



Vascular Pharmacology Lab

Group Heads

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Specific Interests

Our laboratory is interested in vascular regulation, in particular mechanisms of vasorelaxation in small, resistance-like blood vessels. We are particularly interested in endothelium-derived mediators, (such as nitric oxide and endothelium-derived hyperpolarizing factor) and the role of K⁺ channels in vasorelaxation. We study vascular regulation under physiological conditions, and also in cardiovascular disease states such as hypertension and atherosclerosis.

Current projects

Nitric oxide (NO•) vs Nitroxyl anion (NO⁻) Nitric oxide is a well-known endothelium-derived mediator of vasorelaxation. Interestingly, nitric oxide can exist in several different redox forms. To date the vasorelaxant effects of nitric oxide have been largely attributed to the free radical form (NO•). However we have recently shown that the nitroxyl anion (NO⁻) is also a potent vasodilator, and is reported to be produced under physiological and pathophysiological conditions. The aim of this project is to examine and compare the mechanism of vasorelaxation of NO• and NO⁻. Our results thus far have shown that the mechanism of relaxation of NO⁻ is quite different to that of NO•, evidence to suggest that NO⁻ is an important mediator of vasorelaxation in it's own right.

Is NO⁻ an endothelium-derived relaxant factor? Given that NO⁻ can cause vasorelaxation, we are interested in the physiological role of this redox species. NO⁻ is reported to be produced in endothelial cells, therefore the aim of this project is to examine the role of endogenously produced NO⁻ in vasorelaxation responses.

Role of NO⁻ in the coronary circulation In this project we are examining the role of NO⁻ in vasorelaxation in the coronary circulation. Current therapy for angina (insufficient coronary circulation) uses nitrovasodilators that are NO• donors, however these agents are limited in their use by the development of tolerance. Since we have shown that NO⁻ can elicit vasorelaxation through a different pathway to NO•, NO⁻ donors, may be useful therapeutic agents either alone or in conjunction with nitrovasodilators. This project aims to elucidate the mechanism and potency of NO⁻ as a coronary vasodilator, and will also examine the role of NO⁻ in damage caused by ischaemia-reperfusion injury.

Role of NO⁻ in atherosclerosis Atherosclerosis is characterised by the development of lesions within and around blood vessels. These lesions compromise the function of the blood vessel in the least inhibiting endothelium-dependent relaxation, and ultimately by blocking blood flow completely. We have evidence to suggest that NO⁻ may be preferentially produced by blood vessels in a model of atherosclerosis, and this project aims to elucidate the role of NO⁻ as a vasorelaxant mediator in this pathological state.

Members of Laboratory

Funding

National Health & Medical Research Council
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Collaborations

Dr Robert Widdop Dept Pharmacology, Monash University
Dr Tracey Gaspari Dept Pharmacology, Monash University
Dr Karen Andrews Microvascular Research Group, RMIT University
Prof Chris Triggie Smooth Muscle Research Group, University of Calgary
Dr Grant McPherson Dept Pharmacology, Monash University (Honorary Appointment)

Recent selected publications

1. Irvine, J.C., Favalaro, J.L. & Kemp-Harper, B.K. (2003) NO⁻ activates soluble guanylate cyclase and K_v channels to vasodilate resistance arteries Hypertension,41: 1302-1307.
2. Favalaro, J.L., Andrews, K.L. & McPherson G.A. (2003) Novel imidazoline compounds that inhibit Kir-mediated vasorelaxation in rat middle cerebral artery. Naunyn Schmiedeberg's Arch Pharmacol, 367(4):397-405.
3. Favalaro, J.L. & Kemp-Harper, B.K. (2002) Nitric oxide (NO•) and the nitroxyl anion (NO⁻) have differing profiles of relaxant activity in rat mesenteric artery. Proceedings of the Australian Health and Medical Research Congress 2002, 1157.
4. Irvine, J.C., Favalaro, J.L. & Kemp-Harper, B.K. (2002) The nitroxyl anion (NO⁻) mediates relaxation of rat small mesenteric arteries in art via the activation of soluble guanylate cyclase and voltage dependent K⁺ channels. Proceedings of the Australian Health and Medical Research Congress 2002, 2013.
5. Kemp-Harper, B.K., McPherson, G.A. & Favalaro, J.L. (2002) The nitroxyl anion (NO⁻) mediates relaxation of small resistance arteries in part via the activation of soluble guanylate cyclase (sGC) and K⁺ channels. The Pharmacologist, 44 (2), Suppl 1, A214.