Signalling across the blood brain barrier: Implications for blood pressure control

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Our long-term goal is to understand cellular signalling mechanisms involved in the etiology of essential hypertension. Our hypothesis is that this disease may arise, in part, from changes within brainstem circuits controlling arterial pressure, and in particular to occlusion of arterial baroreceptor afferent information at the level of the primary afferent relay within the brainstem. Although it is established that baroreceptors regulate arterial pressure on a moment-to-moment basis, they may also control it long term (Thrasher, 2002). It follows then that desensitisation of this reflex circuit could contribute to high levels of blood pressure. I will discuss the central actions of angiotensin II on neuronal circuitry dedicated to controlling the baroreceptor reflex. Based on *in vivo* somatic gene transfer studies to identify intracellular signalling pathways, and dynamic confocal calcium imaging from cells within the nucleus of the solitary tract (NTS), we hypothesise a novel form of inter-cellular communication, one of *vascular-neuronal signalling*. Our model includes a process whereby angiotensin II stimulates nitric oxide release from the endothelium, which crosses the blood brain barrier to modulate adjacent inhibitory synaptic processes and shunts out incoming afferent information from arterial baroreceptors. Such a signalling process is consistent with that described for the control of GnRH within the median eminence (Prevot *et al.*, 2000). Moreover, using focal genetic approaches to chronically block endothelial cell derived nitric oxide results in an augmentation of baroreceptor reflex function and a fall in arterial pressure towards control levels in a rat model of hypertension. I will demonstrate that the specificity of action of nitric oxide on inhibitory (GABA) transmission in the NTS likely relates to the low concentration of the gas and/or proximity of the nitric oxide synthase isoform to its target (Paton *et al.*, 2002). In conclusion, activation of endothelial nitric oxide synthase within the NTS, which can be induced by physiological levels of angiotensin II, plays a major role in regulating cardiovascular function. Hyperactivity of angiotensin II and/or endothelial nitric oxide synthase within this nucleus may contribute to the persistent elevation of arterial pressure as observed in essential hypertension.

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