophysiology, perinatal hypoxia, synaptic potentials,
hippocampus

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Insults to the fetus resulting in measurable deficit occur in around 10% of pregnancies. The oxygen
and nutrient deficit can be transient, due for example to cord occlusion, or more persistent
throughout the pregnancy, for instance as a result of placental insufficiency. Hypoxia can result in
direct death of neurons, dysfunction of astrocytes (important support cells that are 10-50 times
more numerous than neurons in the central nervous system), and impair blood flow within the
brain. We have experiments that investigate these three issues.
In one study we expose rats to hypoxia and this induces a condition that is similar to infant epilepsy that can occur as a result of perinatal hypoxia during the birth of a baby. We are currently investigating whether various treatments, including the administration of a hormone, can protect against this type of epilepsy. Slices are being used.

In the first study we are investigating the effects of hypoxia and different agents on astrocyte function, using the patch clamp technique. We have already found that astrocytes, that perform major critical “housekeeping” functions in the brain, may be vulnerable to hypoxia, thus leaving neurons more exposed than usual.

In another study we are examining the effects of destructive oxygen species, increased during hypoxia, on vasodilation, and hence on the supply of nutrient to neurons. Here we will perform full functional studies on heart function, then study the coronary arteries within the heart and lastly, test the functionality of arteries in the brain, using techniques described in more detail above.

**Diabetes-induced dementia – what is going on?**

**Key words:** diabetes, obesity, synaptic function, LTP, arterioles, brain slices, electrophysiology, hippocampus

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There is a strong link between diabetes mellitus (DM) and impaired cognition. DM may be directly responsible for 7-13% of all cases of dementia. Cerebrovascular dysfunction occurs early in the development of dementia, and may be an underlying mechanism. It has long been recognized that an increase in neural activity triggers an essential vasodilation of nearby blood vessels. This “neurovascular coupling” involves the active neurons, local astrocytes and the smooth muscle of the vessel wall. The mechanisms involved in neurovascular coupling are incompletely understood. Those with DM or dementia have increases in advanced glycation endproducts (AGEs). AGEs are formed by non-enzymatic glycation of protein and hence are increased in the high glucose milieu of DM. AGE formation is accelerated when food is prepared at high temperatures. A single roast meal containing a high AGE content markedly suppressed endothelium-dependent vasodilator function within 2hr in humans, and the effect persisted for ~6hr. We have shown that AGEs attack blood vessels. Since the endfeet of astrocytes ensheathe most arterioles in the brain, astrocytes must also be exposed to the elevated levels of glucose and AGEs in DM. A key question is whether vasodilator dysfunction in DM is due entirely to the direct injury of blood vessels or whether it is also indirectly caused by impaired function of perivascular astrocytes, perhaps due to a reduced capacity to support neurovascular signalling. In the present study the effects of glucose and AGEs on astrocytes will be examined independently of blood supply in primary cell culture. Astrocytes will be harvested from the hippocampi of rats and grown on coverslips. They will be exposed to control, or high glucose, or high AGEs, or both glucose+AGE.

**Study 1:** An astrocyte-coated coverslip will be attached to the bottom of the recording bath and a drop of freshly isolated vascular smooth muscle applied. Single smooth muscle cells will be studied using patch clamp techniques. Astrocytes will be activated by application of glutamate to stimulate their AMPA receptors. The effects of astrocyte activation on smooth muscle ion channels will be determined. The nature of the ion channels and the diffusible agent(s) released from the astrocytes will be elucidated using standard pharmacological approaches.

**Study 2:** To examine astrocyte-neuron interactions we will take advantage of the knowledge that neural activity induces an increase in cytoplasmic $\text{Ca}^{2+}$ within astrocytes that sweeps as a wave across and between neighbouring astrocytes. Astrocyte-coated coverslips will be loaded with Fluo-4
and placed in our fast confocal imaging system, with continuous solution flow. Neurotransmitter will be picospritzed onto the astrocytes to “simulate” neural release and the Ca^{2+} responses in the astrocytes recorded. We will test glutamate, GABA, acetylcholine, NO donor and elevating K⁺.

**Changes in hippocampal function in relation to cognitive and motor performance after traumatic brain injury in rat**

*Key words:* traumatic brain injury, synaptic function, LTP, electrophysiology, brain slices  
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Traumatic brain injury (TBI) remains a true epidemic of death and disability among healthy adults in their most productive age. The World Health Organisation (WHO) has estimated that motor vehicle accidents are expected to rank third in WHO’s Global Burden of Disease by 2020, above HIV, malaria and tuberculosis. TBI is one of the leading causes of mortality and morbidity in children and young adults in industrialized and developing countries, mostly due to road traffic accidents. In Victoria, over 5,000 people a year are admitted to hospital with TBI, 600 of whom have moderate to severe brain injury. The financial loss for families and the cost of medical care are estimated to be over $100 million annually in Australia. Large efforts have been put into studies of patients suffering severe brain injury to reduce hospital mortality and morbidity.

However, the majority of patients admitted to hospital have mild to moderate brain injury and will fully recover physically. Increasing evidence suggests that memory and cognitive deficit persist following the physical recovery from mild TBI, but these problems receive little attention and remain un-investigated and untreated. This project aims to incorporate into an existing well-established model of induced TBI, sophisticated in vivo testing of behavioural function and in vitro determination of neural function in tissue slices prepared from the same animal. This will provide for the first time a comprehensive model of the consequences of TBI at the level of the intact animal, and at the cellular and molecular level in a brain region – the hippocampus – that is critical for higher functions such as learning and memory.

**Aim 1:** To evaluate memory, cognitive function and behavioural performance after moderate and severe TBI using a range of tests previously validated for rodents by computerized video-tracking software.

**Aim 2:** To quantify TBI-induced changes in synaptic plasticity and neuronal excitability in hippocampal brain slices, using electrophysiology and fast confocal live cell microscopy systems.

**Aim 3:** To identify structures targeted by TBI using immunohistochemistry and molecular biological approaches.

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**BNP rescues LV fibrosis & dysfunction in type 2 diabetes**

*Key words:* diabetes; cardiomyopathy, B-type natriuretic peptide  
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The leading cause of death of patients with diabetes is cardiovascular complications. Diabetic cardiac disease, or diabetic cardiomyopathy is defined as changes in the myocardium independent
of associated coronary vascular disease. The precise cause of diabetic cardiomyopathy in humans is poorly understood, but up to 90% of patients diagnosed with the disorder have type 2 diabetes. Cardiac fibrosis (increased extracellular matrix deposition), cardiomyocyte hypertrophy (an enlarged heart and/or cardiac myocytes) and diastolic dysfunction (impaired cardiac relaxation) are observed in diabetic cardiac disease, and are associated with alterations in myocardial energy metabolism and microvascular changes. These abnormalities are often followed by later onset of systolic dysfunction (reduced cardiac contractile function) and can be worse than predicted from the level of coexistent coronary heart disease or hypertension.

We have previously demonstrated that the cardiac hormone B-type natriuretic peptide (BNP) has acute antihypertrophic actions in the type 1 diabetic heart. Chronic treatment of type 1 diabetic rats with the related peptide, atrial natriuretic peptide (ANP), markedly improves cardiac function and limits cardiomyocyte hypertrophy, but was not able to reduce cardiac fibrosis, which is likely a reactive oxygen species (ROS)-triggered event. The efficacy of the ANP/BNP family has not been investigated in type 2 diabetes. As mice lacking BNP exhibit spontaneous cardiac fibrosis, together with BNP’s ROS-suppressing actions, endogenous BNP is thought to have exciting anti-fibrotic properties. We now propose that chronic BNP treatment rescues diabetes-induced cardiac fibrosis and LV dysfunction in a mouse model of type 2 diabetes in vivo. We predict that the effectiveness of BNP will resemble a combination of its sibling peptide, ANP, and an antioxidant. BNP-based therapies alone or in combination with standard care may provide a more effective means to limit diabetes-induced cardiac fibrosis and hence rescue diabetic cardiac function.

This project will be performed in Dr Ritchie’s laboratory at the Baker IDI Heart and Diabetes Institute in Prahran and will provide the opportunity for learning biochemical (Westerns, ROS detection, ELISA), histological/immunohistochemical, molecular (real-time PCR, Northerns) and physiological techniques (e.g. assessment of cardiac function and blood pressure).

Nitroxyl, a naturally-occurring molecule for treating diabetic heart disease

Key words: diabetes, cardiomyopathy, NO*

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The cardiac dysfunction manifest in patients with diabetes is a major contributor to morbidity and mortality, often exacerbated by underlying LV fibrosis, hypertrophy of cardiac myocytes, and excess generation of ROS such superoxide. The nitric oxide (NO*)/cGMP signalling system is as a powerful cardiac antihypertrophic mechanism. Nitroxyl (HNO), a novel redox sibling of NO*, has several
therapeutic advantages for the treatment of cardiovascular diseases. We have shown that HNO prevents hypertrophy and generation of superoxide in isolated cardiomyocytes. Excitingly, HNO also potentiates cardiac function, in contrast to NO, via the cardiac calcium handling proteins, SERCA2a (sarcoplasmic reticulum Ca\(^{2+}\)ATPase) and the ryanodine receptor RyR2. The activity and expression of these enzymes is abnormally affected by diabetes, and together with the upregulation of ROS is recognised for their causal role in diabetes-induced LV dysfunction. HNO thus is likely to be favourable for treating diabetic cardiac disease.

Our hypothesis is that HNO represents novel pharmacotherapy for the prevention and treatment of diabetes-induced myocardial dysfunction. We aim to demonstrate that (i) HNO is cardioprotective in cardiomyocytes isolated from diabetic hearts; (ii) that HNO acutely enhances cardiac function in the diabetic heart, and (iii) chronic HNO rescues myocardial structure and function in the diabetic heart over the longer-term. Which of these will be included in the scope of this Honours project will depend on the student’s abilities and interests, and may include in vitro techniques (using cardiomyocytes and/or cardiac fibroblasts), ex vivo (Langendorff-perfused isolated rat hearts from diabetic vs. non-diabetic animals) or in vivo models of diabetic cardiac disease. The outcome of this project will be definitive information regarding the mechanism(s) and effectiveness of HNO-mediated rescue of myocardial function specifically in diabetes. Ultimately, HNO-based strategies may offer new treatment options for diabetic cardiac disease, either alone or on top of standard care.

This project, to be performed in Dr Ritchie’s laboratory at the Baker IDI Heart and Diabetes Institute in Prahran will provide the opportunity for learning a range of techniques, including cell culture, biochemical (Westerns, ROS detection, ELISA), molecular (real-time PCR, Northerns) and physiological techniques (e.g. assessment of cardiac function, blood pressure).

**Eating versus sex: how the hormones fight it out in the brain**

*Key words:* leptin, GnIH, electrophysiology, brain slices

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Hormones that regulate reproduction, GnRH and GnIH, may all influence neurons in the arcuate nucleus that regulate satiety and food-seeking behaviours. This project will study the effects of GnRH, GnIH, leptin and insulin, on the electrical properties of these neurons. The neurons involved are the POMC and NPY neurons and these neurons will have been targeted by green fluorescent protein (GRP). This will allow us to see and target the specific neurons of interest during study.
The rise in caesarean deliveries: obesity is the culprit

Key words: uterus, obesity, labour

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The number of caesarean deliveries has doubled in the past ten years, and the increase almost exclusively involves obese women. Obese women go into labour less easily, and require induction. During the process, the labour in obese women has an increased tendency to stall, contractions die away despite infusion of inducing hormone. This necessitates emergency caesarean delivery in labour. This puts subsequent pregnancies at risk of excessive bleeding, misplaced placenta etc. In this project we will study human uterine tissue obtained during these caesarean deliveries, and will also develop a mouse model to enable us to test some therapeutic possibilities.

Mysterious places of uterine regulation

Key words: uterus, ion channels, cell calcium, labour

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Despite much study, our knowledge of how contractions of the pregnant uterus are regulated is still not well understood. In recent studies in our lab, we have found that an important relationship exists between the plasma membrane (PM), the endoplasmic reticulum (ER) that contains an important store of calcium, and mitochondria (Mitos), the powerhouses of cell energy. In this study we will use state-of-the-art techniques, imaging, patch-clamp electrophysiology and siRNA techniques to determine the molecules in the PM, ER and Mitos that are responsible for calcium handling, permitting its availability and removal. The relationship between these three compartments in uterine smooth muscle remains a mystery, with most of our understanding coming from vascular smooth muscle.
Immunity and vaccine development against parasitic diseases

Key words: infection, parasites, vaccines

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Worm parasites such as the liver flukes, blood flukes and gastrointestinal nematodes infect grazing ruminants, particularly in Asia and Africa, resulting in enormous economic loss to the agricultural sector or subsistence farmers and negatively impacting on efficient food production in developing countries. Some of these parasites also cause significant human disease. At present there are few drugs and no molecular vaccines effective against these parasites.

Knowledge of how parasites and hosts interact will provide us with the information we need to understand disease susceptibility and design better vaccines or drugs to prevent and treat parasitic disease. Our projects are integrated and will study both the genetics and protein biochemistry of
parasite molecules involved in pathogenesis as well as host genes and gene products determining host resistance. Students will gain experience in molecular biology, immunology, recombinant protein expression, and vaccine design and development. The Laboratory has a number of international collaborations and frequently hosts visitors from overseas laboratories and Institutes.

How do eosinophils kill parasites and cause allergies?

Key words: infection, parasites, allergies
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The immune response to parasites is characterised by the recruitment of eosinophils to sites of infection. Eosinophils are white blood cells containing specific intracellular granules and lipid bodies which, once activated, are capable of releasing a battery of potent cytotoxic and pro-inflammatory agents including peptide, cytokine and lipid mediators. These effector molecules are thought to contribute to the killing of parasites. This project will focus on determining the cells and molecules responsible for creating a killer eosinophil. Identification of these molecules may lead to new ways to protect humans and animals from a range of parasite infections. In addition, as eosinophils are also key mediators of allergic reactions, these studies may discover new targets for therapy and drug development in allergy and asthma. The student will be exposed to a range of cellular and molecular techniques including tissue culture, flow cytometry, confocal microscopy and gene expression analysis.

Immunostimulation of the mammary gland to cure mastitis

Key words: infection, bacteria, immunity
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Mastitis is an infection of the mammary gland that affects both lactating and non-lactating mammals, and may be caused by a number of bacterial species. Research in our laboratory indicates that certain cells of the immune system known as dendritic cells play an important role in directing the mammary gland to resist infection. Using cattle and sheep, we have found that specific proteins (cytokines) direct the growth and activation of dendritic cells, as well as their ability to respond to mastitic bacteria. In this project the student will conduct in vitro and in vivo studies that aim to improve the ability of the animal to resist mastitis.

Understanding innate immunity for the development of novel vaccines

Key words: vaccines, adjuvants, innate immunity
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The innate immune system detects and responds to many pathogenic invaders as a first line of defence. Following detection of pathogens, the innate immune system activates and instructs the “flexible” adaptive immune system to respond in a more specific manner. Accurate stimulation of the innate immune system is therefore of critical importance for developing vaccines that attempt to mimic a natural immune response. We are studying how new classes of immune stimulators or adjuvants activate the innate immune system. We use unique procedures to harvest dendritic cells from sheep lymphatic vessels and then measure activation using state of the art molecular
biological techniques (microarrays, real time PCR) coupled with cell biology and flow cytometry assays. We have projects available to investigate the innate responses to adjuvants, allergens and bacteria. These projects are aimed at developing an understanding of fundamental pathways involved in shaping the immune system, with implications for vaccine development and treatment of diseases such as allergies and asthma.

**Why are some individuals susceptible to allergies?**

*Key words:* allergy, microarrays, innate immunity

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A proportion of humans are prone to develop allergic reactions to innocuous environmental antigens (allergens), while others do not. We have replicated this variability in responsiveness to allergens in a standardised animal model which also allows detailed examination of the earliest, innate events active in allergen sensitisation. Using state of the art molecular biological techniques (microarrays, real time PCR) coupled with cell biology and flow cytometry assays we will gain insights into the earliest molecular pathways responsible for allergen reactivity in predisposed individuals. These studies may offer new approaches for allergy vaccines and therapies.

**Collaborators:** Prof Robyn O’Hehir and A/Prof Jenny Roland

**Defining the progression to an altered airway smooth muscle phenotype in asthma**

*Key words:* asthma, smooth muscle

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Current drugs are poorly effective at limiting the airway smooth muscle thickening that is associated with deteriorating asthma. Studies to elucidate the onset and critical pathways for the progression of altered muscle properties can only be performed in a relevant animal model amenable to repeated tissue sampling during life. Using our newly developed sheep asthma model, several projects are available to define the progression of airway smooth muscle (ASM) changes in asthma to identify new ways to treat asthma by (1) determining the kinetics of change in ASM proliferative and synthetic properties following chronic airway allergen exposures, (2) correlating altered ASM cell function in vitro with other indices of airway remodelling and lung function decline in vivo; (3) establishing whether airway tissue remodelling, and ASM phenotypic changes in particular, can be reversed or halted with early introduction of targeted anti-asthma therapy.

**Evaluating new approaches for the treatment of asthma**

*Key words:* asthma, immunology, sheep model

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Asthma affects over 2 million Australians with 300 deaths each year. Current treatments are not very specific and have significant side effects with prolonged use. We have developed a novel sheep model of allergic asthma that displays many similarities with human allergic asthma and serves as a valuable tool to study the complex mechanisms underlying the disease. Several projects will be on offer, with work in vitro and in vivo employing a range of cellular, immunological and biochemical/molecular techniques (cell and tissue culture, immunochemistry, ELISA, FACS, protein
chemistry, RT-PCR, gene therapy). The student will gain an in-depth understanding of immunological and physiological interactions, and will be exposed to aspects of drug discovery and biotechnology. Collaborators: Dr Ken Snibson, Melbourne University

**Preventing airway plugging in asthma**

*Key words:* fatal asthma, mucus  
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Mucus plugging of airways is a major cause of fatal asthma attacks in both adults and children, and is due to the abnormal viscosity and adhesiveness of asthmatic mucus. We have discovered a novel molecule that is secreted into the airway mucus of sheep sensitized to the major human allergen, house dust mite. We hypothesize that this molecule may be responsible for changing the properties of airway mucus and for its increased viscosity and adhesiveness. Using specific inhibitors of this molecule, we will examine its effect on airway mucus both in vitro and in vivo using our recently developed sheep asthma model. These studies may result in a new treatment for severe asthma.

**Effects of antenatal corticosteroids on the fetal immune system**

*Key words:* fetal development, immune system  
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Women at risk of preterm birth routinely receive injections of synthetic glucocorticoids to induce fetal maturation. In addition to being critical regulators of prenatal development, glucocorticoids are also potent inhibitors of inflammation. However, the effects of exposure to glucocorticoids on the developing immune system are poorly defined. The aim of this project is to make serial measurements of cellular immune function in fetal sheep, after exposure to maternal glucocorticoid injection.

**Impact of chronic asthma inflammation and airway remodelling on pulmonary drug absorption and distribution in a sheep model of asthma**

*Key words:* asthma, drug delivery  
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The prevalence of asthma in Australia is among the highest in the world: between 10% and 15% of children and between 10% and 12% of adults have asthma. Chronic inflammation in asthma involves marked changes in the composition of airway wall tissues (termed remodelling) which affects. These include: 1) epithelial metaplasia; 2) altered quantity, composition, and distribution of extracellular matrix components; 3) microvascular remodelling; and 4) increases in airway smooth muscle content. How these structural changes affect pulmonary drug disposition and absorption is not well understood. This research project aims to evaluate the impact of asthma-induced airway remodelling on the pharmacokinetic profile of small drug molecules delivered via the lung.
Different aspects of Metabolism are examined by several research groups in the department

**Heating up muscle in obesity**

*Key words:* obesity, energy expenditure, leptin and mitochondrial uncoupling  
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Thermogenesis is the dissipation of energy through the production of heat. This process occurs in specialised cells, including brown fat cells and skeletal muscle. Previous studies in humans have suggested that individual differences in thermogenic potential determine 1. The ability of people to lose weight via dieting and life-style intervention and 2. The ability of people to maintain long-term weight loss. This project will characterise the effects of obesity on post-prandial (after eating) thermogenesis. This project will involve animals that are made obese via dietary intervention; in sheep feeding high energy supplements causes obesity. We will measure temperature in skeletal muscle in animals after feeding and with central administration of leptin. It will involve analyses of gene expression using real-time PCR. This project combines various *in vivo* and *in vitro* techniques to determine whether thermogenic output is blunted in obese subjects.

**Sex, sex steroids and energy expenditure**

*Key words:* estrogen, testosterone, thermogenesis, obesity  
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Adipose tissue exhibits sexual dimorphism whereby females are more likely to accumulate fat subcutaneously and males are more likely to accumulate fat within the viscera. This fat distribution is controlled by the sex steroids. This project will investigate the effects of sex steroids on energy expenditure. To measure energy expenditure we will measure temperature as an index of thermogenesis (the dissipation of energy through heat production). This project combines various *in...
vivo and in vitro techniques to determine how sex steroids regulate energy expenditure. We will measure temperature in skeletal muscle in animals after feeding and with central administration of leptin. It will involve analyses of gene expression using real-time PCR, as well as radioimmunoassay and Western Blotting.

**Fat ain’t fat: identification of novel energy burning cells**

*Key words:* thermogenesis, energy expenditure, obesity  
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Historically two types of fat have been identified. White adipose tissue (WAT) stores energy in the form of triglyceride and brown adipose tissue (BAT) burns energy through the heat producing process of thermogenesis. Recently a third cell type has been identified, the BRITE cell, which appears to be derived by white fat but has energy burning properties. This project will seek to characterise brown fat and BRITE cells in a sheep model of post-prandial (after eating) thermogenesis. The project will combine in vivo recordings of temperature with histological analyses of specific fat depots (retroperitoneal, omental and subcutaneous) as well as skeletal muscle. This project will utilise real time PCR and immunohistochemistry. We will determine whether enhanced heat production occurs via recruitment of BAT and/or BRITE cells. Recruitment of these specific cells types is a novel target for the development of anti-obesity agents.

**Selective leptin resistance and causes of metabolic syndrome**

*Key words:* obesity, metabolic syndrome, cardiovascular disease  
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Obesity is directly linked to many metabolic diseases, including cardiovascular disease and type 2 diabetes. Leptin is the primary signalling hormone from fat tissues and it is considered important for the balance of energy homeostasis.

When humans and other animals become obese, there is an increase of adipose tissue and increase of leptin in blood. However, obese mice lose the ability to regulate body weight in response to leptin. This is called “leptin resistance” and our laboratory has found that some neurons (melanocortin neurons) in the brain of obese mice demonstrate resistance to leptin action. However, the neurons within other parts of the brain are still activated by leptin.
The major aim of this study is to determine if high leptin levels in the blood of obese mammals contributes to pathologically high blood pressure, increased heart rate and diabetes by activating the sympathetic nervous system. Understanding the common cause of these conditions will potentially lead to improvement in patient care and pave the way for new treatments for illnesses in obese humans.

This project will combine whole animal physiology, surgical techniques and animal monitoring; along with experimentation with studies of sympathetic outflow to the fat tissue, energy expenditure, blood pressure, hepatic glucose production and insulin sensitivity.

It will provide the successful applicant with experience in animal handling, collection of blood and tissues samples as well as several physiological and analytical techniques (RIA, IHC, Western Blot, analysis of proteins and real time PCR to assess gene expression) and an opportunity to contribute to the elucidation of molecular/physiological consequence of hyperleptinemia on metabolic syndrome.

**Brain control of blood glucose levels**

*Key words:* obesity, type-2 diabetes

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Diabetes is a failure to properly regulate blood glucose levels and it causes a wide variety of deleterious effects, such as increasing risks for vascular disease, neuropathies and tissue infection. The prevalence of diabetes in Australia doubled between 1990 and 2005. More than one million of Australians are estimated to have diabetes with the number expecting to increase over the coming decade.

Blood glucose levels are controlled on several levels, but it has recently emerged that the brain can regulate glucose production via the liver, which consequently regulates blood glucose levels. Our laboratory recently discovered that a specific group of neurons in the brain detects blood sugar levels (POMC neurons) and these cells produce a transmitter (that can also act as a hormone) called melanocyte stimulating hormone (α-MSH). This regulates the production of glucose by the liver and the use of glucose by tissues in the body. How α-MSH does this is unknown, but we do know stimulation of α-MSH secretion in response to glucose normalizes blood sugar levels in obese diabetic mice. Unfortunately, in diabetic mice glucose is unable to stimulate α-MSH secretion in response to glucose, so the feedback loop fails and blood glucose levels rise catastrophically.

The major aim of our study is to determine the mechanisms of action of α-MSH effects on glucose homeostasis and how glucose sensing in POMC neurons of obese mice and monkeys could be restored. This project will combine whole animal physiology, surgical techniques and animal experimentation with thermogenesis studies, hepatic glucose production and insulin sensitivity.

**Metabolic alterations in a polycystic ovarian syndrome-like mice model**

*Key words:* polycystic ovarian syndrome, obesity, insulin resistance

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Polycystic ovarian syndrome (PCOS) is the most common hormonal disorder affecting women (approximately 10% of adult women). This complex disorder is characterized by excess of
androgens, lack of ovulation and consequently infertility and polycystic ovaries, all of which begins immediately after menarche.

In young women with PCOS, multiple risk factors for cardiovascular diseases, including metabolic syndrome, Type-2 diabetes mellitus and hypertension, may be found. Thus, prevention of future cardiovascular adverse effects is needed.

The mechanisms underlying the development of PCOS have not been identified; nevertheless, several theories have been proposed to explain the syndrome.

Altered sympathetic innervation may contribute to the development of polycystic ovaries. Moreover, a potential contribution of excess nerve growth factor (NGF) to human PCOS can be inferred from these studies, since sympathetic hyperactivity is a hallmark of NGF over-expression in peripheral tissues.

To further study the role of NGF in PCOS we have developed a transgenic mouse model (17NF) which over-expresses NGF in the ovary. These animals show selective over-expression of NGF in thecal/interstitial cells of the ovary and develop hyperandrogenemia, decreased fertility and cystic morphology.

The major aim of this study is to determine if obesity and insulin resistance in association with a previous derangement of the ovary (NGF over-expression) is able to produce cystic follicles and PCOS like alterations in mice. We will also evaluate the hypothesis that metabolic alteration in this PCOS-like mouse model could increase the sympathetic excitation and cause a raise in blood pressure at higher levels compared with obese mice without PCOS.

This project will combine whole animal physiology, surgical techniques and animal experimentation with thermogenesis studies, hepatic glucose production and insulin sensitivity.

The adipocyte as an active participant in the development of metabolic disease

**Key words:** adipose tissue, obesity, diabetes, metabolism

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Obesity is directly linked to the rising incidence of metabolic diseases, including cardiovascular disease and type 2 diabetes. Our understanding of the pathogenesis of obesity has advanced considerably over the past decade. It is now known that the adipocyte produces and secretes a wide variety of hormones and cytokines (termed ‘adipokines’) that influence many biological processes, including substrate metabolism. It is also known that these adipokines can alter feeding behaviour.
Pigment epithelium derived factor (PEDF) is a protein that is highly expressed in the adipose tissue of obese individuals and is released into the circulation. We have previously shown that PEDF contributes to the development of obesity/diabetes by affecting metabolism of glucose and fat (Crowe et al. *Cell Metabolism* 10: 40-47, 2009).

We have now developed a mouse that overexpresses PEDF in the fat (PEDF-aP2). The project will involve the physiological assessment of this transgenic mice, including insulin sensitivity, fat oxidative capacity and feeding behaviour. You will also use a variety of analytical techniques including Western blotting and immunohistochemistry for proteins, quantitative real time polymerase chain reaction (qRT-PCR) to assess gene expression and tissue and blood fatty acid metabolite analysis. This project will provide the successful applicant with a grounding in several experimental approaches and analytical techniques, a stimulating intellectual environment and an opportunity to contribute to the understanding of the development of obesity / type 2 diabetes.

**Does increasing fat breakdown increase the capacity of muscle mitochondria to burn more fat?**

*Key words*: skeletal muscle, fat metabolism, mitochondria

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A decrease in mitochondrial content and an associated reduction in fatty acid metabolism is a major defect in the skeletal muscle of patients with type 2 diabetes. Recent evidence indicates that increasing fatty acid supply to the muscle can cause “mitochondrial biogenesis”, or an enlarged mitochondrial mass. However, it is also known that increasing fatty acid supply to muscles can cause toxicity in the muscle. We hypothesise that increasing the turnover of triglycerides within muscle cells, and thereby liberating fatty acids within the cell, may induce mitochondrial biogenesis without causing toxicity.

To test this hypothesis, the successful applicant will use genetic knockout and overexpression of the protein adipose triglyceride lipase (ATGL) to enhance fatty acid turnover in rodent skeletal muscle. The applicant will then examine markers of mitochondrial biogenesis, the capacity of the muscle cells to oxidize fats and carbohydrates and assess total energy turnover. The cellular and molecular mechanisms underpinning these anticipated changes will be examined.

This project will further our understanding of muscle metabolism and the molecular control of mitochondrial function. It will provide the successful applicant with experience in animal handling, primary culture techniques and a broad array of analytical skills.

**Examining the role of proinflammatory cytokines in the development of a diabetes**

*Key words*: metabolism, fatty acid, cytokine, inflammation, type 2 diabetes

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Obesity is characterised by an increase in proinflammatory cytokine production, which itself is linked to the development of type 2 diabetes. Preliminary data from our laboratory show that several novel cytokines are elevated in patients with type 2 diabetes and that these cytokines influence metabolic processes.

The aim of this project is to examine the effects of proinflammatory cytokines on metabolic processes. Specifically, we will test whether proinflammatory cytokines cause insulin resistance and
the mechanism/s by which this occurs. We will also test whether proinflammatory cytokines cause inflammation in muscle cells and other cell types including macrophages. The project will involve metabolic assessment in cell culture, including insulin sensitivity, and a variety of analytical techniques including Western blotting and for proteins and quantitative real time polymerase chain reaction (qRT-PCR) to assess gene expression. This project will provide the successful applicant with a grounding in several physiological and analytical techniques, a stimulating intellectual environment and an opportunity to contribute to the elucidation of molecular changes that contribute to diabetes development.

**Understanding lipid partitioning in skeletal muscle**

*Key words:* skeletal muscle, obesity, type 2 diabetes, metabolism

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Metabolic diseases such as type 2 diabetes, obesity and others are characterised by the accumulation of lipids in tissues not designed for long-term lipid storage. This accumulation of lipid in tissues including skeletal muscle is thought to be a major mechanism for the development of these metabolic diseases. One of the key questions that needs to be answered is where are lipids that are taken up by the cell partitioned to (i.e. either directly into storage or oxidised in the mitochondria) and thereby where are the key regulatory points of normal lipid metabolism. Characterisation of these pathways will lay the foundations to understand how these process may be perturbed in metabolic pathologies.

This project will use 2 cutting edge technologies, live cell imaging and mass spectrometry, in combination with cell culture techniques to determine the intracellular lipid partitioning of fats taken up from outside the cell. At the end of this project the successful applicant will gain experience in several experimental approaches and analytical techniques, have enjoyed a fun and stimulating intellectual environment, and contribute to scientific knowledge of factors that may be important in the development of type 2 diabetes.

**The role of the lipid ceramide in skeletal muscle insulin resistance**

*Key words:* skeletal muscle, fat metabolism, insulin action, glucose metabolism

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Type 2 diabetes and other components of the metabolic syndrome are characterised by insulin resistance. Insulin resistance is thought to precede the onset of type 2 diabetes and results in the inability of the body to maintain normal blood glucose levels (hyperglycaemia). Skeletal muscle is one of the key tissues responsible for glucose homeostasis and the accumulation of the lipid ceramide in this tissue is thought to be a major mediator of the development of insulin resistance. The aim of this study is to directly test whether a key enzyme responsible for the synthesis of ceramide does contribute to skeletal muscle insulin resistance.

To test this, the successful applicant will use genetic tools to overexpress or knockdown Serine Palmitoyl Transferase LC1 (SPTLC1) to either increase or prevent ceramide synthesis respectively in rodent muscle. The applicant will then examine insulin sensitivity, lipid metabolism and other cellular and molecular mechanisms underpinning these anticipated changes.

This project will determine the role that ceramide synthesis plays in the development of insulin resistance, the molecular mechanisms, and whether SPTLC1 is a potential therapeutic target in the
fight against metabolic diseases. It will provide the successful applicant with experience in animal handling, in vivo and ex vivo techniques and a broad array of analytical skills in a fun and intellectually stimulating environment.

**What causes dopamine cells to die during Parkinson’s disease?**

*Key words:* transgenic mice, brain degeneration, aging  
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The loss of dopamine and dopamine cells in the brain causes Parkinson’s disease. The reason dopamine neurons die is poorly understood but involves impaired mitochondrial function and energy production. This project will use state of the art transgenic mice, in which the AMPK beta 1 gene controlling mitochondrial function and energy production, is genetically removed only in dopamine neurons. Thus, we can assess degeneration of dopamine cells without affecting other non-dopamine cells. This project involves animal handling, immunohistochemistry, western blotting, molecular biology and stereology. These are the first experiments of this kind in the world. This approach will directly answer the question; does AMPK prevent dopamine cell death in Parkinson’s disease. This may identify a new therapeutic target to treat Parkinson’s disease patients.

**How does ghrelin cause insulin resistance?**

*Key words:* obesity, diabetes, fat cells  
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Ghrelin is a hormone that increases food intake and weight gain. Studies show that ghrelin also causes hyperglycemia and insulin resistance in peripheral tissues. This project will directly examine how ghrelin acts on fat cells to cause insulin resistance. Our preliminary data suggests ghrelin inhibits a protein (FXR) that is important for maintaining insulin signalling in fat cells. This project has important implications for the treatment of diabetes and obesity and involves cell culture of fat cells, western blotting for the insulin-signaling pathway and PCR.

**Does ghrelin enhance the rewarding properties of food in diet-induced obesity?**

*Key words:* obesity, reward, motivation, ghrelin, food intake, brain  
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Ghrelin increases food intake in the brain through two different processes. 1) Ghrelin increases the need to eat (i.e. when you are hungry) and 2) ghrelin increases the desire to eat foods that are rewarding (i.e. fats and sugar). This project examines whether ghrelin increases the desire to eat rewarding foods in diet-induced obesity. We hypothesize that ghrelin increases the desire to eat rewarding foods (fats and sugars) and that this contributes to diet-induced obesity. We will use mice that have had the ghrelin gene genetically removed (ghrelin knockout mice). This project
involves animal handling and surgery, transgenic mice, immunohistochemistry, western blotting and monitoring animal behaviour. This project will help us understand why we continue to eat despite sufficient calorie intake and may help identify novel targets to treat obesity.

Ghrelin prevents neuronal cell death after a stroke

**Key words:** hippocampus, neurology, learning and memory, transgenic mice

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Our previous studies show that ghrelin prevents Parkinson’s disease. The mechanism involves decreased free radical production and increased mitochondrial function. As mitochondrial problems are a common cause of neuronal cell death after a stroke, we hypothesized that ghrelin would restrict stroke-induced neuronal cell death. We will use ghrelin knockout mice and a mouse model of stroke in order to examine this hypothesis. Experimental techniques include animal surgery, animal handling, immunohistochemistry, mitochondrial function, western blotting, PCR and stereology. Because ghrelin helps to maintain body weight, this project examines the overall common theme that metabolic states such as obesity or calorie restriction will predispose and prevent neurodegeneration respectively.

Adjustable Gastric Band (AGB) surgery, an animal model – does tightening your belt help to enhance weight loss?

**Key words:** obesity, surgery, hunger, food intake, metabolism

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Laporascopic adjustable gastric band (LAGB) surgery in human patients is emerging as one of the most effective means of initiating and maintaining weight loss. In fact, surgical approaches have created a new “gold standard” where they can offer between 20-30% weight loss (and 60-70% loss of excess weight) whereas the best pharmacological therapies are hovering at about 5% loss of excess body weight. While there is often a misconception that the band which is placed around the upper part of the stomach in the human patient acts solely to limit the amount of food allowed into the stomach, this is not true. The best evidence to date is that there is either a hormonal or neural signal activated by the tightening of the band which alerts the brain to reduce hunger. We have no idea of the nature of this signal or the changes in the brain that it mediates to reduce hunger.
This series of projects uses a miniaturized band fitted to the rat stomach and a range of approaches to map the potential pathways to the brain and the changes in gene expression that are initiated by adjustment of the band. Specifically, individual projects will examine i) the potential activation by the band of neural links between the stomach and the brain via the vagus nerve, ii) the changes in levels of gut derived hormones in the blood that may activate the brain following tightening of the band, iii) the changes in activation of feeding related pathways as shown in fMRI following tightening of the band, iv) the changes in expression of feeding related genes in the brain and expression of incretins and other peptides and hormones in the stomach following tightening of the band v) changes in energy expenditure following tightening of the band. These experimental approaches will provide valuable information about the mechanisms underlying the effectiveness of this approach in human patients.

**Blockade of cannabinoids in the brain – a role in the control of obesity**

**Key words:** cannabinoids, diabetes, appetite, energy expenditure, inflammation

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The cannabinoids have been known for many centuries to increase food intake – most recently recognized as the need to ingest highly palatable foods after smoking cannabis. These largely anecdotal observations have been incorporated into the treatment of patients suffering from cancer and AIDS in order to promote appetite. Over the last few years, blockers of the endogenous actions of the receptors to cannabinoids in the brain, the so called CB1 receptor antagonists, have become the number 1 candidates to combat obesity. This is thought to be largely through changes in food intake but the role of these agents in determining levels of energy breakdown and the level of body fat is unknown. In contrast to the role of the CB1 receptor in appetite and energy expenditure, the CB2 receptor is important for regulation of the immune system. Although poorly understood, obesity is now accepted as a state of inflammation whereby obese individuals have increased circulating and adipose tissue expression of inflammatory markers, similar to what is seen during an infection. This opens the possibility that CB2 receptor agonists, known to inhibit the immune system, may prove beneficial for the treatment of obesity-related inflammatory conditions such as type 2 diabetes.

**The biological basis of anorexia nervosa? Impact of an animal model**

**Key words:** eating disorders, anorexia nervosa, animal models of human disease

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While obesity and its related issues occupy centre stage amongst so called eating disorders, anorexia nervosa is situated at the other end of the spectrum and represents a very significant problem amongst affected individuals. Nearly 20% of those diagnosed with restrictive anorexia nervosa will die as a result of the disorder. There is no effective treatment and there is only a sketchy understanding of the etiology of the disorder. It is clear that psychological and environmental issues play a role but what is not apparent is the extent to which there is an underlying biological basis of anorexia nervosa. In this vein, insight into these mechanisms or the brain regions involved may enable the development of therapeutic strategies.

This series of projects is based on an activity based rodent model of anorexia which mimics a number of the key characteristics of the disease. It is our intention to exploit this model to
investigate the biological substrates involved as well as the potential to pharmacologically reverse the weight loss associated with anorexia nervosa.

**Antipsychotic drug (APD) induced weight gain – understanding the mechanisms behind the increases in weight and development of diabetes in schizophrenic patients taking APDs**

*Key words:* drug treatments for schizophrenia, drug side effects, obesity  
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Commonly overlooked when considering individuals who are overweight or obese are those who gain weight and develop diabetes directly as a result of taking medications for psychoses including schizophrenia. This is a debilitating situation which often results in patients discontinuing medications or running the risk of developing metabolic syndrome. These disadvantages are tolerated because of the effectiveness of the drugs in alleviating antipsychotic symptoms.

We have a series of projects based in animal models and possibly in a human intervention study that will look at the mechanisms involved and the potential to reverse these adverse effects with adjunct therapies.

**The potential for opioids and other peptides in the central nervous system to alleviate the mood related effects of endocannabinoid receptor antagonists**

*Key words:* obesity, drug therapy, mood, depression  
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Until recently, the endocannabinoid receptor “antagonist”, rimonabant was considered one the brightest hopes for a human anti-obesity therapy. Unfortunately, large scale human trials revealed an adverse effect on mood and a tendency to increase suicide rates. This intolerable adverse effect profile has lead to the removal of the drug but research continues to find ways to preserve the significant positive effects of the drug on weight loss and diabetic status.

This series of experiments looks in animal models at possible adjunct treatments where other compounds, namely opioids and the antagonists of the orexigenic hormone MCH, are co administered with rimonabant in an attempt to circumvent the unwanted effects on mood while preserving or even adding to anorexigenic outcomes.
The role of the fusimotor system in proprioception

Key words: position sense, exercise, muscle spindle

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Our ability to tell where our limbs are in space, if we are not looking at them, depends on signals from sensors in our muscles, the muscle spindles. In this project we want to test the idea that when, during a voluntary contraction, spindles become activated through their motor supply, they no longer signal limb position and movement. To do that, a movement illusion will be generated in elbow flexor muscles using vibration. The size of the illusion will be measured in the relaxed arm and when it is contracting voluntarily. We predict that the illusion generated in the relaxed arm will fade as the muscles contract. The illusion will be measured in muscles before and after elbow flexors have been exercised to reduce their contraction strength by 30%. It is hypothesised that during fatigue, the smaller contractions will result in a proportionately greater suppression of the vibration illusion.

Muscle fatigue and limb position sense

Key words: position sense, movement sense, fatigue

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We have recently shown that when a muscle is fatigued, a subject’s sense of limb position is disturbed. This is an important finding because it implies that the effects of muscle fatigue associated with exercise are not just a matter of the muscles having reduced force output, but that neural mechanisms of movement and postural control have also been affected. Here we want to measure a subject’s ability to detect changes in position sense of the forearm before and after experimentally inducing muscle fatigue or loading. The forearm will be moved through a range of angles and subjects will be asked to indicate the new position by matching it with the other arm. A comparison will be made between matching accuracy before and after induction of muscle fatigue.
or loading. This kind of experiment will have important implications for reducing the effects of muscle fatigue on performance in exercise and sport. It may also gain insight into improving strategies to reduce falls and debilitating injuries in the elderly.

**Effect of stretch on passive and active tension in human skeletal muscle**

*Key words:* passive tension, warm-up, muscle torque

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To an athlete the risk to performance of even mild muscle damage is significant. The potential benefits of a warm-up stretch protocol with respect to both preventing injury and improving performance are still unclear. This is because our understanding of the mechanisms involved remains fragmentary. After some forms of exercise, like eccentric exercise, where the contracting muscle lengthens actively, there is some muscle damage and this leads to delayed muscle soreness, a reduction in active force, and an increase in passive tension. The rise in passive tension is associated with the damage process. A common warm-up strategy before training is to stretch the involved muscles. This lowers passive tension for some time. Does this reduce the risk of muscle injury? Does it impair muscle performance? The aim of this study is to measure the size and time-course of changes in passive and active tension after large passive stretches. Measurements will include passive torque, joint angle, electromyogram (EMG), and active torque (voluntary and twitch).
Development of new classes of memory enhancers

*Key words:* Alzheimer’s disease, drug development, memory

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This body of work will build on our laboratory’s successful drug discovery program to identify new classes of cognitive enhancers using state of the art techniques including *in silico* drug screening, high throughput fluorimetric assays and whole animal behavioural tests.

Mechanism of action of IRAP inhibitors

*Key words:* genetically modified mice, drug development, memory

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Although it is well-established that modulation of insulin-regulated aminopeptidase (IRAP) facilitates memory, the mechanism of action has not been elucidated. It has not been clearly established which stages of memory formation process (acquisition, consolidation and/or recall) the IRAP inhibitors were most effective at. The availability of the small molecule IRAP inhibitors and generation of knockout-transgenic mouse lines provide the essential tools to address this question.

Role of IRAP in Alzheimer’s Disease

*Key words:* Alzheimer’s disease, insulin-regulated aminopeptidase

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Our newly discovered IRAP inhibitors are currently being developed as potential therapeutic agents for symptomatic treatment of Alzheimer’s disease (AD). However, it is not known if IRAP contributes to the pathophysiology of AD by regulating the levels of Aβ (in its role as a peptidase), altering the trafficking of amyloid precursor protein or Aβ in neurons (in its role as a regulator of vesicular transport) or participating in the inflammation process.

Role of IRAP in ischemic damage

*Key words:* stroke, brain damage, ischaemia-reperfusion injury

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Stroke is Australia’s second greatest cause of death after coronary heart disease and is a leading cause of disability. We have three independent observations that provide clear evidence for the involvement of IRAP in ischemic damage (1) markedly reduced damage in the brains of the IRAP KO mice following middle cerebral artery occlusion, (2) IRAP inhibitor treatment attenuating volume of ischemic damage and (3) the detection of IRAP immunostaining in activated astrocytes and microglia after damage. This project will elucidate a role for IRAP in the brain following focal or global ischemia and develop the concept of IRAP inhibitors as a potential treatment.
Role of IRAP in cardiovascular function

Key words: atherosclerosis, heart disease, insulin-regulated aminopeptidase

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We have preliminary data implicating a role for IRAP inhibitors in retarding the development and progression of atherosclerosis. We recently observed that the IRAP KO mice have enhanced vascular reactivity to vasodilators and decreased ability to retain and deposit fat in response to a Western high fat diet. This project, conducted in collaboration with A/Prof Rob Widdop and Dr Tracey Gaspari from the Department of Pharmacology, will investigate the cardiovascular phenotype of the IRAP KO mice and investigate the effect of IRAP inhibitors on disease progression in atherosclerosis.

Importance of IRAP in the kidney

Key words: vasopressin, water balance, insulin-regulated aminopeptidase

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Recent exciting evidence indicates that IRAP plays a role in the degradation of vasopressin in vivo. The most important physiological function of vasopressin is the maintenance of water homeostasis through interaction with V2 receptors in the kidney. These studies will investigate the role of IRAP in the kidney in regulating vasopressin actions. In the kidney, the vasopressin-responsive water channel, aquaporin-2, plays a key role in maintaining water balance. An important outcome of this project will be the exposition that IRAP is part of a vasopressin negative feedback loop regulating aquaporin-2 movement; a system vital for normal fluid homeostasis.

Does IRAP regulate neurogenesis?

Key words: brain development, neurogenesis, memory loss

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We recently found high concentrations of IRAP expression in the subventricular zone of the developing mouse brain and that our IRAP knockout mouse expressed abnormalities in cortical and hippocampal brain development. In this project, we will test the hypothesis that the premature onset of age-related memory deficits observed in our IRAP knockout mice is likely to result from abnormalities caused by the absence of IRAP during critical stages of brain development.

Role of IRAP in glucose and fat metabolism

Key words: obesity, fat absorption, fat metabolism, insulin-regulated aminopeptidase

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In characterising the phenotype of the (IRAP) knockout mice, we observed that these mice, when placed on a Western high fat diet, were not susceptible to weight gain, in contrast to their wildtype controls. We postulate that IRAP plays a role in the absorption and deposition of fat and in the absence of IRAP (either with gene deletion or inhibition of its activity), the mice have impaired fat absorption and/or enhanced fat clearance. This project will investigate if the IRAP KO mice or mice treated with the IRAP inhibitors, are protected against the health complications associated with diet-induced obesity.
Is there a sex difference in kisspeptin and/or GnIH expression in the brain?

**Key words:** fertility, puberty, reproductive neuroendocrinology  
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Kisspeptins are the endogenous products of the Kiss1 gene, which is expressed in the hypothalamus and plays a vital role in the neuroendocrine regulation of reproduction. Not surprising then is that kisspeptin are critical for the onset of puberty. Despite this, it is unclear how kisspeptin expression changes over the course of puberty. Moreover, the onset of puberty differs between males and females. Sex differences are apparent in Kiss1 expression (in rats and mice) but these have not been examined prior to puberty and have not been examined at all in sheep, which appear to be more similar to humans. This project will involve collection of brains pre- and post puberty in male and female sheep. Kiss1 mRNA and kisspeptin protein expression will be measured (by in situ hybridisation and immunohistochemistry). Data obtained from this study will provide insights into the role of kisspeptin in the onset of puberty.

Are the effects of stress on the reproductive system mediated by kisspeptin signalling?

**Key words:** infertility, stress, reproductive neuroendocrinology  
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It is well known that stress has an inhibitory effect on fertility. Increased plasma concentrations of cortisol (in response to stress) inhibit normal reproductive function by suppressing gonadotrophin secretion, but the mechanisms involved are largely unknown. This project aims to determine whether the neuropeptide kisspeptin plays a role in mediating the effects of stress on the reproductive system. The project will involve measurement of Kiss1 mRNA (the kisspeptin gene) in the brains of animals subjected to acute psychosocial stress. Furthermore, the response to kisspeptin treatment will also be determined in stressed animals. Techniques will include collection of both peripheral and hypophysial portal blood samples with subsequent analysis by LH and GnRH radio-immunoassay. Collection of brain tissues from sheep will also be performed for subsequent in situ hybridization and immunochemistry analysis.
Do pheromones activate the reproductive system by stimulating kisspeptin cells in the hypothalamus?

**Key words:** fertility, reproductive neuroendocrinology

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The ability of olfactory cues to alter the reproductive system in humans has sparked interest in the possibility of pheromonal communication in humans. In sheep, reproductive activity is seasonal, being activated by short-day photoperiod and inhibited by long days. In this species, pheromones produced by the male can induce out-of-seasonal ovulation in anoestrous females, the so-called 'ram effect.' Because the initial endocrine event following reception of the pheromone is the stimulation of pulsatile luteinising hormone (LH) secretion we believe kisspeptin signalling may play a critical role in this phenomenon. This project will examine the activation of kisspeptin cells in anestrous female sheep subjected to the 'scent' of a male ram. Techniques will include collection of blood samples with subsequent analysis by LH and GnRH radio-immunoassay. Collection of brain tissues from sheep will also be performed for subsequent in situ hybridization and immunochemistry analysis.

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**Hypo-responsiveness to stress in lean individuals: what are the mechanisms for this and can we treat anxiety and depression by reducing body weight?**

**Key words:** depression, anxiety, stress-disorders, weight regulation

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Some individuals are naturally less responsive to stress, such as during late-pregnancy, lactation, or in cases of low visceral fat. We have several projects available in which we aim to examine some of the mechanisms for this hypo-responsiveness. Lean animals display reduced responses to stress compared with normal and overweight animals. There is also, conversely, a clear effect of stress on propensity to gain weight, a phenomenon that can lead to a cycle where bigger stress responses leads to obesity leads to bigger stress responses. We aim to investigate this phenomenon by manipulating litter sizes in the rat thus creating ‘fat’ versus ‘thin’ phenotypes from genetically identical animals. We will then examine various aspects of the “stress” hypothalamic-pituitary-adrenal (HPA) axis, and its responses to stressful situations, utilizing surgical and immunohistochemical techniques, in situ hybridization and radioimmunoassay.

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**Does being obese from an early age make you more susceptible to disease?**

**Key words:** infection, fever, weight regulation

**Supervisors:** Dr Sarah Spencer (Rm F228), Dr Zane Andrews (Rm F215)
The perinatal environment is essential in programming long-term physiology. It has been established that animals, including humans, that are overfed in early life become overweight from an early age and go on to become obese adults. We have recent novel evidence from our laboratory that overfeeding during this early period also influences immune system integrity long-term. Thus, neonatally overfed rats have markedly exaggerated fevers and hypothalamic-pituitary-adrenal (“stress”) axis responses in adulthood to the bacterial infection mimetic lipopolysaccharide (LPS). Recent discoveries have suggested that immune responsive toll-like receptor (TLR)4 may be dysregulated in obesity. TLR4 initiates responses to specific stimuli such as LPS or free fatty acids (elevated in obesity). Importantly, TLR4 expression can be permanently altered by neonatal events. These findings suggest a potential mechanism for exaggerated immune responses in adults that were overfed as neonates. In this project we will investigate alterations in TLR4 in neonatally overfed rats with the aim of determining how adult immune responses are affected by neonatal overfeeding.

**Protecting against learning and memory deficits associated with obesity**

**Key words:** learning and memory, weight regulation  
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Early life overfeeding can lead to obesity and type II diabetes that last a lifetime. However, the perinatal period is one of significant plasticity in a number of aspects of physiology, and the long term effects of obesity and type II diabetes acquired in childhood may differ from those of obesity and type II diabetes acquired later on. We have preliminary evidence that the neonatal period may be protective against the negative effects of obesity and type II diabetes on amygdala-dependent learning and memory. We have seen that performance in a test of contextual fear conditioning is enhanced rather than impaired in male rats that were made obese and type II diabetic during the early postnatal period. Overfeeding during the neonatal period may therefore confer protection against the amygdala-dependent learning and memory deficits usually associated with obesity and type II diabetes. We will test this hypothesis by investigating whether neonatal overfeeding affects amygdala and hippocampus-based memory differently, comparing these in the same study with animals made obese as adults and will identify the role of neurogenesis in these memory effects.

**Postnatal programming of brain pathways regulating metabolism**

**Key words:** early life programming, metabolism, weight regulation  
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Overfeeding in early life can lead to obesity that lasts a lifetime. Animals are particularly vulnerable to environmental factors during the neonatal period, but we do not know how overfeeding at this time influences the brain and body to cause permanent obesity. In this project we will aim to determine how neonatal overfeeding changes the brain circuitry that determines metabolism and weight regulation throughout life. We will focus on the role of a key hormone, leptin, in development of feeding circuitry in animals that are overfed during early life. We will use a variety of techniques from whole body in vivo physiology to examination of neuronal development in brain slices to investigate the role of leptin in this regard.
Macrophage phenotypes and the physiological consequences of perinatal brain injury

Key words: immunology, neurodevelopment, schizophrenia, cerebral palsy, glia

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Neurodevelopmental diseases such as schizophrenia and cerebral palsy are thought to be caused by viral infection (e.g. influenza) of the mother during pregnancy or by brief episodes of hypoxia (lack of oxygen) and/or ischemia (lack of blood flow) endured by the fetus during development or birth. Initially in response to brain trauma, both macrophages and glia seem to exacerbate the damage, as interventions that inhibit the immune response to brain trauma have a beneficial effect on overall outcome. However an innate, beneficial characteristic of macrophages and glia is the ability to promote tissue repair. In particular to macrophages, recent studies have highlighted a number of macrophage subtypes, termed polarization states M1, M2a, M2b, and M2c. The M1 phenotype is the classic pro-inflammatory (Th1 cellular response) macrophage phenotype; the M2a phenotype is pro-inflammatory but associated with Th2 cellular responses; the M2b phenotype is immunoregulatory; the M2c phenotype is anti-inflammatory and associated with tissue repair. The project will focus on characterising the role of macrophages in neurodevelopmental brain injury and disease, and focus on the therapeutic potential of manipulating macrophages to heal the injured brain, using animal models of maternal stress such as exposure to viral mimic and fetal hypoxia/ischemia during development or birth. Techniques utilised include fetal surgery, monitoring of fetal physiology (heart rate, blood pressure, brain electrical activity, brain blood flow), immunohistochemistry, flow cytometry, cell culture techniques, real-time PCR and other molecular biological techniques, and an understanding of neuroanatomy.
Neuroimmune regulation of the obese mother and her offspring  

Key words: prostaglandin, neuropeptide, immunology, metabolism, appetite, obesity

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The incidence of obesity in adults and children is dramatically increasing. Obesity-related complications such as metabolic disturbances, diabetes and cardiovascular disease are soon to be the major causes of death in westernised countries. With the increased incidence of obesity in adults, there has been a concomitant increase in the incidence of obese, pregnant women. The long-term consequences on the offspring of the obese, pregnant woman are not known but initial studies, both in humans and in rodent models, suggest that there are long-term changes in the offspring’s regulation of body weight and food intake, predisposing the offspring to developing metabolic disturbances, diabetes and cardiovascular disease. Obesity can be characterised as a state of low-grade inflammation, and during pregnancy these inflammatory factors can influence fetal development, having long-term consequences on offspring’s ability to regulate energy intake (e.g. feeding and appetite) and energy expenditure (e.g. the utilisation of fat for energy, body temperature). The project will focus on characterising the neuroimmune link between obese mother and her offspring, as well as the neuroimmune regulation of energy intake, energy expenditure, cardiovascular function and immune function in the offspring. Techniques utilised include surgery, monitoring of maternal and offspring physiology (heart rate, blood pressure, food intake, activity, and oxygen consumption), immunohistochemistry, real-time PCR and other molecular biological techniques, and an understanding of neuroanatomy.
Understanding how the brain computes the motion of objects

Key words: neuroscience, vision, physiology, cerebral cortex

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The aim of this study is to discover the specific contributions of different parts of the brain to visual sensation. By analysing the electrical responses (action potentials) to different types of visual stimuli, we try to understand how the information is processed at the different stages of the visual pathway, until an accurate conscious perception emerges. This type of information has the potential to help improve the quality of life of visually impaired people, through the creation of accurate models of visual processing, which will help the design of electrical stimulation devices (“bionic eyes”). Among the questions we will be examining are the physiological differences between central and peripheral vision. For example, in what ways the brain cells that process high acuity information (e.g. when you are examining a picture) differ from those involved in detecting sudden motion in your peripheral visual field. If you are interested in this type of study, you will receive training in surgical techniques, simple histological preparations, and electrophysiological techniques. A certain level of computer literacy will be a distinct advantage. This project provides exciting opportunities for students with a background in computing, mathematics, or engineering.

Study of the connections of areas of the cerebral cortex

Key words: neuroscience, anatomy, connections, cerebral cortex, plasticity

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The long-term aim of this study is to create an accurate “wiring diagram” of how different areas of the cerebral cortex are connected to each other, and to other parts of the brain. This type of information will allow the modelling of the information flow through the brain, and allow the development of better artificial systems capable of vision. In 2011, we will also be studying the consequences of brain lesions early in life- how the neuronal circuits reorganise to make use of the parts of the brain that are not affected. This has direct implications for future attempts to cure
certain types of blindness. These experiments use fluorescent tracer substances which, when placed in a point of the brain, migrate along the axons to reveal the cells that send information there. If you are interested in this type of study, you will be trained in surgical techniques, histological techniques, and microscopy, including image processing techniques. These projects also offer exciting opportunities for students with interest in computer graphics, through the development of better tools for the visualisation of complex networks of data.

**Visual control of behaviour in honeybees**

*Key words:* behaviour, decision-making, invertebrate, cognition

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This area of research is devoted to examining how an animal with a very small brain (fewer than 1 million nerve cells) can solve complex tasks like navigating mazes, discriminating between similar shapes and colours, and even recognising human faces. Our recent work shows that individual bees make high level decisions, and can balance speed for accuracy when solving difficult tasks, and we are currently working to understand how these processes occur.

Psychophysics of Speed Accuracy Tradeoffs for solving impossible tasks: Bees allocate more time to tasks of increasing difficulty, but currently it is not known what mechanisms in the brain control this and what the miniature brain does when the task is made impossible (big-brained primates do a rule switch and make fast random choices, but can an insect possibly learn the new rules?). This project will tackle these important questions and reveal important insights into how brains manage the complexities of difficult and impossible tasks. Students who choose to work on this project will have the opportunity to perform studies both in the laboratory and outdoors, at our on campus field station. You will learn to do psychophysics, behavioural training, statistical analysis, and preservation of samples for genetic studies.

**Noise in the brain**

*Key words:* neuroscience, vision, perception, eye movements

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You could try to throw a ball the same way 100 times and your actions would be subtly different every time. Similarly, you could see a picture 100 times and your perception would be slightly different with each look. What does this variability, or noise, tell us about how visual information is processed in the brain, and what limitations there may be on our perception and on the accuracy of our movements?

In this project, you will perform psychophysical testing of human visual perception. You will record a subject’s reflexive eye movements and their perception of moving stimuli presented on a computer monitor. This will give insights into how visual sensory information is represented in the brain, and the reliability of this sensory processing. During this project, you will learn how to design and implement psychophysical tests of human perception, computational analyses, and how to accurately track and quantify human eye movements.
Visual adaptation: how does what we perceive now, depend on what we saw then?

Key words: neuroscience, vision, perception, eye movements
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Our perception of the world is innately coloured by what we have experienced previously. For example, you may have noticed that driving at 60 km/hr can seem ridiculously slow after being on a freeway, but quite fast after waiting at traffic lights. Although less obvious, after driving at 100 km/hr, you actually become more sensitive to small deviations in speed. These perceptual changes probably arise because sensory neurons in the brain dynamically “adapt”, matching their sensitivity to prevailing environmental conditions. This allows the brain to more accurately and efficiently encode the world.

Using psychophysical studies of human observers, this project will characterise how human perception of motion depends on what has recently been seen. This gives us insights into flexibility of motion encoding in the brain, and whether adaptive mechanisms in the brain are likely to have evolved simply to conserve energy, or whether they convey behavioural or perceptual benefits. During this project, you will learn how to design and implement psychophysical tests of human perception and how to perform computational analyses or perceptual performance.

Sensory encoding by populations of neurons

Key words: neuronal populations, touch, sensory perception
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Our perception of the world depends on the activity of populations of sensory neurons in the brain. However, like any population, the votes of individual neurons can only influence the final percept – it is the collective activity of the population that is critical for making a decision. While much is known about how single neurons encode specific attributes of the world, we know relatively little about how small groups of neurons work together to create perception. For example, if we double the number of sensory neurons, are we now twice as sensitive to a stimulus, or are there fundamental limits on how much information can be processed by the brain?

This project will make use of novel electrophysiological methods such as electrode arrays, which allow us to simultaneously record the extracellular activity of multiple neurons in the whisker barrel cortex of rodents. Previously, it has been more common to record from only one neuron at a time. You will investigate how small groups of neurons collectively encode whisker movements and how information encoding capacity scales with the number of neurons. This project is a blend of physiological and engineering approaches. Students will learn surgical and electrophysiological techniques, and will also learn to perform sophisticated computational analyses.

Integrating visual information across space and time

Key words: neuroscience, vision, perception, short term memory
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You will make at least 5 small eye movements, or saccades, while reading this sentence. Similarly, when looking around the world, you continually make small eye movements to build up your mental representation of the scene. Although these behaviours seem simple and automatic, it is not
clear how the brain integrates visual information across space and time. This project will involve tracking the eye movements of human subjects while they play a computer game requiring them to memorise the location of objects. You will investigate how a subject’s perceptual performance depends both on task difficulty and on the pattern of eye movements that they make. Further, you will examine if a subject’s performance can improve if they are told specific strategies. During this project, you will learn how to design and implement psychophysical tests of human perception, computational analyses, and how to accurately track and quantify human eye movements.

**Audio-visual integration in working memory for speech**

*Key words:* neuroscience, hearing, vision, integration

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Our senses have dedicated peripheral systems to process the specific stimulus for which they are specialized and dedicated “labelled line” neural pathways to send the information to specialised brain areas. Ultimately, input from the different senses must be integrated to provide a holistic view of the world. We depend on multi-sensory integration vitally when input from one sense is distorted or degraded as in noisy parties where we use lip-reading to assist our ability to follow a conversation. We critically need it when during development and in learning complex tasks such as reading, writing, walking; deficiencies in this skill have been linked to dyslexia. In this study we will characterize the ability of people to carry out multi-sensory integration to utilise redundancy of information across the senses. The questions we will address are how well people carry out such integration in working memory for speech and whether different people show different degrees of dependency on multi-sensory integration. We will examine the integration of audio-visual inputs under conditions where there is no cognitive load and conditions with varied cognitive load.

**Does expertise in simple tasks assist in learning complex tasks?**

*Key words:* neuroscience, hearing, speech, training

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Our ability to understand speech, especially in the noisy backgrounds that typify a modern technological society, draws on skills ranging from extracting low-level information (e.g., using spectral or temporal mismatches to segregate the speech of interest from background noise) to use of more complex speech-based information (e.g., more efficient use of cues such as prosody) and all the way through to high-level language (e.g., predictively using contextual cues in the speech stream) and attention processes (e.g., learning where to focus attention to most efficiently extract speech from background noise). Unsurprisingly speech-in-noise identification therefore requires use of very widespread brain areas ranging from primary auditory cortex through to high-order language and attention areas. In central auditory processing disorder, children have difficulty in understanding speech in noise and the deficits have been linked to a number of low-level as well as high-level skills. In this study we will examine whether training in low-level auditory discrimination tasks can help improve the ability of adults to understand natural whole speech in noisy backgrounds. The questions we will address are how well people training under easy and difficult background conditions assists in subsequent speech-in-noise processing.
Telmisartan in the management of abdominal aortic aneurysm (TEDY)

Key words: clinical trial, heart disease, angiotensin receptor blockers

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Abdominal aortic aneurysm (AAA) is responsible for ~1,500 deaths and 10,000 hospital admissions per year in Australia. Surgery is the only therapy for AAA but is costly and associated with high morbidity and mortality. No medical therapy has been approved for AAA, highlighting the need for a better understanding of its pathophysiology to implement novel management strategies.

Evolving evidence suggests that angiotensin II (AngII) plays a crucial role in aneurysm formation (1,2). This pro-aneurysmal pathway can be antagonised by angiotensin II type 1 receptor (AT1) antagonists.

A project is offered in conjunction with a large scale clinical trial which is currently underway with collaborators from Queensland. The aims of the clinical trial are to investigate the efficacy of the AT1 antagonist Telmisartan to:

- Reduce AAA growth assessed by computed tomography angiography
- Reduce circulating concentrations of pro-aneurysmal biomarkers.

This clinical trial will be the first to assess the value of a promising medication with significant preliminary data to suggest it can slow aortic destruction, and thus offers the possibility of identifying a new treatment modality for an increasingly common condition.
Does a high fat diet initiate an epigenetic program for diabetes?

*Key words:* diet, lifestyle factors, obesity, diabetes

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The “pandemic” of metabolic disease is recognized as one that is caused by an interaction between genes and the environment. This study investigates the role of epigenetic modification induced by exposure to a high fat diet (both directly and prenatally) on gene expression and metabolic control. The study incorporates cell, animal (rabbit and rat) and human studies with genome wide histone modification and gene expression analyses. Current projects include studies of offspring from rabbit and rat mothers fed high fat diets. These animals undergo extensive physiological metabolic investigations at the whole body and tissue level as well as epigenetic and gene expression analysis of metabolic tissues (muscle, adipose, liver). Results from our animal investigations will be interpreted in conjunction with parallel data from human vastus lateralis and adipose biopsies (healthy and obese patients with various stages of metabolic disease). A project is offered in relation to both the rat and human aspects of this program in 2011.

Metabolic and anti-inflammatory actions of HDL

*Key words:* metabolism, good cholesterol, inflammation, diabetes

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Recent studies in our laboratory have identified novel actions of HDL cholesterol in relation to glucose and fat metabolism which provide new opportunities for therapies to prevent and treat type 2 diabetes.

In a combination of *in vitro* molecular investigations and a clinical trial of reconstituted HDL (rHDL) infusion, we have recently shown that HDL lowers blood glucose through both stimulation of insulin release from pancreatic β cells and activation of the key metabolic regulatory enzyme, AMP-activated protein kinase in skeletal muscle. Our current studies also support a third mechanism involving enhanced insulin sensitivity via anti-inflammatory actions in both metabolic tissues and macrophages. These findings provide a rationale for therapeutic approaches to raise levels of circulating HDL to manage the metabolic syndrome and type 2 diabetes.

This exciting work is progressing on multiple fronts including:

- A drug company collaboration to examine the effects of chronic HDL elevation on glucose metabolism both *in vitro* and in a clinical trial of type 2 diabetic patients
- Examination of novel HDL signalling pathways in human skeletal muscle and macrophage cultures using approaches including gene array and phosphoprotein proteomics.
- Determination of metabolic and functional actions of HDL in the heart using cell culture, isolated heart models and human biopsy material.

Both PhD and Honours projects are offered in all the above areas.
Development of brown adipose tissue for treatment of obesity

Key words: clinical trial, obesity, metabolism

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Fundamentally, obesity results from an imbalance between energy intake and expenditure. Current preventative and therapeutic approaches have been either unsustainable or result in significant negative side effects. Increasing brown adipose tissue (BAT) content and activity is currently considered one of the most promising strategies to increase energy expenditure and combat obesity. Projects focusing on the following areas are offered in 2011:

a) gene activation targeted to drive BAT formation in immature stems cells from human muscle and adipose tissues,

b) pharmacological activation of brown adipose tissue in humans,

c) examination of the capacity of precursor cells in human tissue to form BAT cells when comparing lean and obese humans.

Steroid Receptor Biology Group: Prince Henry’s Institute, Monash Medical Centre

Understanding the mechanisms of cardiac failure using cardiac selective knockout mice: the role of the mineralocorticoid receptor

Key words: cardiac failure, hormones and heart disease, mineralocorticoid receptor, tissue-selective knockout mice

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The mineralocorticoid receptor (MR) is best known as a regulator of salt and water homeostasis in the kidney. We now know that the MR has novel and important functions in the cardiovascular system and in particular it plays an important role in the development of heart failure making it an attractive therapeutic target. However, current drugs that block the MR have side effects in many patients which limit their use. Cardiac specific MR blockers would avoid these problems.

We have now used the Cre-Lox technique to delete mineralocorticoid receptor (MR) expression in (separately) cardiomyocytes, endothelial cells to identify which cells types are critical for the development of vascular inflammation and cardiac fibrosis. These studies have identified important and novel roles for the MR in macrophages and cardiomyocytes, i.e. our first study in tissue selective MR knockout mice has shown that deleting the MR in macrophages prevents the development of cardiovascular disease and hypertension.

There are 2 specific projects in this section:

1. Animal study: Determine the cardiovascular responses to tissue selective knockout (cardiomyocyte, macrophage or endothelial cell) of the MR in the DOC/salt model of heart failure.
This will involve the molecular and immunohistochemical analysis of mice already generated by a specific breeding program.

2. Cell culture studies: Using primary cultures of cells from wild type and knockout mice we wish to determine and characterise the specific MR response to different hormones and mechanisms that regulate receptor activation such as salt and oxidative stress. These studies aim to determine the important cellular signalling pathways that are regulated by the MR and other environmental factors that lead to cardiovascular disease. For example in macrophage MRKO mice, given that we have shown that tissue selective knockout of the MR in macrophages changes the normal physiological profile of macrophage specific markers, we will characterise responses under normal and stimulated (LPS, oxidative stress etc) conditions using primary cell culture, ELISA assays and western blotting. We will further examine the differences in macrophage response to various steroid ligands that can bind the receptor. Primary cell culture, cell lines, immunohistochemistry and RT PCR are some techniques that will be involved in this work.
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