Neuroimmune crosstalk in the pathophysiology of hypertension

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Abstract | Hypertension is an important risk factor for cardiovascular morbidity and mortality and for events such as myocardial infarction, stroke, heart failure and chronic kidney disease and is a major determinant of disability-adjusted life-years. Despite the importance of hypertension, the pathogenesis of essential hypertension, which involves the complex interaction of several mechanisms, is still poorly understood. Evidence suggests that interplay between bone marrow, microglia and immune mediators underlies the development of arterial hypertension, in particular through mechanisms involving cytokines and peptides, such as neuropeptide Y, substance P, angiotensin II and angiotensin-(1–7). Chronic psychological stress also seems to have a role in increasing the risk of hypertension, probably through the activation of neuroimmune pathways. In this Review, we summarize the available data on the possible role of neuroimmune crosstalk in the origin and maintenance of arterial hypertension and discuss the implications of this crosstalk for recovery and rehabilitation after cardiac and cerebral injuries.

Hypertension affects millions of patients and is recognized as a major risk factor for cardiovascular events and cardiovascular mortality[1,2]. Hypertension is the result of a complex interaction between environmental factors, genetic influences[3], unhealthy lifestyle and abnormalities in control mechanisms of the cardiovascular system[4]. Consequently, identifying a specific cause for this condition is not possible in many patients, which explains the common use of the terms essential or primary hypertension.

Many mechanisms have been proposed to explain the occurrence of a rise in blood pressure (BP) levels in an individual, such as abnormalities in salt and water handling by the kidneys, in particular via the intrarenal and systemic renin–angiotensin–aldosterone system, and an imbalance of the neural autonomic modulation of the cardiovascular system[5–7]. These mechanisms are not mutually exclusive and might all contribute to the increase in BP in many patients with essential hypertension. Studies in the past 10 years have suggested that endothelial dysfunction and inflammation also contribute to the development of a hypertensive condition[8,9] and that the crosstalk between the autonomic nervous system (ANS) and the immune system might have an important role in hypertension[10–14]. Several studies have shown that angiotensin II (ANGII) increases the immune response and is closely interrelated with the sympathetic nervous system, which also has a pro-inflammatory effect[9,10]. By contrast, the parasympathetic system elicits anti-inflammatory responses[15] and seems to protect against the development of target-organ damage in various models of hypertension with different aetiologies[16].

However, the available data do not allow the respective roles of these mechanisms in the elevation of BP to be determined: the ANS has a fundamental role in collecting and spreading information throughout the body, whereas immune mediators have the dual function of carrying information to the ANS and, conversely, of mediating responses directed from the ANS and from other organs to peripheral cells. In this Review, we summarize the crosstalk between the ANS, the central nervous system (CNS) and the immune system. We also explore the role of microglia, bone marrow, neuropeptides and inflammatory cytokines, and their reciprocal interaction, in the development and modulation of hypertension.

Experimental evidence

Microglia, bone marrow and inflammation

Several studies have shown that bone marrow and microglia are involved in the regulation of BP[17,18]. The bone marrow is a lymphoid tissue that has an important role in managing the crosstalk between the immune system and the peripheral organs in mammalian systems, whereas microglia are cells of mesodermal origin in the CNS, the function of which has often been considered to be that of a local immune system. However, many findings indicate that microglia have the very complex physiological role of maintaining neuronal homeostasis in the CNS and contributing to the interplay between the CNS, bone marrow and peripheral tissues[18,19].

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Key points

- A proposed interplay between the bone marrow, microglia and immune mediators could underlie the development of arterial hypertension.
- Brain microglia activation is a hallmark of neuroinflammation in hypertension; the bone marrow contributes to hypertension by increasing the extravasation of peripheral inflammatory cells into the brain.
- Chronic psychological stress increases the risk of hypertension through a mechanism involving the bone marrow and sympathetic nervous system.
- Cytokines, neuropeptides and peptides including neuropeptide Y, substance P, angiotensin II and angiotensin-(1–7) seem to act as messengers between immunity, the central nervous system and the cardiovascular system to regulate blood pressure homeostasis.
- Genome-wide association studies have identified links between three pairs of genes related to inflammation and diastolic blood pressure and between *BDNF* (encoding a neurotrophic factor implicated in neuropeptide Y modulation) and hypertension.
- Clinical evidence shows that neuroimmune factors are involved in changes in the regulation of the cardiovascular system underlying arterial hypertension.

Evidence supports the existence of a pathway in which sympathetic activation induces the extravasation of haematopoietic stem and progenitor cells (HSPCs) from the bone marrow to the periphery, where the HSPCs can differentiate into endothelial progenitor cells (EPCs) or inflammatory cells, with reparatory and inflammatory functions, respectively[20]. Inflammatory cells can also infiltrate the brain to become bone-marrow-derived microglia and contribute to the development of hypertension, as suggested in several studies[18,21,22]. Chronic infusion of ANGII has been reported, in addition to the expected effects on BP and sympathetic drive, to increase the activation of microglia in the hypothalamic periventricular nucleus, a brain area regulating cardiac homeostasis and BP[23]. Other investigators also reported that microglia activation in autonomic brain regions is a hallmark of neuroinflammation in neurogenic hypertension and that the bone marrow contributes to hypertension by increasing the number of peripheral inflammatory cells and their extravasation into the brain[24]. Of note, spontaneously hypertensive rats (SHRs) that received bone marrow from normotensive Wistar Kyoto (WKY) rats after bone marrow ablation had a decrease in mean arterial BP, inflammation and microglial activation compared with SHRs that received SHR cells, whereas WKY rats that received bone marrow from SHRs had an increase in the same parameters compared with WKY rats that received WKY cells[21]. Moreover, treatment with minocycline, an inhibitor of microglial activation, attenuated hypertension both in the SHRs and in animals chronically treated with ANGII[21].

Several factors, including chronic psychological stress and CNS perturbation, can induce bone-marrow-derived inflammatory cells to cross the blood–brain barrier (BBB) and reach the brain, where they transform into bone-marrow-derived microglia and start inflammatory processes[25,26]. Bone-marrow-derived microglia accumulate in the brain locally, releasing pro-inflammatory cytokines at the site of the injury or of the perturbation (for example, in the paraventricular nucleus during chronic stress, which is interestingly the same area infiltrated by bone-marrow-derived microglia after infusion of ANGII)[25,27–29]. Inflammation in cardioregulatory brain areas might lead to cardiovascular dysregulation and the possible development of hypertension. The mechanism underlying this inflammatory process involves the action of CC-chemokine ligand 2 (CCL2) on its receptor CC-chemokine receptor 2 (CCR2)[30] (TABLE 1). Neurons in the CNS produce CCL2 and create a CCL2 gradient that attracts bone-marrow-derived cells across the BBB[21,31,32], a process followed by the transformation of the cells into activated bone-marrow-derived microglia. Both SHRs and patients with hypertension have an imbalance in the EPC:inflammatory cell ratio of bone-marrow-derived cells compared with healthy individuals; this imbalance is caused by a decrease in the pool of EPCs and an increase in the pool of inflammatory cells[18,33].

ANGII might alter BBB permeability[34]; a study showed that chronic treatment with ANGII increases cerebral microvasculature inflammation via oxidative stress and leads to greater interaction between endothelial and immune cells and higher BBB permeability in mice[35].

Microglia activation in the presympathetic cardioregulatory brain area might precede an increase in both sympathetic drive activation and BP values[18]. Studies have suggested that prohypertensive stimuli activate both microglia and specific neurons, which alters neuronal activity in the hypothalamus and the brainstem. These central neural responses have been reported to be accompanied by an increase in sympathetic drive at the peripheral level[18,22,26,36].

In summary, sympathetic activation might induce the extravasation of inflammatory and progenitor cells from the bone marrow; the cells then reach the brain and differentiate into bone-marrow-derived microglia. At the same time, hypertensive stimuli might activate the resident microglia in the CNS, triggering inflammation that is widely distributed across the CNS. A subsequent increase in cytokine production from both bone-marrow-derived and resident-activated microglia might further increase neuroinflammation and create a vicious cycle (FIG. 1). All these processes seem to be strongly associated with hypertension. Kapoor and colleagues have reported that changes in BP can induce morphological transformations in microglia, which become activated[17,24]. Given that little evidence is available to support the involvement of microglia in the pathophysiology of cardiovascular diseases in humans, this important area of research requires further investigation.

The question of which is the main event triggering the onset of the vicious cycle linking neuroinflammation and prohypertensive mechanisms (FIG. 1), even in the absence of any apparent pathological condition, is relevant in this context. The role of microglia in maintaining such a vicious cycle has been supported by the observations that microglia function as sensors, not only of inflammatory stimuli from the environment but also of synaptic activity[17]. Microglia and neurons are in constant communication, an interaction that depends on the presence on the surface of microglia of receptors for neurotransmitters, including dopamine, substance P, neuropeptide Y (NPY), glutamate and GABA, and of receptors for several peptides, including the type 1 angiotensin II receptor (AT_1),

Table 1 | **Cytokines involved in the regulation of blood pressure**

Cytokine	Receptor	Main function	Role in hypertension	Refs
CCL2	CCR2	Recruitment of monocytes, memory T cells and dendritic cells	Important role in inducing macrophage influx and development of chronic renal damage in a mouse model of hypertension induced by renal artery stenosis	87
CXCL12	CXCR4	Mobilization of stem cells from bone marrow	Hypertensive effect when injected in rats; *CXCL12* polymorphisms have been associated with hypertension	73,89–91
IL-1	IL-1R	Increases the expression of adhesion factors on endothelial cells to enable transmigration of immunocompetent cells	Early initiator of inflammation in hypertension; can act on immune and nonimmune cells (vascular endothelial and smooth muscle cells) to induce inflammation and other prohypertensive effects	73,195
IL-6	Type I cytokine receptor complex	Mediator of the acute phase response and leukocyte development	Promotes angiotensin-II-induced hypertension	75
IL-17	IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE	Pro-inflammatory responses; commonly associated with immune responses	Promotes angiotensin-II-induced hypertension; promotes vascular dysfunction through T cell recruitment and increases blood pressure	70,74
TNF	TNFR1 and TNFR2	Regulation of immune cells	Promotes hypertension; production increased with angiotensin-II-induced hypertension	73,82
IL-10	IL-10R	Inhibition of pro-inflammatory cytokine production, including IFNγ, TNF, IL-1β and IL-6; prevention of dendritic cell maturation	Protective role; decreases oxidative stress and vascular dysfunction induced by angiotensin II and reduces levels of the pro-inflammatory cytokines TNF and IL-6	76,196
MIF	CD74 and CXCR4	Regulation of macrophage function	Protective role; antagonizes angiotensin II at the central level	77–79

CCL2, CC-chemokine ligand 2; CCR2, CC-chemokine receptor 2; CXCL12, CXC-chemokine ligand 12; CXCR4, CXC-chemokine receptor 4; MIF, macrophage migration inhibitory factor; TNF, tumour necrosis factor; TNFR, TNF receptor.

type 2 angiotensin II receptor (AT_2) and Mas receptor[37–41]. After acute hypertension, the number of synapses in neurons in contact with microglia increases in the regions of the brainstem involved in cardiovascular regulation[19]. Conversely, acute hypotension causes microglia to reduce the number of synaptic contacts. Analysis of microglial morphology revealed that BP changes induce an alert state, which suggests an active cooperation between the microglia and cardiovascular neurons in the brainstem to maintain a healthy and receptive state[19].

AT_1, AT_2 and Mas receptors are expressed on the cell surface of the microglia of rodents, monkeys and humans[41,42]. AT_1 and AT_2 receptors have also been identified in the microglia of monkeys and in the substantia nigra compacta of humans[43,44]. In 2017, a study showed that the major components of the renin–angiotensin–aldosterone system are expressed in striatal projection neurons in rats and monkeys[44]. Nevertheless, activated microglial cells showed more intense nuclear labelling for AT_1 and AT_2 receptors compared with cytoplasm[42,45]. The expression of the Mas receptor was detected in microglial cultures prepared from the hypothalamus of normotensive Sprague–Dawley rats[38].

What could happen to this fine-tuned communication in the event of an increased stress load is another relevant question. A study showed that chronic psychological stress stimulated the expression of the pro-inflammatory chemokine CCL2 in the paraventricular nucleus of mice, reduced the expression of CXC-chemokine ligand 12 (CXCL12) — an immune mediator strongly associated with hypertension — in the bone marrow, increased the number of CXC-chemokine receptor 4 (CXCR4)-expressing monocytes in the peripheral circulation and induced the infiltration of bone-marrow-derived microglia into the paraventricular nucleus[25] (FIG. 1; TABLE 1). This finding has an important implication: changes in the psychological state might deeply affect synaptic activity and trigger a neuroinflammatory state, even in the absence of a commonly recognized prohypertensive stimulus acting as a first trigger. The complexity of human behavioural and emotional aspects could be another piece in the puzzle of hypertension. The combination of genetic factors together with environmental and psychophysiological factors could, therefore, be a complex stimulus interacting with the bone marrow–microglia neuroimmune network. These experimental data could explain the common clinical observation that patients in stressful conditions have higher BP and that, sometimes, better BP control is obtained by adding anxiolytic drugs to common antihypertensive drugs.

Immunity, neuropeptides and other peptides

Neuropeptides are small protein-like molecules produced by neurons. Neuropeptides are important mediators in the communication between neurons and seem to connect the neural system to the immune system as well as to other organs[46,47]. The immune system acts via the release of cytokines — small molecules that are involved in cell signalling[48]. Cytokines are the main regulatory mediators of immunity and are the ideal mediators in the communication between the neural and immune systems, given that cytokines can cross the BBB, as can some neuropeptides[49–51]. Several studies have described the role of the neuropeptides NPY and substance P and of several cytokines in modulating cardiovascular processes[52–56], supporting the possible involvement of these molecules in the onset and maintenance of a hypertensive condition. The ubiquitous expression of cytokines, NPY and substance P in peripheral organs and in the blood, together with their capacity to cross the BBB, strongly suggest that these molecules act as messengers

between the CNS, immune cells and the cardiovascular system, thereby contributing to BP homeostasis.

ANGII and angiotensin-(1–7) (ANG-(1–7)) are also involved in the immune response. Activation of the classic renin–angiotensin system (angiotensin-converting enzyme (ACE)–ANGII–AT_1) has been associated with an increase in the release of pro-inflammatory cytokines and chemokines, leading to cell senescence, inflammation and the development of autoimmune dysfunction. Conversely, the ACE2–ANG-(1–7)–Mas receptor axis

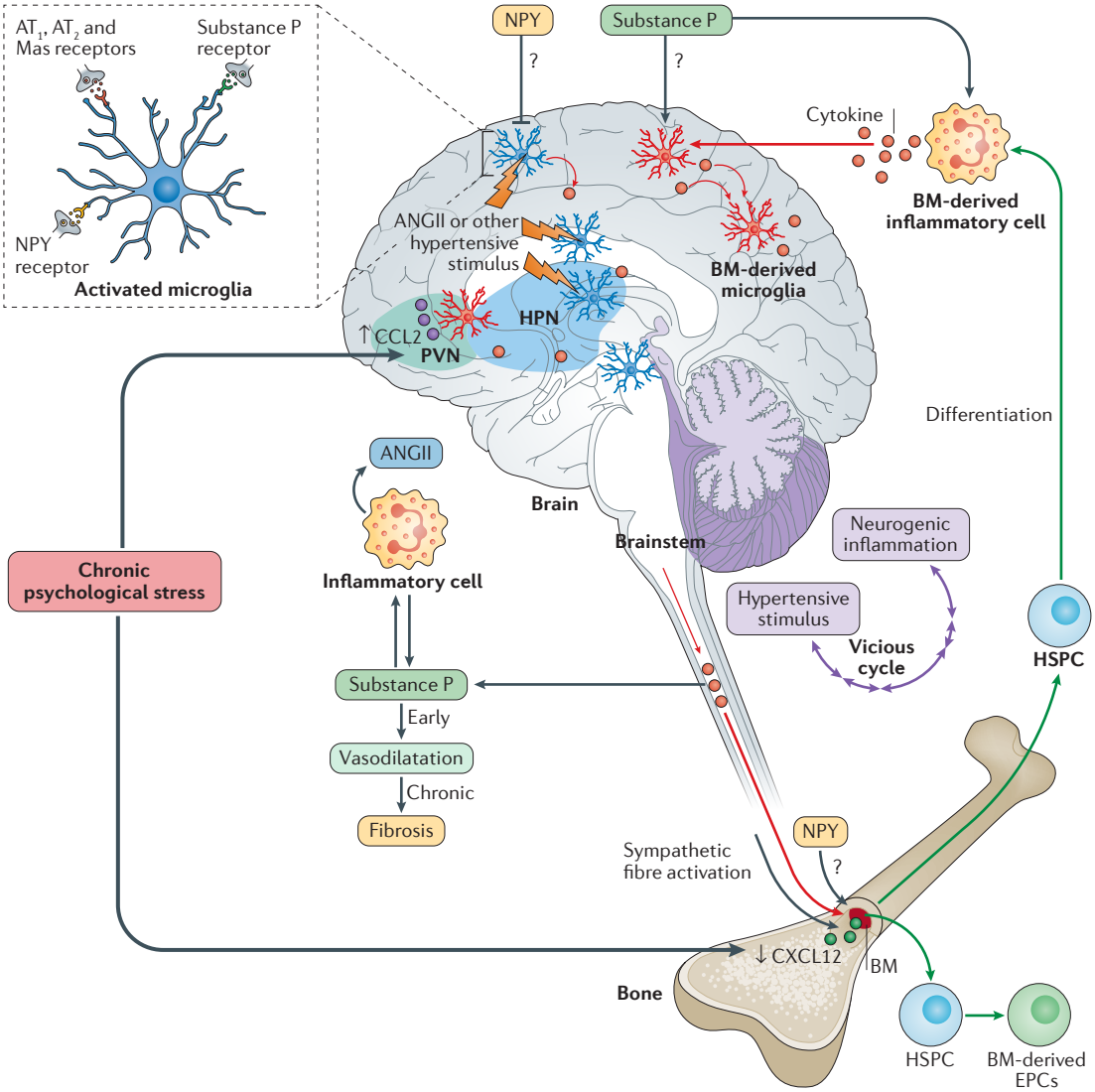

Fig. 1 | **Proposed interaction between the bone marrow, microglia and immune mediators in arterial hypertension.** The figure illustrates the possible vicious cycle linking neuroinflammation and prohypertensive stimuli, such as angiotensin II (ANGII). This schematic is based on a few studies describing a neuroimmune pathway in which sympathetic activation induces extravasation of haematopoietic stem and progenitor cells (HSPCs) from the bone marrow (BM). HSPCs can differentiate into endothelial progenitor cells (EPCs) and inflammatory cells; inflammatory cells can reach the brain and differentiate into BM-derived microglia. A subsequent increase in cytokine production from the activated microglia, both resident and BM-derived, further increases neuroinflammation, which is considered to be a hallmark of neurogenic hypertension. Chronic stress, which stimulates inflammation in the paraventricular nucleus (PVN) in mice and induces the infiltration of BM-derived microglia into the PVN, could promote hypertension by increasing neuroinflammation. Neuropeptide Y (NPY) might modulate blood pressure (BP) by directly inducing vasoconstriction and through its action on the BM and microglia. NPY inhibits cytokine and nitric oxide production from microglia and regulates the extravasation of inflammatory cells into the brain by influencing the EPC:inflammatory cell ratio in the BM. Substance P is released by the terminals of specific sensory nerves, is present in the brain and spinal cord and is secreted by inflammatory cells. In rats, substance P stimulates inflammatory cells to produce ANGII in the heart and causes a BP increase when injected intravenously. Substance P has prohypertensive properties through neuroimmune modulation at peripheral organs. Substance P might also have a direct effect on the central nervous system through possible crosstalk with microglia. Interestingly, on their surface, microglia express type 1 angiotensin II (AT_1) and type 2 angiotensin II (AT_2) receptors and Mas receptors as well as NPY receptors and substance P receptors. CCL2, CC-chemokine ligand 2; CXCL12, CXC-chemokine ligand 12; HPN, hypothalamic paraventricular nucleus.

acts as a counter-regulator of the effects of the classic ANGII-mediated effects[57].

Immune system. The role of the immune system in hypertension is well recognized and has been extensively reviewed[58–62]. For example, Singh and colleagues found that thymus transplantation from neonatal normotensive rats to prehypertensive SHRs delayed the onset of hypertension from 5 weeks to 32 weeks and that transplanted SHRs had reduced BP levels when they reached adult age[10]. We aim to summarize the literature on this topic and focus on data relating to the crosstalk between immunity, the nervous system and hypertension.

When stimulated by the sympathetic nervous system or by ANGII, the spleen and thymus directly contribute to hypertension by increasing cytokine production and by favouring T cell activation. Activated T cells and cytokines reach the blood vessels and the kidneys and contribute to hypertension by inducing vasoconstriction, tissue damage and an increase in sodium and water absorption[63,64]. Carnevale and colleagues showed that the spleen is an essential organ for the development of hypertension and that splenic placental growth factor (PlGF) has an important role in hypertension when activated by sympathetic drive through fibres stemming from the coeliac ganglion. PlGF induces the activation and egression of T cells from the spleen reservoir to blood vessels and the kidneys, where they contribute to hypertension and tissue damage[64]. The same group linked the PlGF–sympathetic connection with the cholinergic anti-inflammatory pathway by showing that mice lacking the α7-nicotinic cholinergic receptor, the main receptor for this pathway, were protected from ANGII-induced hypertension and T cell egression[65]. The investigators also provided evidence of the existence of a specific brain-cell network that produces rhythmical discharges in the splenic nerve through the vagus connection and proposed that the parasympathetic system activates a neural splenic stimulation inducing T cell egression from the spleen under hypertensive challenges, although the parasympathetic modulation of the cardiovascular system has usually been believed to be anti-inflammatory[66]. These data suggest that different pathological conditions, including hypertension and inflammatory diseases such as sepsis, affect the same neuroimmune connections[65].

T cells (BOX 1), dendritic cells and macrophages (BOX 2) and neutrophils seem to have important roles in hypertension[67–69]. Activation of T lymphocytes potentiates hypertension through the induction of reactive oxygen species and cytokines that subsequently affect vascular function and renal sodium handling. Moreover, the pro-inflammatory cytokine IL-17 seems to mediate ANGII-induced hypertension by increasing T cell recruitment[70]. ANGII can activate several immune mediators in a self-sustaining process by which the immune system translates the hypertensive signal into cell and organ damage[67,71,72]. ANGII-dependent hypertension in mice significantly upregulated the transcription levels of the pro-inflammatory mediators tumour necrosis factor (TNF) and IL-1, of the chemokines CCL2 and CXCL12 and of profibrotic factors[73]. These mediators have been associated with hypertension together with IL-6, IL-10, IL-17, macrophage migration inhibitory factor (MIF) (TABLE 1) and Toll-like receptor 4 (TLR4) and TLR9 (REFS[70,74–83]). TLR9 is of particular interest for neuroimmune crosstalk, given that TLR9 is a negative regulator of cardiac vagal tone and baroreflex function[84]. TLR4 was upregulated after ANGII infusion in mice[85]. Interestingly, under hypertensive conditions, TLR4-deficient mice had an increase in BP similar to that observed in control animals, but the consequences of hypertension were blunted[86]. Indeed, cardiac hypertrophy, vascular remodelling and perivascular fibrosis were not observed in TLR4-deficient mice, and the levels of reactive oxygen species and of the pro-inflammatory and profibrotic chemokine CCL2 were similar to those observed in mice without ANGII treatment. This observation demonstrates the critical role of the immune system in translating the biological signals triggered by the rise in BP into pathophysiological effects. Without the activation of the immune system, the complex network involving the nervous system, neuropeptides and bone marrow would probably not cause many of the deleterious consequences associated with hypertension. A 2015 study partially confirmed this hypothesis by showing that in mice that develop hypertension after undergoing renal artery stenosis, those treated with a CCR2 inhibitor had reduced renal atrophy compared with control mice[87].

CXCL12 mediates the homing of progenitor cells in the bone marrow and regulates their mobilization into peripheral tissues upon injury or stress[88]. Several preclinical studies have supported the involvement of CXCL12 in hypertension: injection of CXCL12 increased BP in rats[89], and platelets of hypertensive hamsters produced significantly more CXCL12 than did those of normotensive animals[90]. Polymorphisms in *CXCL12* and *CNNM2*, which encodes a protein with an important role in magnesium homeostasis, were associated with hypertension in a case–control study[91]. In addition, in patients with chronic kidney disease, higher plasma levels of CXCL12 were associated with risk factors for cardiovascular disease and were predictive of incident myocardial infarction and death[92]. In 2018, another study on patients with chronic kidney disease showed a positive correlation between CXCL12 and average 24 h systolic BP, daytime systolic BP and nocturnal systolic BP[93].

CXCL12 is considered to be an important regulator of the sympathetic nervous system and of haemodynamic function in normal and pathological conditions. CXCL12 contributes to neural and humoral activation in heart failure, the main pathological consequence of hypertension. The potential role of brain chemokines in regulating haemodynamic, sympathetic and neuroendocrine mechanisms was investigated in a rat model of ischaemia-induced heart failure[89]. The study showed that CXCL12 was highly expressed in the hypothalamic paraventricular nucleus and subfornical organ and that CXCL12 expression was significantly increased in rats that developed heart failure compared with control animals. In addition, intracerebroventricular injection of CXCL12 induced substantial and long-lasting increases in BP, heart rate and renal sympathetic nerve activity in both experimental groups, but responses were

augmented in rats with heart failure[89]. Another study showed that acute activation of the sympathetic nervous system leads to HSPC egress by reducing CXCL12 expression in the bone marrow via NPY[94]. NPY-null mice stimulated with agents that induce HSPC mobilization had reduced numbers of mobilized HSPCs in the peripheral blood and expressed higher levels of CXCL12 in the bone marrow than wild-type mice[94]. Altogether, these findings suggest that, in response to a hypertensive stimulus, CXCL12 acts as a messenger in the crosstalk between the ANS, bone marrow and microglia.

Neuropeptide Y. NPY is secreted by the brain or sympathetic nerves in response to various stressors and has important roles in a variety of physiological processes, such as appetite, energy storage, anxiety and pain[94,95]. NPY might plausibly also have a role in cardiovascular physiology, given that NPY is the most abundant neuropeptide found in the heart and that it was first identified in intramural sympathetic nerves in close association with myocytes and coronary blood vessels[96]. NPY has been associated with hypertension: findings from transcriptome analysis of kidneys from rat models with programmed hypertension identified *Npy* as one of the differential genes related to the regulation of BP[97]. NPY is a strong vasoconstrictor agent with positive chronotropic and inotropic effects on the guinea pig heart[98–100]. A common genetic variation at the human *NPY* locus increases NPY transcription and secretion, systemic vascular resistance and heritable responses to environmental stress, resulting in elevated resting BP[101]. Over the past 30 years, several studies have shown that NPY is involved in various cardiovascular conditions, such as myocardial infarction, heart failure and cardiac hypertrophy[102–104]. NPY is ubiquitously expressed in cardiovascular, nervous and immune organs and is, therefore, an attractive candidate to study the neuroimmune crosstalk in hypertension[105,106].

Evidence shows that both immune cells and the ANS synthesize NPY and that immune cells can also respond to NPY stimulation through tissue-specific expression of different receptor subtypes, such as NPY receptor type 1 (NPY1R) and type 2 (NPY2R)[107]. In general, NPY1R has anti-inflammatory properties, as described in *Npy1r*-knockout mice, whereas NPY2R stimulates leukocyte migration and adhesion[47,108–111]. NPY1R has a particularly important role in decreasing cytokine release from microglia. An in vitro study showed that NPY inhibits IL-1 and nitric oxide production from

Box 1 | **Role of T cells in hypertension**

Among the immune cells that are likely to be involved in hypertension, T cells seem to have the most important role; however, macrophages, neutrophils and dendritic cells also have an important function[67] (BOX 2).

T cell subsets

- T cells can be separated into two subpopulations, $CD4^+$ T cells and $CD8^+$ T cells, depending on the glycoproteins expressed on the cell surface.
- $CD4^+$ T cells can differentiate into T helper 1 (T_H1), T_H2, T_H17 and regulatory T (T_{reg}) cells in response to antigen and cytokine stimulation.
- T_H1 cells secrete IFNγ, IL-2 and tumour necrosis factor (TNF), which activate macrophages and are responsible for cell-mediated immunity and phagocyte-dependent protective responses.
- T_H2 cells secrete IL-4, IL-5, IL-10 and IL-13, which are responsible for strong antibody production, eosinophil activation and inhibition of several macrophage functions; therefore, T_H2 cells provide phagocyte-independent protective responses.
- T_H17 cells secrete IL-17, a potent pro-inflammatory cytokine that induces the recruitment of leukocytes, especially neutrophils, thereby creating a link between innate and adaptive immunity. T_H17 cells have an important role in the pathogenesis of diverse immune-mediated diseases[185].
- T_{reg} cells suppress T cell proliferation and cytokine production by regulating target T cells and antigen-presenting cells, especially dendritic cells. T_{reg} cells also inhibit macrophage accumulation and the expression of matrix metalloproteinase and pro-inflammatory cytokines, promote anti-inflammatory cytokine production, preserve aortic medial smooth muscle cells, suppress apoptosis and reduce oxidative stress. IL-10 is an important effector cytokine produced by T_{reg} cells.
- $CD8^+$ T cells are cytotoxic cells and important mediators of adaptive immunity against foreign pathogens. $CD8^+$ T cells exert their effects mainly via two mechanisms: cytolytic attack on target cells or secretion of interleukins and cytokines, such as IFNγ, TNF and IL-2, as well as many chemokines that promote recruitment of other cells to sites of infection.

T cells in hypertension

Both $CD4^+$ and $CD8^+$ T cells have been implicated in blood pressure control. In female spontaneously hypertensive rats, $CD8^+$ T cells infiltrate into the kidney, an important organ in blood pressure control[186]. T cell infiltration into the kidney and vasculature promotes hypertension and end-organ damage[187,188]. *Rag1*$^{-/-}$ mice, which lack a recombinase-activating protein essential for the generation of mature T cells, were protected against hypertension, vascular dysfunction and oxidative stress induced by angiotensin II or desoxycorticosterone acetate (DOCA) salt[187]. Similar results were reported in Dahl salt-sensitive rats[188,189]. Experimental studies have shown that activation of T cells potentiates hypertension through the induction of reactive oxygen species and cytokines, which modulate blood pressure through effects on vascular function and renal sodium handling[141].

T_{reg} and T_H17 cells in particular seem to be strongly involved in hypertension and related end-organ damage[83]. *Il17*-deficient mice are protected against hypertension induced by chronic angiotensin II infusion, and patients with hypertension have an increased number of T_H17 cells in the plasma, suggesting that T_H17 cells promote blood pressure elevation[70,190]. DOCA salt increases blood pressure and levels of renal and cardiac IL-17 and T_H17 cells in male Sprague–Dawley rats, and treatment with an IL-17-neutralizing antibody attenuates the increases in blood pressure[83]. Accordingly, patients with diabetes mellitus and hypertension have plasma IL-17 A levels threefold higher than those of individuals without hypertension[70].

By contrast, T_{reg} cells seem to have a protective role against hypertension. Adoptive transfer of exogenous T_{reg} cells or expansion of endogenous T_{reg} cells effectively attenuates the progression of many cardiovascular diseases. T_{reg} cells protect endothelial function, whereas reduced T_{reg} cell numbers contribute to endothelial dysfunction and the development of hypertension[191]. T_{reg} cells can improve microvascular endothelial function in hypertension via IL-10 release, which can attenuate NADPH oxidase activity and ameliorate endothelium-dependent relaxation[191]. Deficiency in T_{reg} cells exaggerates angiotensin-II-induced artery resistance, endothelial dysfunction and remodelling, oxidative stress and inflammation by modulating innate and adaptive immunity[192]. T_{reg} cells use an immunosuppression-independent mechanism to counteract renal and possibly cardiac damage during angiotensin-II-dependent hypertension[193]. T_{reg} cells directly cause apoptosis of tissue-resident neutrophils and constitute a first protective barrier against hypertension-driven tissue fibrosis[193].

Box 2 | **Dendritic cells and macrophages in hypertension**

Dendritic cells

Dendritic cells are bone-marrow-derived cells originating from both myeloid and lymphoid precursors. Dendritic cells present antigens to activate macrophages and T cells to secrete IL-17 and other pro-inflammatory cytokines[67]. Dendritic cells also secrete cytokines to regulate immune responses. Several studies have shown dendritic cell involvement in the pathophysiology of cardiovascular diseases, such as atherosclerosis, hypertension and heart failure, and most notably after heart transplantation[68,194]. Dendritic cell involvement in hypertension is due to increased oxidative stress in the kidney and the vasculature, which leads to the formation of altered proteins and prohypertensive inflammation[68].

Macrophages

Macrophages are specialized cells involved in the detection, phagocytosis and destruction of harmful organisms and apoptotic cells. Macrophages originate from blood monocytes leaving the circulation to differentiate in the tissues. Macrophages can also present antigens to T cells and initiate inflammation by releasing cytokines that activate other cells.

M1 macrophages. A macrophage subset that is induced by Toll-like receptor ligands, such as lipopolysaccharide, IFNγ and granulocyte–macrophage colony-stimulating factor. M1 macrophages express pro-inflammatory cytokines, such as IL-1β, IL-12, IL-18, IL-23 and tumour necrosis factor, and inducible nitric oxide synthase. This cytokine release contributes to driving the antigen-specific inflammatory responses of T_H1 and T_H17 cells.

M2 macrophages. A macrophage subset that is induced by cytokines, such as IL-4, IL-10, IL-13 and transforming growth factor-β, fungal cells, immune complexes, helminth infections, complement components, apoptotic cells and macrophage colony-stimulating factor. M2 macrophages are characterized by their involvement in parasite control, tissue remodelling, immune regulation, tumour promotion and efficient phagocytic activity. M2 macrophage activation leads to the secretion of large amounts of IL-10 and low levels of IL-12.

Microglia. Phagocytic cells of myeloid origin that are involved in the innate immune response in the central nervous system. Microglia are the only true parenchymal macrophages of the central nervous system. Microglia are extremely plastic and have been classified into three different subsets: M0 (resting and/or monitoring stage), M1 (inflammatory neurotoxic phase) and M2 (tissue repair and neuroprotective stage).

lipopolysaccharide-stimulated microglial cells by activating NPY1R on the cell surface[112]. As mentioned above, in neurogenic hypertension, microglial cells are activated and produce several cytokines, which amplifies neuroinflammation; therefore, NPY might inhibit cytokine production from microglia activated by hypertensive stimuli and have a protective role in this particular situation.

Experimental models have indicated that NPY has a role in the bone marrow haematopoietic stem cell microenvironment[94,113,114]. Both SHRs and patients with hypertension have an imbalance in the ratio of bone-marrow-derived cells, caused by a decrease in the pool of EPCs and an increase in the pool of inflammatory cells[18,33]. Interestingly, NPY regulates the trafficking of HSPCs[94,114] and protects fibres of the sympathetic nervous system in the bone marrow in a model of chemotherapy-induced nerve injury[113]. In addition, NPY upregulates the production of CXCL12 — the chemokine responsible for the homing of progenitor cells in the bone marrow — in mesenchymal stem cells[103].

Both activated microglia and bone-marrow-derived inflammatory cells have a role in increasing BP in animal models; therefore, NPY might have a role in modulating hypertension by affecting these cells[97,105–107], although whether NPY antagonizes the extravasation of inflammatory cells into the brain and the occurrence of neurogenic hypertension is not yet clear (FIG. 1).

Kourtesis and colleagues found that NPY expression in the locus coeruleus of SHRs was higher than in normotensive rats and suggested that noradrenaline–NPY co-transmission is increased in specific brain areas in hypertension[115]. Given that the locus coeruleus is related to stress, panic attack and the release of noradrenaline, overproduction of NPY in this brain area in spontaneous hypertension is intriguing. Conversely, in transgenic rats overexpressing NPY, NPY was mainly expressed in the paraventricular, suprachiasmatic and supraoptic nuclei, which are areas related to the release of atrial natriuretic peptide, oxytocin and vasopressin[116]. One might speculate about a possible different location of the sympathetic transmitters noradrenaline and NPY in the brain of patients affected by essential hypertension, although this finding was not reported in the studies.

Finally, in rats, chronic stress doubled plasma levels of NPY, increased BP and macrophage infiltration in the intima and induced carotid artery occlusion, secondary to angioplasty[117]. These effects were prevented by NPY1R inhibition. In summary, considering the involvement of NPY in neuroimmune crosstalk and the important biological effects of NPY on all the systems involved in BP regulation, the precise role of NPY in hypertension should be examined.

Substance P. Substance P, the other neuropeptide involved in cardiovascular processes, is released from the terminals of specific sensory nerves, is present in the brain and spinal cord and has been associated with inflammatory processes and pain[118]. Although substance P has been described as a peptide of neuronal origin, studies in rodents have demonstrated that substance P is also secreted by inflammatory cells, such as macrophages, eosinophils, lymphocytes and dendritic cells, and acts by binding to the substance P receptor (SPR), which is expressed in a variety of cells[119]. The interaction between substance P and SPR induces different responses depending on the tissue expressing SPR. Immunoreactivity for substance P was observed in arterioles in humans. Substance P seems to have no direct effect on heart muscle[118] but acts as a potent vasodilator inducing vasodilatation and hypotensive responses via activation of SPR in large arterial vessels and release of nitric oxide from the endothelium[120,121].

Substance P elicits local vasodilatation and alters vascular permeability, which increases local immune responses, specifically stimulates the chemotaxis of leukocytes and fibroblasts and is involved in the resolution of inflammation and tissue repair[119]. Substance P is also expressed near the coronary vessels. Dehlin and colleagues studied adverse cardiac remodelling associated with hypertension and found that *Tac1*, the gene encoding substance P, was upregulated when BP increased in SHRs; despite an initial vasodilator effect, substance P was associated with inflammation and fibrosis in the long term[56] (FIG. 2). This observation was confirmed by Melendez and colleagues, who demonstrated that substance P acts as a primer on cardiac fibroblasts by upregulating genes that encode extracellular matrix

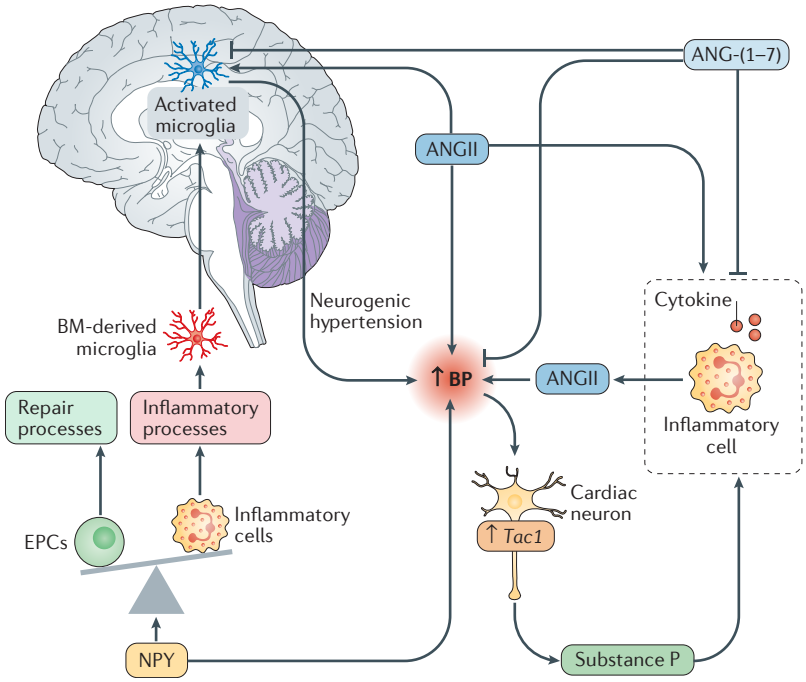

Fig. 2 | **Interactions between ANGII, ANG-(1–7), NPY, substance P and the immune system in hypertension.** Angiotensin II (ANGII), angiotensin-(1–7) (ANG-(1–7)) and neuropeptide Y (NPY) can influence blood pressure (BP) through direct actions or through modulation of inflammation. Studies have shown that ANGII increases the production of pro-inflammatory cytokines and reactive oxygen species and can activate microglia. ANG-(1–7), by contrast, has anti-inflammatory and antihypertensive effects and opposes ANGII-mediated effects. ANG-(1–7) also inhibits microglial cell activation. NPY can either directly induce vasoconstriction or act by modifying the endothelial progenitor cell (EPC):inflammatory cell ratio in the bone marrow (BM), although whether NPY antagonizes or promotes the extravasation of inflammatory cells into the brain and the subsequent occurrence of neurogenic hypertension is not yet clear. *Tac1*, encoding substance P, is upregulated in cardiac neurons in rats as BP increases, resulting in an increase in substance P levels. Substance P induces inflammation and an increase in ANGII production in inflammatory cells, which further increases BP. Despite an initial vasodilator effect, substance P is associated with inflammation and fibrosis in the long term.

proteins[122]. After intravenous injection of substance P, BP and renal nerve firing increased more in SHRs than in normotensive rats, suggesting a selective increase in substance-P-mediated effects on sympathetic ganglia in SHRs[123].

A study showed that substance P modulates hypertensive conditions by directly affecting the immune system. In SHRs, substance P stimulated a mixed population of isolated cardiac inflammatory cells to produce ANGII[124] (FIGS 1,2). In the same animals, surgical sympathectomy significantly attenuated cardiac fibrosis and hypertension and normalized left ventricular mass[124]. These results suggest that these effects are mediated through a reduction in the production of substance P and the normalization of myocardial levels of IFNγ, IL-6 and IL-10.

ANGII and ANG-(1–7). Activation of the pressor arm of the renin–angiotensin–aldosterone system, comprising ANGII and AT_1, might drive pro-inflammatory responses of macrophages during neuroinflammation via regulation of chemokines[125]. ANGII was shown to increase the production of reactive oxygen species and pro-inflammatory cytokines (IL-1β, IL-6 and TNF) while simultaneously decreasing the production of IL-10 (REF.[80]). By contrast, the depressor and protective arms of the renin–angiotensin–aldosterone system, comprising ANG-(1–7) and the Mas receptor, might counteract some of the ANGII–AT_1-mediated effects.

ANG-(1–7) induces vasodilatation, natriuresis and diuresis; increases cardioprotection; inhibits angiogenesis and cell growth; and opposes the pressor, proliferative, profibrotic and prothrombotic actions mediated by ANGII. Centrally, ANG-(1–7) induces changes in mean arterial BP, an effect that might be linked to its inhibitory neuromodulatory action on sympathetic neurotransmission[126,127]. ANG-(1–7) has anti-inflammatory and antifibrotic effects in different acute and chronic inflammatory conditions and several cardiovascular diseases[128–133].

Microglial cells are the target of the anti-inflammatory effect of ANG-(1–7). ANG-(1–7) elicited significant decreases in basal expression levels of mRNAs for the pro-inflammatory cytokines IL-1β and TNF and of the microglia–macrophage marker αM integrin (also known as CD11b) and significant increases in basal levels of mRNA for the anti-inflammatory cytokine IL-10 (REF.[38]). In addition, ANG-(1–7) treatment resulted in a 50% reduction in the number of activated microglial cells induced by the pro-inflammatory Shiga-toxin-2-producing enterohaemorrhagic *Escherichia coli*[134].

In macrophages, the ANG-(1–7)–Mas pathway has beneficial effects on neuroinflammation via modulation of macrophage polarization, migration and T cell activation[125]. Finally, in a model of obstructive sleep apnoea, which is highly relevant to patients with hypertension, ANG-(1–7) had a protective effect in the kidneys that seemed to be mediated, at least in part, by inhibiting the release of pro-inflammatory cytokines and ameliorating oxidative stress and fibrosis[132].

Together, these data clearly demonstrate that the depressor arm of the renin–angiotensin–aldosterone system elicits anti-inflammatory actions, modulates microglia activation and counteracts the pro-inflammatory effect of ANGII[38,126,127,132] (FIG. 2; TABLE 2).

Clinical evidence

Immune system and hypertension

Stress-related hypertension and neuroinflammation. In a review of the literature on the psychosocial risk factors for hypertension, Cuffee and colleagues reported the associations identified between several psychosocial stress factors (including occupational problems, life events or sleeping problems) and BP increase[135]. Higher job insecurity and low annual wages, for example, have been associated with incident hypertension as well as with social isolation and sleep disorders. Of note, a study involving 9,224 individuals showed that assembly line work and long work hours were significantly associated with an increased risk of hypertension; similar results were observed with downsizing and job insecurity in a study of 13,000 individuals. Low wages were associated with hypertension in 17,295 individuals, and higher loneliness scores at baseline were associated with a 3.6 mmHg increase in systolic BP each year in

Table 2 | **Neuropeptides, peptides and immunity in hypertension**

Peptide	Effects	Role in inflammation and hypertension
Neuropeptide Y	• Vasoconstrictor • Positive chronotropic and inotropic actions • Protects fibres of the sympathetic nervous system • Inhibits microglial IL-1 production and the release of nitric oxide • Increases the expression of CXC-chemokine ligand 12 • Regulates the trafficking of bone-marrow-derived cells (endothelial progenitor cells and inflammatory cells)	Modulation of hypertension through action on endothelial progenitor cells and inflammatory cells; the role of neuropeptide Y in the occurrence of neurogenic hypertension is not yet clear
Substance P	• Vasodilator • Decreases blood pressure • Increases the generation of angiotensin II • Increases the expression of genes encoding extracellular matrix proteins	Pro-inflammatory action in the long term
Angiotensin II	• Vasoconstrictor • Increases reactive oxygen species • Increases the expression of tumour necrosis factor, IL-1β and IL-6 • Decreases the expression of IL-10 • Increases blood pressure	Prohypertensive and pro-inflammatory actions
Angiotensin-(1–7)	• Decreases fibrosis and reactive oxygen species • Decreases IL-1β and nuclear factor-κB • Decreases microglial activation • Increases IL-10 • Decreases blood pressure	Antihypertensive and anti-inflammatory action

229 patients, resulting in a 14.4 mmHg greater increase in BP at 4-year follow-up in these individuals than in individuals with a low loneliness score at baseline. Finally, individuals with chronic insomnia had a four-fold increase in incident hypertension compared with normal sleepers who slept ≥6 h, and individuals who reported poor sleep had about double the likelihood of developing hypertension over the 7.5 years of follow-up.

Two studies have identified neuroinflammation as a pathway likely to be involved in the mechanism of action of stress-related hypertension[136,137]. The neurobiology of stress consists of impulses that arise from high cortical centres of the brain and are transmitted to the hypothalamus through the limbic system, the so-called hypothalamic–pituitary–adrenal axis. In this axis, hypothalamic cells, activated by mediators such as noradrenaline, serotonin and acetylcholine, produce corticotropin-releasing hormone, the coordinator of the stress response, which activates a cascade producing adrenocorticotropic hormone. The subsequent production of corticosteroids, glucagon, growth hormone and catecholamine by the sympathetic nervous system complete the biochemical arsenal that can respond to a stress insult. Substance P and the renin–angiotensin–aldosterone system also participate in the stress response[136]. In chronic stress conditions, continuous activation of the hypothalamic–pituitary–adrenal axis triggers an increase in shear stress and cytokine production in blood vessels[137,138], which can impair endothelial function and lead to atherosclerosis and hypertension[137]. Studies that reported clinical evidence of stress-related inflammation described an association between IL-6, TNF and C-reactive protein expression and work-related stress and burn-out, as well as between IL-6 expression and caregiver stress in a 6-year study[138,139]. Interestingly, a positive correlation was found between these cytokines and pulse wave velocity — an index of arterial stiffness — in essential hypertension[140].

Clinical research on biochemical patterns of neuroinflammation associated with hypertension is not as extensive as preclinical research because of the impossibility of performing invasive experimental procedures on humans. Nevertheless, the evidence for an association between inflammation and hypertension has been described in patients by several investigators[141–144]. The identification of neuroimmune patterns as one of the mechanisms of stress-induced hypertension is convincing evidence to support the targeting of neuroinflammation for the screening and management of high BP.

Neuropeptides and hypertension. Neuropeptides have been associated with hypertension in humans. In a small group of patients with hypertension, increased plasma levels of NPY were associated with high BP[145]. In addition, genetic polymorphisms were identified in *NPY*, located on chromosome 7p15.1, in individuals who had an increased sympathetic response after exercise[100]. Faulhaber and colleagues postulated and demonstrated in a small clinical study that substance P contributes to the pathogenesis of human hypertension and has a role in therapeutic mechanisms[146]. The investigators showed that substance-P-like immunoreactivity was significantly lower in patients with essential hypertension than in normotensive individuals and that mental stress could influence substance-P-like immunoreactivity. Of note, whereas the level of substance P increased in the plasma of normotensive individuals under a standardized mental arithmetic test, a decrease from already lower baseline levels could be measured in the plasma levels of substance P in patients with hypertension. In addition, antihypertensive treatment also increased plasma levels of substance P.

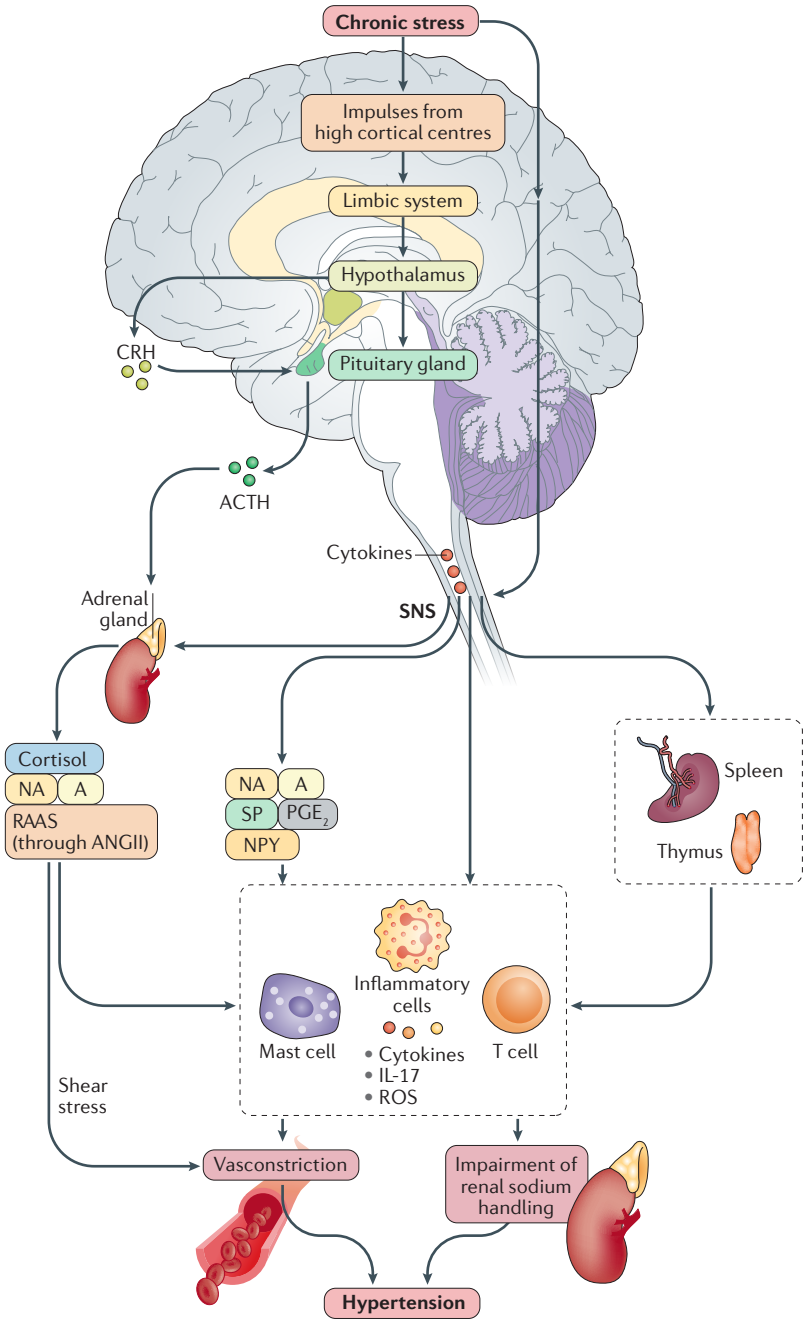

Fig. 3 | **Proposed link between stress-related hypertension and neuroinflammation.** Chronic stress induces impulses that arise from high cortical centres of the brain and are transmitted to the hypothalamus through the limbic system (the hypothalamic–pituitary–adrenal (HPA) axis). In this axis, hypothalamic cells, activated by mediators such as noradrenaline (NA), serotonin and acetylcholine, produce corticotropin-releasing hormone (CRH), the coordinator of the stress response, which activates a cascade leading to the production of adrenocorticotropic hormone (ACTH). In chronic stress conditions, continuous activation of the HPA axis induces shear stress and cytokine production in blood vessels. The subsequent involvement of the adrenal glands, thymus, spleen and neuropeptides triggers inflammatory processes, which lead to hypertension by impairment of renal sodium handling and vasoconstriction. Chronic stress can also induce cytokine production in the sympathetic nervous system (SNS) through direct central activation and, in turn, the SNS can activate systemic inflammatory processes. NA and adrenaline (A) are secreted by both the SNS and the adrenal glands and can cause vasoconstriction by inducing increased shear stress that impairs endothelial function or by influencing immune cells together with substance P (SP), prostaglandin E_2 (PGE_2) and neuropeptide Y (NPY). ANGII, angiotensin II; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species.

The investigators suggested that lower plasma levels and decreased responsiveness to substance P could indicate increased stress sensitivity in primary hypertension[146].

Role of NPY, TNF and microglia in hypertension. In an interesting study, Li and colleagues evaluated plasma levels of NPY and TNF in patients with hypertension, with or without obstructive sleep apnoea[147]. The main finding was that the plasma levels of these factors were higher in hypertension than in a normotensive condition. Moreover, patients with hypertension and obstructive sleep apnoea had the highest levels of both mediators. Despite an intriguing approach, the investigators did not discuss the precise mechanisms of the interaction between NPY and TNF in patients with hypertension and obstructive sleep apnoea; therefore, the nature of the interaction between the two factors in this pathological context remains unresolved.

A small clinical study provided indirect evidence of the involvement of microglia in hypertension. Patients with diabetes mellitus and obesity who presented with hypertension and diabetic retinopathy were treated with minocycline for 10 months together with an appropriate diet to decrease body weight[148]. All patients reported improved visual acuity, important weight loss and decreased BP values. The investigators suggested that, together with the beneficial effect of the weight loss, the mechanisms underlying the remarkable outcomes observed might be due to anti-inflammatory actions of minocycline on the brain. Minocycline is an antibiotic that easily crosses the BBB, is neuroprotective and inhibits microglial activation and brain inflammation[148]. Given the difficulty of investigating neuroinflammation in patients, several investigators consider this study to be a partial confirmation of the role of microglia in hypertension in humans, as previously observed in animal studies[32,148].

In conclusion, although a precise description of the neuroimmune crosstalk involved in human hypertension is still lacking, results from animal studies and clinical evidence suggest several mechanisms of action involved (FIG. 3) and allow us to plan future clinical research.

GWAS data on the immune system in hypertension. Primary hypertension is considered to be a complex polygenic disorder resulting from the interaction between genomic and environmental factors. A positive family history of hypertension is a well-known risk factor for the development of hypertension, and studies have estimated that genetic factors explain 30–50% of interindividual variation in BP[149]. Therefore, in the past decade, several genetic studies have been published to elucidate such a genetic predisposition; genome-wide association studies (GWAS; see the GWAS Catalog) exploring thousands of common single-nucleotide polymorphisms (SNPs) across the entire genome have been conducted. The advantage of such studies is the absence of an a priori hypothesis, which allows the identification of novel targets. Interestingly, some of the SNPs identified in association with hypertension through GWAS are related to immune responses and inflammation. Among these SNPs, rs3184504 in *LNK* is noteworthy[150]. *LNK* encodes

SH2B adaptor protein 3 (SH2B3), a member of the SH2B family of adaptor proteins that functions as a regulator in signalling pathways associated with haematopoiesis, inflammation and cell migration[151]. SH2B3 is expressed mainly in haematopoietic cells and endothelial cells, reduces cell proliferation and cytokine signalling and, therefore, has an anti-inflammatory action[152].

A 2015 study used GWAS data from the Framingham Heart Study to evaluate SNP–SNP interactions for their possible association with BP[153]. The identification of three interactions involving six genes linked to inflammation (*IKBKB–NFKBIA*, *IKBKE–CHUK* and *ADIPOR2–RETN*) showed evidence of an association between inflammation and diastolic BP. Finally, the minor allele of a SNP (rs13333226) in the promoter region of *UMOD* (encoding uromodulin) has been associated with lower risk of hypertension, reduced uromodulin urinary excretion and better renal function[154]. Uromodulin protects the kidney from ischaemic injury by decreasing inflammation and by altering the expression of TLR4 (REF.[155]). In 2017, Warren and colleagues performed a GWAS analysis of systolic, diastolic and pulse pressure in >140,000 individuals of European ancestry and identified additional loci associated with hypertension[156]. Among these loci, the *BDNF* gene, encoding brain-derived neurotrophic factor, is of great interest because of its involvement in the development and survival of the arterial baroreceptor system[157] and in the modulation of BP[158,159] and of NPY expression[160–162]. Furthermore, an Ingenuity Pathway analysis of the genes identified in the Warren study showed enrichment in the α-adrenergic pathway, the CXCL12–CXCR4 signalling pathway and the endothelin system–angiotensin receptor pathway[163].

In conclusion, GWAS support the role of genetic predisposing factors in the genesis of hypertension, including variants for genes involved in renal salt handling, ion transport, corticosteroidogenesis and vascular tone[164]. Genes influencing inflammatory responses and neuromodulation have also been identified, which supports the role of neuroimmune crosstalk in the pathophysiology of hypertension.

Hypertension in immune diseases

The immune system is known to protect self-homeostasis against any potential non-self-modification, such as the attack of infectious agents or neoplastic cells. Two main disorders of the immune system have been identified: autoimmunity with responses against the self and immunodeficiencies characterized by the inability to generate effective responses against the non-self. As mentioned above, evidence from experimental models supports the existence of cellular and soluble neuro-endocrino-immune effectors that interfere with arterial BP regulation. This finding raises the question of whether these pathways are altered in autoimmune or immunodeficiency disorders.

Autoimmune disorders. The most common examples of autoimmune diseases are the systemic autoimmune rheumatic diseases (SARDs). SARDs affect up to 3–5% of the general population. Patients with SARDs are a heterogeneous group, and their common feature is the presence of chronic inflammation sustained by autoimmune responses against different tissues or organs. Rheumatoid arthritis and lupus-like syndromes are the most common SARDs. A large amount of evidence indicates that the prevalence of hypertension is increased in these patients compared with an age-matched and sex-matched population[165]. Autoimmune disorders mainly affect the regulation of arterial BP through immune-mediated endothelial damage. Independently of the nature of the initial disorder, autoimmune responses always involve the production of pro-inflammatory mediators, such as cytokines or chemokines, and frequently lead to activation of the complement system[165]. All these mediators are locally produced at the site of the autoimmune attack but also spread out in the circulation, generating a systemic effect. The endothelium, which expresses cell membrane receptors specific for these different soluble pro-inflammatory mediators, is therefore a preferred target of the autoimmune response[166–168]. An additional mechanism includes the formation of circulating immune complexes that bind to the endothelium or the formation of autoantibodies directed against autoantigens present on the membrane of the endothelial cell.

In all cases, endothelial perturbation is then followed by the appearance of a pro-inflammatory phenotype that can influence the regulation of arterial BP. Direct involvement of the CNS is frequent in SARDs, particularly in systemic lupus erythematous through thrombotic vasculopathy or inflammatory vasculitis. Both mechanisms might lead to an endothelial pro-inflammatory phenotype through the local release of pro-inflammatory cytokines or chemokines targeting neurons and glia. Evidence suggests that brain-resident immune cells, such as microglia, are also sensitive to elevated levels of circulating cytokines that can trigger effector pathways involved in the regulation of BP[169,170]. Autoimmune processes might also cause organ damage that subsequently triggers hypertension. This mechanism can be observed when the kidney is involved, particularly in patients with systemic lupus erythematosus[165]. Moreover, inflammatory cytokines might also impair BP control by modulating the expression and activity of sodium transporters along the nephron, the bioavailability of nitric oxide and the activity of the renin–angiotensin–aldosterone system[171–173]. Consequently, kidney disorders might simultaneously be the cause and the result of hypertension.

Conversely, hypertension can affect the endothelium. Indeed, high BP and increased shear stress might trigger endothelial perturbation, which might promote a pro-inflammatory phenotype and arterial stiffness[165]. The effect on arterial BP of some drugs commonly used to treat SARDs should also be taken into account. Corticosteroids are the most common therapy for SARDs, and their role in hypertension and/or in increased risk of cardiovascular disease is widely accepted and closely correlated with the cumulative dosage[174,175]. Moreover, prolonged use of NSAIDs and the use of cyclosporine and leflunomide have also been associated with an increased risk of hypertension[165].

Immunodeficiencies. The basis of immunodeficiency disorders is a qualitative and/or a quantitative defect in immune responses, with an increased risk of infectious processes, including infections by opportunist agents. Several gene products have been characterized as effectors or mediators of the immune system; whenever the expression or function of one of these products is genetically impaired, a primary immunodeficiency occurs. Primary immunodeficiencies can involve all the types of immune response, from innate to adaptive, cell differentiation and effector function and regulation[176]. The defect of the immune system in primary immunodeficiency does not seem to be associated with the presence of hypertension. However, an increased prevalence of hypertension has been reported in acquired immunodeficiencies such as the HIV-associated immunodeficiency. However, the data remain conflicting[177]. Several studies have demonstrated that, in a population with HIV infection, hypertension correlates with older age, male sex, hypertriglyceridaemia, diabetes, high BMI, low $CD4^+$ T cell count and long-term exposure to anti-retroviral treatment[177]. Increased prevalence of hypertension and increased risk of cardiovascular disease[178] in patients with HIV infection might be caused by chronic immune activation and inflammation[178]: higher levels of inflammatory markers, including C-reactive protein, IL-6 and TNF, have been reported among individuals with HIV infection[179], and all these mediators have an important role in endothelial perturbation. Of note, emerging evidence supports that HIV can enter the brain early in the course of infection and establish a reservoir in resident microglia and astrocytes[180]. HIV in the CNS might also mediate direct damage of neurons via glycoprotein 120 and protein Tat[181]. Together, these mechanisms might lead to the synapsis deregulation responsible for the multiple neurological disorders observed in patients with HIV infection and might also involve cells and pathways associated with BP regulation.

Conclusions

Progress in the field of immunity and inflammation in the past 2 years[182–184] has revealed new perspectives for a deeper understanding of the pathophysiology of arterial hypertension. However, the role of neuroinflammation in the pathogenesis of hypertension is still difficult to explore given the great complexity of the interaction between neural, cardiovascular and immune mechanisms. On the basis of the studies summarized in this Review, decoding the neuroimmune crosstalk in hypertension to better understand and treat the condition remains an enormous challenge that requires further experimental studies and clinical observations.

Although a large number of studies support the existence of an important neuroimmune reciprocal interaction in hypertension, critical knowledge gaps still need to be addressed. Most of the evidence comes from animal studies and from only one small clinical study on the effect of minocycline in patients, which indicated a possible involvement of microglia in BP regulation. Little is known about bone marrow–microglia crosstalk in humans. However, given that GWAS clearly indicate a correlation between neuroimmunity and hypertension, the missing links between genetic expression and biochemical phenotype in patients with hypertension should be investigated.

A comprehensive understanding of the reciprocal role of the immune system and neuropeptides, in particular NPY and substance P, in hypertension is also still lacking. Further studies are needed to investigate in detail the crosstalk between neuropeptides and immune mediators in both experimental and clinical settings with an appropriate methodological approach. First, these studies require multiple observations in the same subject, in both animal and human studies, given that simple measurement of one or a few parameters cannot unravel the complexity of the multiple interactions. Such a study design implies the need for a multidisciplinary approach. Second, both behavioural and emotional aspects should be considered when exploring immune factors in hypertension. In rats and mice, stress is associated with inflammation and hypertension, which is in accordance with the evidence in humans that the psychological background might also have an important role in neuroimmune regulation of BP. Finally, although SHRs and stroke-prone SHRs remain the most useful experimental models to date to study hypertension, the development of 3D tissue models might allow more specific biochemical determination of the link between the neuroimmune system and hypertension.

While waiting for further progress in research, the data summarized in this Review seem nevertheless substantial enough to draw more attention to the association between arterial hypertension, related cardiovascular complications, the occurrence of neuroimmune crosstalk and chronic inflammatory diseases. All these factors should, therefore, be considered when estimating the level of cardiovascular risk in any individual with high BP.

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L.C. researched the data for the article. All the authors discussed its content, wrote the manuscript and reviewed and edited it before submission. G.P. conceived the idea of the paper and coordinated the revisions.

Competing interests
The authors declare no competing interests.

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