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Neuroscience



Metabolic Disease
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The renin angiotensin system is one of the major hormonal systems regulating blood pressure and general cardiovascular status. Increased activity of the renin angiotensin system is likely to contribute to a range of cardiovascular diseases including hypertension, heart failure, atherosclerosis and stroke. There are a number of angiotensin receptor subtypes that are activated by endogenous angiotensin peptides as well as by synthetic compounds. The AT₁ receptor subtype mediates most of the classical effects of angiotensin II. While blockade of AT₁ receptors by sartan-type compounds has proven very successful in the treatment of diseases such as hypertension, other non-AT₁ receptors are now thought to counter-balance overactivity of AT₁ receptors and exert protective actions in their own right.

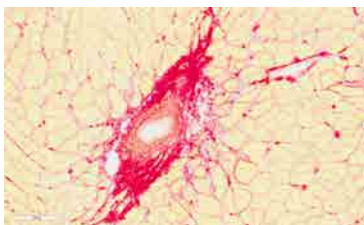
Therefore, a major focus of our laboratory has been to elucidate the (patho) physiological role(s) of AT₂ receptors, Mas receptors and insulin-regulated aminopeptidase (IRAP), and their interactions with angiotensin peptide fragments (e.g. Ang II, Ang 1-7, Ang III, Ang IV). Drug discovery programs in each of these areas provide mechanistic data, from initial drug screening through to *in vitro/in vivo* preclinical testing, on potential drug targets for a range of cardiovascular diseases including hypertension, heart failure, stroke, atherosclerosis, aortic aneurysms and ageing itself. In particular, prevention and reversal of organ fibrosis, inflammation and cardiovascular remodelling are seen as key features of novel drug therapies.

Research Projects

1. **Novel therapeutic strategies to reverse hypertension, organ fibrosis and remodelling**
2. **Drug discovery programs (new molecules) for testing AT₂ and Mas receptor function**
3. **Acid sensing ion channels (ASIC) as a novel target for stroke**



Heart Imaging



Cross-section heart- fibrosis (collagen) around coronary artery and in heart (red)

Selected significant publications:

1. McCarthy CA, Rash LD, Chassagnon IR, King GF, **Widdop RE**. 2015. PcTx1 affords neuroprotection in a conscious model of stroke in hypertensive rats via selective inhibition of ASIC1a. *Neuropharmacology*, 99, 650-657.
2. Chow BS, Kocan M, Bosnyak S, Sarwar M, Wigg B, Jones ES, **Widdop RE**, Summers RJ, Bathgate RA, Hewitson TD, Samuel CS. 2014. Relaxin requires the angiotensin II type 2 receptor to abrogate renal interstitial fibrosis. *Kidney Int*, 86, 75-85.
3. Gaspari T, Liu H, Welungoda I, Hu Y, **Widdop RE**, Knudsen LB, Simpson RW, Dear AE. 2011. A GLP-1 receptor agonist liraglutide inhibits endothelial cell dysfunction and vascular adhesion molecule expression in an ApoE^{-/-} mouse model. *Diab Vasc Dis Res*, 8, 117-24.
4. Bosnyak S, Welungoda IK, Hallberg A, Alterman M, **Widdop RE**, Jones ES. 2010. Stimulation of angiotensin AT₂ receptors by the non peptide agonist, Compound 21, evokes vasodepressor effects in conscious spontaneously hypertensive rats. *Brit J Pharmacol*, 159, 709-71.
5. **Widdop RE**, Jones ES, Hannan RE, Gaspari TA. 2003. Angiotensin AT₂ receptors: cardiovascular hope or hype? *Brit J Pharmacol*, 140, 809-824.