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 a literature review, 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 written critiques of departmental
seminars, a journal club presentation, a statistics assignment and two exams which test 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 have 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, at the discretion of the convenors, 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. At least one of your supervisors must be a member (or honorary member) of the Department of Physiology.

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. There is also an index at the back to help you find particular topics and researchers. We have endeavoured to provide you with photos wherever possible to help you identify the researchers of interest.

Once you have 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 18th NOVEMBER (internal students) or 25th 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 18th 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.

Membrane Physiology & Cellular Signalling

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.

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.
**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.

**Neuronal Degeneration, Metabolism & Repair**

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).

**Obesity & Metabolic Physiology**

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, Metabolism, Pharmacology, Electrophysiology and Immunology. 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 and the liver produces and secretes proteins that can then circulate and affect metabolic processes in other peripheral tissues including muscle and liver

Projects will 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.
Parasite Infections, Allergies & Vaccinations

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.

Sensory & Cognitive Neuroscience

The laboratories in the Sensory and Cognitive Neuroscience Group study the structure and function of sensory systems in the brain. The laboratories have specific strengths in studying the auditory, somatosensory and visual systems. Lines of investigation include understanding how individual neurons represent sensory stimuli in the environment, the functional connectivity that exists between brain regions and how neuronal activity contributes to perception and action. The Group is also involved in efforts to develop a cortical visual prosthesis - a bionic eye. With over 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 sensory systems neuroscience groups in Australia.
BakerIDI & Diabetes Institute: Metabolic & Vascular Physiology

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
- 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.

BakerIDI & Diabetes Institute: Human Neurotransmitters Laboratory

The Human Neurotransmitters Laboratory is a sub-group of the Vascular Biology and Hypertension division and focus on the sympathetic nervous system, with a particular emphasis on neuronal activity, brain function and end organ consequences of sympathetic nervous activation in conditions such as obesity, hypertension, depression and orthostatic intolerance.

Prince Henry’s Institute: Cardiovascular Endocrinology Group

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.

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Does the renin-angiotensin system determine the severity of cardiovascular outcomes with obesity?

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

**Supervisor:** Dr Russell Brown (Rm F259)
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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.

**Impact of acute sleep deprivation on maternal cortisol levels and offspring birthweight**

**Key words:** fetal programming, sleep deprivation, glucocorticoids, psychological stress, adult cardiovascular risk

**Supervisor:** A/Prof Kate Denton (Rm F266)
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This project focuses on the impact of acute sleep deprivation during pregnancy. Evidence shows that sleep duration in the population is declining, with sleep disorders one of the most frequent, yet most commonly overlooked disorders leading to health problems. Sleep complaints are twice as prevalent in women as men and two-thirds of pregnant women report abnormal sleep. Short-term fetal exposure to elevated maternal cortisol in early gestation has been shown to alter renal growth and to be linked with an increase in cardiovascular risk in the adult—there is strong evidence for this in both human and animal studies. Sleep deprivation has been shown to increase plasma cortisol levels, and increased cortisol levels are a predictor of low birthweight. This project will demonstrate that a clinically relevant maternal stress, sleep deprivation, in early pregnancy can drive fetal programming cardiovascular disease (CVD), similar to models of endogenously administer GCs.

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

*Key words:* arterial pressure, kidney function, renin-angiotensin system

*Supervisors:* Dr Lucinda Hilliard (Rm F259), A/Prof Kate Denton (Rm F266)

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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 vasodilation 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 and kidney function in both males and females.

**Factors regulating kidney oxygenation**

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

*Supervisors:* A/Prof Roger Evans (Rm F274), Dr Gabriela Eppel (Rm F259), Dr Amany Abdelkader (Rm FG12)

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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.
Maternal obesity and programming of the fetal kidney

Key words: kidney, obesity, pregnancy, hypertension, kidney disease
Supervisor: Dr Michelle Kett (Rm F114)
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As a result of the obesity epidemic, obesity or being overweight affects over 50% of females of reproductive age. Despite the fact that obesity reduces fertility, recent data from the US has found that 20% of women who gave birth were obese. It is well recognised that maternal obesity programmes cardiovascular and metabolic disorders in offspring, however there is very little information regarding how maternal obesity affects the development of the fetal kidney. Further, it is unclear what the renal consequences are for the offspring of obese mothers as they mature to adulthood. Studies include examination of the impact of obesity on the mouse during pregnancy, the impact on the placenta, the changes that occur to the fetal kidney, and the impact on the adult kidney and cardiovascular system.

Investigating circulatory control in diabetes and heart failure with synchrotron microangiography

Key words: diabetes, coronary dysfunction, lipotoxicity, endothelial function, x-ray imaging
Supervisors: Dr James Pearson (Rm F206), Dr Amanda Edgley (St Vincent’s)
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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 type-1 and type-2 diabetes, ischaemic disease and hypertrophy and 2) how new therapies (e.g. Stem Cell transplantation) 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.
Understanding the contribution of the Y chromosome in blood pressure regulation

Key words: arterial pressure, Y chromosome, renal function, genetics

Supervisors: Dr Amanda Sampson (Baker IDI), Prof Jaye Chin-Dusting (Baker IDI), A/Prof Kate Denton (Rm F266)

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Mortality rates from cardiovascular disease between the ages of 20 to 60 are double the rate in men than in women. High blood pressure, (hypertension) is one of the leading risk factors for the development of cardiovascular disease, with males showing a higher blood pressure than women between the ages of 20-60. Given the documented differences in arterial pressure between males and females and the obvious genetic difference in the sex chromosomes between the sexes, we and others suggest that the Y chromosome plays an integral role in the development of hypertension. In fact, the Y chromosome accounts for around 15-20mmHg difference in arterial pressure. Our research aims to investigate the contribution of the genes located on the male sex chromosome, the Y chromosome, to the development of high blood pressure. In particular, we are looking at the interaction of the Y chromosome with the renal renin-angiotensin system in rats. We are seeking an honours student who would enjoy learning animal surgical techniques for in vivo investigations as well as in vitro molecular analysis techniques.

Can L-arginine restore renal perfusion and function in heart failure?

Key words: heart failure, kidney, nitric oxide, L-arginine

Supervisors: Dr Niwanthi Rajapakse (Baker IDI), A/Prof Roger Evans (Rm F274), Prof David Kaye (Baker IDI)

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The cardiorenal syndrome can generally be defined as a disorder of the heart and the kidney, where primary dysfunction or injury in one organ leads to secondary dysfunction of the other organ. That is, chronic or acute heart failure can lead to secondary dysfunction of the kidney and vice versa creating a vicious cycle which is injurious to both organs. Approximately 25% of patients with chronic heart failure have renal dysfunction. Even small reductions in glomerular filtration rate are associated with significant increases in mortality risk in these patients. In addition, progressive renal dysfunction per se may ultimately necessitate dialysis at the end stage.

L-arginine is the substrate for nitric oxide (NO) formation. Roles of NO in regulating renal perfusion and function are now well established. We have previously shown that L-arginine transport in the kidney plays a critical role in regulating renal NO bioavailability. Reduced NO bioavailability and impaired renal function are well established as contributors as well as prognostic features in the cardiorenal syndrome. Professor David Kaye’s previous work indicates that heart failure patients have impaired arginine transport in the heart. In this project we aim to assess whether reduced renal L-arginine transport contribute to impaired renal function and perfusion in a mouse model of heart failure and whether L-arginine supplementation can improve renal function in this animal model. The project will involve histology, immunohistochemistry, western blots, arginine transport assays and/or in vivo animal studies.
L-arginine transport in obesity induced hypertension: a new therapeutic target

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

**Supervisors:** Dr Niwanthi Rajapakse (Baker IDI), Prof Geoff Head (Baker IDI), A/Prof Roger Evans (Rm F274)

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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.

L-arginine is the substrate for NO formation. We have previously shown that L-arginine can greatly reduce hypertension (by about 45%) and greatly reduce related renal damage in a rat model of hypertension. Currently, the efficacy of L-arginine in reducing hypertension in humans remains limited as arginine transport is impaired in human essential hypertension. We are investigating the potential for using therapies that increase arginine transport in the treatment of hypertension, using a newly developed transgenic mouse model with increased L-arginine transport. With the use of this new mouse model, we aim to determine whether increasing arginine transport can reduce obesity induced hypertension and related kidney damage. 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.

Characterisation of female Schlager hypertensive mice

**Key words:** hypertension, gender, stress, central nervous system

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Studies in spontaneously hypertensive mouse show that hypertension in these mice is a neurogenic form, most likely driven by a specific part of the brain. Thus far our studies have been limited to male mice and the female of this strain is relatively under studied. However characterisation of the females could reveal further details of mechanisms driving the hypertension. Therefore the current project will use radio-telemetry to examine the cardiovascular differences between the genders.

We will perform a series of stress tests to assess if gender differences in cardiovascular response to stress. The metabolic profile of female mice will also be investigated using metabolic caging. Finally we will fix the brain for histology to establish any gender differences of brain regions driving the hypertension. The project involves surgery, animal handling, computerised monitoring and analysis using special software and immunohistochemistry. Experimental work for the project will be carried out at BakerIDI in Prahran.
What can be learnt from a clinical trial feasibility study?

**Key words:** cardiovascular disease, clinical trial, stroke, feasibility, risk factors

**Supervisors:** A/Prof Amanda Thrift (Monash Medical Centre), A/Prof Dominique Cadilhac (Monash Medical Centre), A/Prof Roger Evans (Rm F274)

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This is a project to test the feasibility of undertaking a clinical trial of risk factor management by general practitioners. Patients were recruited to this study following admission to hospital for a stroke. The patients were then randomised to an intervention or control group. The intervention involves development of a management plan for patients so that high quality management is maintained once patients return home. There is also an education component to teach patients about their risk factors and how to manage them.

The aim of this project is to determine how representative the patients recruited are of all patients that attend hospital for stroke. We also aim to see which patients tend to drop-out and which patients tend to remain in the study for its duration. The overall aim is to determine which patients should be targeted for such a clinical trial.
Factors determining regional susceptibility to vascular complications of diabetes

Key words: diabetes, arteries, vascular disease, endothelium

Supervisors: Dr Marianne Tare (Rm F131), A/Prof Helena Parkington (Rm F133)

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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.
Role of interstitial cells of Cajal (ICC) cells in intercellular communication in smooth muscle

Key words: cellular communication, pacemaker cells, urinary tract, uterus prostate, aging, obesity
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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, prostate, 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 involving 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.

Prostate: The prostate gland commonly enlarges in ageing or obese 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. In this project the spontaneous activity of the isolated prostate gland, in adult lean or obese animals will be investigated using video imaging, organ bath or electrophysiological techniques. Furthermore, the effects of nerves and agents that affect neurotransmission or the mechanisms underlying the spontaneous activity of the prostatic ICC-like cells will also be studied.

Effects of obstruction on ureteric peristalsis

Key words: hydronephrosis, 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.

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 range of hormones, 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

Supervisors:  Dr Harry Coleman (Rm F131), A/Prof Helena Parkington (Rm F133), A/Prof Stephen Robinson (Psych), Dr V Srikanth (Southern Clinical School)
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 Ca2+ 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 Ca2+ 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.

### Development of inhibition in the hippocampus – the GABA switch

**Key words**: traumatic brain injury, synaptic function, LTP, electrophysiology, brain slices

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In adults, GABA is the major inhibitory neurotransmitter in the brain. However, during development GABA is excitatory. The timing of the GABA excitation-to-inhibition switch has been described only for rats, whose brain is very much less well developed at birth than the brain of humans. The importance of knowing the timing of the GABA excitation-to-inhibition switch emerges from our recent observations that administration of a hormone, normally present in the brain, can protect the brain from exposure to low oxygen in the fetus in late pregnancy. This hormone acts on GABA receptors. We have NHMRC funding to determine the timing of the GABA excitation-to-inhibition switch in guinea-pigs, in which the brain is more developed at birth. We also seek to explore the timing of the switch in marmosets.

Experiments will involve recording electrophysiological activity in neurons of guinea-pig and marmoset hippocampus. Molecular biological approaches will be used to determine the mechanisms implicated in the switch.

### New strategies to rescue diabetes-induced cardiac dysfunction

**Key words**: diabetes, heart failure

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Diabetes is Australia’s fastest growing chronic disease; one million Australians have been diagnosed, with close to one million more yet to be identified. Most of these patients will eventually die from cardiovascular causes. As diabetes induces left ventricular (LV) dysfunction, this increases the risk of death from heart failure in affected patients. Patients with diabetes are 2.4-fold more likely to develop heart failure, even when adjusted for age and coronary artery disease. Onset of heart failure occurs at a younger age in diabetic patients, with heart failure prevalence increased five- to eight-fold in middle-aged patients. New therapies for restoring cardiac function in the diabetic heart are thus highly desirable. In most forms of non-diabetic heart failure, systolic (contractile) dysfunction is the first and predominant functional abnormality. The aetiology of diabetic heart disease is distinct from other causes of LV dysfunction, as it is characterised initially by diastolic dysfunction, where relaxation of the cardiac muscle following contraction is prolonged. Diabetes-induced cardiac dysfunction is often exacerbated by underlying LV fibrosis (increased extracellular matrix deposition), hypertrophy (abnormal pathological growth) of cardiac myocytes, and excess generation of reactive oxygen species (ROS) such as superoxide.

Our laboratory has demonstrated that antioxidant and/or ROS-suppressing approaches, as well as activation of cardioprotective signalling and negative regulators of LV hypertrophy, are beneficial for treating the cardiac complications of type 1 and type 2 diabetes, in the intact heart. We are now offering an exciting student research project in 2012, exploring a novel potential therapeutic strategy for rescuing cardiac function and structure in the diabetic heart. This project will determine whether post-translational protein modifications induced by high glucose and implicated in insulin resistance play a causal role in the development of diabetic cardiomyopathy, and investigate whether pharmacological and/or gene-based strategies targeted at limiting these modifications can prevent diabetes-induced LV dysfunction and remodelling. The scope of this project will be tailored depending on the student’s abilities and interests, and will provide the opportunity for learning a range of techniques, including physiological (e.g. isolated rodent hearts ex vivo or in vivo models of diabetic cardiac disease, for assessing cardiac function and blood pressure) biochemical (Westerns, ROS detection, ELISA), molecular (real-time PCR, Northerns) and/or histological techniques. This project will be performed in A/Prof Ritchie’s laboratory at the Baker IDI Heart and Diabetes Institute in Prahran. Ultimately, treatment strategies that may emerge from these studies may provide significant benefits alone or in combination with current standard care, to ultimately reduce progression to heart failure and death in diabetic patients.

Nitroxy, a relative of NO, is a naturally-occurring cardioprotective molecule

Key words: heart disease, diabetes

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The nitric oxide (NO•)/cGMP signalling system is 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 (abnormal pathological growth) 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 Ca2+ATPase) and the ryanodine receptor RyR2. The activity and expression of these enzymes is abnormally affected in cardiac pathologies (LV hypertrophy, heart failure,
diabetes), and together with the upregulation of ROS is recognised for as playing a causal role in the development of LV dysfunction. HNO thus is likely to be favourable for treating these cardiac pathologies.

We are now offering an exciting student research project in 2012, exploring whether HNO or related strategies represent novel pharmacotherapy for the prevention and treatment of myocardial dysfunction, induced by chronic LV hypertrophy, heart failure or diabetes. The project will examine whether the mechanisms by which HNO acutely enhances cardiac function in intact heart are different to those that prevent hypertrophy and elicit ROS suppression, and determine if acute or chronic HNO treatment is cardioprotective in isolated cardiomyocytes and the intact myocardium in vivo in settings of chronic cardiac impairment.

The scope of this project will be tailored depending on the student’s abilities and interests. It will provide the opportunity for learning a range of techniques, including cell culture (cardiomyocytes and/or cardiac fibroblasts), physiological/pharmacological (e.g. isolated rodent hearts ex vivo or in vivo models of cardiac disease, for assessing cardiac function and blood pressure) biochemical (Westerns, ROS detection, ELISA, real-time PCR) and/or histological techniques. The outcome of this project will be definitive information regarding the mechanism(s) and effectiveness of HNO-mediated rescue of myocardial dysfunction. This project will be performed in A/Prof Ritchie’s laboratory at the Baker IDI Heart and Diabetes Institute in Prahran. Ultimately, HNO-based strategies may offer new treatment options for cardiac disease, either alone or on top of standard care.

**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.
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.
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).
Neuroendocrinology

Gonadotropin inhibitory hormone and stress

Key words: stress, reproduction, hormones
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Gonadotropin inhibitory hormone (GnIH) is a peptide that is produced in cells of the dorsomedial nucleus of the hypothalamus and the peptide is secreted into the hypophysial portal blood to inhibit gonadotrope function. This holds significant potential as a negative regulator of reproduction. Stress inhibits reproductive function, at least in part, by action on the gonadotropes. The hypothesis to be tested in this project is that chronic high levels of cortisol stimulate the synthesis and secretion of GnIH. You will treat animals chronically with stress hormones and sample hypophysial portal blood to measure GnIH levels. You will also examine gene expression for GnIH in animals exposed to chronically high levels of stress hormones. This project involves some work with animals and some laboratory work.

Estrogen regulation of Gonadotropin inhibitory hormone

Key words: reproduction, estrogen
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Gonadotropin inhibitory hormone (GnIH) is a peptide that is produced in cells of the dorsomedia nucleus of the hypothalamus and the peptide is secreted into the hypophysial portal blood to inhibit gonadotrope function. The function of GnIH neurons are reduced in the follicular phase of the estrous cycle, to permit ovulation. GnIH holds significant potential as a negative regulator of reproduction. The hypothesis to be tested in this project is that estrogen negatively regulates GnIH expression. Preliminary data show that a high percentage of GnIH cells express ERβ, which may be how negative regulation occurs in the follicular phase of the estrous cycle. In this project you will infuse ERβ-specific agonists into the lateral cerebral ventricle and recover brains for in situ hybridisation. You will measure gene expression. This project involves some work with animals and some laboratory work.

Gonadotropin inhibitory hormone and reproductive failure

Key words: reproduction, gene expression
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Gonadotropin inhibitory hormone (GnIH) is a peptide that is produced in cells of the dorsomedial nucleus of the hypothalamus and the peptide is secreted into the hypophysial portal blood to inhibit gonadotrope function. The function of GnIH neurons are reduced in the follicular phase of the estrous cycle, to permit ovulation. The hypothesis to be tested in this project is that high producing, lactating dairy cows have elevated GnIH expression, which would cause reproductive failure. You will be given brains from lactating and non-lactating cows and you will measure gene expression by in situ hybridisation. In another model, being that of the lean sheep, you will measure GnIH gene expression and, if time permits, conduct some sampling of hypophysial portal blood to measure GnIH secretion. This project involves some work with animals and some laboratory work.

Is there a sex difference in kisspeptin and/or GnIH expression in the brain?

**Keywords:** 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?

**Keywords:** 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.
**The effect of kisspeptin on energy expenditure**

*Keywords*: neuroendocrinology, reproduction, obesity, metabolism

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Recent data from our laboratory demonstrate no effect of central kisspeptin treatment on accumulative food intake in sheep. Despite this, kisspeptin results in the activation of NPY cells in the hypothalamus. Electrophysiological data also suggests kisspeptin regulates the activity of NPY, and also POMC neurons. Taken together, these data strongly suggest kisspeptin has effects on energy expenditure. Experiments will be conducted to measure the direct effect of kisspeptin and kisspeptin antagonist on energy expenditure (measured via examination of the thermogenic properties of skeletal muscle and visceral fat). Calorimetry experiments in rats will also be conducted (time permitting). Finally, if kisspeptin effects on NPY and/or POMC neurons were direct, kisspeptin receptor expression must be expressed in these neurons. Double label in situ hybridization experiments will be conducted to determine this. Results from these experiments will shed light on the known link between the reproductive system and metabolism and will, potentially, offer novel therapeutic alternatives for the treatment of obesity and related metabolic disorders.

**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.

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

*Key words*: infection, fever, weight regulation

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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.
Impact of neuroendocrine stress responses on health and welfare

Key words: stress, cortisol, reproduction, mental health, hypothalamo-pituitary adrenal axis, behaviour

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Physiological stress responses are designed to deal with challenges and they are generally an every day event. They are important for a normal healthy life but if stress responses are repeated frequently, or prolonged there can be detrimental impacts on the body. This can make humans and animals ill. When animals are chronically stressed their welfare is at risk. We are interested in understanding neuroendocrine responses to stress so that we can use the knowledge to improve human health and animal welfare. Various projects are available to investigate how stress hormones impact physiology and behaviour. Some projects will focus on human health, including mental illness, while others will focus on animal welfare.
Development of new classes of memory enhancers

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

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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 targeting the enzyme insulin-regulated aminopeptidase (IRAP) using state-of-the-art techniques including *in silico* drug screening and docking, high throughput fluorimetric assays and whole animal behavioural tests. In this project, the student will work closely with medicinal chemists to investigate the structure-activity relationship of different classes of IRAP inhibitors.

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 also 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). We recently found that one of the IRAP inhibitors developed in the lab significantly reduced amyloid plaque deposition in a mouse model of AD as well as reversing the cognitive deficit. The aim of this project is to investigate the role of IRAP in the pathogenesis of AD. Our hypothesis is that IRAP participates in the inflammatory process associated with AD progression by regulating the release of pro-inflammatory cytokine from activated astrocytes that infiltrate the damaged regions of the brain.

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 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.

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.

**Does ghrelin promote rebound weight gain after diet-induced weight loss?**

*Keywords:* ghrelin knockout mice, appetite control, hypothalamus

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When obese humans are placed on a diet-induced weight loss program, it is common to observe rebound weight gain over time. The brain mechanisms that control this phenomenon are unknown. Our previous studies show that diet-induced weight loss increases plasma ghrelin concentrations. Because ghrelin is a hormone that acts in the brain to increase food intake and weight gain, we hypothesized that increased ghrelin contributes to rebound weight gain after diet-induced weight loss. We will use ghrelin knockout mice (mice that do not produce ghrelin) to test this hypothesis. If ghrelin promotes rebound weight gain, ghrelin knockout mice will not show rebound weight gain after diet-induced weight loss. These studies may identify a new target to prevent rebound weight gain after diet-induced weight loss.

**How does the central actions of ghrelin prevent starvation?**

*Keywords:* ghrelin receptor green fluorescent protein, hypothalamus, brainstem, Fos

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Ghrelin is a hormone that increases food intake and weight gain. Recent studies show that ghrelin primarily acts to prevent starvation by increasing food intake, weight gain and blood glucose. However, the key brain areas in which ghrelin acts to prevent starvation remain unknown. This
The project will use a novel ghrelin receptor green fluorescent protein (GFP) reporter mouse to visualize ghrelin receptors in the brain. We will identify novel areas of the brain containing the ghrelin receptor, which are activated by starvation. This project will increase our understanding of appetite control.

**How do hypothalamic POMC neurons control appetite?**

*Keywords:* obesity, POMC, leptin, food intake, brain

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The brain plays a critical role in body weight gain by balancing appetite-inducing and appetite-suppressing signals. An imbalance in this process causes obesity, promotes diabetes and cardiovascular disease. The aim of this research is to identify how appetite-suppressing brain POMC cells function and prevent obesity progression. We will use state-of-the-art cre/lox transgenic animals to selectively delete the CPT1 gene in POMC neurons. CPT1 is a mitochondrial protein that controls cellular energy levels, by deleting CPT1 in POMC neurons we predict the POMC cells will not have sufficient energy supply to function properly and predispose these mice to obesity and diabetes. This project will identify new molecular targets to treat obesity and associated diseases such as type-2 diabetes.

**Hormonal regulation of NPY neurons in the hypothalamus**

*Keywords:* hypothalamus, obesity, leptin, insulin

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The activation of NPY neurons in the brain increases appetite and thus, understanding how hormones regulate NPY neurons is critical to appetite regulation. In this proposal we will examine how multiple hormones and nutrients feedback to regulate the function of NPY neurons. This is a significant advance in the field as most studies only measure a single hormone at a single time point and therefore neglect the regulation of NPY neurons in a physiological context. In these studies we will use NPY-green fluorescent protein (GFP) neurons to examine signalling properties in response to multiple hormonal inputs such as leptin, insulin and glucose. We believe understanding the hormonal regulation of NPY neurons in a physiological context will provide an important framework on which we can design more effective anti-obesity therapies.

**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.

**Adipokines, ghrelin and oestrogens in obesity and breast cancer**

*Key words:* obesity, breast cancer, aromatase, adipokines, ghrelin  
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Obesity increases the risk of breast cancer in older women. The goal of our laboratory is to understand how metabolic dysregulation leads to increased risk of breast cancer and specifically, how oestrogens are regulated in the context of obesity and postmenopausal breast cancer. We believe that this association is mediated in large part through the regulation of aromatase, the enzyme responsible for the biosynthesis of oestrogens, within the human breast. This effort builds on our previous work to understand the regulation of aromatase expression within the postmenopausal breast, which is the major source of oestrogen driving breast cancer development in the postmenopausal woman. Adipokines are factors produced by the adipose tissue and ghrelin is produced by the stomach. Both are regulated in response to changes in energy availability and are dysregulated in obesity. The focus of this project will be to characterise the effect of adipokines and ghrelin on oestrogen production within the breast.
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 mitochondria  
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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.

**Energy expenditure in PCOS- a translational approach**

*Key words:* energy expenditure, infertility, thermogenesis, obesity  
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This project will combine clinical and animal research to examine the dysregulation of energy expenditure with polycystic ovarian syndrome. PCOS affects 12-21% of young women and is characterised by reproductive, metabolic and psychological features. Excess weight exacerbates all features of PCOS and weight loss is considered first line therapy in overweight and obese patients. In spite of this, patients with PCOS have a higher body weight, and require greater reduction in caloric intake to achieve weight loss, which is often not sustainable. Understanding the mechanisms underpinning the greater propensity to obesity and the physiology that impairs weight loss will improve clinical outcomes in this common and costly condition. This work will characterise changes in thermogenesis in both PCOS patients and in a sheep model of PCOS. It will involve animal work and *in vivo* analyses of thermogenic output (temperature recordings), which will be coupled to analyses of gene expression using real-time PCR, as well as radioimmunoassay and Western Blotting techniques.

**How do amphetamines cause weight loss?**

*Key words:* obesity, metabolic syndrome, neuroscience  
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Obesity is continuing to increase globally with no cure in sight. It contributes to serious chronic diseases including cardiovascular disease and type-2 diabetes. One drug class that can have beneficial weight loss actions are amphetamines. Amphetamines are psycho stimulating drugs and are normally used recreationally and to increase wakefulness, however amphetamines also cause weight loss. We currently do not know how amphetamines cause weight loss, or where in the brain amphetamines act to cause weight loss.
The major aim of this study is to determine how amphetamines cause weight loss. Determining the neurons in the brain that amphetamines act through and the pathways it activates to produce its weight reducing action. Determine if this pathway is still active in obesity and determine whether this pathway could be targeted as a potential obesity drug treatment if the pathways associated with the adverse or dangerous effects of amphetamines could be excluded. Understanding the actions of amphetamines will help increase our understanding of how the body regulates body weight and could pave the way for new treatments for weight loss in obese humans.

The project will involve the physiological assessment of genetically modified mice and experimental procedures including assessment of glucose and insulin sensitivity, body weight change and feeding behaviours including food preference. A variety of analytical techniques will be used including immunohistochemistry, Western blotting, radio immunoassays, PCR. This project will provide the successful applicant with grounding in several experimental approaches and analytical techniques, a stimulating intellectual environment and an opportunity to contribute to the understanding of the complex regulation of body weight.

What is it about fat that causes the development of metabolic syndrome?

Key words: obesity, fat distribution, metabolic syndrome, cardiovascular disease

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Obesity is directly linked to many metabolic diseases, including cardiovascular disease and type-2 diabetes. The body mass index (BMI) (ratio between weight and height squared) is widely used for ranking the risk of metabolic diseases. BMI however fails to account for individuals who are heavy due to muscle or those who have a normal body weight but still have excess abdominal adiposity. Excess abdominal fat is associated with risk of morbidity and mortality than is excess of subcutaneous fat. Physiologically not all adipose tissue deposits are the same, they have different adipogenic, metabolic, pro-atherogenic and pro-thrombic characteristics. Reductions of equal amount of visceral and subcutaneous fat do not have the same effect on glucose homeostasis and cardiovascular disease. Around 15-20 % of adult humans with normal body weight have an increased accumulation of abdominal fat and this is connected to metabolic disorders.

Obese rodent models are a powerful tool for discovering molecular mechanisms of body weight regulation. However, there has been minimal research into discriminating what excess fat and specifically what specific regional accumulation of fat does to the regulation of body weight. Using a new mouse model this project will search to understand how a differential distribution of adipose tissue is connected to metabolic disorders (the risk to develop diabetes and cardiovascular disease).

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 excess fat on the development of metabolic syndrome.
The role SOCS3 in Leptin resistance. What can we learn from blocking the main inhibitor of the pathway of the hormone that regulates appetite receptor?

**Keywords:** obesity, brain signalling, leptin resistance

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Obesity and overweight affect up to 70% of Australians and are directly linked to many metabolic diseases, including cardiovascular disease and type 2 diabetes. Leptin is the primary signalling hormone produced in fat tissue and acts as a negative feedback loop in the brain to regulate appetite and energy balance.

When humans and other animals become obese, there is an increase of adipose tissue and therefore an increase of Leptin levels in blood. However, obese individuals lose their ability to regulate body weight in response to Leptin. This state 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.

This project is aimed at understanding what mechanisms contribute to Leptin resistance in some neurons and thus, contribute to develop treatments for obesity.

Given that some studies have shown that the appetite regulating neurons, namely POMC and AgRP, express high levels of Suppressor of Cytokine Signalling (SOCS3), an inhibitor of Leptin receptor signalling pathway, we want to test the role of SOCS3 in the inhibition of Leptin actions in the AgRP neurons.

For this purpose, we will create a mouse model that lacks SOCS3 in their AgRP neurons. This project will take advantage of mouse manipulation, surgical and physiology techniques as well as tissues and cell signalling studies.

**Inflammation and metabolic alterations in a polycystic ovarian syndrome mice model**

**Keywords:** polycystic ovarian syndrome, obesity, insulin resistance

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Polycystic ovarian syndrome (PCOS) is the most common hormonal disorder affecting 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 theca/interstitial cells of the ovary and develop hyperandrogenemia, decreased fertility and cystic morphology.

Insulin resistance (IR) and its consequent hyperinsulinemia are also thought to be important etiological factors in PCOS. An emerging hypothesis exists proposing that inflammation is the link between obesity and metabolic disease. TNF-α has a key role in the inflammatory process and is increased in IR and obesity. We demonstrated that TNF-α is increased in the ovaries of 17NF mice, independent of their metabolic status. Furthermore, we believe that TNF-α is mediating the deleterious effect of NGF in the ovary. This hypothesis will be evaluated by determining the expression of inflammatory markers in this model.

This project will combine whole animal physiology, surgical techniques, animal experimentation and test of insulin sensitivity.

Understanding how fat causes diabetes

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 (fat tissue) 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. Our previous honours student showed that PEDF contributes to the development of obesity/diabetes by affecting metabolism of glucose and fat.

We have now developed a mouse that overexpresses PEDF in the fat (PEDF-aP2). The project will involve the physiological assessment of this transgenic mouse, 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.

How does the protein OXPAT affect fat metabolism?

Key words: skeletal muscle, fat metabolism, mitochondria

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Our lab has spent many years studying how fat metabolism is regulated in skeletal muscle and how defects in fat metabolism contributes to the development of insulin resistance and type 2 diabetes.
A protein called OXPAT was recently discovered and is thought to influence fat breakdown in cells. Surprisingly, another laboratory suggests that OXPAT is important for storing fat. The aim of this project is to understand how OXPAT affects fat metabolism in skeletal muscle, and whether OXPAT expression influences insulin sensitivity.

To test this hypothesis, the successful applicant will use genetic knockdown and overexpression of OXPAT in muscle cells and use established techniques to examine fatty acid metabolism, insulin sensitivity and mitochondrial function. The biochemical and molecular changes that accompany these anticipated changes will be examined.

This project will further our understanding of muscle metabolism and the control of fat metabolism. It will provide the successful applicant with experience in cell culture techniques, genetic manipulations and a broad array of analytical skills.

What is the cellular localization of ghrelin O-acyltransferase in the anterior pituitary?

Key words: obesity, metabolic syndrome, neuroscience

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Ghrelin is a 28 amino acid peptide that is produced primarily by endocrine cells in the stomach, and released into the circulation. A member of the membrane-bound O-acyltransferase family (mBOAT4) was recently identified to specifically acylate ghrelin and subsequently renamed Ghrelin O-acyltransferase (GOAT). A number of mild phenotypes have been reported for mice that are genetically deficient in GOAT and we have recently identified significant changes in bile acid metabolites and supporting changes in bile acid transporters within the gastrointestinal-biliary system, indicating a role in the regulation of bile acid metabolism. Additional phenotypes are likely to be found under the right challenge conditions. A cursory analysis of Goat expression using a lacZ reporter expression system on whole tissues revealed a surprisingly strong expression pattern within the anterior pituitary. The anterior pituitary gland secretes a number of peptide hormones regulating important physiological functions, however it lacks significant expression of ghrelin.

The major aim of this study is to determine the cellular localization of Goat in the anterior pituitary of a diverse group of species (mice, rats, sheep, monkeys) as a way to show conservation of function. Additional studies will be conducted on mice to examine pituitary GOAT expression in different metabolic states such as fasting, caloric restriction, and diet induced obesity. The project will involve the immunohistochemical assessment of multiple species including mice that have been genetically modified to express the β--galactosidase gene from the endogenous Goat locus. A variety of analytical techniques will be used including immunohistochemistry, western blotting, PCR. This project will provide the successful applicant with grounding in several experimental approaches and analytical techniques, a stimulating intellectual environment and an opportunity to contribute to the understanding of the physiological role of the Ghrelin/GOAT system.
The role of the brain prostaglandin system in regulating energy balance during sickness

Keywords: sickness, prostaglandins, neuropeptides, hypothalamus, energy balance, food intake

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Chronic infections such as cancer and AIDS result in deleterious alterations in energy balance including anorexia (lack of drive to eat) and cachexia (muscle wasting). Increased circulating and brain-derived inflammatory mediators in states of chronic infection likely signal through brain neuropeptide systems to promote a state of negative energy balance, i.e. reductions in energy intake (eating) with concomitant increases in energy expenditure (fever, increased O2 consumption). The primary hypothalamic neuropeptide systems that regulate energy balance include the pro-opiomelanocortin (POMC) neurons and neuropeptide Y (NPY) neurons of the arcuate nucleus, and the orexin (ORX) and melanin-concentrating hormone (MCH) neurons of the lateral hypothalamus. The expression and signalling of these neuropeptides within the brain maintain energy balance; however during inflammatory states the expression of these neuropeptides are altered—e.g. increased POMC and decreased NPY expression—driving changes in energy balance. The prostaglandin system includes lipid-based signalling molecules of which prostaglandin E (PGE) is a primary inflammatory factor associated with regulating energy balance. The 2 primary enzymes responsible for the production of PGE are a ubiquitously expressed cyclooxygenase-1 (COX-1) and an inducible COX-2. There are 4 PGE receptor subtypes termed EP1-4, which are functionally diverse and expressed throughout the brain on both neurons and glia. The distribution patterns of EP receptors within the brain are known but the cellular co-localisations are predominantly unknown. Lipopolysaccharide (LPS) is a cell-surface component of gram-negative bacteria and is used to produce an acute inflammatory response and a state of negative energy balance. LPS induces the increased production of PGE through the rapid up-regulation of COX-2 within glial, macrophages and endothelial cells. The actions of PGE within the brain are largely responsible for the LPS-induced state of negative energy balance, although the role of the EP receptors in mediating the changes in energy balance requires further investigation. The project will focus on characterising the neuroimmune link between prostaglandins and neuropeptides regulating energy balance. Techniques utilised include surgery, monitoring of physiology (food intake, activity, and oxygen consumption), immunohistochemistry, in situ hybridisation, real-time PCR and other molecular biological techniques, and an understanding of neuroanatomy.

Cytokines on the brain? Understanding the interactions between cytokines and neuropeptides which regulate metabolism during infection

Keywords: sickness, cytokines, neuropeptides, hypothalamus, energy balance, food intake

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Chronic illnesses such as cancer and AIDS are associated with anorexia and cachexia (muscle wasting) which are debilitating side effects that reduce quality of life. Pro-inflammatory cytokines (IL-1β, TNF-α) are responsible for the range of physiological and behavioural changes that are collectively referred to as ‘sickness’. Ant-inflammatory cytokines (IL-10) are also produced in response to infection and act as endogenous ‘brakes’, ensuring survival. The interaction of pro- and
anti-inflammatory cytokines at the level of the brain modulates neuropeptide expression and secretion, subsequently regulating metabolism. This project investigates the central actions of both pro- and anti-inflammatory cytokines and the role of neuropeptide systems during models of acute infection and the metabolic consequences of these interactions. The neural systems of interest include the neuropeptide Y, melanocyte stimulating hormone, orexin, and melanin concentrating hormone systems of the hypothalamus. The project involves surgical procedures such as implantation of cerebral cannula and telemetric devices, physiological measurements such as telemetric recording of body temperature and indirect calorimetry, and post-hoc analysis of tissue that includes immunohistochemistry and quantitative real-time PCR.

**Controlling macrophage function in the brain to heal the damaged perinatal brain**

*Keywords:* macrophage, endotoxin, cytokines, apoptosis, brain damage  
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Infection in the perinatal period is a major cause of brain injury, of which disruptions in brain hemodynamics have a significant role. Brain hemodynamics is regulated by a myriad of factors, including inflammatory cytokines and nitric oxide (NO). Perivascular macrophages and endothelial cells within the brain are prime candidates to investigate the mechanisms underlying endotoxemia-related brain injury because these cells are significant regulators and contributors of inflammatory cytokines and NO within the brain. Perivascular macrophages in the brain provide inhibitory control over endothelial cells during acute endotoxemia, limiting the ability of endothelial cells to produce inflammatory mediators. During chronic or repeated endotoxemia, as observed clinically in the human neonate and induced experimentally in the fetal and newborn lamb, the perivascular macrophages may lose the inhibitory control over the endothelial cells because these specialised macrophages become activated independently. Our preliminary data suggests that repeated endotoxemia in the lamb results in a robust activation of inducible nitric oxide synthase (iNOS) in macrophages and a simultaneous inhibition of endothelial NOS (eNOS). Because nitric oxide is a key regulator of brain hemodynamics and also a likely contributor to brain damage during endotoxemia, this project will involve investigation into the role of macrophages in endotoxemia-related brain damage in the fetal and newborn lamb. Techniques utilised include fetal surgery, monitoring of fetal physiology (heart rate, blood pressure, brain electrical activity, brain blood flow), immunohistochemistry, real-time PCR and other molecular biological techniques, and an understanding of neuroanatomy.

**Fat is not just fat? Central estrogen receptors in regulating metabolism and fat distribution**

*Keywords:* estrogen, hypothalamus, energy balance, food intake  
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Abdominal fat which is more developed in males than females is more dangerous because it is the major correlate of metabolic syndrome with all of its pathologies such as heart disease, diabetes, stroke, etc. Subcutaneous fat on the other hand is far less of a problem and is found more in pre-menopausal women. The answers to why abdominal fat but not subcutaneous fat correlates well with deadly obesity-related pathologies are not known. One potential explanation is the central actions of the sex hormone estrogen, as the fat distribution of women changes to a more male-like
distribution post-menopause when circulating estrogen levels drop significantly. In addition, male animals treated with estrogen develop a female compartmentalisation of fat. As most obesity research has focused on the mechanisms behind the development of obesity and means of reversing obesity, the present project aims to understand the central mechanisms behind the distribution of fat. The project will incorporate both pharmacological and transgenic approaches to manipulate the central regulation of estrogen receptors, including transgenic mice lacking estrogen receptors only within the brain as well as viral techniques to selectively up- or down-regulate estrogen receptors selectively within brain nuclei. The project involves surgical procedures such as implantation of cerebral cannula and telemetric devices, physiological measurements such as telemetric recording of body temperature and indirect calorimetry, laser capture microscopy, and post-hoc analysis of tissue that includes immunohistochemistry, quantitative real-time PCR and Western Blots.

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
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 therapeautic 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.
Parasite Infections, Allergies & Vaccinations

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.
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 2012, 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.

**What does the claustrum do?**

*Key words: neural connections, primate, behaviour*

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The mammalian claustrum is a small but important region of the brain, as evidenced by its widespread pattern of neural connections. Despite many years of study however, its function remains unknown. Recent studies employing functional neural imaging have implicated regions connected with the claustrum in an array of complex behavioural and cognitive processes. In this project, we will analyse the pattern of connections of the claustrum in the marmoset brain, employing neural tracers, 3-D volumetric reconstruction, and quantitative fluorescence microscopy to identify the functional connections of the claustrum. This project is well suited for someone interested in microscopy, brain anatomy, and computer imaging. You will also be exposed to histological methods and microscopic photography.

**Pharmacological manipulation of visual discrimination learning in honeybees**

*Key words: behaviour, drug effects, pharmacology, invertebrate, cognition*

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This project will employ a number of neuroactive compounds, including caffeine, nicotine, and other psychostimulants, to investigate the neurotransmitter systems involved in colour discrimination learning. We have recently shown that caffeine affects the acquisition and accuracy of colour learning in bees, and that the effect is dose-dependent. However, the duration of effect, effects on memory, and possible interactions of caffeine with other drugs remain unknown. The student will be learn how to train bees on a discrimination task, administer pharmacological agents, record behavioural data, and analyse drug effects. This project involves a large amount of outdoor work and the ability to work with honeybees. Thus, persons suffering from pollen or bee sting allergies, or insect phobias, would not likely be comfortable working on this project. Due to the seasonal nature of honeybee behavioural research, it is essential that you contact one of the supervisors as early as possible if you think you would be interested in participating in this project.

**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 using a reflexive eye movement called ocular following. Using moving visual stimuli presented on a computer monitor, you will record the subject’s perception of the stimulus speed and direction, as well as any subconscious, reflexive eye movements generated by the stimulus. By manipulating the visual stimuli, this project 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 they have seen over the previous few seconds. 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, computational analyses, 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.

**How does working memory allocate attentional resources in demanding multi-tasking?**

*Key words:* neuroscience, working memory, divided attention, multi-sensory competition, brain  
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Working memory is the store we use for online processing in tasks we are undertaking at that moment. It is also the neuronal “workbench” where conscious awareness is played out. The most widely-accepted WM model is Alan Baddeley’s multi-component model which postulates separate components for processing acoustic input (for language) and for processing visual and spatial input, with a controller (a central executive) that directs attention as needed for the task, and a multi-dimensional storage buffer which integrates multi-dimensional information for immediate use. How WM copes with allocating attention resources when we have competing information is not well known — e.g., at a party, how do we converse with a boss when we can see that elsewhere in the room the drinks tray is being rapidly depleted; how do you listen to a friend offering unsolicited advice on your love life just at the moment when the evil Orcish leader Ner’Zhul is about to zork you? Many brain disorders (e.g., autism spectrum disorders, schizophrenia, ADHD) result in disordered WM functioning and it highly likely that this is particularly problematic in conditions when attention has to focused on one specific task against another equally demanding one. This project aims to understand how WM allocates attention resources in everyday demanding tasks that we do effortlessly such as the online processing of speech in noise.
Brain processes in learning language

Key words: neuroscience, language, dual stream processing, voice templates, brain schema

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We live in a dynamic world and one major way that the brain can cope with the plethora of stimuli and experiences we encounter is by forming templates for stimuli and experiences. This allows for more efficient brain processing as it means we can often simply match a stimulus to an existing template rather than have to learn it afresh. (Of course templates can also be the source of perceptual errors through mis-alignment of a novel stimulus and a pre-existing template.) Template formation is also critical in allowing us to learn language; learning language appears to involve two parallel brain cortical streams: one for extracting the meaning of what is being uttered, the other for extracting information on who is saying it and how they are doing so. The second process, i.e., the formation of a brain template for the speaker’s voice, appears to be critical in guiding our understanding of what is being said. Our recent work using a perceptual learning paradigm, reveals that formation of a template for who is speaking is critical in guiding us in the everyday task of understanding speech in the presence of noise. This type of template formation is attributed to the mirror neuron system, a set of neurons believed to be involved in processes such as socialization, in development of empathy, and of language – and disorders to this system have been postulated to underlie the difficulties seen in Autism Spectrum Disorders. This project seeks to elucidate the brain processes that underlie the formation of templates for speakers, in learning language. We will examine how factors such as pitch, speed, tempo and gender are used by the brain to form that template and how this schema for voice guides access to long-term memory language (lexical) stores.

Sensory encoding of fine sensory discriminations in a complex environment

Key words: neuronal signalling, touch, fine discriminations, brain processes

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In every sensory system we routinely process information while there is distractor or competing input occurring at the same time in the same or another modality. Somehow neurons in our brain are able to – generally – extract information of importance against the other “noise”. In this project we will examine how neurons in the brain’s cortex allow us to do this. We will examine how sensory cortex neurons can signal the critical relevant information required to navigate the world, and how this neuronal processing varies between neurons at different hierarchical levels of signal processing (e.g., neurons that simply relay information to the cortex; neurons that process and send output to guide movement responses; neurons involved in processing input for learning and memory). As in most brain processes, neuronal activity that leads to us carrying out careful discrimination tasks must involve processing carried out by large populations of sensory neurons in the brain. Hence, we will examine how small groups of neurons work together to carry out the signalling of important features of the world. In the project you will learn how to undertake the most sophisticated and elaborate method of understanding brain activity: electrophysiological recordings from neurons. You will also acquire skills in histology and image processing.
Where is the best site to activate cortex for functional outcomes? (Bionic Vision project)

*Key words:*  
cortical activation, blindness, electrical stimulation

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The Systems Neuroscience Group is part of a Monash University consortium that has been funded to develop a cortical implant to restore some functional vision to blind people. This project is part of the pre-clinical studies that will help develop that prosthetic device. The prosthetic device will be implanted in visual cortex and electrical stimulation used to activate neurons. However, at this stage it is not known which is the best layer in visual cortex in which those electrodes should be implanted to produce the most effective percepts. In this project we will use the rat’s motor cortex as a model to help answer this question. Electrodes will be used to activate neurons in the region of motor cortex that causes movement of the whiskers – thus there will be a clearly identifiable outcome from the stimulation. We will then systematically examine what layers and stimulation protocols are most effective at producing a response (whisker movement). This information will be used to assist in other studies directed to the best cortical prosthesis to evoke visual perceptions.

Qualitative exploration of how visually impaired people perceive vision restoration experimentation.

*Key words:*  
bionic eye, visual prostheses, qualitative methodology, informing clinical recovery

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This project is a human studies project in the Monash Vision Group and is designed to obtain information that will eventually feed into the development of the bionic vision implant as well as the rehabilitation programs to be used for blind people in the implant program. The development of the bionic ear has provided the capacity for people with otherwise impaired auditory processing to experience sound, in many cases within a range that can facilitate the development of speech or restoration of aural communication. The development of the bionic eye offers a similar capacity to facilitate the restoration of vision in adults who have lost visual functioning. However, while the protocols for preparing, surgically inserting and rehabilitating patients following implantation of the bionic ear are robust and well known, far less is known about how best to prepare and provide support following the implantation of a bionic eye. The Monash Vision Group is a Monash University consortium that has been funded to develop a cortical implant to restore some functional vision to blind people. As part of ensuring the best outcome for selected bionic eye candidates, the current project is offered as an honours project to qualitatively explore how people who have lost visual functioning perceive the potential to be a bionic eye candidate. Perceived benefits and challenges will be explored, along with thoughts about who would be a good candidate and what would be needed to support someone in recovery following implantation.
Does training in simple perceptual tasks help to optimise performance in complex tasks?

Key words: neuroscience, figure-ground segregation, speech processing, training, brain

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Our ability to understand speech in the noisy backgrounds that typify a modern 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 prosody etc) through to high-level language (e.g., using contextual cues in the speech stream) and attention processes (e.g., learning where to focus attention to most efficiently extract speech from noise). Given the breadth of skills and processes required therefore to effortlessly understand speech in competing noise, it is not surprising that speech-in-noise identification is affected in a range of brain disorders. In auditory processing disorders, 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. We have found that people with autism spectrum disorders also show deficits in processing speech-in-noise but adults and children with ASD show different patterns of deficits, but in both cases apparently linked to poorer discrimination abilities. In this study we will examine whether training in a range of simpler auditory discrimination tasks can help improve the ability of normally-developed adults to understand natural whole speech in noisy backgrounds, i.e., can it improve the discrimination “filters” used to separate the speech of interest from the background noise. This research is directed to identifying the optimal training schemes for improvements in segregating complex speech from noise.
TElmisartan in the management of abdominal aortic aneurysm (TEDY)

Key words: abdominal aortic aneurysm, ACE inhibition
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Abdominal aortic aneurysm (AAA) is responsible for approximately 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. 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:

1. Reduce AAA growth assessed by computed tomography (CT) angiography
2. 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.

Evaluation of reduced sedentary time on peripheral arterial disease risk factors and symptoms

Key words: peripheral artery disease, claudication, sitting, physical inactivity
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Peripheral Arterial Disease (PAD) currently affects approximately 15% of Australian adults aged ≥40 years and 30% of those >70 years and will increase in prevalence with rising obesity rates and an ageing population. The consequences of PAD are two-fold. Firstly, PAD increases cardiovascular
morbidity and mortality. Secondly, PAD significantly reduces quality of life as a result claudication, walking impairment and related complications such as limb loss.

Formal exercise programs are the best non-pharmacological therapy for claudication and also reduce cardiometabolic risk factors, but adherence to such programs is poor. Recent evidence suggests that interrupting sedentary time with short bursts of low and moderate intensity activity has cardiometabolic benefits additional to purposeful exercise, but the efficacy of sedentary avoidance behaviour has not been examined in an intervention trial in patients with cardiovascular disease. PAD is a condition of particular interest in this context as sedentary avoidance behaviour has the potential to both improve cardiometabolic risk factors as well as claudication and walking ability. Furthermore the long term sustainability of sedentary avoidance behaviour is likely to exceed that of formal exercise programs.

This proposal is for a randomised, controlled trial in patients with PAD which evaluates reduced sedentary time with and without a formal gym-based exercise program over 12 months. Major endpoints include conventional cardiometabolic risk factors, ankle-brachial index, walking ability, quality of life and sustainability of interventions.

If positive, this study will provide a new evidence-based alternative to current treatments that will influence guidelines and policies in the management of this debilitating disease. Moreover patients can potentially expect an improved quality of life with a less invasive and cost effective treatment that promotes self-autonomy in health care.

**Development of brown adipose tissue for treatment of obesity**

*Key words:* obesity, brown adipose tissue, energy expenditure

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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. Brown adipose tissue (BAT) is unique with respect to its sole function of burning potentially great quantities of energy, therefore increasing BAT content and activity is currently considered one of the most promising strategies to increase energy expenditure to combat obesity. BAT function in small animals is well described, however in humans knowledge is limited due to only recently being conclusively identified in adults and the identification of novel techniques to measure its activity. Our ongoing studies therefore provide opportunities to explore the possibility of combating obesity related disease through one of the most novel and exciting approaches in research settings ranging from the laboratory to the clinic.

**Projects focusing on the following areas are offered in 2012:**

a) Pharmacological activation of BAT in humans

b) Examination of the capacity of precursor cells in human tissues to form BAT cells in lean and obese humans

c) Novel treatments to enhance BAT differentiation and function.
Impact of Sympathetic Nervous System activity in generating end organ damage in obesity

Key words: obesity, organ damage, sympathetic nervous system

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There is a very strong case to indicate that obesity, in particular abdominal obesity, unfavourably affects blood pressure regulation, the heart, the kidneys and endothelial function at an early stage, even in the absence of hypertension or demonstrable metabolic abnormalities. My recent work strongly indicates that these early signs of organ damage are closely related to the activation of the sympathetic nervous system (SNS). Alterations in the SNS seem to contribute to the dysregulation of blood pressure and to the development of organ damage; therefore targeting the SNS may be an attractive and potentially important avenue for the pharmacological prevention of obesity related illnesses. This project is clinically based and will examine the effects of reducing SNS activity on organ damage in young obese subjects by using different approaches (a) the centrally acting sympatholytic agent moxonidine, (b) by weight loss alone, and (c) by combining weight loss and moxonidine.

The project involves patient recruitment, data acquisition and analysis. The clinical work for the project will be carried out at the Alfred Hospital & Baker Institute in Prahran.

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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Cellular localization of mineralocorticoid receptor-mediated vascular inflammation and cardiac fibrosis: we have used the Cre-Lox technique to delete MR expression (i.e. gene knockout) in a cell-specific manner in the cardiovascular system to identify the cells types critical for the development of vascular inflammation and cardiac fibrosis. Identification of the critical cell types will allow a focused investigation of the cellular mechanisms involved in the establishment and progression of cellular inflammation and cardiac fibrosis.
this pathology. We have shown that MR signalling in the context of high salt leads to inflammation, fibrosis and ultimately heart failure. The cardiovascular remodelling is a direct effect of MR activation in the heart and blood vessels.

Our first study in tissue-selective MR knockout mice has shown that deleting the MR gene knockout in macrophages (immune cells) prevents the development of cardiovascular disease and surprisingly hypertension. A current research theme is to further investigate the role of MR in macrophages.

There are 3 possible Honours projects:

1. Tissue-selective deletion of the MR in the heart and protection against heart disease: this will involve histological, molecular and immunohistochemical analyses of hearts, aortas and kidneys from transgenic mice generated by a specific breeding program and subject to treatment that causes heart failure. Tissue selective knockout lines are currently being investigated for their responses to different models of heart disease and include endothelial cell (vessel wall)-specific, macrophage-specific and cardiomyocyte-specific knockouts.

2. Identification of cell signalling pathways that regulate MR activation in response to pathological stimuli: this cell culture-based project aims to determine and characterise, in cell types shown to be critical in the development of cardiac fibrosis, the specific MR response to inactivation of the MR-protective enzyme 11bHSD2, oxidative stress, hypoxia and high salt. 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.

3. The role of the molecular clock in heart failure: a diurnal rhythm has been shown for many physiological parameters. It is well known that certain cardiac pathologies (e.g. heart attack) occur more often in the early hours of the morning. An intrinsic molecular clock has now been described for virtually all mammalian cells include cardiomyocytes and that this is retained in primary cultures of cells and include Cry, Per, CLOCK, Bmal and several other factors that are regulated in a cyclical manner. Dysregulation of the molecular clock has now been described for several models of heart, kidney and metabolic disease, highlighting the importance of this relatively recently described regulatory system. Our preliminary data suggests a role for cardiomyocyte MR signalling in regulating the intrinsic molecular clock. This project will investigate pathological signalling pathways in a model of heart failure in mice in which the molecular clock is not functioning.
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