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Stress-Dependent Hypertension and the Role of T Lymphocytes

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Abstract

Hypertension is a significant global health burden associated with an increased risk of stroke, atherosclerosis and other cardiovascular diseases. Several risk factors including high dietary salt, obesity, genetics, race as well as behavioral and psychological factors contribute to development of this complex disease. Various hypertensive stimuli enhance sympathetic drive and promote autonomic dysfunction leading to elevated blood pressure. In further understanding the pathogenesis and end organ damage associated with hypertension, mounting evidence also highlights the role of inflammation in this process, and in particular the role of the adaptive immune system and T cells in this process. This review will discuss recent findings regarding the role of the central nervous system, T lymphocytes and the impact of cardiovascular risk factors such as psychological stress in hypertension.

Keywords

Inflammation; stress; hypertension

Introduction

Despite extensive study, the etiology of most cases of human hypertension remains unknown. Increasing evidence suggests that inflammation and adaptive immunity play a significant role in the pathogenesis of hypertension (Harrison *et al.*, 2011; Muller *et al.*, 2011). Previous studies from our laboratory have shown that mice lacking lymphocytes (RAG1^{-/-}) are resistant to various forms of experimental hypertension and that adoptive transfer of T cells but not B cells restores their hypertensive phenotype (Guzik *et al.*, 2007; Marvar *et al.*, 2010). In these and other studies we demonstrate that hypertensive stimuli such as angiotensin II, high salt, catecholamines and more recently chronic psychological stress, cause T cell activation and entry of activated T cells into the peripheral blood vessels and kidney (Lob *et al.*, 2010; Madhur *et al.*, 2010; Marvar *et al.*, 2010; Marvar *et al.*, 2012). Recent work from other groups have extended these findings and provide further evidence of a role for T lymphocytes in salt-sensitive, pregnancy related, and pulmonary forms of

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hypertension (Rodriguez-Iturbe, 2010; Cuttica *et al.*, 2011; De Miguel *et al.*, 2011; Wallace *et al.*, 2011). The severe combined immunodeficiency (SCID) mouse model also exhibits a blunted hypertensive response to chronic angiotensin II (Crowley *et al.*, 2010). Therefore, independent of the type of experimental hypertension or the experimental model studied the adaptive immune response is important. The precise mechanism for how T cells become activated and contribute to hypertension is unknown and is currently being investigated by a number of research groups.

Neural Control of Blood Pressure in Hypertension and Inflammation

The central nervous system (CNS) is essential for processing and integrating neurohumoral signals from the periphery, modulating autonomic nervous activity to maintain blood pressure and fluid homeostasis (Guyenet, 2006). In both human hypertension and animal models of hypertension there are several lines of evidence supporting neural mechanisms that can be considered a contributing cause or consequence of neurogenic hypertension (Grassi *et al.*, 2010). For example, elevated sympathetic nerve activity (Anderson *et al.*, 1989), altered baroreceptor sensitivity (Matsukawa *et al.*, 1991; Chappleau *et al.*, 2001), enhanced norepinephrine turnover (Rumantir *et al.*, 2000), angiotensin II and dietary salt (Osborn *et al.*, 2007), inflammation (Waki *et al.*, 2011) as well as environmental factors such as psychological stress (Esler *et al.*, 2008; Davern & Head, 2011). Although these are all considered important factors in neurogenic hypertension their complex interactions and precise mechanisms are a matter of great debate. This brief review will be focused on the renin angiotensin system, psychological stress and implications in immune cell signaling and vascular inflammation in hypertension.

Autonomic control of blood pressure is largely regulated by distinct nuclei in the hypothalamic forebrain (ie; circumventricular organs) and brainstem (McKinley *et al.*, 2003) including the subfornical organ, the organum vasculosum of the lamina terminalis, the area postrema, and the median eminence (Figure 1). The circumventricular organs have an incompletely formed blood brain barrier and can therefore sense circulating hormones like angiotensin II. Importantly, circulating angiotensin II activates angiotensin type 1 (AT₁) receptors in circumventricular organs (Brody, 1988), which in turn sends projections to hypothalamic areas, leading to long-term activation of hypothalamic neurons and increased sympathetic vasomotor activity (Davern & Head, 2007). This has been previously demonstrated in both animal (DiBona & Jones, 2001) and humans (Johansson *et al.*, 1999) suggesting that circulating angiotensin II is a major signal to the CNS contributing to neurogenic hypertension.

Importantly, activation of the above mentioned central pathways have also been shown to elicit a peripheral immune response. Ganta *et al* demonstrated that administration of angiotensin II in the lateral cerebral ventricles increased mRNA expression of pro-inflammatory splenic cytokines such as IL-1 beta and IL-6 (Ganta *et al.*, 2005). Interestingly, splenic sympathetic denervation abrogated these responses, suggesting that central angiotensin II can elicit a peripheral immune response via the autonomic nervous system.

There is evidence to suggest bi-directional communication between the CNS and immune systems (Nance & Sanders, 2007). The spleen and lymph nodes receive substantial sympathetic innervation and most immune cells possess adrenergic receptors (Sanders & Straub, 2002). Studies have demonstrated that neuro-immune mechanisms contribute to the neurogenic component of hypertension (Paton & Waki, 2009; Shi *et al.*, 2010; Yu *et al.*, 2010). Paton and colleagues have shown that inflammatory cells and cytokines are increased in the brainstem in experimental hypertension, and that these inflammatory cells can impair central autonomic control of blood pressure regulation (Paton & Waki, 2009), (Waki *et al.*, 2010). Moreover, angiotensin II increases blood brain barrier permeability and causes cerebral microvasculature inflammation, which could allow inflammatory cells and cytokines to gain entry to the brain (Zhang *et al.*, 2010). Microglial cells, a type of specialized macrophage in the CNS, are also activated in hypertension, and inhibition of these cells reduces blood pressure (Shi *et al.*, 2010). Taken together these data support the concept that the CNS can serve as both a target for inflammatory cells in hypertension as well as mediator of inflammation through its communication with the immune system. Angiotensin II is a key contributor to these processes in the setting of hypertension. Figure 2 illustrates the relationships between hypertensive stimuli, their sites of action in the CNS, (ie; circumventricular organs), and the neuroimmune system in hypertension.

Circumventricular Organs (CVOs): Important CNS sites in T lymphocyte Mediated Hypertension

The anteroventral third ventricle (AV3V) region contains a high density of AT₁ receptors and receives input from the SFO, a CVO, and sends efferent projections to key cardiovascular regulatory brainstem sites such as the nucleus of the solitary tract (NTS) and rostral ventrolateral medulla (RVLM) (Brody *et al.*, 1978) (Figure 1). Earlier studies have shown that electrolytic ablation of this region abolishes all central actions of angiotensin II including drinking behavior, sympathetic outflow, vasopressin release as well as preventing and/or reversing several forms of experimental hypertension (Brody *et al.*, 1978; Brody & Johnson, 1980). In support of these early studies, we demonstrated that the hypertensive response to a 2-week infusion of angiotensin II is attenuated by AV3V lesioning (Marvar *et al.*, 2010). Interestingly, AV3V lesions also completely prevented activation and vascular infiltration of T cells. This demonstrated that the central pressor actions of angiotensin II are required for T cell activation and peripheral vascular inflammation in the setting of hypertension caused by this octapeptide. We went on to show that this effect was specific to the AV3V region as norepinephrine infusion, a peripherally acting hypertensive stimulus, caused hypertension and T cell activation independent of the lesion. To determine whether these effects were due to the central actions of angiotensin II or a result of blood pressure lowering from the lesion, we blocked the rise in blood pressure to angiotensin II with hydralazine, which prevented the T cell activation and vascular inflammation. Our findings are compatible with a pathway in which central stimuli such as angiotensin II cause modest elevations of blood pressure, which lead to T cell activation, and ultimately more severe hypertension. These data also suggest that the adaptive immune response can be triggered in hypertension irrespective of the type of hypertensive stimulus.

Psychological Stress, Angiotensin II and Inflammation

Psychological stress has been considered for years to be a risk factor for hypertension (Esler *et al.*, 2008). Many clinical and epidemiological studies have shown that behavioral and psychological factors are involved in the pathogenesis of human hypertension (Matthews *et al.*, 2004; Gasperin *et al.*, 2009). In addition, psychological stress can profoundly affect the immune system, promoting inflammation and cardiovascular disease (Glaser & Kiecolt-Glaser, 2005; Black, 2006; Pickering, 2007). Despite substantial clinical data, the mechanisms by which stress causes hypertension remain poorly understood. Current evidence suggests that increased sympathetic neural activity and central actions of angiotensin II likely have an important role (Saiki *et al.*, 1997; Esler *et al.*, 2008; Groeschel & Braam, 2011). Moreover, recent pre-clinical data show that angiotensin II receptor blockers reduce manifestation of stress, including brain inflammation and ischemia (Saavedra *et al.*, 2011).

Given our previous data supporting a role of inflammation and adaptive immunity in hypertension, we recently asked the question of whether stress-related hypertension could promote T cell activation in a similar fashion and whether angiotensin II could augment these effects (Marvar *et al.*, 2012). Repeated exposure of mice to the stressors of repeated cage switching and restraint produced anxiety like behavior and modest elevations in blood pressure after 1 week. Interestingly, circulating T cells these animals exhibited a greater percentage of activation markers and their vascular tissue contained an increased number of leukocytes including total leukocytes and T cells. Interestingly, we found that RAG-1^{-/-} mice, which lack lymphocytes, were protected from stress-induced hypertension and that reconstitution of T cells into the RAG1^{-/-} mice by adoptive transfer restored the hypertensive response to repeated stress. These data support our previous findings in other hypertensive models and suggest that the hypertensive stimulus of chronic stress contributes to T cell mediated vascular inflammation in hypertension (Marvar *et al.*, 2012).

Another important factor in development of stress-related hypertension is the renin-angiotensin system (Raasch *et al.*, 2006; Groeschel & Braam, 2010; Liu *et al.*, 2012). Angiotensin II not only exerts the central effects mentioned above to increase sympathetic outflow, but has direct effects on post-ganglionic fibers to enhance release of catecholamines (Weiner, 1979; Dendorfer *et al.*, 2002). It also promotes vasoconstriction (Evans *et al.*, 2010) and is a potent stimulus for pro-inflammatory and pro-oxidative events (Suzuki *et al.*, 2003; Guzik *et al.*, 2007) (Ferrario & Strawn, 2006). Circulating levels of renin and angiotensin II are elevated during stress (Clamage *et al.*, 1976; Carrasco & Van de Kar, 2003) and AT₁ receptors are located in a number of brain regions related to the emotional stress response (Aguilera *et al.*, 1995). For example, the amygdala, bed nucleus stria terminalis and other limbic brain regions involved in the stress response contain AT₁ receptors (von Bohlen und Halbach & Albrecht, 1998). Interestingly, projections from these regions extend to critical autonomic control sites including OVLT and SFO (Sunn *et al.*, 2003) (Figure 1). Moreover, Krause *et al.*, recently demonstrated that restraint stress increases circulating levels of angiotensin II which in turn activates neurons in the SFO. The authors also showed that lentiviral knockdown of the AT₁ receptor in the SFO attenuated the humoral and behavioral responses to the stress paradigm (Krause *et al.*, 2011). Mice lacking

the AT₁ receptor, exposed to aversive stress exhibit decreased cardiovascular reactivity, and this effect appears to be centrally mediated as well (Davern *et al.*, 2009). These data highlight the central actions of angiotensin II as an important neurohumoral stimulus in stress related hypertension.

Angiotensin II can affect T-cell-mediated inflammation in hypertension (Hoch *et al.*, 2009) and has angiogenic properties that can influence behavior (Gard, 2002). To further understand the interactions between chronic stress and angiotensin II, we recently examined the effects of a chronic low dose infusion of angiotensin II combined with chronic stress on T cell mediated inflammation (Marvar *et al.*, 2012). Low dose angiotensin II infusion markedly augmented the blood pressure response to repeated stress as well as the vascular inflammation. Studies in both humans (Nyklicek *et al.*, 2005) and animals (McDougall *et al.*, 2005) have shown that following repeated chronic stress, exposure to additional acute stressors elicits an exaggerated acute pressor response likely due to increased cardiovascular/autonomic sensitivity. Similarly, the animals exposed to stress and angiotensin II in our study displayed an exaggerated hypertensive response to a bout of acute cage switch stress (Marvar *et al.*, 2012). In these studies we did not examine indices of autonomic function to determine if greater sympathetic activity was the driving force behind these enhanced effects, however, Moretti *et al.*, recently showed that chronic low dose angiotensin II enhances renal sympathetic nerve activity in rabbits. These authors also showed that animals exposed to angiotensin II and stress displayed greater neuronal Fos-related antigen immunoreactivity in circumventricular organs, suggesting that these enhanced peripheral autonomic responses are likely mediated within the CNS via AT₁ receptors (Moretti *et al.*, 2012). Overall, these data provide evidence that the circumventricular organs are key targets for angiotensin II and that external stimuli such as stress converge on these sites to enhance sympathetic activity, contributing to elevations in blood pressure and vascular inflammation.

Taken together, we propose that hypertensive stimuli such as angiotensin II, salt and chronic stress act on the CNS to increase sympathetic outflow in part via the circumventricular organs. Increased sympathetic outflow to the kidneys and vasculature leads to a modest elevation in blood pressure, which promotes the formation of unknown antigens that are processed by antigen presenting cells, leading to T cell activation. Activated T cells infiltrate the vasculature and kidney, interacting with monocyte/macrophages and promote pro-inflammatory cytokine release, endothelial dysfunction, further vasoconstriction, salt /water retention and ultimately severe hypertension.

Conclusion

Blood pressure control is influenced by many factors including vasoactive substances that control vascular tone, renal regulation of electrolytes and volume and the central nervous system. We and others have shown that the CNS, in particular the CVOs play a critical role in the setting of hypertension, and the accompanied T cell activation and vascular inflammation. These hypothalamic brain regions are also heavily influenced by psychological stress, which on its own can influence the immune response. Further understanding the role of psychological stress on central control of blood pressure and the

associated inflammatory responses could provide the potential for the development of new treatment strategies for hypertension.

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New Findings

This review will discuss:

- Recent findings regarding the central nervous system in hypertension, the role of T lymphocytes, angiotensin II and the impact of cardiovascular risk factors such as psychological stress.
- This review highlights data that provides new insight for our understanding in the role of inflammation in hypertension.

Central Hypertensive Stimuli (Angiotensin II, Salt, Psychological Stress)

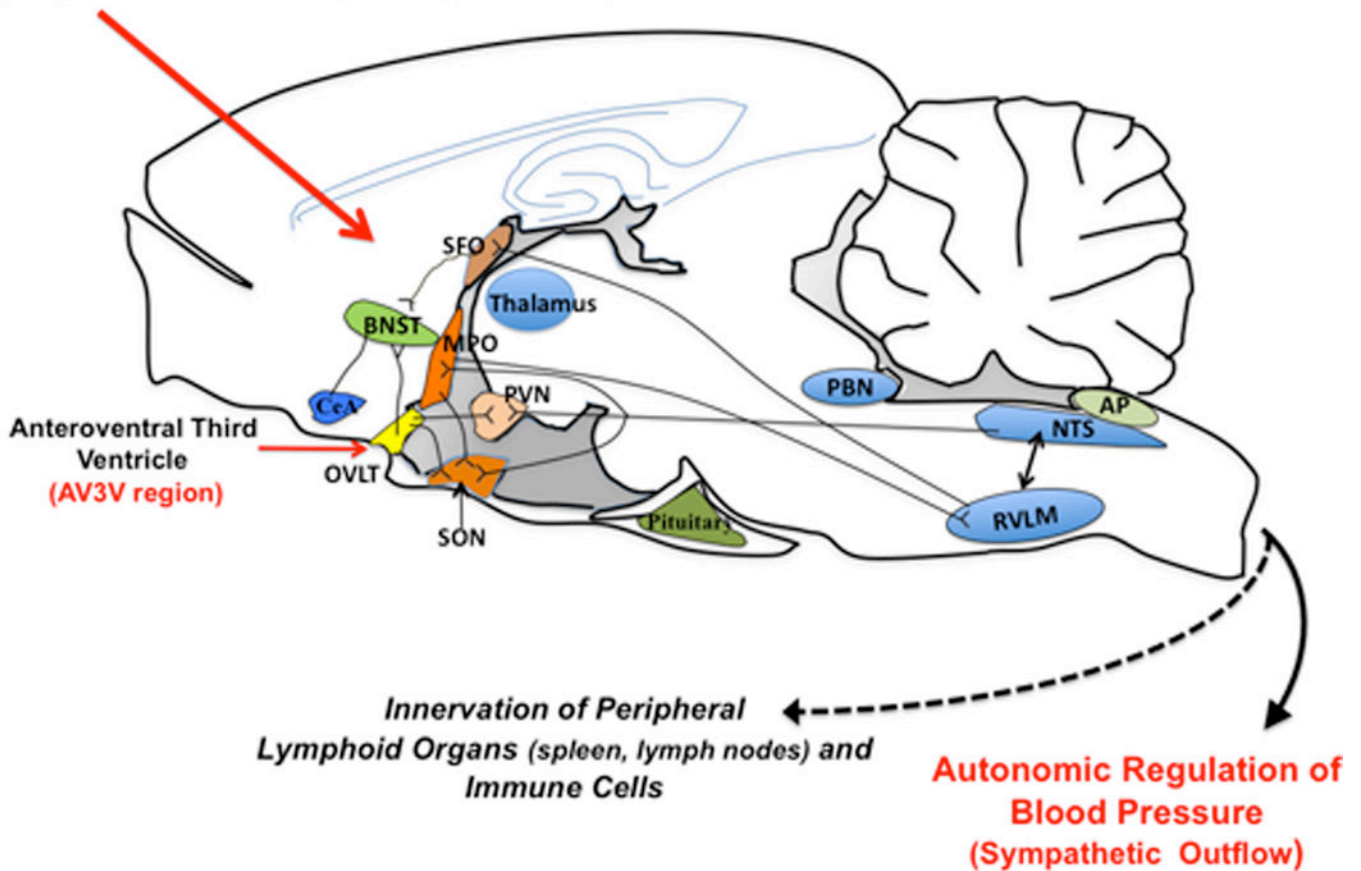


Figure 1.

Schematic showing location and connections of some of the primary hypothalamic structures responsible for central angiotensin II signaling and the integration of the stress response. SFO, Subfornical organ; BNST, Bed nucleus stria terminalis; MPO, Median preoptic nucleus; PVN, paraventricular nucleus; CeA, Central amygdala; NTS, the nucleus of the solitary tract; RVLM, rostral ventrolateral medulla; PBN, parabrachial nucleus; AP, area postrema.

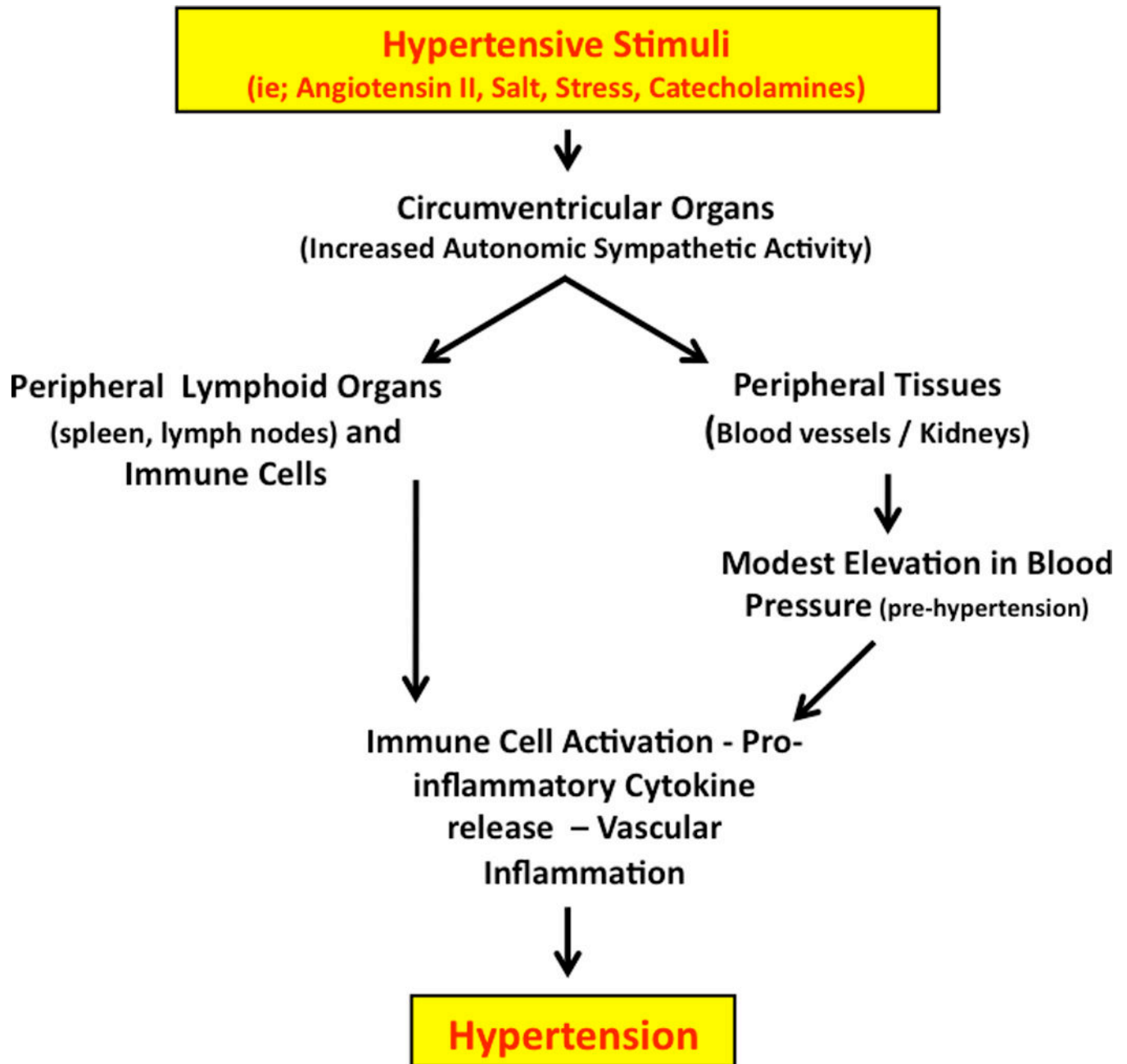


Figure 2.

We propose that hypertensive stimuli such as angiotensin II, salt and chronic stress act on the CNS to increase sympathetic outflow in part via the circumventricular organs. Increased sympathetic outflow to the kidneys and vasculature leads to a modest elevation in blood pressure, which promotes the formation of unknown antigens that are processed by antigen presenting cells, leading to T cell activation. Direct autonomic innervation of lymphoid tissue and immune cells may also contribute to this pathway. Activated T cells infiltrate the vasculature and kidney, interacting with monocyte/macrophages and promote pro-

inflammatory cytokine release, endothelial dysfunction, further vasoconstriction, salt /water retention and ultimately severe hypertension.

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