

## Hypertension Research at the University of Sydney

The University of Sydney is a fitting start for a series of articles about Hypertension Research in Australia. The Department of Physiology founded around 1890 has had a long history of research into cardiovascular disease and hypertension. Notably Past HBPRCA President, [Professor Paul Korner](#) graduated from The University of Sydney in Science and Medicine in the early 1950s, and obtained his clinical training at Royal Prince Alfred Hospital. He spent further periods in the Department of Physiology before moving to Melbourne in 1975 to head the Baker Institute. More recently, he has returned to Sydney and has been writing a major work on hypertension entitled "The Neurogenic Basis of Essential Hypertension" which is in the very final stages with the publisher. [Professor John Chalmers](#), also a past president of the society, who is now the Senior Director of "The George Institute" and the director of the newly established "The George Foundation for International Health" is also a graduate of The University of Sydney and established the Hypertension Research Group there in 1996. John's contributions to hypertension with both basic and clinical studies are too many to list but his studies in central autonomic pathways and neurotransmitters regulating the sympathetic nervous system stand out in the field. His recent work with the "[PROGRESS](#)" study is well known to hypertension researchers world wide. Today hypertension research in The University of Sydney is a major feature of a number of Laboratories, all of which are part of the Discipline of Physiology and the Institute for Biomedical Research.

The [Cardiovascular Neuroscience](#) laboratory, headed by **Professor Roger Dampney**, investigates the control of blood pressure and sympathetic nerve activity by the brain, both under normal conditions and under abnormal conditions such as high blood pressure. The Laboratory has a particular interest in the role of angiotensin II, as well as other hormones such as leptin and aldosterone, all of which can act directly on brain neurons to cause increased sympathetic activity and other changes leading to high blood pressure. There is good evidence that the levels of brain angiotensin II are increased in certain types of high blood pressure as well as heart failure.

Similarly, the levels of the hormone leptin, which is released from fat tissue, are increased in obesity, and this leads to increased sympathetic activity, which could be a major factor causing obesity-related hypertension. A noted visiting hypertension researcher **Dr Virginia Brooks**, from the Oregon Health & Science University in the United States is currently based in The Department of Physiology at The University of Sydney with the support of the Australian-American Fulbright Commission. She has been studying the role of osmolarity sensors in regulating fluid balance, salt sensitivity and the level of blood pressure. Her recent publication in [CEPP](#) highlights her studies in the area and explains her teaming up with "brain expert" Roger Dampney. She proposes that increased salt intake causes salt retention and raises plasma sodium concentrations, which activate sodium/osmoreceptors to trigger sympathoexcitation. Often the increase in osmolality is not detectable but can drive significant sympathoexcitation, because salt-sensitive individuals exhibit increased sensitivity to the sympathoexcitatory effects of increased osmolality. While her visit is now nearly complete, she has summarized her experience as follows: "My seven months in Australia have been extremely stimulating and enriching. I've especially enjoyed the opportunity to interact with Roger and his lab on an almost daily basis, which has allowed me to greatly expand my knowledge of the brain and its regulation of the sympathetic nervous system. I've been particularly impressed with the breadth of and comradery within the Australian Neuroscience community. A highlight of my stay has been the new and stronger connections I've been able to make with colleagues not only here in Sydney, but also in Adelaide and Melbourne. In fact my visit to Melbourne was prompted by a fantastic one day symposium, organized by Dmitry Mayorov and Geoff Head, at which those of us in Australia and New Zealand informally exchanged our newest ideas about mechanisms underlying neurogenic hypertension. (It also gave me the chance to attend an Australian Rules Football game at the MCG!). I thank my Aussie friends, new and old, for making my stay so memorable."



Virginia Brooks and Roger Dampney

The [Hypertension & Stroke Research Laboratories](#) (HSRL) are based at the Royal North Shore Hospital (Dept of Neurosurgery) in Sydney and are a part of the Discipline of Physiology at the University of Sydney. The HSRL is run by **Dr Paul M. Pilowsky** (Head of HSRL, NHMRC PRF, A/Prof in Physiology and Pharmacology) and **Dr Ann K. Goodchild** (Senior Lecturer in Physiology and High Blood Pressure Research Foundation Fellow). The group is interested in all aspects of how the brainstem and spinal cord organize the intake and distribution of oxygen into the body and tissues, and the removal of carbon dioxide: the ABC of medicine -

Hypertension & Stroke Laboratory



airways, breathing and circulation. To investigate these phenomena in health and disease, the HSRL have established a facility in which many areas can be investigated from the molecular to the clinical level (from the nucleotide to the bedside), where we study changes in gene expression following physiological or pathophysiological stimuli including hypertension, haemorrhage and renovascular hypertension.

In our pharmacological and physiological studies we investigate the effects of changing neurotransmitter pathways in the

brainstem on the reflex control of the cardiovascular system. For example we recently demonstrated that mu opioid agonists in the rostral ventrolateral medulla of the brainstem attenuate the arterial sympathetic baroreflex but not the somatosympathetic reflex whilst delta opioid agonists have the reverse action having no effect on the baroreceptors, but attenuating the somatosympathetic reflex. We also have a very active molecular group that examines gene expression using analysis of mRNA using real-time PCR, and by in situ hybridization combined with immunocytochemistry. We now have a facility for radiotelemetry in conscious rats permitting continuous recording of blood pressure temperature, ECG and activity. At the clinical level we are investigating patients in the intensive care unit who have arterial catheters and whose ECG is continuously monitored. The data is collected and analysed for heart rate variability and baroreflex sensitivity using the sequence method.

Running parallel to these investigations into the central control of the cardiovascular system is studies on cardio respiratory integration and studies into respiratory rhythm generation and respiratory motor control. It is the view of our Laboratory that these two systems are so inextricably linked that they cannot really be considered as separate homeostatic systems. Since the group was established in 1996 when Dr Pilowsky, Dr QJ Sun and Prof. JP Chalmers moved to Sydney from Adelaide the team has grown significantly and now comprises about 17 people including 6 senior people, 5 postgraduate students, 1 post doctoral fellow and 3 honours students as well as a research assistant and an administrative assistant. The group has won several honours and awards, and our work has resulted in the publication of one major specialist book (PM Pilowsky, 2004, Serotonin neurons in the brainstem and spinal cord: diverse projections and multiple functions in 'Neural Mechanisms of Cardiovascular Regulation:' Dun NJ, Machado BH & Pilowsky PM eds, Kluwer Academic Publishers, Boston, Dordrecht and London.) 56 full papers and 4 commentaries in peer reviewed journals since 1996.

The [Basic & Clinical Genomics Laboratory](#), headed by **Professor Brian Morris**, has had a long standing interest in hypertension research. Their work on the regulation of renin gene expression at the transcriptional and post-transcriptional level is unravelling the complex genetic control mechanisms that regulate this important enzyme. Projects that the Laboratory is currently conducting include (i) Whether a strong far-upstream enhancer controls on/off switching of the renin gene. (i) The identification and mechanism of action of proteins that bind to the 3'-UTR of human renin mRNA to control stability. (ii) Characterization of several proteins that the Lab has found control alternative splicing of pre-mRNA and (iv) changes in gene expression in human cells as they age and in response to agents that increase lifespan of other species. The Lab published the first ever study on the molecular genetics of hypertension (in 1988), which was followed by numerous papers on this topic. Recent research highlights include completion of a genome scan to find loci for essential hypertension (June 2005 issue of *Am J Hypertens*), a project that began in 1992. Another long-running project that is near completion involves a study of the role of a far-upstream enhancer in control of the renin promoter in a variegated manner. Fluorescence activated cell sorting and immunohistochemistry experiments are supporting this hypothesis. Geoff Head and Jay Chin-Dusting at the Baker have provided physiological support on enhancer knock-out mice. The Lab also identified several proteins that bind to the 3'-UTR of human renin mRNA and showed how cyclic AMP modulates their effect on stability of this mRNA (*J Biol Chem* 2003). Prof Morris has an extensive review coming out in a forthcoming issue of *J Hypertens* on the molecular basis of longevity.



The [David Read Laboratory](#) at The University of Sydney, headed by **Professor Colin Sullivan** (also the director of the Australian Centre for Advanced Medical Technology on Obstructive Sleep Apnoea at Royal Prince Alfred Hospital) has made a major contribution to the problem of **sleep apnea induced hypertension**. Professor Sullivan pioneered nasal CPAP as an effective treatment for sleep apnoea syndrome and has over 90 scientific publications in the area. Notably, in the field of hypertension research, the work of his team has been instrumental in showing the effectiveness of this treatment for reducing blood pressure in sleep apnea in patients ([see Wilcock et al 1998](#)).

The [Muscle Cell Function Laboratory](#), headed by **Professor David Allen**, is concerned with the regulation of intracellular ions, particularly calcium, sodium and protons, and with their effects on muscle function. The Laboratory is particularly interested in situations where ionic regulation has major effects on cell function, for instance in cardiac pacemaker cells, in the heart during ischaemia and reperfusion and in skeletal muscle during fatigue. Much of the focus is on single cells in which ionic concentrations can be measured using fluorescent methods and the distribution of ionic changes can be studied using confocal microscopy. Professor Allen developed the first method for measuring intracellular calcium in cardiac muscle using the luminescent protein aequorin. Current research involves studies on **Pacemaker cells** where the Laboratory is examining the mechanisms which control the firing rate of pacemaker cells and have discovered that the Na/Ca exchanger acts as a pacemaker current. **Ionic regulation in the heart during ischaemia and reperfusion** is another focus where hearts which are reperfused after ischaemia become loaded with calcium and this contributes to cell damage. The main mechanism involved is the coupled activation of the Na/H exchanger and the Na/Ca exchanger stimulated by the proton accumulation during ischaemia (Park et al. 1999). The Laboratory is also studying the regulation of the Na/H exchanger during ischaemia and

reperfusion. Langendorff-perfused rat hearts are loaded with fluorescent indicators for sodium or protons (Xiao & Allen, 1999). These ideas are of increasing clinical interest because patients with heart attacks often have their ischaemic myocardium reperfused, so it is important to prevent the ionic changes which can occur as these trigger some of the cardiac damage. Using a confocal microscope, Professor Allen's group have examined **calcium sparks in the heart during acidosis and ischaemia**. These sparks give information about the state of calcium release sites and calcium stores in the heart. During acidosis and ischaemia, arrhythmias are more common and seem to be related to changes in calcium handling which can be studied by observing the frequency and magnitude of the calcium sparks (Balnave & Vaughan-Jones, 2000).