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Central angiotensinergic mechanisms associated with hypertension

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ABSTRACT

Following its generation by both systemic and tissue-based renin–angiotensin systems, angiotensin II interacts with specific, G-protein coupled receptors to modulate multiple physiological systems, including the cardiovascular system. Genetic models in which the different components of the renin–angiotensin system have been deleted show large changes in resting blood pressure. Interruption of the generation of angiotensin II, or its interaction with these receptors, decreases blood pressure in hypertensive humans and experimental animal models of hypertension. Whilst the interaction of angiotensin II with the kidney is pivotal in this modulation of blood pressure, an involvement of the system in other tissues is important. Both systemic angiotensins, acting via the blood–brain barrier deficient circumventricular organs, and centrally-generated angiotensin modulate cardiovascular control by regulating fluid and electrolyte ingestion, autonomic activity and neuroendocrine function. This review discusses the pathways in the brain that are involved in this regulation of blood pressure as well as examining the sites in which altered angiotensin function might contribute to the development and maintenance of high blood pressure.

1. General introduction

Hypertension is common within the human population and a major contributor to the development of cardiovascular diseases, such as ischemic heart disease and stroke (Lloyd-Jones et al., 2009). Whilst hypertension can be a result of known, primary causes, such as renal artery stenosis, the majority of people fall into the category of 'essential' hypertension, where the cause is unknown and likely due to an interaction of multiple genetic and lifestyle factors. Amongst multiple factors, there is strong evidence implicating dysregulation of the renin–angiotensin system (RAS) in up to 70% of cases of human essential hypertension, leading to altered renal fluid and electrolyte handling (Laragh, 1985; Hansson et al., 1999; Yusuf et al., 2000). Whilst peripheral actions of the renin–angiotensin system are important in the pathogenesis of hypertension, there is also considerable evidence pointing to an involvement of the brain renin–angiotensin system. The data supporting this are the focus of this review.

2. The Renin–angiotensin system

The RAS was initially described as a systemic enzymatic cascade that results from the action of a renal enzyme, renin, on the hepatic glycoprotein angiotensinogen (AGT) to form an inactive peptide, angiotensin 1–10 (Ang I). This is then cleaved by angiotensin converting enzyme (ACE) to produce the active peptide angiotensin 1–8 (Ang II). Ang II is highly conserved throughout evolution, appearing in humans, rodents, avian and reptile species and its predominant role in these species is in the regulation of fluid and electrolyte balance and blood pressure (Nolly and Fasciolo, 1973; Laurent et al., 1995; Nishimura, 2001; Fournier et al., 2012). In mammals, these actions occur via the activation of specific G-protein-coupled receptors, the angiotensin type 1 and type 2 receptors (AT_1R and AT_2R). In rodents, there are two subtypes of the AT_1R, type A ($AT_{1A}R$) and type B ($AT_{1B}R$) (Timmermans et al., 1993; Hunyady and Catt, 2006).

In addition to this systemic humoral system, the existence of independently regulated tissue-based RAS has now been described in many organs, including in the brain (Paul et al., 2006). Furthermore, the complexity of this cascade continues to grow. Renin, and its precursor prorenin, bind to the (Pro)renin receptor with the subsequent activation of prorenin as an enzyme and increased catalytic efficiency of renin (Nguyen et al., 2002; Campbell, 2008). In addition to increasing enzymatic activity it is observed that ligand binding to the (Pro) renin receptor induces cell signaling (Campbell, 2008). Whilst considered the RAS, it is also known that other enzymes are able to cleave angiotensin peptides from AGT, including cathepsin D (Sakai and Sigmund, 2005). Thus renin-independent production of Ang II might occur. The recent detection of angiotensin 1–12 in several tissues, including the brain, and the demonstration that angiotensin 1–12 can be processed to yield a ligand that activates the AT_1R indicate that these alternative pathways may be functionally important (Nagata et al., 2006; Arnold et al., 2010). In addition, chymase is able to generate Ang II and may be physiologically important in some tissues

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(Prosser et al., 2009). Whilst Ang II and des-Asp Ang II (Ang III) have been considered the principal, active ligands of this system other active components are now known. Alternative processing pathways, which include the ACE homolog ACE2, form angiotensin 1–7 which is relatively inactive at the AT_1R and AT_2R but has effects via the *mas* receptor (Santos et al., 2003; Xu et al., 2011). Finally enzymatic processing of Ang III results in the formation of angiotensin 3–8 which selectively modulates the activity of insulin-regulated amino peptidase (Chai et al., 2004).

3. Angiotensin and blood pressure regulation

A comprehensive discussion of data supporting a role for the RAS in blood pressure regulation and hypertension is beyond the scope of this review. Considerable evidence supports an involvement of the RAS in determining the resting level of blood pressure. Mice with targeted deletion of renin (Yanai et al., 2000), AGT (Kim et al., 1995), ACE (Esther et al., 1996; Krege et al., 1997) and $AT_{1A}R$ (Ito et al., 1995) all have decreased levels of resting blood pressure. Whilst it might be difficult to disentangle the effect of the RAS on development – for example, all these models show significant impairment of renal development – from the direct effect on blood pressure, the results do point to an important role for Ang II acting via the $AT_{1A}R$.

The activity of the AGT gene and its relative abundance in plasma has direct effects on blood pressure in both animal models and humans. Whilst the levels of AGT are often overlooked in favor of renin, as the assumed rate-limiting step in the RAS cascade, the concentration of AGT in plasma is close to the Michaelis–Menten coefficient for renin levels (Morgan et al., 1996), suggesting that even with normal renin availability, altering AGT expression will affect Ang II levels. Studies in humans and experimental animals demonstrate a direct link between AGT gene expression and blood pressure (Jeunemaitre et al., 1992; Yang et al., 1994; Kim et al., 1995; Inoue et al., 1997). Multiple copies of the AGT gene at its normal locus in transgenic mice increased plasma AGT levels and blood pressure proportional to the number of extra copies of the AGT gene (Kim et al., 1995). In humans, an association between molecular variants of the AGT gene and essential hypertension has been reported (Jeunemaitre et al., 1992). This variant is associated with increased AGT gene promoter activity and elevated plasma AGT (Jeunemaitre et al., 1992, 1997). Similarly animal models with overexpression of renin develop hypertension (Mullins et al., 1990; Sinn et al., 1999).

Whilst blood pressure is proportional to the level of AGT expression, such an association is not demonstrated for the $AT_{1A}R$. Over-expression of the $AT_{1A}R$, either globally (Le et al., 2003) or throughout the brain (Lazartigues et al., 2002) does not result in changes in basal blood pressure. More recently several studies have examined blood pressure in mouse models with conditional cell selective deletion of the $AT_{1A}R$. Whilst the determination of resting blood pressure clearly involves $AT_{1A}R$ expression in the kidney, and in particular the renal proximal tubules, this does not fully account for the decrease in blood pressure observed in total $AT_{1A}R$ knockout mice (Crowley et al., 2005; Gurley et al., 2011; Li et al., 2011). Selective deletion of the $AT_{1A}R$ from vascular smooth cells of large arteries (Sparks et al., 2011), T cells (Zhang et al., 2012) or catecholaminergic cells (Allen and Jancovski, unpublished observation) also does not affect basal blood pressure. This argues for an important role of the $AT_{1A}R$ in other tissues in determining resting blood pressure.

Dysregulation of the RAS clearly contributes to hypertension in both humans and animal models and RAS blockade is a frontline therapy for many cardiovascular disease. RAS blockade can prevent end-organ damage and reduce cardiovascular events in patients (Volpe, 2012). These observations extend to the rodent models of essential hypertension, such as the spontaneously hypertensive (SH) rat, which shows large decreases in blood pressure in response to the inhibition of the RAS. Interestingly, early life inhibition of the RAS in SH rats leads to life-long attenuation of their blood pressure, suggesting a developmental role of the RAS in determining adult blood pressure (Harrap et al., 1990).

4. Brain angiotensin II and blood pressure regulation

Early studies observed that the pressor response to systemic Ang II involved a central action (Bickerton and Buckley, 1961; Dickinson and Lawrence, 1963; Bonjour and Malvin, 1970; Lowe and Scroop, 1970; Fischer-Ferraro et al., 1971) due to the increased secretion of vasopressin (Bonjour and Malvin, 1970; Mouw et al., 1971; Keil et al., 1975), inhibition of baroreflex-mediated withdrawal of cardiac parasympathetic activity (Lumbers et al., 1979) and stimulation of sympathetic vasomotor activity (Ferrario et al., 1972; Fukiyama, 1972). These actions occurred through the circumventricular organs which express high levels of AT_1R (Ferrario et al., 1972; Gildenberg et al., 1973; Mangiapane and Simpson, 1980; Mendelsohn et al., 1984). Subsequently, it was shown that Ang II is produced in the brain (Ganten et al., 1983) and that AT_1R and AT_2R are expressed behind the blood–brain barrier in many regions known to influence the central regulation of cardiovascular function (Mendelsohn et al., 1984; Song et al., 1992; Allen et al., 2009). Further studies showed that Ang II, acting via the AT_1R influences blood pressure when microinjected into several regions, including the lateral septum (Saad et al., 2004); anterior hypothalamus (AHA) (Hagiwara and Kubo, 2004); median preoptic nucleus (MnPO) (Ferreira-do-Vale et al., 1995; Budzikowski and Leenen, 2001); hypothalamic paraventricular nucleus (PVN) (Bains et al., 1992); nucleus of the solitary tract (NTS) (Casto and Phillips, 1984; Rettig et al., 1986); dorsal motor nucleus of the vagus (DMX) (Diz et al., 1984); rostral ventrolateral medulla (RVLM) (Andreatta et al., 1988; Allen et al., 1988b); caudal ventrolateral medulla (CVLM) (Allen et al., 1990); and intermediolateral cell column (IML) (Suter and Coote, 1987).

In most cases, high concentrations of Ang II are required to elicit these responses and so the results need to be treated with some caution. Several factors could influence this issue. Angiotensin is rapidly degraded by extracellular peptidases (Abhold et al., 1987) and thus the effective concentration might be considerably lower than that injected. The concentration of endogenous Ang II at a synapse is not known, as the mechanism by which it is generated remains unknown. Measurement of AGT concentrations in human cerebrospinal fluid indicates that it is present at approximately 60 nM and this equates to nearly 1% of total cerebrospinal fluid protein (Genain et al., 1984). Conceivably, high concentrations of Ang II could be locally generated in or near a synapse. Most of the microinjection studies have also been performed in anesthetized experimental animals where it is likely that activity in different pathways is altered compared to the conscious state. Of note, is the observation that intracisternal administration of the femtomole concentrations of Ang II induces a pressor response in conscious, sino-aortically denervated rabbits (Head et al., 1988). Finally it should be noted that microinjections of selective AT_1R antagonists into several of the regions noted above induce changes in blood pressure opposite to those of Ang II (Bains et al., 1992; Muratani et al., 1993; Matsumura et al., 1998; Allen, 2001; Hagiwara and Kubo, 2004) and thus support the view that this receptor plays a role in the neural regulation of cardiovascular function.

5. Brain RAS

As mentioned above, all components of the RAS are synthesized within the brain, although the cellular mechanism and pathway by which Ang II production occurs remain unclear. AGT mRNA is predominantly localized to astrocytes and exhibits regional heterogeneity of expression (Stornetta et al., 1988; Bunnemann et al., 1992). Mouse transgenic reporter approaches also demonstrate AGT expression in a limited number of neurons (Yang et al., 1999). Immunohistochemical approaches demonstrate AGT in neurons (Thomas and Sernia, 1988),

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