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Review

Neuroinflammation and sympathetic overactivity: Mechanisms and implications in hypertension

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ABSTRACT

Essential hypertension is a multifactorial disorder with a strong genetic predisposition. Although anti-hypertensive medications have drastically reduced cardiovascular diseases mortality and morbidity rates, a significant percentage of hypertensive individuals currently on anti-hypertensive therapy, remain hypertensive. In spite of the emergence of transgenic animals and sophisticated tools to study the pathophysiology of hypertension, unraveling the causal mechanisms remains a challenge. Research on borderline hypertensive humans and/or prehypertensive rat models revealed an elevation in centrally-mediated sympathetic activity and a heightened neuroinflammatory state. Hyperactive brain renin angiotensin system (RAS), oxidative stress and neuroinflammation in brainstem cardiovascular centers and other brain regions are implicated as key factors in augmenting sympathetic activity in hypertension and other cardiovascular abnormalities. Angiotensin (Ang) II, the main RAS effector peptide, has been shown to trigger significant upsurges in pro-inflammatory cytokines and reactive oxygen species (ROS). Both microglial and astroglial cells, via a host of different mechanisms, contribute to pro-inflammatory states and ROS generation in the brain. Hence, it becomes essential to understand the impact of Ang II and neuroinflammatory mediators on the impairment of cardioregulatory centers in the brain, and to investigate the role of glia in Ang II-mediated sympathoexcitation. Understanding the mechanisms leading to an elevation in neuroinflammatory states, and the possible ways of counteracting it, could aid in devising better therapeutic strategies for the treatment of cardiovascular diseases and hypertension. This review primarily focuses on the molecular aspects of hypertension from a neuroinflammatory standpoint within brainstem cardiovascular centers.

1. Introduction

Elevated sympathetic tone is observed in a significant percentage of individuals diagnosed with essential hypertension (Esler et al., 2010; Esler et al., 1988). Evidence suggests that an augmented central sympathetic outflow is not only a consequence of hypertension, but can be a crucial triggering mechanism (Fisher et al., 2009; Mancia et al., 1999). In addition to oxidative stress being a crucial factor, inflammatory states in the brainstem cardiovascular centers have also been described as important contributors to hypertensive states (Waki et al., 2008a; Paton and Waki, 2009; Waki et al., 2011; Waki and Gouraud, 2014; Winklewski et al., 2015; Gowrisankar and Clark, 2016; Haspula and Clark, 2017a). The purpose of this review is to highlight the implications of augmented sympathetic activity, followed by the role of centrally elevated inflammatory states, on hypertension and cardiovascular disorders. In addition, the role of pro-hypertensive systems that are known to elevate pro-inflammatory states, such as the renin angiotensin system (RAS), is also highlighted in both cardiovascular and neurological disorders.

2. Current status of hypertension and treatment

Hypertension has the dubious distinction of being termed the silent killer. In addition to being a peerless risk factor for cardiovascular diseases, hypertension is associated with minimal, if any, visible symptoms during the initial stages of disease progression (Sawicka

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ADHD, attention deficit hyperactivity disorder; Ang, angiotensin; AT1R, angiotensin type 1 receptor; AT2R, angiotensin type 2 receptor; CNS, central nervous system; CVLM, caudal ventrolateral medulla; IL, interleukin; JAM-1, junction adhesion molecule 1; MCP-1, monocyte chemotactic 1; MIF, migration inhibitory factor; NTS, nucleus tractus solitaris; PVN, paraventricular nucleus; RAS, renin angiotensin system; RVLM, rostral ventrolateral medulla; SAD, sinoatrial denervation; SFO, subfornical organ; SHR, spontaneously hypertensive rat; TLR4, toll like receptor 4

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et al., 2011). Before the start of this decade, about 1 billion people were diagnosed with hypertension worldwide, and the numbers are expected to rise to 1.5 billion by 2025 (Kearney et al., 2005; Chockalingam, 2007). Since 1975, there has been more than a 50% increase in the number of adults diagnosed with high blood pressure (Zhou et al., 2017). Antihypertensive drug therapy is hailed as one of the most significant medical breakthroughs to come out of the 20th century, considering that its impact on lowering mortality rates, is second only to antibiotics (Kaplan, 1980). Since the introduction of antihypertensive drug therapy, as per the National Institutes of Health, death rates associated with cardiovascular diseases have significantly dropped by 72% in the United States (https://www.nhlbi.nih.gov/files/docs/research/2012_ChartBook_508.pdf). In spite of these giant strides, more than 30% of the United States population who are currently receiving anti-hypertensive drug therapy, continue to remain hypertensive (Calhoun et al., 2008). Although mortality rates associated with hypertension have been on the decline during the period from 2003 to 2010, less than half of the estimated 66.9 million hypertensive U.S. adults were able to keep their blood pressure under control (Tu et al., 2008; Cohen and Townsend, 2013). Given the availability of multiple classes of antihypertensives, one would expect to achieve a higher remission rate of hypertension. Apart from a lack of compliance to antihypertensive drug therapy being a major factor (Fadl Elmula et al., 2014), another plausible reason could be that individuals remain refractory to prescribed drugs (Fisher and Fadel, 2010). Refractory or resistant hypertension accounts for about 30% of all hypertensive cases (Calhoun et al., 2008). A lack of effectiveness of traditional anti-hypertensive medications, necessitates identification of viable therapeutic targets for hypertension (Fisher and Fadel, 2010). Since a multifactorial, polygenic disorder like hypertension may have multiple blood pressure regulatory mechanisms compromised at different stages of the disorder (Sleight, 1971), singling out mechanisms that are critically intertwined with disease progression, becomes an uphill task. Identification of effective therapeutic targets hinges on understanding the mechanisms that are impaired at the very early stages of hypertension. These may well be the drivers of hypertension, and treating these impairments at the earliest stages would result in a better response to drug therapy.

3. Role of sympathetic hyperactivity in the pathogenesis of hypertension

Since regulation of blood pressure is orchestrated by multiple mechanisms encompassing both neurogenic and non-neurogenic origins, the task of isolating hypertension trigger mechanisms remains a challenge. Evidence of autonomic dysfunction in hypertension came from studies conducted in borderline hypertensive individuals, where an elevated cardiac output was observed in young hypertensive individuals (Widimsky et al., 1957). By employing direct and indirect parameters of sympathetic activation in humans (Safar et al., 1974; Julius and Esler, 1975), researchers were able to identify autonomic dysfunction as a crucial mechanism for the development of hypertension. A meta-analysis of plasma catecholamine levels in hypertensive individuals revealed a high correlation between younger hypertensive individuals, rather than older hypertensive individuals, with hypertension (Goldstein, 1983). Possible neural involvement in hypertensive states was also theorized (Mancia et al., 1983; Reis, 1981). Seminal works of Anderson and Julius, published in the late 1980's and early 1990's, not only established the importance of sympathetic overactivation as a significant factor in the initiation of hypertension (Julius et al., 1991), but also provided convincing evidence of central nervous system (CNS) involvement (Anderson et al., 1989). Additionally, sympathetic hyperactivity was not just associated with essential hypertension, but it was demonstrated to be a decisive factor in other cardiovascular risk factors and cardiovascular diseases (Leimbach et al., 1986; Huggett et al., 2003; Smith et al., 2004; Graham et al., 2004; Grassi et al., 2005; Fisher et al., 2009). Traditional antihypertensives, other than centrally acting sympatholytics, have been demonstrated to have both a minimal/neutral effect (Grassi et al., 1998), and also an exacerbatory effect (Fu et al., 2005) on central sympathetic outflow. Since an elevated central sympathetic outflow is a key underlying determinant of cardiovascular diseases and their risk factors, it is essential that we explore the molecular mechanisms that lead to an impairment in cardiovascular parameters.

4. Causes and consequences of augmented central sympathetic activity

Sympathetic activity that is centrally-mediated is tightly regulated by the baroreceptors and the CNS cardioregulatory centers, both of which form important components of the baroreflex (Guyenet, 2006). In the CNS, the cardioregulatory centers of the brainstem and hypothalamus play a critical role in the homeostatic regulation of blood pressure over shorter and longer periods of time (Dampney et al., 2002; Thrasher, 2004; Osborn, 2005; Zanutto et al., 2010; Lohmeier and Iliescu, 2015). Nucleus of the tractus solitarius (NTS), located in the medulla, is a major command center for the integration of inputs from arterial baroreceptors, chemoreceptors, and also cardiopulomonary receptors (Dampney, 1994; Guyenet, 2006). It also receives inputs from the amygdala and the hypothalamic paraventricular nucleus (PVN). A rapid rise in blood pressure activates baroreceptors, both carotid and aortic, which then relay the signal to the cardioregulatory centers in the CNS through the nerve of Hering, and the aortic depressor nerve (Timmers et al., 2003). This sets into motion a negative feedback loop which lowers heart rate by activating the parasympathetic tone (efferent arm) (Guyenet, 2006; Fisher and Paton, 2012). Activation of the peripheral baroreceptors serves to depress the rostral ventrolateral medulla (RVLM) activity, the major pressor center in the brain, leading to a decrease in sympathetic activity (Dembowsky and McAllen, 1990). This action is achieved through baroreceptor afferents that terminate into the NTS, whose primary function is to keep a check on the RVLM, via its activity on the major inhibitory center, the caudal ventrolateral medulla (CVLM). Additionally, afferent inputs from chemoreceptors and projections from PVN also terminate into the RVLM which further regulate the sympathetic tone (Colombari et al., 2001) (Dampney et al., 2002). RVLM neurons, terminate in the intermediolateral cell column, from which arises the sympathetic preganglionic neurons. Its activation has been demonstrated to result in an increase in sympathetic efferent activity to heart, arteries and kidneys, resulting in an increase in heart rate, vasoconstriction, and an increase in renin release (Kumagai et al., 2012). Hence, optimum functioning of the peripheral baroreceptors and the brainstem cardioregulatory centers, along with the higher brain regions such as hypothalamus, have a crucial role in the regulation of baroreflex (Guyenet, 2006; Waki, 2012). Elevation of sympathetic activity that is observed in hypertensive states could be either due to an impairment in baroreceptor and chemoreceptor afferent input to the brainstem, or a processing error in brainstem cardiovascular centers (Guyenet, 2006).

Baroreflex serves to normalize fluctuations in blood pressure, either via a reflex inhibition of heart rate and sympathetic activity in response to heightened blood pressure, or a disinhibition of inhibitory control over the aforementioned cardiovascular parameters in response to a fall in blood pressure. Changes in heart rate or sympathetic activity buffering capacity in response to arterial pressure changes, is referred to as baroreflex resetting. Resetting of the baroreflex is an important pathophysiological abnormality of essential hypertension (Folkow, 1982). Both peripheral (baroreceptor) and/or central (cardioregulatory centers) impairments have been postulated as important contributors (Chapleau et al., 1989). The baroreflex has long been considered to have a primary role in regulating acute changes in blood pressure. For instance, although sinoatrial denervation resulted in an acute increase in blood pressure, stabilization in blood pressure was observed over