NTS AT1a receptor on long-term arterial pressure regulation: putative mechanism

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Online publish-ahead-of-print 17 September 2013

This editorial refers to ‘Cardiovascular role of angiotensin type1A receptors in the nucleus of the solitary tract of mice’ by B. Abegaz et al., pp. 181–191, this issue.

Studies over the last 50 years have demonstrated the major role of the central nervous system and renin–angiotensin system (RAS) acting together to control cardiovascular haemodynamic and blood fluid homoeostasis. It is well accepted that the combination of CNS and RAS is the major regulator of blood pressure in both normal and pathophysiological conditions. Considered one of the most important nuclei of the brain stem, the nucleus of the solitary tract (NTS), located at the dorsal brainstem, is the first synaptic relay station in the CNS for cardiovascular and respiratory afferent fibres, among other afferents, and contributes in mediating the hypertension and sympathoexcitiation observed in spontaneously hypertensive rats.

Most of the classical actions of central Ang II are exerted via the angiotensin II (Ang II) type 1 (AT1) receptor, which activates intracellular signalling cascades resulting in neuronal excitation. A single gene encodes the AT1 receptor in humans but in rodents two AT1 receptor genes are expressed resulting in two subtypes of AT1 receptors: AT1a and AT1b. In the murine CNS an overlapping and divergent localization of the AT1 receptor subtypes can be observed. Studies from Davison et al. have identified divergent functional roles for AT1a and AT1b in the actions of Ang II in the brain. While the dipsogenic effect of Ang II requires the presence of AT1b, the cardiovascular effects were selectively dependent on the AT1a Ang II subtype of receptor.

A study by Abegaz et al. (in this issue of Cardiovascular Research), is therefore timely, and sheds important light on how Ang II acts on AT1a receptors within the NTS and how these receptors are involved in a novel mechanism that may modulate arterial pressure in the long term. Such a demonstration was obtained with a very elegant set of experiments. In brief, they delivered lentiviruses to induce expression of the wild-type AT1a receptor in AT1a−/− mice, targeting the intermediate NTS, i.e. the most relevant NTS subregion in cardiovascular studies due to high concentrations of AT1 receptors and catecholaminergic neurons. This novel approach is very useful in examining the cardiovascular role of AT1a receptors in specific brain regions in conscious and unrestrained animals. Recent studies from the same group demonstrated that the sustained pressor response to aversive stress is diminished in AT1a−/− mice, whereas the replacement of AT1a receptor in the rostral ventrolateral medulla (a key region in the brainstem that contains a group of sympathoexcitatory neurons) of these mice significantly increased the sustained pressor response to aversive stress, hence mimicking the pressor response observed in wild-type mice exposed to the same conditions.

AT1a−/− mice are characterized as having low basal arterial blood pressure, and Abegaz et al. provide clear information that overexpression of AT1a receptors on neurons in the NTS of these mice can be activated by endogenous Ang II, causing a sustained elevation in blood pressure. This response is independent of the sympathetic outflow and does not affect the baroreflex sensitivity. The pressor responses elicited by aversive stress are possibly augmented by mechanisms involving central Ang II activating AT1a receptors on neurons located in the NTS enhancing the forebrain activation induced by stress. Since such responses appear to be independent of an increase in the sympathetic outflow, it could be possible that this occurs by way of an over-activation of the hypothalamic pituitary axis. Abegaz et al. observed an outstanding neuronal activation detected by Fos in several brain regions, which include the well-known nuclei involved in mediating the behavioural, hormonal, and cardiovascular responses to stress, the paraventricular nucleus (PVN) of the hypothalamus among them. A major inhibitory pathway from the NTS to vasopressin neurons in the PVN has previously been demonstrated. Therefore, a putative mechanism involving activation of Ang II-AT1a receptor in the NTS could be the removal of such inhibition in the NTS. The data presented by Abegaz et al. are the first to determine the role of AT1a receptors in the hindbrain and propose a putative mechanism involved in long-term blood pressure regulation. Such advances in cardiovascular research put into perspective new experimental approaches regarding this mechanism involving central Ang II activating AT1a receptors on neurons located in the NTS. This activation could amplify forebrain activation induced by stress and/or in the development and maintenance of hypertension.

Conflict of interest: none declared.

Funding

E.C. and D.S.A.C. are supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP: 09/54888-7; 11/20040-1; 11/50770-1; 13/...
50121-9) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq: 473108/2011-9; 305372/2010-6).

References


