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Neuroimmune communication in hypertension and obesity: A new therapeutic angle?

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ABSTRACT

Hypertension is an epidemic health concern and a major risk factor for the development of cardiovascular disease. Although there are available treatment strategies for hypertension, numerous hypertensive patients do not have their clinical symptoms under control and it is imperative that new avenues to treat or prevent high blood pressure in these patients are developed. It is well established that increases in sympathetic nervous system (SNS) outflow and enhanced renin–angiotensin system (RAS) activity are common features of hypertension and various pathological conditions that predispose individuals to hypertension. More recently, hypertension has also become recognized as an immune condition and accumulating evidence suggests that interactions between the RAS, SNS and immune systems play a role in blood pressure regulation. This review summarizes what is known about the interconnections between the RAS, SNS and immune systems in the neural regulation of blood pressure. Based on the reviewed studies, a model for RAS/neuroimmune interactions during hypertension is proposed and the therapeutic potential of targeting RAS/neuroimmune interactions in hypertensive patients is discussed. Special emphasis is placed on the applicability of the proposed model to obesity-related hypertension.

Contents

Abbreviations: ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; AGT, angiotensinogen; Ang-II, angiotensin-II; Ang-(1–7), angiotensin (1–7); AT1R, angiotensin type-1 receptor; AT2R, angiotensin type-2 receptor; ARC, arcuate nucleus of the hypothalamus; BBB, blood–brain barrier; CCL2, C–C chemokine ligand type-2; CCR2, C–C chemokine receptor type-2; CVO, circumventricular organ; GFAP, glial fibrillary acidic protein; IL-10, interleukin-10; IL-1β, interleukin-1β; IL-6, interleukin-6; IML, intermediolateral cell column; Iba-1, ionized calcium binding adaptor molecule 1; MIF, macrophage migration inhibitory factor; MCP-1, monocyte chemotactic protein-1; NTS, nucleus of the solitary tract; PVN, paraventricular nucleus of the hypothalamus; PRR, pro-renin receptor; RAS, renin–angiotensin system; RVLM, rostral ventral lateral medulla; SFO, subfornical organ; SHR, spontaneously hypertensive rat; SNS, sympathetic nervous system; TPOR, thiol-protein oxidoreductase; TNFα, tumor necrosis factor-α.

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1. Introduction

Hypertension is an epidemic health concern and a major risk factor for the development of cardiovascular disease, the leading cause of death in the USA. It has long-been established that high blood pressure is often accompanied by enhanced activities of the renin–angiotensin system (RAS) and the sympathetic nervous system (SNS) and, over several decades, research efforts have led to the development and refinement of countless pharmacological antihypertensive therapeutics targeting these systems. Despite these efforts, which successfully reduce blood pressure in many hypertensive subjects, numerous patients remain unresponsive to available pharmacological interventions and are left with severely high blood pressure (Egan et al., 2010). A large proportion of these patients have increased sympathetic outflow, parasympathetic withdrawal, and norepinephrine spillover, and surgical denervation of the kidney has shown promise as an effective intervention for these patients (Krum et al., 2009; Schlaich et al., 2009a, 2009b; Esler et al., 2010; Schlaich et al., 2012). The implication is that their hypertension arises from neurogenic origins (Fisher & Fadel, 2010; Grassi, 2010; Grassi et al., 2010).

The frequent ineffectiveness of available antihypertensive pharmacotherapies coupled with the neural origins of uncontrolled hypertension underscores the urgent need to develop new avenues for the pharmacological treatment or prevention of neurogenic hypertension. One promising prospect in this regard, stems from the relatively recent realization that hypertension is also an immune condition (Harrison et al., 2008; Shi et al., 2010; Zubcevic et al., 2011; Marvar et al., 2012). The nervous and immune systems are intricately connected and their reciprocal communication may contribute to the etiology of hypertension. Here we review the intimate relationship between these systems in the regulation of blood pressure and the potential roles of the SNS and RAS in these interactions.

Before discussing this RAS/neuroimmune connection, we first briefly review the current understanding of the roles of the SNS and RAS in blood pressure control. Then, subsequent sections will consider the reciprocity between the nervous and immune systems, and how the RAS and SNS mediate these interactions. The role of the RAS, SNS and immune system in facilitating the causal relationship between obesity and hypertension is also considered. Finally, based on the reviewed studies a model for RAS/immune interactions in the neural control of blood pressure will be proposed and the clinical relevance of these regulatory systems for the development of new antihypertensive therapeutics will be discussed.

2. The brain renin–angiotensin system, sympathetic outflow and hypertension

Before discussing how the RAS, SNS and immune systems may interact to cause hypertension, it is appropriate to first review the roles of the SNS and RAS in blood pressure regulation. The SNS plays a key role in the pathophysiology of cardiovascular disease (Goldstein, 1983; Guyenet, 2006; Fisher & Fadel, 2010; Grassi, 2010; Grassi et al., 2010). Hypertensive animals and patients exhibit elevated SNS outflow (Goldstein, 1983; Grassi, 1998; Guyenet, 2006; Joyner et al., 2008) as well as, heightened vascular reactivity, characterized by greater vasoconstrictor responses to norepinephrine (Ziegler et al., 1991).

Various environmental factors, such as exposure to stressful stimuli and high-fat diet-induced obesity, and humoral factors, including those synthesized by the RAS activate the SNS and lead to an increased susceptibility to hypertension (Oparil et al., 2003; Dorresteijn et al., 2012; Marvar & Harrison, 2012) and pharmacotherapies that target the SNS and RAS reduce blood pressure in many patients. Furthermore, a therapy that has recently proven effective for some individuals resistant to available antihypertensive pharmaceutics is surgical denervation of the kidney (Krum et al., 2009; Schlaich et al., 2009a, 2009b; Esler et al., 2010). This surgical intervention is minimally invasive, as it uses a percutaneous catheter-based approach to ablate both afferent and efferent renal nerves, and it is highly effective, as it reduces sympathetic outflow to the kidney, reduces plasma renin activity and increases urine output, thereby reducing blood pressure without causing long-term adverse events (Krum et al., 2009; Schlaich et al., 2009a; Esler et al., 2010; Krum et al., 2011).

The effectiveness of this surgical intervention solidifies the importance of the nervous system in uncontrolled hypertension and understanding the mechanism(s) by which the nervous system regulates blood pressure under normal conditions may therefore guide the refinement of existing and/or the development of new pharmacological therapeutics for this pathology. In this section, we review the neural circuitry controlling sympathetic outflow and blood pressure regulation and the impact of the RAS on these pathways.

2.1. The renin–angiotensin system

First, it is essential to outline the current understanding of the RAS. Classically, the RAS has been viewed as an endocrine system regulating cardiovascular function and hydromineral balance. Angiotensin-II (Ang-II) is considered the principle effector peptide of the system, which is formed from liver-derived angiotensinogen (AGT) through proteolytic cleavage first by kidney-derived renin (the rate-limiting enzyme for Ang-II synthesis) and then by lung-derived angiotensin-converting enzyme (ACE). Ang-II then acts predominantly at its type-1 receptor (AT1R), in variety of tissues to impact blood pressure regulation. Although this is the best characterized and perhaps the dominating pathway of the RAS, several additional nuances of the RAS have been revealed, that allow it to impact blood pressure in diverse ways.

This includes several endogenous mechanisms that counteract the hypertensive actions of AT1R. For example, AT1R activation can be opposed by stimulation of the angiotensin type-2 receptor (AT2R; Huang et al., 1996; Bosnyak et al., 2010; Steckelings et al., 2012) and by the ACE2-Ang-(1–7)-Mas axis (Donoghue et al., 2000; Katovich et al., 2005; Der Sarkissian et al., 2006; Diez-Freire et al., 2006; Santos et al., 2008). We have also determined that macrophage migration inhibitory factor (MIF) can oppose many of Ang-II's pathophysiological actions mediated by AT1R, working intracellularly via its thiol-protein oxidoreductase (TPOR) activity (Busche et al., 2001; Sun et al., 2007; Li et al., 2008; Freiria-Oliveira et al., 2013).

Moreover, it is now acknowledged that the RAS is also an autocrine/paracrine system within various tissues including adipose tissue (Yiannikouris et al., 2012a, 2012b) and the brain (Lenkei et al., 1997; McKinley et al., 2003; Cuadra et al., 2010). Components of the RAS are present within brain regions that control cardiovascular function, but are protected from the circulating RAS by the blood brain barrier (BBB) suggesting that brain-derived Ang-II may contribute to SNS activity and may act as a neurotransmitter in these regions (Bains et al., 1992; Li & Ferguson, 1993). Pharmacological or genetic manipulations of the RAS in these protected brain regions have profound effects on physiology and behavior, further supporting the prevalence of a functional brain-specific RAS (Morimoto et al., 2002; McKinley et al., 2003; Grobe et al., 2008; Grobe et al., 2010; de Kloet et al., 2011; Yamazato et al., 2011). However, the level of renin within the CNS is low at best (Bader & Ganten, 2002; Lavoie et al., 2004), calling into question the mechanism/source of Ang-II's presence in the brain. In this regard, the (pro)renin receptor (PRR) which is highly expressed in the brain may mediate extracellular generation of Ang-II in the brain by binding and sequestering (pro)renin, thereby increasing its catalytic activity and propagating localized cleavage of AGT (Cuadra et al., 2010).

2.2. Neural circuitry controlling the sympathetic nervous system and blood pressure

Sympathetic stimulation of the heart, vasculature and kidneys increases blood pressure by elevating cardiac output, vascular

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