Angiotensin in the ventrolateral medulla

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The ventrolateral medulla contains groups of neurons that regulate autonomic functions such as respiration and cardiovascular control. This presentation will concentrate on two of these groups, the caudal and rostral ventrolateral medulla (CVLM and RVLM respectively). These nuclei contain catecholaminergic and non-catecholaminergic cells, which regulate sympathetic vasomotor nerve activity and neuroendocrine function. The CVLM contains a group of GABA-ergic interneurons that are involved in the sympathetic component of the baroreceptor reflex, and noradrenergic A1 neurons that project to the magnocellular neurosecretory neurons of the hypothalamus to modulate vasopressin release. The RVLM contains spinally-projecting neurons (some of which are adrenergic (C1 cells)) whose activity is essential for the tonic and reflex regulation of sympathetic vasomotor tone.

Angiotensin AT_1 receptors occur throughout the ventrolateral medulla in all mammals, including humans. In the human the AT_1 receptors are associated with the catecholaminergic neurons. Angiotensin II-like immunoreactivity also occurs in the region of the catecholaminergic neurons in the rat suggesting that neuronally released angiotensin might act in this region (see Allen *et al.*, 1992).

Microinjections of angiotensin into the ventrolateral medulla of anesthetized animals induce decreases in blood pressure and vasopressin release in the CVLM and increases in blood pressure from the RVLM. Studies *in vitro* support this observation with angiotensin II increasing the activity of presumed C1 RVLM neurons via activation of an AT_1 receptor (Li & Guyenet, 1995).

Microinjections of the selective AT_1 receptor antagonists into the RVLM of anesthetized animals have little effect under basal conditions. Interestingly these agents elicit a pressor response from the RVLM of conscious animals – the mechanism responsible for this is not yet elucidated (Fontes, *et al.*, 2000). However, there are some situations in which endogenous angiotensin does elicit an excitatory action in the RVLM. These include the sympathetic excitation following airjet stress (Mayorov & Head, 2003) or activation of the hypothalamic paraventricular nucleus (Tagawa & Dampney, 1999), and in several models of hypertension including the spontaneously hypertensive rat (Allen, 2001), the transgenic (mREN2) rat (Fontes, *et al.*, 2000) and the Dahl salt sensitive rat (Ito, *et al.*, 2003). Interestingly microinjection of an AT_1 receptor antagonist into the RVLM of the L-NAME-induced hypertensive rat does not affect blood pressure indicating that not all forms of hypertension involve activation of AT_1 receptors in the RVLM (Bergamaschi *et al.*, 2002).

Thus, via activation of AT_1 receptors, angiotensin acts as an excitatory neuromodulator in the ventrolateral medulla to regulate cardiovascular function. The physiological role of this angiotensinergic input is still being elucidated but the input to the RVLM is activated in several forms of hypertension, contributing to the sympathetic activation observed in some forms of this disease.

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