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Title:
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Date:
2019-06-01

Citation:
Carnagarin, R., Matthews, V., Zaldivia, M. T. K., Peter, K. & Schlaich, M. P. (2019). The bidirectional interaction between the sympathetic nervous system and immune mechanisms in the pathogenesis of hypertension. British Journal of Pharmacology, 176 (12), pp.1839-1852. https://doi.org/10.1111/bph.14481.

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The bidirectional interaction between the Sympathetic Nervous System and Immune mechanisms in the pathogenesis of hypertension

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Word count: 5797 words (excluding references)

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bph.14481

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Abstract

Over the last few years, evidence accumulated to suggest that hypertension is at least in part an immune mediated inflammatory disorder. Multiple links between immunity and hypertension have been established and provide a complex framework of mechanistic interactions contributing to the rise in blood pressure. These include immune mediated inflammatory processes affecting regulatory brain nuclei and interactions with other mediators of cardiovascular regulation such as the sympathetic nervous system. Sympatho-excitation differentially regulates T cells based upon activation status of the immune cell as well as the resident organ. Exogenous and endogenous triggers activate signalling pathways in innate and adaptive immune cells resulting in pro-inflammatory cytokine production and activation of T lymphocytes in the cardiovascular and renal regions, now considered major factors in the development of essential hypertension. The inflammatory cascade is sustained and exacerbated by the immune flow via the brain - bone marrow - spleen -gastrointestinal axis and thereby further aggravating immune mediated pathways resulting in a vicious cycle of established hypertension and target organ damage. This review summarizes the evidence and recent advances in linking immune mediated inflammation, sympathetic activation and their bi-directional interactions with the development of HTN.

Keywords: Hypertension, immunity, sympathetic nervous system, inflammation, cytokines.

Non-standard abbreviations:

HTN: Hypertension

SHR: spontaneously hypertensive rat

Ang II: angiotensin II

APCs: antigen presenting cells

TLRs: Toll-like receptors

CVO: circumventricular region

CVD: cardiovascular disease

CKD: chronic kidney disease

Introduction

Hypertension (HTN) is a major cause of mortality and morbidity worldwide affecting more than one billion adults. It is the most common modifiable risk factor for cardiovascular events and death. With an underlying cause established for only ~10% of cases (i.e. secondary hypertension), the majority of the hypertensive population suffers from essential hypertension, which is frequently characterized by sustained sympathetic activation. More recently, immune mechanisms have been proposed to contribute to the development of hypertension. Immune reactivity in experimental and human hypertension was initially believed to be a consequence rather than a cause of blood pressure elevation. It has now become clear that immune-mediated oxidative stress can initiate renal interstitial inflammation, loss of peritubular capillaries and medullary hypoxia which in turn causes impaired pressure-natriuresis and increased blood pressure [Franco et al 2013, Guyton et al

1972]. These findings laid the foundations for further investigations into the role of immunity induced pathways as a causal mechanism in the development of hypertension. Indeed, Franco et al demonstrated a close relationship between renal immune cell infiltration and impaired pressure natriuresis, which was preventable by mycophenolate mofetil-dependent reduction of immune infiltration in a salt-sensitive HTN rat model [Franco et al 2013].

There has since been a shift from the perception of HTN and HTN-mediated end organ damage merely being the result of elevated pressure on the vessel wall to a much more complex scenario involving immune mechanisms. Experimentally, immunological approaches for the treatment of blood pressure have revealed promising results and provided evidence for a concerted interplay of innate and adaptive immunity. The objective of this review is to summarize the evidence and recent advances in linking immune mediated inflammation, sympathetic activation and their bi-directional interactions with the development of HTN.

Immunity and Hypertension: Compelling evidence for immune-mediated hypertension

Experimental suppression of immune mechanisms is an elegant approach to explore their role in blood pressure regulation. Indeed, immunosuppression or thymectomy blunted the development and maintenance of HTN [Harrison 2014, Okuda & Grollman 1967, White & Grollman 1964]. Blood pressure and urinary excretion of inflammatory cytokines was decreased in hypertensive patients treated with mycophenolate mofetil for rheumatoid arthritis or psoriasis over a 3-month period, despite unchanged antihypertensive therapy or

salt intake, but reverted when treatment was discontinued [Herrera et al 2006]. Human Immunodeficiency Virus positive patients with low $CD4^+$ T-cell counts were less prone to HTN than those on antiretroviral therapy with normal $CD4^+$ T cell counts, who developed HTN to a similar degree as the normal population [Seaberg et al 2005]. Thymic transplantation from normotensive Wistar Kyoto rats reduced HTN in spontaneously hypertensive rats (SHR) [Ba et al 1982]. The requirement of a functional thymus for the maintenance of HTN and the inability of thymectomized or athymic nude mice with renal infarction to maintain HTN [Svendsen 1977, Svendsen 1976, Batalliard et al 1986] support a pathogenic role of the immune system in hypertension. Moreover, mice with severe combined immunodeficiency were protected from developing HTN [Crowley et al 2010]. The passive transfer of lymphocytes from hypertensive rat models to normotensive rats induced HTN [Okuda & Grollman 1967]. Furthermore, HTN was suppressed by anti-thymocyte serum or immunosuppressive cyclophosphamide in SHR [Bendich et al 1981, Dzielak 1991] suggesting that inflammation is a cause rather than merely a consequence of HTN.

In another important line of research it was demonstrated that recombinase activating gene 1 ($Rag1^{-/-}$) mice, which lack T and B lymphocytes failed to develop HTN when chronically exposed to Ang II [Guzik et al 2007]. Rag1 deletion also attenuated HTN in Dahl salt-sensitive rats [Mattson et al 2013] further supporting a role of immune cells in HTN development. However, in a more recent publication Ji et al reported that these RAG null mice on a C57BL/6J background lost their resistance to angiotensin II-induced HTN, which

was independent of T cells [Ji et al 2017]. Enhanced sensitivity and upregulation of the renal angiotensin type 1-receptor activity was identified as the most likely explanation and this was attributed to the universal drive for genetic variation in inbred animals. Clearly, this phenotypic change in B6. *Rag1*$^{-/-}$ -M has implications for investigators using this strain to study mechanisms of T-cell modulation of Ang II-dependent blood pressure control, however, it does not necessarily compromise the findings from studies investigating the role of T- cell modulation in Ang II-induced HTN prior to this occurrence. Furthermore, there is strong evidence that T cells modulate other important physiological processes mediated by Ang II such as endothelial dysfunction and microvascular injury [Mian et al 2016]

T cells as critical immune players in the genesis of HTN

Sympathoexcitation differentially regulates T lymphocytes and it has been shown that sympathetic stimulation induces norepinephrine mediated T cell activation and vascular inflammation [Marvar et al 2010]. The activation of T lymphocytes involves two-steps: 1) T cell receptor interaction with antigen presented by the major histocompatibility complex and 2) co-stimulation via CD28, bound by the B7 ligands, CD80 and CD86 of the antigen presenting cells (APCs) – the absence of which induces T cell apoptosis [Frauwirth &Thompson 2002]. Depletion of neutrophils and monocytes with diphtheria toxin in mice eliminates the hypertensive response to Ang II and HTN is restored with repletion of monocytes but not granulocytes, highlighting the important role of monocyte-antigen presentation to T cells [Wenzel et al 2011, Harrison 2014]. Inhibition of co-stimulation by

CTLA4-Ig, a pharmacological agent which binds B7 ligands on APCs, attenuated the associated blood pressure rise as well as T cell activation, vascular infiltration, and T cell-mediated tumor necrosis factor-alpha (TNF-α) and Interferon-gamma (IFN-ɣ) production in both Ang II and deoxycorticosterone acetate (DOCA) HTN models [Vinh et al 2010]. HTN as a T-cell driven inflammatory process became evident when passive transfer of T cells and not B cells restored HTN following Ang II infusion accompanied by elevated levels of memory and circulating T cell markers including CD69+, CCR5+, $CD44^{high}$ [Guzik et al 2007]. Furthermore, the role of T-cells in the pathogenesis of HTN has recently been confirmed in humanized mice, in which the murine immune system is replaced by the human immune system [Itani et al 2016].

In all models of salt sensitive hypertension, the tubulo-interstitium of rat kidney is intensively infiltrated with lymphocytes and macrophages, which correlates with the degree of HTN [Rodriguez-Iturbe et al 2004, Heijnen et al 2014]. Lymphocyte infiltration was also seen in perivascular aortic tissue in Ang II-induced HTN, DOCA-salt HTN and aldosterone-induced HTN [Guzik et al 2007, Kasal et al 2012]. Significant immune infiltration precedes HTN and intensifies with increasing severity of HTN suggestive of a likely cause and effect relationship [Rodríguez-Iturbe et al 2004, Franco et al 2013]. Blocking of immune infiltration using mycophenolate mofetil prevents HTN in various animal models such as SHR [Rodriguez-Iturbe et al 2001], Dahl salt sensitive rats [De Miguel et al 2011], salt driven HTN models induced by protein overload glomerular disease [Alvarez et al 2002], and in the

Page kidney model when the renal parenchyma is subjected to external compression [Vanegas et al 2005].

A distinct infiltrating T cell phenotype characterised by amplified C-C chemoligand 2 (CCL2) production promotes leukocyte recruitment, enhances reactive oxygen species (ROS) and generation of cytokines thereby intensifying the local and advanced inflammation causing organ dysfunction and overt HTN [Wei et al 2014]. Elevated CCL2 levels were found in organs regulating blood pressure [Bush et al 2000] and T cells were identified to be an important source of CCL2 contributing to inflammation associated with hypertension. Leukocytes express the CCL2 receptor (CCR2) which binds to CCL2 and several other chemokines such as CCL8, CCL13 and CCL27. CCR2 inhibition reduces vascular macrophage accumulation and reverses the pressor responses in DOCA-salt induced HTN [Chan et al 2012]. CCR2- deficient mice exhibit decreased macrophage and monocyte infiltration into the arterial wall during Ang II-induced HTN [Bush et al 2000] suggesting a crucial role of CCR2-CCL2 signalling in immune-mediated inflammation of HTN and associated organ dysfunction which may be initially driven by infiltrating T cells leading to a pro-inflammatory cascade.

B cells as additional players in the genesis of HTN

Whereas a plethora of evidence is available supporting an important role for T cells, the role of B cells has been less well documented. Only quite recently did Chan et al. demonstrate that B cells and the associated IgG production contributed to Ang II-induced hypertension.

Interestingly, a clinically available anti-CD20 antibody approach reduced HTN, providing an interesting potential therapeutic perspective for HTN [Chan et al. 2015].

The concerted interplay of adaptive and innate immunity in the development of HTN

The T cell dominant adaptive immune response in HTN, initiated and coordinated by the innate immune components such as phagocytes, dendritic cells, monocytes/macrophages, natural killer cells, and the pattern recognition receptors Toll-like receptors (TLRs), are critical to the induction and sustenance of HTN. These events are mediated through the downstream immune components such as ROS and reactive nitrogen species [Ryan 2013]. The peripheral blood monocytes of the hypertensive patients have elevated mRNA levels of TLR2 and TLR4 which are reduced by intensive antihypertensive treatment, indicative of a relevant role of the innate immune response [Hartupee et al 2007].

Oxidative stress has been observed in all experimental models of HTN. ROS act as second messengers in Ang II signalling and intracerebral ventricular (ICV) injections of adenovirus encoding for superoxide dismutase (SOD) ablated Ang II-dependent changes in heart rate and blood pressure [Zimmerman et al 2002]. Furthermore, SOD deletion in the circumventricular organs increases baseline blood pressure and augments the Ang II-dependent hypertensive response and promotes T cell and leukocyte infiltration as well as vascular inflammation, partly by modulating sympathetic outflow. [Lob et al 2010]. With respect to ROS, a feedforward loop between nicotinamide adenine dinucleotide phosphate oxidase (NOX) and mitochondria results in the induction and maintenance of diffuse

inflammation in organs regulating blood pressure [Datla & Griendling 2010, Dikalov & Nazarewicz 2013]. This inflammatory milieu is characterised by elevated levels of Ang II, aldosterone, cytokines and altered mechanical forces, stimulated enzyme sources such as the NOXs, uncoupled nitric oxide synthase and the mitochondrial ROS which contribute to the development of hypertension [Harrison & Gongora 2009].

Several cytokines are implicated in the pathogenesis of HTN. Inflammatory markers [Chae et al 2001, Engstrom et al 2002] and T cell specific cytokines such as IL-4, IL-6, IL-7, IFN-γ-inducible protein-10 (IP-10), TNF-α and IL-17 [Stumpf et al 2011, Madhur et al 2010] are elevated in patients with essential hypertension. IL-17 infusion has been demonstrated to cause endothelial dysfunction and HTN in mice [Nguyen et al 2013] and also induced oxidative stress in the placenta of pregnant rats thereby promoting HTN [Dhillion et al 2012]. The TNF-α antagonist Etanercept effectively prevented HTN in animal models [Venegas-Pont et al 2010, Tran et al 2009] and IL-6 deficient mice appear to be protected in certain HTN models [Brands et al 2010, Lee et al 2006, Schrader et al 2007]. Short-term administration of pressor doses of angiotensin II (Ang II) resulted in renal infiltration and activation of immune cells with subsequent development of salt-sensitive hypertension in male Sprague-Dawley rats [Rodriguez-Iturbe et al 2001]. The Ang II-induced vascular dysfunction and arterial hypertension was driven by IFN-γ-mediated immune recruitment and activation of natural killer cells and monocytes [Kossmann et al 2013]. Furthermore, IFN-γ is upregulated in kidneys of hypertensive mice [Crowley et al 2010] and IFN-γ receptor deletion prevents AngII-dependent end organ damage [Marko et al 2012].

The ongoing metabolic and oxidative cellular damage in HTN can result in the oxidative modification of endogenous molecules, exposure of intramolecular sites by protein cleavage that are otherwise not exposed to the immune system and release reactive intracellular molecules further propagating the damage [Harrison et al 2011]. Highly reactive oxidatively modified isoketals accumulate in the dendritic cells and activate T cell mediated immuno-inflammation and promote HTN in mice [Kirabo et al 2014]. Certain molecules such as oxidized low-density lipoprotein, heat shock proteins (HSP) and platelet glycoproteins have been suggested to elicit immune responses in atherosclerosis [Gotsman et al 2008]. Abnormal HSP responses have been noted in patients with essential HTN [Pockley et al 2003, Pockley et al 2002, Kunes et al 1992, Li et al 2009] and increased expression of HSP70 has been observed in circulating lymphocytes of hypertensive subjects [Kunes et al 1992] that caused clonal expansion of CD4+ T cells and induced delayed hypersensitivity in models of salt sensitive HTN [Pons et al 2013]. HSP70 gene polymorphisms, namely HSPA1A, HSPA1B and HSPA1L, predispose to HTN in individuals of Uygur ancestry [Li et al 2009]. Furthermore, auto-antibodies against Ang II type1-receptors (AT1R) and alpha1-adrenergic receptors have been detected in patients with HTN [Liao et al 2002] indicative of a role for protein modification. Agonistic antibodies directed to the second extracellular loop of AT1R, initially described in preeclampsia, have also been detected in patients with essential HTN [Fu et al 2000, Wei et al 2011]. Circulating anti-endothelial Immunoglobulin (Ig) G and IgM have also been observed in HTN [Papadopoulos et al 2006, Frostegard et al 1998]. Taken together, the “first hit” phase is likely initiated by cytokine-dependent oxidative damage and

protein modification resulting in the generation of neoantigens which contribute to the initiation of the inflammatory cascade of HTN **(Figure 1).**

Interaction of the sympathetic nervous system and immunity in the development of hypertension

Physiological integration and processing of the interaction between the autonomic nervous system and the immune system determines the balance of the sympathetic responses at the peripheral sites including the lymphoid targets. Neural and non-neural communication pathways keep the central autonomic nervous system informed of the peripheral immune status. In addition, the microenvironment created by diverse signalling mechanisms mediated through neurotransmitters and neuromodulators including adrenergic receptors, immune cells, cytokines and pathogens maintain the neural communication. Importantly, immune cells express adrenergic and nicotinic receptors, which bind the sympathetic neurotransmitters to initiate immunomodulatory responses. Of interest in this context is the observation that bilateral ablation of renal sympathetic nerves with phenol prevented immune activation, renal inflammation and attenuated Ang II- induced HTN in mice [Xiao et al 2015]. Furthermore, catheter-based renal denervation applied to lower BP by reducing sympathetic nervous system activation has recently been demonstrated to reduce monocyte activation and inflammatory markers in patients with essential hypertension [Zaldivia et al 2017].

Essential HTN is a clinically heterogeneous entity and current evidence supports the notion that immunomodulation is specifically relevant in regards to three major factors contributing

to the blood pressure rise including (i) increased sympathetic tone, (ii) enhanced sodium and fluid overload and (iii) activation of the renin-angiotensin-aldosterone (RAS) cascade. In cases involving high sympathetic activation, a low-grade systemic inflammatory environment is established by the amplified release of inflammatory cells into the blood circulation [Heidt et al 2014]. The cells of the innate immune system, monocytes in particular, are implicated in the pathogenesis of hypertension. Acute and long-term BP elevation is linked to pre-activated monocytes in animals and patients with HTN [Dörffel et al 1994, Wenzel et al 2011]. In fact, genetic depletion of LysM+ monocytes resulted in blunted Ang II-induced HTN in mice, whereas adoptive transfer of proinflammatory monocytes restored the BP elevation, supporting the notion of an important role of monocytes in hypertension development [Wenzel et al 2011]. α_1-adrenergic stimulation has a proinflammatory effect on immune system responses and positively regulates the expression of inflammatory cytokines in the innate immune cells during stress or injury-dependent release of catecholamines [Grisanti et al 2011]. In addition, adrenergic activation-dependent proinflammatory cytokine release in a number of chronic inflammatory disease states [Maestroni 2000, Heijnen et al 2002, Pere et al 2009]. For example, in chronic polyarticular juvenile rheumatoid arthritis IL6 release from mononuclear cells in peripheral circulation is dependent on α1-AR expression [Heijnen et al 1996] while α1-AR activation was found to be important for enhanced inflammatory responses in an established model of multiple sclerosis [Brosnan et al 1985].

Sympathetic activation of the bone marrow and the spleen and the associated release of hematopoietic cells into the systemic circulation has been identified to play an important role

in the pathogenesis of HTN [Heidt et al 2014]. Sympathetic nerves densely innervate the bone marrow and upon activation can release progenitor cells seeding to the spleen with a subsequent increase in monocyte production [Dutta et al 2012, Felten et al 1985, Felten et al 1984]. Enhanced T cell infiltration and increased sympathetic discharge has also been identified in the carotid body of hypertensive patients [Mcbryde et al 2013]. Exaggerated RAS activation [Rudermiller et al 2016] with T cells and monocytes/macrophages accumulation in the kidney and vasculature mediates tissue injury and deleterious remodelling in HTN [Madhur et al 2010]. Sympathetic nervous system activation differentially regulates the immune system based upon activation status of the immune cell as well as the resident organ [Case & Zimmerman 2016]. Release of norepinephrine from the sympathetic nerve terminal potentiates the effects of the activated T-lymphocytes in these cardiovascular-related organs. In norepinephrine-infused mice increased T-lymphocyte numbers and activation has been observed in the aorta [Marvar et al 2010] whereas T-lymphocytes from the spleen in this model_demonstrated decreased proliferation that was accompanied by a reduction in IFN-γ and TNF-α [Case & Zimmerman 2015]. Whilst norepinephrine stimulation of Th1 cells generated from naïve CD4+ lymphocytes enhances IFN-γ production by more than 2- to 4-folds [Swanson et al 2001], norepinephrine is also known to cause mitochondrial superoxide-dependent modulation of the canonical activation of splenic T lymphocytes in a model of sympathetically-driven HTN [Case & Zimmerman 2015]. Short-term norepinephrine administration has been shown to augment the number of CD8+ circulating T-lymphocytes, but long-term administration resulted in decreased T-lymphocyte numbers [Maisel & Michel 1989]. Taken together, the available evidence

suggests that norepinephrine can elicit differential immunomodulatory effects on different subclasses and stages of differentiated T-lymphocytes. Naïve unchallenged T-lymphocytes are suppressed by norepinephrine stimulation whereas the functionality of pre-existing activated T-lymphocytes is exacerbated under different conditions such as specific systemic infections, stress, or targeted T-lymphocyte differentiation [Alaniz et al 1999].

On the contrary, alterations in sympathetic nervous system activity have been proposed to be implicated in stroke-induced immunosuppression. In experimental stroke both activation of the hypothalamic pituitary axis (HPA) and the sympathetic nervous system, as well as β-receptor blockade have been shown to substantially affect stroke induced immunomodulation [Prass et al 2003]. It has been suggested that brain injury induced generation of inflammatory cytokines such as tumor necrosis factor-*a*, interleukin-1β and interleukin-6 interferes with the autonomic-immune circuits to result in immune dysfunction [Dirnagl et al 2007]. Direct measurement of sympathetic activation in humans following a stroke using gold standard techniques such as microneurography or noradrenaline spillover (Schlaich et al 2010, Lambert et al 2008) have not been applied but would likely shed some light into the relevance of these findings in a clinical setting. Overall, these findings are indicative of relevant cross talk between the sympathetic and the immune system to sustain the immune-mediated inflammation in HTN **(Figure 2)**.

The immunomodulatory brain-bone marrow-spleen-gut axis:

Neuroinflammation is a hallmark of hypertension

The sympathetic nervous system is an integrative interface between the brain and the immune system and modulates both hemodynamic and immune responses [Elenkov et al 2000]. Immune infiltration and enhanced inflammation of neural regulatory centres have been suggested to be key players in the interaction between the immune and sympathetic nervous system as demonstrated in the nucleus tractus solitarii of the SHR [Gouraud et al 2011]. Similarly, in Sprague-Dawley rats chronic Ang II infusion has been demonstrated to activate microglia and increase proinflammatory cytokines in the paraventricular nucleus causing neurogenic HTN. This effect was attenuated by minocycline, an antibiotic that passes the blood brain barrier and has been shown to act as an inhibitor of microglia [Shi et al 2010]. Furthermore, ICV infusion of Ang II increases sympathetic discharge of the splenic nerve and increases the expression of IL-1, IL-2, IL-6, IL-16 and TGF-β1 in splenocytes, an effect that can be abrogated by splenic sympathectomy, thereby linking the CNS to peripheral immune reactivation [Ganta et al 2005]. Anteroventral third ventricle lesions impair the activation of lymphocytes and their homing to the arterial walls and thereby ameliorate Ang II–induced HTN [Marvar et al 2010]. Indeed, lesions in this region appear to prevent any form of experimental HTN [Brody et al 1978]. Chronic ICV infusion of neuropeptides such as substance P and Ang II enhance T cell populations in experimental rodents [Fannon et al 1991].

The circumventricular regions (CVO) lack a blood brain barrier making it susceptible to the influence of circulating hormones and cytokines. The CVO has abundant AT1 receptors and NOX in the subfornical organ that produces ROS to enhance sympathetic outflow. SOD

knockdown induces oxidative stress in the subfornical organ of the hypothalamus and increases vascular infiltration of activated lymphocytes which is associated with worsening HTN [Lob et al 2010]. Administration of a dominant negative Ras-related C3 botulinum toxin substrate 1 (Rac1) has been shown to prevent NOX activation, highlighting the requirement of Rac1-dependent Ang II effects in the brain [Zimmerman et al 2004]. Similarly, Ang II receptor knockout in the subfornical organ of the brain ameliorates HTN in DOCA-salt HTN [Hilzendeger et al 2013]. Suppressing the inflammation of the subfornical organ with minocycline or induction of IL-10 overexpression ameliorates HTN [Lob et al 2013]. ICV infusion of etanercept inhibits brain TNF-α and protects against Ang II–induced HTN in rats by restoring the anti-inflammatory balance and alleviating oxidative stress in the paraventricular nucleus [Venegas-Pont et al 2010, Sriramula et al 2013]. The elevation of circulating inflammatory markers characteristic of HTN [Chae et al 2001, Engstorm et al 2002], may well be relevant for inflammatory processes in the CNS thereby sustaining and further exaggerating the overall systemic inflammation [Wu et al 2012].

The reciprocal impact: Bone marrow-derived inflammatory cells in HTN

The bone marrow (BM) is extensively innervated by the sympathetic nervous system [Katayama et al 2006], which regulates immunomodulation [Scheiermann et al 2013], stem cell niche homeostasis and haematopoiesis [Hanoun et al 2015]. BM from hypertensive subjects is characterised by altered adrenergic signalling with exaggerated sympathetic tone, elevated levels of norepinephrine, loss of circadian rhythmicity and impaired mobilisation of

haematopoietic stem and progenitor cell populations [Katayama et al 2006, Afan et al 1997]. The sympathetic overdrive of HTN shifts the BM equilibrium towards the generation of myeloid progenitor cells which induce peripheral inflammation and migrate to the brain to differentiate into brain macrophage/microglia to induce and sustain neuroinflammation [Sanisteban et al 2016]. Cytokines, chemokines and ROS generated as a consequence of inflammation, further accentuate the sympathetic overdrive centrally as well as in the peripheral organs, thereby further perpetuating hypertension. Impaired autonomic input to the BM has been associated with altered inflammatory responses in SHR [Zubcevic et al 2014]. The extravasation of inflammatory progenitors from the BM into the cardioregulatory centres of the brain results in microglial/macrophage activation to cause and sustain HTN [Santisteban et al 2015]. The inflammatory progenitors from the BM migrate to the brain parenchyma in a CCL2-CCR2 axis dependent manner to exacerbate neuroinflammation [Ataka et al 2013, Lampron et al 2013] and infiltrate critical peripheral organs such as the heart and vasculature, carotid body, spleen, kidneys and gut to induce systemic inflammation [Rodriguez-Iturbe et al 2004, Gonzalez et al 2015]. It is pertinent to note that the CCL2-CCR2 chemokine axis is a crucial player in the migration of T lymphocytes, monocytes and natural killer cells in rheumatoid arthritis and type 2 diabetes [Madrigal & Caso 2014]. Moreover, Ang II directly stimulates CCL2 production in vascular smooth muscle cells [Chen et al 1998], monocytes [Tsou et al 2007] and in hypothalamic neurons [Santisteban et al 2013] via an AT1-receptor mediated pathway [Dai et al 2007, Koh et al 2004, Marketou et al 2011]. However, the resting microglia of the adult brain expresses AT1-receptors only when primed by pro-hypertensive signals [Miyoshi et al 2008].

The Spleen: a neuro-immune hub differentially involved in cardiovascular and metabolic diseases

The spleen contains half of the body's monocyte population and mapping of the genetic, molecular and neurophysiological basis of HTN-induced inflammatory reflexes converge in the spleen [Rosas-Ballina et al 2008, Rosas-Ballina et al 2011]. The spleen acts as a reservoir of pathogenic T cells and activation of adrenergic splenic neurons regulate a T cell subset in the white pulp that eventually migrates to organs regulating blood pressure. Moreover, the pro-HTN signals such as Ang II regulate haematopoietic stem cell proliferation (HSPCs) in the BM and enhance $CCR2^{+}$ HSPCs, myeloid progenitors and inflammatory monocytes in the spleen thereby contributing to HTN [Kim et al 2016]. Hypertensive challenges activate splenic sympathetic discharge to prime the immune response, specifically the vagus-splenic drive mediated by nicotinic cholinergic receptor (α7nAChR) which links the brain and spleen [Rosas-Ballina et al 2008]. The α7nAChR deficiency in Apolipoprotein E knockout mice or splenic parasympathectomy increases the inflammatory profile characterized by elevated leukocyte counts and increased pro-inflammatory cytokine expression within the spleen [Kooijman et al 2015]. The neural circuits that modulate the lymphocytes reveal that the action potential generated in the vagus nerve is transmitted to the celiac ganglion (the origin of the splenic nerve) to inhibit macrophage production of TNF-α and other cytokines [Andersson and Tracey 2012]. Indeed, TNF-α production is not inhibited by vagus nerve stimulation in splenectomised animals during endotoxemia [Huston et al 2006] and intravenous administration of lipopolysaccharide increased efferent activity in the splenic and

splanchnic sympathetic nerves in rats to induce a strong systemic inflammatory response [Martelli et al 2014, Martelli et al 2016] indicating an essential role for the spleen in mediating inflammatory signalling.

Ang II infusion increases the expression of tyrosine hydroxylase, the rate-limiting enzyme of norepinephrine biosynthesis in adrenergic neurons and norepinephrine levels in the spleen. Splenectomy or splenic nerve ablation prevents the recruitment, activation and egression of pathogenic T cells from the spleen and consequent target organ infiltration [Carnevale et al 2016]. Splenic placental growth factor (P1GF)-sirtuin 1 (SIRT1) signalling was found to mediate HTN development in mice. Furthermore, splenic reimplantation from wild type donors restored the hypertensive response to Ang II whereas mice reimplanted with spleen from PlGF-deficient spleen donors continued to be protected against the hypertensive effects of Ang II [Carnevale et al 2014]. Chronic administration of the Ex-527 selective SIRT1 inhibitor and genetic silencing of SIRT1 in PlGF-deficient splenocytes restored the hypertensive response to Ang II [Carnevale et al 2014]. Cumulatively, these data suggest that the spleen is a bidirectional communication hub between the nervous and immune system and neural signals culminate in increased PIGF production and increased norepinephrine release resulting in the release of T cells and its downstream effectors thereby contributing to HTN and tissue damage. Therapeutic strategies targeting the sympathetic innervation of the spleen may be of interest.

The Gastro-intestinal connection

Recent findings suggest that gut related mechanisms may also be of relevance. Indeed, HTN in rodents is accompanied by gut dysbiosis [Santisteban et al 2017, Yang et al 2015, Durgan et al 2016] and a high fiber diet induced changes in the gut microbiota and prevented the development of HTN and heart failure in hypertensive mice [Marques et al 2017]. Furthermore, faecal microbial transplantation from HTN patients to germfree mice resulted in increased BP suggesting that alterations in gut microbiota may precede the onset of HTN [Li et al 2017]. Significant changes in the gut microbiome characterised by decreased butyrate and acetate producing bacterial populations and altered Firmicutes/Bacteroidetes ratio has been linked with high BP. Treatment with minocycline not only reduces the neuroinflammation [Shi et al 2010] but also rectified the gut dysbiosis both in animal and human hypertension and expanded both acetate and butyrate producing bacteria and lowered BP [Yang et al 2015] indicative of its potential in hypertension therapeutics.

Reductions in the lactobacillaceae and prevotellaceae populations were identified in patients with CKD, an important and common consequence of HTN [Vaziri et al 2013]. Interestingly, patients on maintenance haemodialysis have ~100 time's higher enterobacteria and enterococci levels than controls [Hida et al 1996].

Sympathetic overdrive is associated with chronic gut inflammation which in turn enhances gut permeability, dysbiosis and altered microbial metabolites in the systemic circulation. The HSPCs from the BM also migrate to the gut causing local inflammation and immune responses [Santisteban et al 2016]. Intrinsic gut mechanisms regulate the activation of T-helper 17 cells which was found to be elevated in HTN inducing marked gut microbial dysbiosis and an increase in circulating inflammatory cells [Kim et al 2015]. The changes in

gut microbiota in HTN was associated with changes in gut inflammatory status [Santisteban et al 2017]. Germ-free mice were protected from AngII-induced arterial HTN, vascular dysfunction, and HTN-induced end-organ damage. This protection was mediated by inhibition of recruitment and activation of the inflammatory myelomonocytic cells in the vasculature and altered cytokine signalling [Karbach et al 2016]. Short-chain fatty acids (SCFAs) are metabolites of gut microbiota primarily comprised of acetate, propionate and butyrate and have been implicated in host-microbiota immune-inflammatory responses [Maslowski et al 2009, Samuel et al 2008, Xiong et al 2004].

SCFAs directly activate the sympathetic nervous system and are not detectable in the plasma of germ-free mice [Perry et al 2016] indicating that all circulating SCFAs are microbial in origin and any changes in SCFAs indicate an involvement of the gut microbiota. Recent studies analysing different SCFA receptor-null mice such as olfactory receptor 78 (Olfr78) and Gpr41, G-protein–coupled receptor 41(expressed in renal vasculature) suggest a role of SCFAs in BP regulation [Pluznick 2017]. Olfr78-null mice have lowered plasma renin levels and lowered baseline BP consistent with its localisation in the site of renin storage and secretion (renal afferent arteriole) and in vascular smooth muscle cells of large vessels. Gpr41-null animals display altered vascular tone, functionally stiffer vessels and isolated systolic HTN [Natarajan et al 2016]. Surprisingly transplantation of caecal contents from salt-resistant (R) to salt-sensitive (S) Dahl rats resulted in consistent and significant elevation in BP during the remaining lifespan of the recipient rat, and also shortened lifespan. The genome of R rats was resistant to BP alterations when microbiota was transplanted from the S to the R type. These effects were speculated to be mediated by SCFAs as both acetate and

hetanoate were higher in the R to S transfer group [Mell et al 2015]. Population based studies have found that interventions that alter SCFAs production correlate with changes in BP [Khalesi et al 2014] indicative of the potential roles of SCFAs in influencing phenotypic changes to regulate BP.

Yet another microbial metabolite that has drawn significant attention is trimethylamine derived from dietary phosphatidylcholine or l-carnitine, metabolised in the liver following absorption to form trimethylamine N-oxide (TMAO) and excreted by the kidneys [Tang et al 2013, Wang et al 2011]. Accumulation of circulating TMAO results in adverse effects such as macrophage/foam cell activation, platelet hyperresponsiveness, vascular and endothelial cell dysfunction and leads to atherosclerosis, thrombosis and cardiorenal impairment [Wang et al 2011] as well as prolonging the hypertensive effect of AngII [Ufnal et al 2014]. Also, TMAO concentrations in plasma correlated positively with CVD in humans [Koeth et al 2013, Wang et al 2015]. Moreover, plasma TMAO levels (r=0.43) were inversely related to vascular endothelial function as assessed by brachial artery flow-mediated dilation, whereas they were positively correlated with systolic arterial levels (r=0.47; R.A. Gioscia-Ryan and D.R. Seals, unpublished data, 2017). TMAO was found to be high in chronic kidney disease (CKD) patients and directly contributed to progressive renal fibrosis and dysfunction in animal models [Tang et al 2015]. Taken together, these studies indicate that the gut microbiome may have: (1) A different interaction with the immune system in the prehypertensive and hypertensive states compared to the normotensive state; (2) dysbiosis of the gut microbiota increases sympathetic activity and the consequent immune responses are likely to contribute to the chronic systemic inflammation associated with HTN.

Effect of sympatho-inhibitory therapy on immune-mediated inflammation in hypertension.

In addition to its well described effects on cardiovascular control, data from laboratory and clinical studies provide substantial evidence for the role of sympathetic nervous system-mediated immune mechanisms in the pathogenesis of hypertension. Inhibition of sympathetic overdrive in hypertension can be achieved by a number of strategies including weight reduction and exercise, pharmacotherapy, and device-based therapeutic approaches. Disorders such as obesity and metabolic syndrome are associated with increased sympathetic nerve activity and circulating markers of oxidative stress and inflammation which can be markedly improved with exercise and weight loss [Festa et al 2000, Schlaich et al 2015]. Exercise training downregulates TLR signalling, attenuates oxidative stress and sympathetic activation and prevents the increase in weight, arterial pressure and white adipose tissue accumulation in rats fed a high fat diet [Li et al 2014]. Pharmacologic sympathetic inhibition can be achieved by inhibiting sympathetic outflow at the level of the rostral ventral medulla by means of imidazoline I1 agonists such as moxonidine which has been demonstrated to exert anti-inflammatory properties in postmenopausal hypertensive women [Pöyhönen-Alho et al 2008] in addition to its beneficial effects on blood pressure and metabolic parameters [Chazova et al 2006]. Another relevant relationship in the current context is the sympathetic nervous system- induced increase in expression of the sodium glucose co-tranporter-2 (SGLT-2). Interestingly, SGLT-2 inhibition with empagliflozin has been shown to reduce glucotoxcity-induced inflammation and fibrosis in human proximal tubular cells [Matthews et

al 2017, Panchapakesan et al 2013]. Interventional approaches to target sympathetic overactivity include device based therapeutic strategies such as renal denervation and carotid body ablation. Both carotid body deafferentation and renal denervation have been demonstrated to reduce T-cell infiltration in brain tissue and aorta of spontaneously hypertensive rats [Mcbryde et al 2013]. The beneficial effects of catheter-based renal sympathetic denervation applied in patients with resistant hypertension appear at least in part to be mediated by immunomodulation via inhibition of monocyte activation and inflammation [Zaldivia et al 2017].

Overall, these findings suggest that targeting sympathetic overactivity as a therapeutic principal has an impact on the immune system on various levels which may at least in part account for the beneficial cardiovascular and metabolic effects observed with these approaches.

Conclusion

The sympathetic nervous system plays a vital role in both activating and limiting immune-inflammatory responses. This, in turn, encourages thinking that fine-tuning of the immune-inflammatory mechanisms responsible for enhanced sympathetic activity may be useful in the management of hypertension. However, to develop successful therapeutic interventions, an even better understanding and more research focussing on this link is warranted. Another important issue is to determine how modulation of sympathetic nerve activity could be

exploited therapeutically to beneficially influence immune-inflammatory responses. Finally, understanding the immune flow via the brain-BM-spleen-gut axis that perpetuates the immune cascade including immune infiltration and immune-mediated inflammatory damage in the organs regulating blood pressure will be important. New technologies for manipulating the SNS are already being investigated in clinical trials. Investigating the full impact of the new modalities used in the treatment of resistant hypertension such as renal denervation and carotid body ablation on the immune system are likely to yield relevant insights and are currently being explored.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander *et al.*, 2017).

Competing Interests: None

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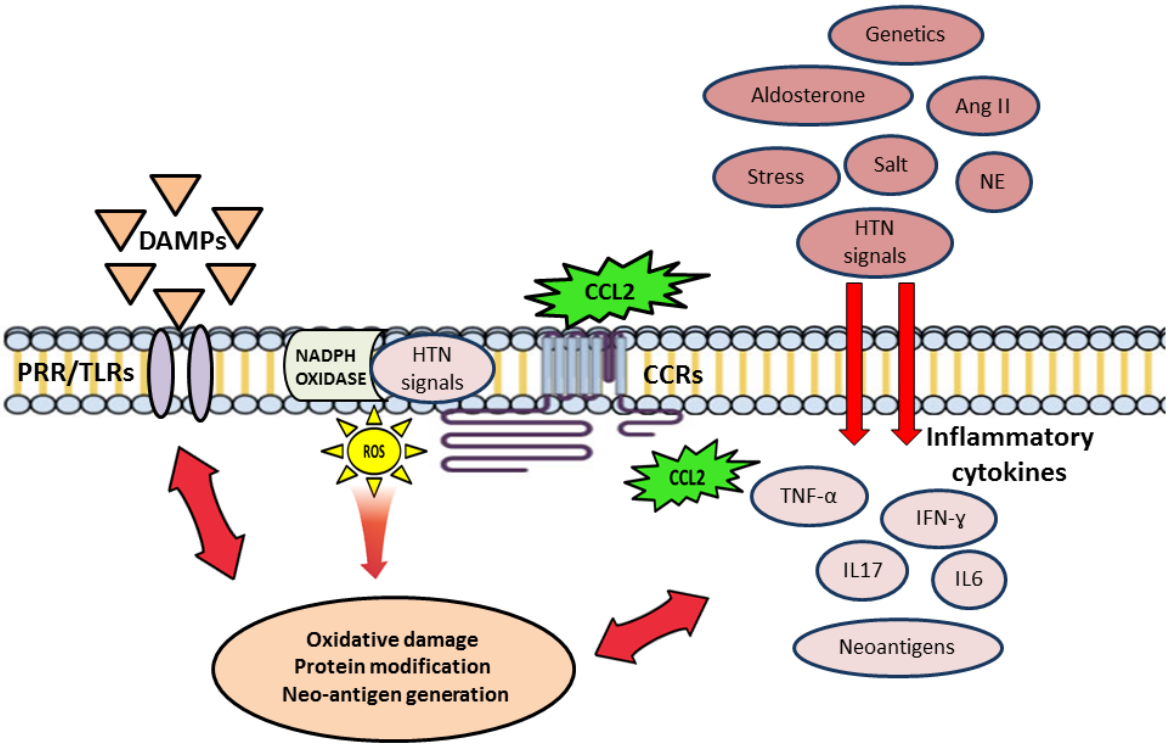
Figure Legends

Figure 1: The 'first hit proinflammatory phase' of prehypertension: Hypertensive signals, damage-associated molecular patterns (DAMPs) and cytokine-dependent reactive oxygen species (ROS) signalling causes protein modification generating new neoantigens such as oxidized low-density lipoprotein, modified receptor proteins, heat shock proteins (HSP) and platelet glycoproteins that elicit an immunological response in the cardiovascular target tissues via the activation of T cells. This phase initiates the inflammatory cascade in organs associated with blood pressure regulation.

Figure 2: The sympathetic – immune cross talk results in established hypertension: The Brain-BM-Spleen-GI axis perpetuates and further exaggerates the immune cascade by causing immune infiltration and immune-mediated inflammatory damage in the organs regulating blood pressure, ultimately resulting in established HTN.



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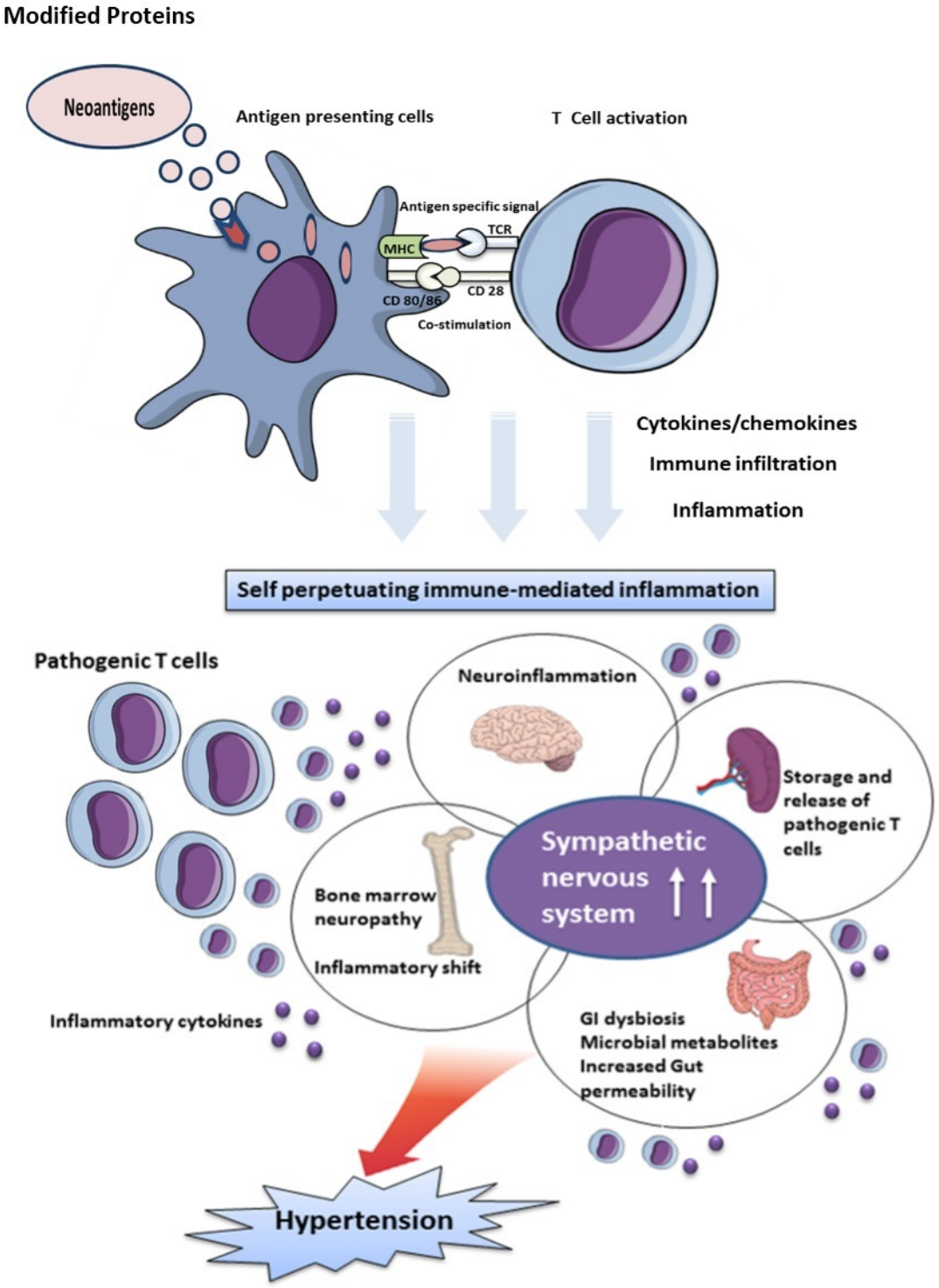

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