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Hypothalamic and inflammatory basis of hypertension

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Abstract

Hypertension is a major health problem with great consequences for public health. Despite its role as the primary cause of significant morbidity and mortality associated with cardiovascular disease, the pathogenesis of essential hypertension remains largely unknown. The central nervous system in general, and the hypothalamus in particular, are intricately involved in the development and maintenance of hypertension. Over the last several decades, the understanding of the brain's role in the development of hypertension has dramatically increased. This brief review is to summarize the neural mechanisms of hypertension with a focus on neuroendocrine and neurotransmitter involvement, highlighting recent findings which suggest that hypothalamic inflammation disrupts key signaling pathways to affect the central control of blood pressure, and therefore suggesting future development of interventional strategies that exploit recent findings pertaining to the hypothalamic control of blood pressure as well as the inflammatory-sympathetic mechanisms involved in hypertension.

Keywords

central nervous system; hypothalamus; hypertension; inflammation

Introduction

Hypertension is characterized by a chronic elevation in arterial pressure and is a major risk factor for many common causes of morbidity and mortality including stroke, myocardial infarction, congestive heart failure, and end-stage renal disease in many segments of the population (1). In the United States alone, high blood pressure affects an estimated 65 million individuals (2, 3) and contributes to the deaths of as many as 360,000 Americans every year. Globally, hypertension is the biggest contributor to disease burden and mortality in the world, accounting for 9.4 million deaths each year (4). Over the next decade, the global prevalence of hypertension is predicted to increase by 60% (5), despite advancements in awareness, antihypertensive therapy, and control of high blood pressure (6). For this reason, preventive strategies for those at risk and methods to both identify the undiagnosed and manage uncontrolled hypertension are urgently needed. Resolving these issues requires

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a deeper understanding of the physiology of blood-pressure regulation, the genetic traits that contribute to hypertensive phenotypes, and the identity of environmental factors that confer risk in susceptible individuals. Pertinently, attempts to study the pathogenic mechanisms of hypertension increasingly point to alterations in central nervous system (CNS) regulation of arterial pressure as a critical modulating factor (7). Many of these functional changes are concentrated in the hypothalamus (8), an area of the brain consisting of several nuclei that acts as the interface between the nervous and endocrine systems. The hypothalamus plays a crucial role in coordinating and integrating the activity of neural networks that control central blood pressure (9, 10). The intent of this brief review is to highlight recent findings that implicate the nervous system and the hypothalamus in particular in the pathogenesis and maintenance of hypertension. Particular emphasis is placed on recent findings that point to hypothalamic inflammation as a potential driver of pathogenic hypertension and therefore likely to inform new translational advances in the field.

Brief overview on pathophysiology of blood pressure regulation

Hypertension is broadly categorized as primary or secondary depending on the underlying pathogenic mechanism (11). Primary or essential hypertension represents the majority of cases, typically arising in middle or old age as a result of the interaction between non-specific genetic and environmental factors. A genetic link is supported by high heritability of blood pressures, elevated sibling recurrence-risk ratio, and higher concordance of blood pressures among monozygotic twins in comparison to dizygotic twins (12). Although rare mendelian hypertensive phenotypes are associated with mutations in a single gene (13–17), the genetic risk seems to be more commonly derived from variations in at least 65 distinct loci affecting blood pressure, each of modest effect size (18–22). Progression from a normotensive to hypertensive phenotype among genetically-predisposed individuals is likely to be influenced by a combination of environmental, behavioral and dietary factors. Common determinants of primary hypertension include aging, obesity, insulin resistance and excessive intake of salt, calories, and alcohol (11). Other potential risk factors that have garnered attention in recent years include sedentary lifestyle, stress, depression, low potassium intake, low calcium intake, intrauterine programming and early life events. In contrast to essential hypertension, secondary hypertension affects far fewer patients, develops at an earlier age, and is linked to an identifiable cause such as renal or endocrine disorder and oral contraceptive use. Notwithstanding the insights into the multi-factorial nature of hypertension, the precise cellular and molecular mechanisms that influence physiology to raise blood pressure remain poorly understood.

Unraveling the etiology of hypertension requires consideration of different systems that contribute to short-term blood pressure control. These include the well-characterized interactions between the vasculature, the kidney, and the central and sympathetic nervous systems (SNS), mediated by various, often shared, receptors and ligands. Mechanisms that maintain normotensive arterial pressure include baroreceptors that sense acute changes in blood vessel pressure and decrease or increase sympathetic nervous system (SNS) activity; activation of the renin-angiotensin system (RAS) due to a fall in renal perfusion pressure; adrenergic receptors (or adrenoceptors) that bind catecholamines and increase heart rate; factors produced by endothelial cells that cause vasodilation (e.g. nitric oxide) or

vasoconstriction (e.g. endothelin); secretion of natriuretic peptides in response to increased pressure; and the kinin-kallikrein system, which influences vascular tone and renal salt handling (Figure 1). Many of these systems function autonomously to locally regulate blood flow (via alterations in cardiac output and blood volume), resistance (via arterial contraction and relaxation) and ultimately blood pressure.

At the same time, the nervous system integrates signals from peripheral organs and helps to coordinate homeostatic responses (23, 24). The contributions of central pathways are perhaps best exemplified in the pathophysiological hallmarks of “neurogenic” essential hypertension. This form of hypertension is due to autonomic nervous system abnormalities originating in the afferent arm (e.g. baroreceptors, chemoreceptors and renal afferents) or in the central circuitry without a primary vascular or renal defect (10). Studies in animals – in which the contribution of causal factors and pathways underlying hypertension can be studied in a more systematic manner – reveal that circumventricular organs (CVOs), the hypothalamus, and the brain stem are critical regulatory regions. Some of the earliest studies in experimental models found that damage to the brain stem or the afferent components of the baroreceptor reflex pathway that terminate within the nucleus tractus solitarius (NTS) produce short-term (25) and long-term elevations in arterial pressure (26–28). Mechanistically, the increased arterial pressure is caused by increased regional vascular resistance (29) as a result of enhanced sympathetic tone (30) that is normally suppressed by inhibitory baroreceptor input. Thus, activation of carotid baroreceptors (31) or chemical stimulation of the NTS with adrenaline, noradrenaline and dopamine (32) decreases arterial pressure and heart rate. These early studies were instrumental in documenting neural mechanisms that could lead to enhanced central sympathetic outflow in hypertension.

Central modulation of blood pressure also involves the RAS. As mentioned above, it is well studied that peripheral RAS activation controls fluid and electrolyte balance when renal blood flow is reduced. However, components of the RAS (i.e. renin, angiotensinogen, angiotensin, angiotensin converting enzyme, angiotensin II, and angiotensin II receptor subtypes) are also found in the brain (33) and compelling evidence suggests the RAS can contribute to hypertension by modulating cardiovascular effects through the CNS (34, 35). In particular, angiotensin II (Ang II) stimulates the organum vasculosum and the subfornical organ, CVOs surrounding the anterior part of the third ventricle (36). Both sites are highly vascularized and lack a blood-brain barrier (BBB) making them responsive to both locally-produced (37) and circulating Ang II (38). Indeed, high levels of circulating Ang II induce the development of hypertension, which is mediated by increased production of reactive oxygen species (ROS) in the subfornical organ (39, 40). Most of the known actions of Ang II are mediated by angiotensin II type 1 (AT_1) receptors. Their activation in hypertension is likely to have an effect on multiple brain structures in the network that controls SNS outflow including the paraventricular nucleus (PVN) in the hypothalamus, the median preoptic nucleus, and the rostral ventrolateral medulla in the brain stem (24, 41–43). Consistent with this point, several studies suggest that oxidative stress in the rostral ventrolateral medulla is a potent factor in the dysregulation of sympathetic outflow that accompanies the spontaneous development of hypertension (44–46). Ang II derived from the brain’s RAS (as opposed to circulating Ang II) is likely to play similar roles in the development of hypertension (47), but the factors that regulate this pathway’s activity remain unknown.

Salt sensitivity is one such factor that is likely to affect this pathway. High salt intake acutely reduces circulating renin-angiotensin activity and aldosterone concentration (48, 49). A third of essential hypertension patients with high-sodium consumption have lower plasma renin activity (50, 51), but are responsive to RAS inhibitors (52). One hypothesis to reconcile this apparent discrepancy is that the brain's RAS response to salt intake may differ from the body's RAS response (50, 53). High sodium intake in rats leads to a sustained increase in renin gene expression in the hypothalamus, despite reduced renal renin expression (54). In line with this evidence, angiotensin-converting enzyme (ACE) and AT_1 expression in the hypothalamus and brain stem are elevated in salt-sensitive hypertension, particularly following activation of sodium channels in the brain (55). Blocking these sodium channels reduces blood pressure and SNS hyperactivity induced by hypertonic saline loading in the brain (56, 57). These results suggest high sodium loading increases brain RAS activity locally, which in turn increases sympathetic outflow to promote hypertension.

Central hypertensive regulation is also tightly coordinated by mineralocorticoid receptor (MR) expression and ligand responsiveness. Upon ligand binding, neuronal MRs enter the nucleus, forming dimers that complex with transcription factors to activate or repress target gene expression that culminates in increased SNS activity (58–60). Importantly, they have similar affinity to physiologic mineralocorticoids (aldosterone) and glucocorticoids (cortisol and corticosterone). However, aldosterone-targeted cells express both the MR and localized 11-β-hydroxysteroid dehydrogenase 2 (11βHSD2), an enzyme which converts cortisol and corticosterone into inactive metabolites; this increases relative aldosterone concentrations in close proximity to MRs (61). 11βHSD2 utilizes NAD^+ as a cofactor, producing NADH and depleting MR-proximal concentrations of NAD^+ (62). In the brain, 11βHSD2 is expressed at low levels apart from aldosterone-target neurons in the BBB-deficient zone of the NTS that influences sodium appetite (62–64). With sodium intake, these neurons quiesce resulting in decreased sodium appetite (64). However, NADH generated from 11βHSD2 activity limits the transcriptional activity of glucocorticoid-bound MRs. In the absence of 11βHSD2, increased NAD^+ is thought to change the conformation of glucocorticoid-bound MR allowing it to have similar transcriptional activity to aldosterone-bound MR (62). Oxidative stress mimics this NADH-depleted state by redox imbalance, impairing normal MR function and activating glucocorticoid-bound MRs (65). Additionally, plasma levels of glucocorticoids are 1000 fold (total) or 100 fold (free) higher than that of aldosterone, and brain levels of these hormones have been shown to be similar (61, 62). Thus, neuronal MRs are bound and activated by basal glucocorticoids in normal physiological conditions.

MRs also work in congruence with AT_1 receptors in the brain to drive SNS activity and subsequent hypertensive drive in the presence of excess mineralocorticoid (66). Both MR and the AT_1 receptor in the subfornical organ increase Ang II-induced ROS production in the PVN and rostral ventrolateral medulla (67). Ang II activates NADPH oxidase to drive ROS production (68, 69), potentiating SNS hyperactivity (70). ACE mRNA and AT_1 receptor mRNA are upregulated by aldosterone in hypothalamic tissue, further increasing Ang II production and subsequent ROS formation to drive hypertension (71).

Interestingly, the glucocorticoid receptor (GR) has only 1/10 the affinity to glucocorticoids that the MR does. Despite their widespread expression in the brain, GRs are thought to only

be occupied with ligand during stress or the zenith of the circadian cycle for this reason (62, 72). The highest concentration of MRs is localized to the hippocampus, and activated GRs help to regulate the MR-mediated non-genomic stress response (73, 74) as well as hippocampal explicit memory formation (75). Imbalance between MR and GR function and expression contributes simultaneously to psychopathological disorders such as anxiety and PTSD and loss of cognitive function by dysregulating the hypothalamic-pituitary-adrenal axis (HPA axis) (75, 76). Increased GR increases HPA axis activity, while decreased GR decreases HPA axis activity. Due to the diurnal levels of glucocorticoids, the MR regulates HPA axis activity basally, and the GR during stressed conditions (77). In the hippocampus, MR and GR signal to inhibit or stimulate respectively secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) from the PVN of the hypothalamus (78). Taken together, these studies demonstrate the complexity of action and signaling of glucocorticoids, mineralocorticoids, and their respective receptors in the nervous system.

Hypothalamic mechanisms of hypertension

Regulation of vasopressin secretion in hypertension

Accumulating evidence implicates increased AVP signaling in the pathogenesis of hypertension. AVP is produced by magnocellular neurons in the PVN and supraoptic nucleus (SON) of the hypothalamus and stimulates water reabsorption in the kidney to help maintain blood pressure. The concentration of circulating AVP is normally too low to have a measureable effect on blood pressure, but the AVP neuronal activity is dysregulated (79) fairly early in the development of hypertension (80). This effect on AVP neurons may be attributable, at least in part, to reduced inhibitory GABAergic input from baroreceptors in response to high salt intake (81). More recent findings suggest that such impairments in inhibitory signaling are mediated by brain-derived neurotrophic factor leading to increased excitability of hypothalamic AVP-secreting neurons. This in turn drives excess AVP release, which elevates arterial pressure (82, 83). Indeed, increased AVP expression is critical in the maintenance of hypertension in several experimental models involving RAS hyperactivity (79, 84–86). Although the precise mechanisms by which excess AVP secretion drives high blood pressure remain an ongoing topic of discussion, several pathways may be implicated including sympathoexcitation via V_{1a} receptors in the PVN (87), brain RAS hyperactivity via V_2 receptors (88), and peripheral vasoconstriction via V_1 receptors (Figure 2) (82).

Hypertensive effect of steroid hormones in hypothalamus

Although the mechanisms underlying the centrally-mediated hypertensive responses to aldosterone have been well studied (89), the central effects of glucocorticoids are less understood. For example, intracerebroventricular injection of hydrocortisol increases SNS activity and induces hypertensive responses that are reversible with pretreatment using an Ang II antagonist or ACE inhibitor (90). As discussed previously, under normal conditions, cortisol can be converted to inactive metabolites by 11βHSD2 before acting on MRs (50, 91). While MRs are expressed in the hypothalamus, 11βHSD2 is barely detectable (92, 93), suggesting that circulating cortisol can act on the hypothalamus directly through the third ventricle, to increase sympathetic activity and blood pressure. Recent findings suggest that MR stimulation by cortisol may also modulate RAS activity downstream (91, 94). Thus,

hypothalamic MRs sit at a delicate interface between glucocorticoid and mineralocorticoid stimulation.

Leptin-induced SNS activity in hypertension

Leptin is a hormone produced by adipose cells that helps to regulate energy balance by inhibiting hunger. Leptin levels are increased in obese humans (95) and have been shown to drive hypertension in rats (96). In addition, peripheral administration of an anti-leptin antibody decreases blood pressure and SNS activity in obese mice fed with a high fat diet (97). Although the leptin receptor (LepR) is expressed in multiple sites in the brain, leptin's effects on SNS activity prominently involve the ventromedial hypothalamus, arcuate nucleus (ARC), and dorsomedial areas in the hypothalamus (97, 98). LepR deletion in the ARC attenuates leptin-induced increases in renal sympathetic discharge and resolves increased arterial pressure in diet-induced obese mice (99). In fact, ablation of LepR specifically in proopiomelanocortin (POMC) neurons, a major type of neuron in the ARC, can effectively reduce blood pressure (100). Recent evidence suggests that leptin-evoked increases in SNS activity are mediated by intracellular AMP-activated protein kinase (101) and mammalian target of rapamycin (mTORC1) signaling pathways (102), thus offering potential therapeutic targets to treat obesity-associated hypertension in the future.

Melanocortin receptor 4 (MC_4) signaling in hypertension

MC_4 is a member of the G-protein coupled receptor family and is activated by alpha-melanocyte-stimulating hormone (α-MSH). POMC neurons in the ARC send projections to the PVN and lateral hypothalamus where they release α-MSH. Thus, MC_4 expression in POMC neurons is a critical component in the melanocortin system's actions on feeding behavior, regulation of metabolism, SNS activation, and blood pressure homeostasis (103). Microinjection of a MC_4 agonist into the PVN increases renal SNS activity and blood pressure in rats (104), while pharmacological blockade of MC_4 in the PVN attenuates lumbar sympathetic nerve activity due to hyperinsulinemia (105). Intracerebroventricular injection of an MC_4 antagonist markedly reduces blood pressure in spontaneously hypertensive rats in an SNS-dependent manner, irrespective of body weight fluctuations (106). Renal SNS activity due to central leptin and insulin administration on can be attenuated and abolished in heterozygous and homozygous MC_4 knockout mice, respectively (107). Taken together, MC_4 in POMC neurons plays a key role in several forms of hypertension.

Hypertension caused by circadian rhythm in the hypothalamus

It is well-known that cardiovascular functions, including blood pressure, show diurnal oscillation. Incidences of life-threatening cardiovascular events, such as stroke and acute myocardial infraction, also display a diurnal pattern, with increased incidence during the morning (108). The suprachiasmatic nucleus of the hypothalamus is the "central clock" that regulates physiological functions through the autonomic nervous system and humoral mediators. Clock genes are expressed in a circadian manner in the SCN; circadian variations associated with blood pressure are related to modifications in clock gene-regulated endogenous sleep-wake rhythms (109). Indeed, acute changes in blood pressure brought on by morning or sleep surge can modify cardiovascular risk (110). The underlying mechanism

is hypothesized to involve multiple components including increased circulating blood volume due to salt sensitivity, excessive salt intake, autonomic nervous dysfunction, abnormal clock genes, and/or altered secretion of melatonin (109). The generation and maintenance of circadian rhythms involves two flavoproteins: cryptochrome-1 (Cry1) and cryptochrome-2 (Cry2) (111). Cry1 and Cry2-deficient mice are prone to salt sensitive hypertension due to increased activity of the adrenocortical aldosterone-producing enzyme, 3 beta-hydroxyl-steroid dehydrogenase (111). Recent studies also suggest that melatonin has multiple beneficial effects on the cardiovascular system; melatonin administration at bedtime reduces blood pressure in hypertensive patients (112). Thus, it is possible that alterations in circadian rhythm may affect melatonin levels resulting in autonomic nervous dysfunction, increased aldosterone, and subsequent hypertension.

Hypothalamic inflammatory mechanisms of hypertension

As detailed above, the hypothalamus acts as the central regulator of energy homeostasis – it senses metabolic cues and in turn modulates neurohormonal and neurotransmitter systems via endocrine signaling, inflammatory signaling, and neuronal plasticity (113–115). POMC and neuropeptide Y/agouti-related peptide (AGRP) neurons are the two major cell types in the mediobasal hypothalamus that play a vital role in energy balance. They reciprocally regulate energy homeostasis via anorexigenic and orexigenic effects, respectively. In addition, both POMC and AGRP neurons are regulated by leptin in opposite manners to affect energy homeostasis via negative and positive energy balance (116–119). Mounting evidence from experimental and clinical studies unequivocally has shown overnutrition is an important environmental factor capable of promoting neuroinflammation (120, 121). Obesity-associated hypertension is associated with the activation of pro-inflammatory signaling pathways (122) that promote the development of metabolic syndromes in several tissues (123–127). Metabolic inflammation chronically and negatively impacts neuronal regulatory functions including leptin and insulin signaling. This results in altered regulations, including central leptin and insulin resistance, that can drive increased blood pressure and energy imbalance (97, 128). Over activity of the hypothalamic IKKβ/NF-κB pathway has been recently shown to be as a critical modulator of hypothalamic inflammation (Figure 3). In particular, IKKβ/NF-κB driven hypothalamic inflammation induces blood pressure imbalance and insulin resistance in an obesity-independent manner (129–133). This inflammation seems to originate from the network of neurons, astrocytes and microglia, representing a new perspective on central inflammatory metabolic disorders (134, 135). The following describes the hypothalamic mechanisms of hypertension from a few bases that have been consistently connected with hypothalamic inflammation.

Hypothalamic cytokines in hypertension

Cytokines orchestrate all phases of the immune response and function in highly complex networks to maintain homeostasis. A dynamic balance between pro and anti-inflammatory cytokines is required, and this contributes to changes in CNS physiology that promote hypertension. Circulating pro-inflammatory cytokines can pass through leaky blood vessels in CVOs or in areas where the BBB is disrupted. Alternatively, neuroactive cytokines including tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) can increase the

activity of cyclooxygenase-2 in perivascular macrophages to generate prostaglandin E_2. This chain of events results in increased discharge from PVN neurons, which regulate adrenocorticotropic hormone release, sympathetic outflow, and ultimately blood pressure elevation (136–138). Increased expression of pro-inflammatory cytokines in the hypothalamus is also associated with hypertension, including RAS-mediated blood pressure increases in rats (139). Bilateral NF-κB inhibition within the PVN attenuates Ang II-induced hypertensive response by reducing pro-inflammatory cytokines and ROS (140). Central administration of the ROS scavenger tempol attenuates Ang II-induced hypertension by decreasing the expression of pro-inflammatory cytokines in PVN (141). These findings highlight how pro-inflammatory signal transduction involving ROS drives central RAS-mediated hypertension.

Several pathways have been implicated in this response. Inhibiting the P44/42 mitogen-activated protein kinase (MAPK) signaling pathway in the PVN lessens Ang II-induced hypertension by reducing SNS activity (142). However, the expression of pro-inflammatory cytokines in this study failed to decrease after disruption of PVN P44/42 MAPK signaling, suggesting an alternative source for these cytokines. Possible cytokine-secreting cell types that contribute to the development of hypertension include glia and neurons (143–145). Supporting this, overexpression of anti-inflammatory IL-10 reduces both activated microglia and blood pressure in rats (146). Interestingly, Ang II can directly pass through the BBB to affect neuronal circuits (147, 148), or alternatively, increase BBB permeability, further contributing to baroreceptor reflex dysfunction and hypertension (149). IL-1β and TNF-α can also increase BBB permeability via disruption of tight junctions (150, 151). This finding is particularly intriguing considering that prorenin can increase the expression of TNF-α and IL-1β in the NTS via the NF-κB complex (152). TNF-α stimulation of the NF-κB pathway in POMC neurons leads to increased blood pressure by increasing SNS outflow (131, 132). Taken together, Ang-II and prorenin increase the expression of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) and decrease the expression of anti-inflammatory cytokines in the hypothalamus. Subsequent activation of NF-κB signaling augments the pro-inflammatory response and increases permeability of BBB in the Ang-II-induced hypertension. This results in further inflammation and SNS activity further increasing blood pressure.

Hypothalamic endoplasmic reticulum (ER) stress in hypertension

The ER is a cellular organelle that regulates protein synthesis and secretion. The unfolded protein response (UPR) is an intracellular stress response to a buildup of newly synthesized, unfolded proteins in the ER. Several inflammatory signaling systems, including JAK-AP1 and NF-κB pathways, interact with the three prototypical branches of the UPR that regulate metabolism and SNS activity (153–158). Overnutrition-related ER stress in the hypothalamus activates NF-κB and is sufficient to cause insulin and leptin resistance, which increases SNS outflow and hypertension (131, 132). Similarly, reduced ER capacity in the hypothalamus of mice on a high-fat diet results in severe leptin resistance and leads to increased obesity (159). Intracerebroventricular injection of the ER stress inducer thapsigargin induces systemic insulin resistance and hypertension (132), while blocking ER stress induces leptin sensitization (159) and reduces obesity-related hypertension (132). In line with these findings, acute induction of hypertension by hypothalamus ER stress can also

be abrogated by NF-κB inhibition (132). In summary, brain ER stress is likely involved in some form of hypothalamic inflammation and certain aspects of neurogenic hypertension involving increased SNS activity.

Hypothalamic oxidative stress in hypertension

As mentioned above, ROS help to drive hypertension both locally and systemically. Mitochondrial oxidative stress is frequent in overnutrition conditions and high levels of ROS in the PVN can modulate SNS activity as well as hypertension (160). Chronic Ang II infusion into the PVN leads to membrane mobilization of $p47^{phox}$, a cytoplasmic NADPH oxidase subunit required to initiate ROS production (161). ROS reduce nitric oxide signal transduction in the PVN and increase glutamatergic signaling, which can contribute to neural dysfunction. However, enhanced nitric oxide signaling reduces blood pressure, decreases SNS activity, and shows anti-hypertensive effect via adrenomedullin receptors (162). Anti-oxidative treatments, such as overexpression of superoxide dismutase 1 (SOD1), or bilateral infusion of the radical scavenger tempol into the PVN inhibit ROS-driven SNS activation and hypertension (163). Regarding the mechanisms involved, inflammation is likely involved in the mitochondrial dysfunction (164). Mitochondrial dysfunction itself can also directly lead to the overexpression of pro-inflammatory cytokines, resulting in a feedforward loop characterized by increasing neuronal dysfunction. Notably, NF-κB inhibition in the PVN also abrogates the ROS production, which reduces inflammation in the hypothalamus and attenuates Ang II-dependent hypertension (140).

Hypothalamic pro-inflammatory IKKβ/NF-κB signaling in hypertension

Hypothalamic inflammation is frequently observed in overnutrition or obesity and is associated with IKKβ/NF-κB signaling pathway activation in the brain (131). Besides various cytokines and various intracellular stress responses that lead to activation of hypothalamic NF-κB, it can also be activated by excess leptin (165). Thus, while leptin's anorexic effects are blunted in obese mice (166), the resultant chronic elevation of leptin levels may contribute to activating the NF-κB pathway in the hypothalamus. Activation of the NF-κB complex is a critical modulator for the expression of the suppressor of cytokine signaling 3 (SOCS3), which plays an important role in the development of leptin and insulin resistance in feeding dysregulation (167), as indeed SOCS3 deficiency in the hypothalamus causes elevated leptin sensitivity and resistance to diet-induced obesity (168–170). Activation of IKKβ/NF-κB pathway is also responsible for the upregulation of protein tyrosine phosphatase 1B (PTP1B), which further inhibits leptin and insulin signaling in a manner similar to SOCS3 (170). Therefore, there appears to be a vicious cycle consisting of inflammation, leptin resistance and pathological increase in leptin release. Of interest, while leptin resistance caused by hypothalamic IKKβ/NF-κB activation leads to impaired function in controlling appetite, the action of leptin in elevating blood pressure is abnormally augmented under this inflammatory condition of obesity. The underling divergence remains puzzling, but possibly involves different downstream molecular events and neural circuitries in the hypothalamus and brain.

Control of hypertension via targeting inflammatory-sympathetic mechanism

As hypothalamic and neuroinflammation related hypertension continues to attract more attention by researchers, treatments targeting central mechanisms of hypertension may be promising in the near future. The animal studies discussed above support the potential for novel pharmacological therapies and lifestyle modifications. Given that high sodium-mediated activation of RAS leads to expression of pro-inflammatory cytokines (55, 56), one promising option includes local inhibition of epithelial sodium channels in the CNS to prevent hypertension (171). Inhibition of RAS by renin inhibitors, ACEIs, angiotensin receptor blockers or MR blockers already shows benefit in clinical practice and treatment with such drugs can prevent future cardiovascular complications (171). Animal studies indicate that systematic administration of an angiotensin receptor blocker has anti-hypertensive effects that also prevent the SNS hyperactivity (172). Additionally, a leptin antagonist was recently shown to reduce blood pressure independent of body weight changes (97). ROS scavengers and immunosuppressive agents can also reduce blood pressure and have shown promise in both experimental models and humans (173, 174). Finally, epigallocatechin-3-O-gallate is a polyphenol present in green tea that is currently being tested for its antioxidant and anti-inflammatory properties. It has been shown to prevent hypertension and sympathetic outflow (175).

Conclusion

Over the last several decades, the understanding of the brain's role in the development of hypertension has dramatically increased. Current understanding postulates that neurogenic hypertension involves dysregulation of different neural cell types and signaling pathways. As outlined in this review, hypothalamic inflammation is one such signaling pathway that can result in cellular dysfunction that is detrimental to blood pressure homeostasis. Future studies should be aimed at delineating hypothalamic inflammatory pathways and their cross talk as it pertains to neurogenic hypertension. Further recognition of the underlying mechanisms of hypertension will help generate more therapeutic targets for further treatment of human hypertension.

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Acronyms

11βHSD2	11beta-hydroxy steroid dehydrogenase 2
α-MSH	Alpha-melanocyte-stimulating hormone
ACE	Angiotensin converting enzyme
ACEI	Angiotensin-converting enzyme inhibitor

AGRP	Agouti-related peptide
Ang II	Angiotensin II
AP-1	Activator protein-1
ARC	Arcuate nucleus
AT1	Angiotensin II type 1
AVP	Arginine vasopressin
BBB	Blood-brain barrier
CNS	Central nervous system
CVO	Circumventricular organ
ER	Endoplasmic reticulum
GABA	Gamma-amino butyric acid
GR	Glucocorticoid receptor
HPA	Hypothalamic-pituitary-adrenal
IKKβ	Inhibitor of nuclear factor-kappa B kinase subunit beta
IL-1β	Interleukin-1β
IL-10	Interleukin-10
JAK	Janus kinase
MC4	Melanocortin receptor 4
MR	Mineralocorticoid receptor
NF-κB	Nuclear factor-kappa B
NTS	Nucleus tractus solitarius (solitary nucleus)
PVN	Paraventricular nucleus
PTSD	Posttraumatic stress disorder
POMC	Proopiomelanocortin
PTP1B	Protein tyrosine phosphatase 1B
RAS	Renin-angiotensin-system
ROS	Reactive oxygen species
SCN	Suprachiasmatic nucleus
SOCS3	Suppressor of cytokine signaling 3

SON	Supraoptic nucleus
SNS	Sympathetic nervous system
TNF-α	Tumor necrosis factor-alpha
UPR	Unfolded protein response

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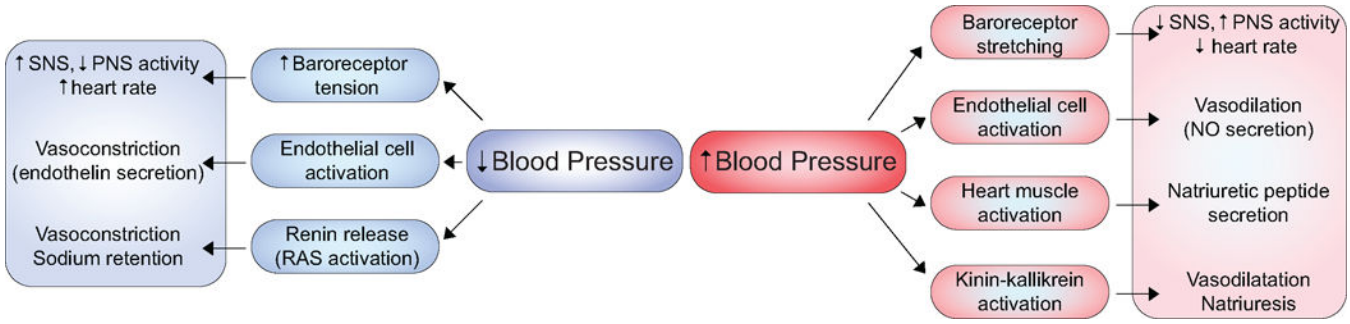

Figure 1. Systemic responses to blood pressure change

The body responds to changes in blood pressure by activating multiple homeostatic mechanisms. In response to decreased blood pressure, baroreceptors immediately sense decreased tension and signal for increased SNS outflow and decreased PNS outflow, effectively increasing heart rate. Concurrently, endothelial cells secrete endothelin, which constricts blood vessels. Renin released from juxtaglomerular cells of the kidney activates the RAS. In response to increased blood pressure, baroreceptors detect stretching and signal increased PNS outflow and decreased SNS outflow, effectively decreasing heart rate. Endothelial cells secrete nitric oxide, which dilates blood vessels. Cardiac muscle secretes natriuretic peptides in conjunction with activation of the kinin-kallikrein system to promote natriuresis and vasodilatory effects.

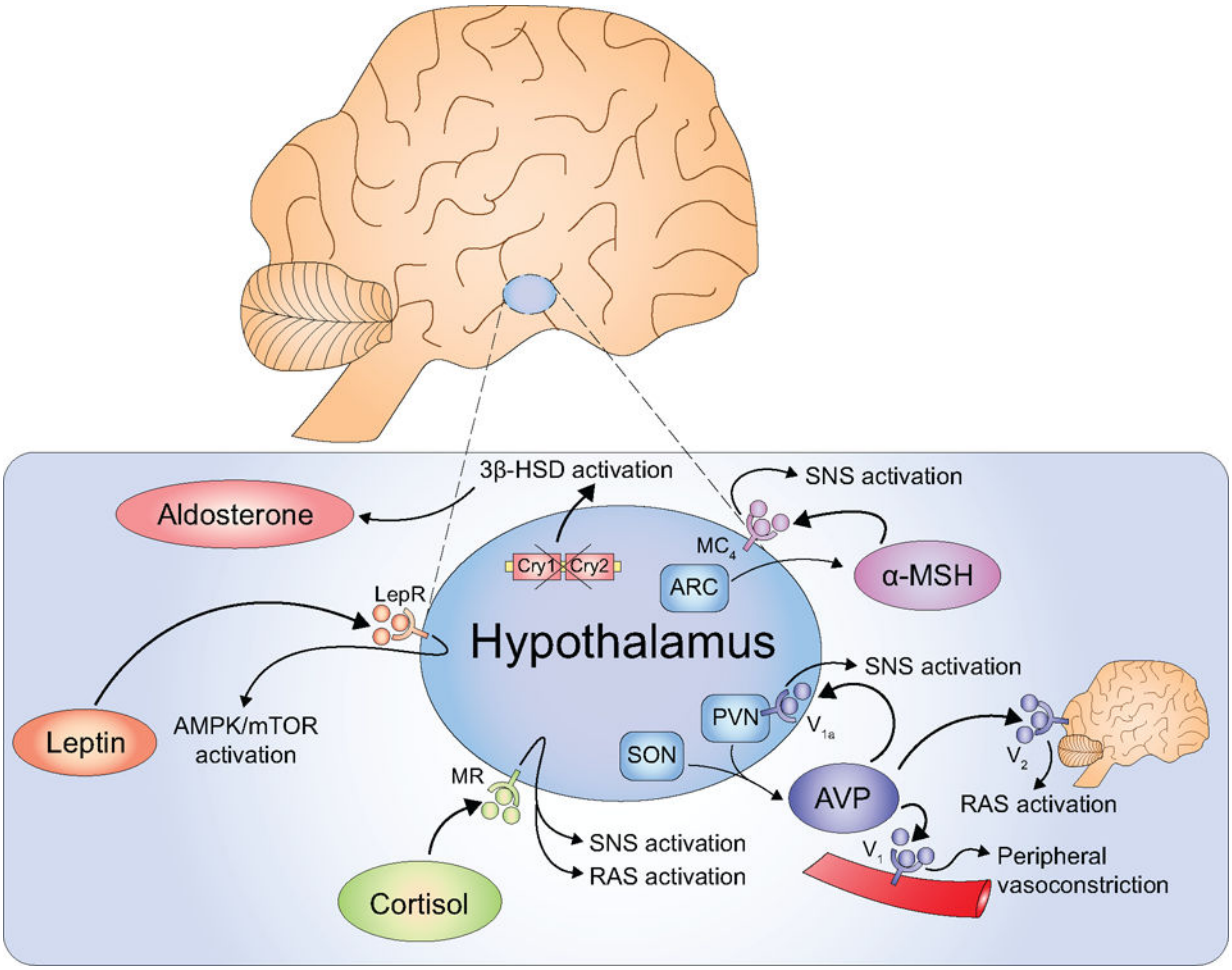

Figure 2. Hypothalamic mechanisms of hypertension

The hypothalamus activates the SNS and other pathways contributing to the pathogenesis of hypertension. Dysregulated AVP neurons in the SON and PVN produce excess AVP, which activates hypothalamic V1a, brain V2, and peripheral V1a receptors, thus activating the SNS, RAS, or endothelial cells, respectively. Circulating cortisol activates MRs in the hypothalamus to simultaneous stimulate the SNS and RAS. Leptin binds to the LepR to activate AMPK and the SNS. The ARC produces α-MSH, which binds to the MC_4 in the hypothalamus to increase SNS outflow. Dysregulated clock gene expression promotes aldosterone production leading to salt-sensitive hypertension.

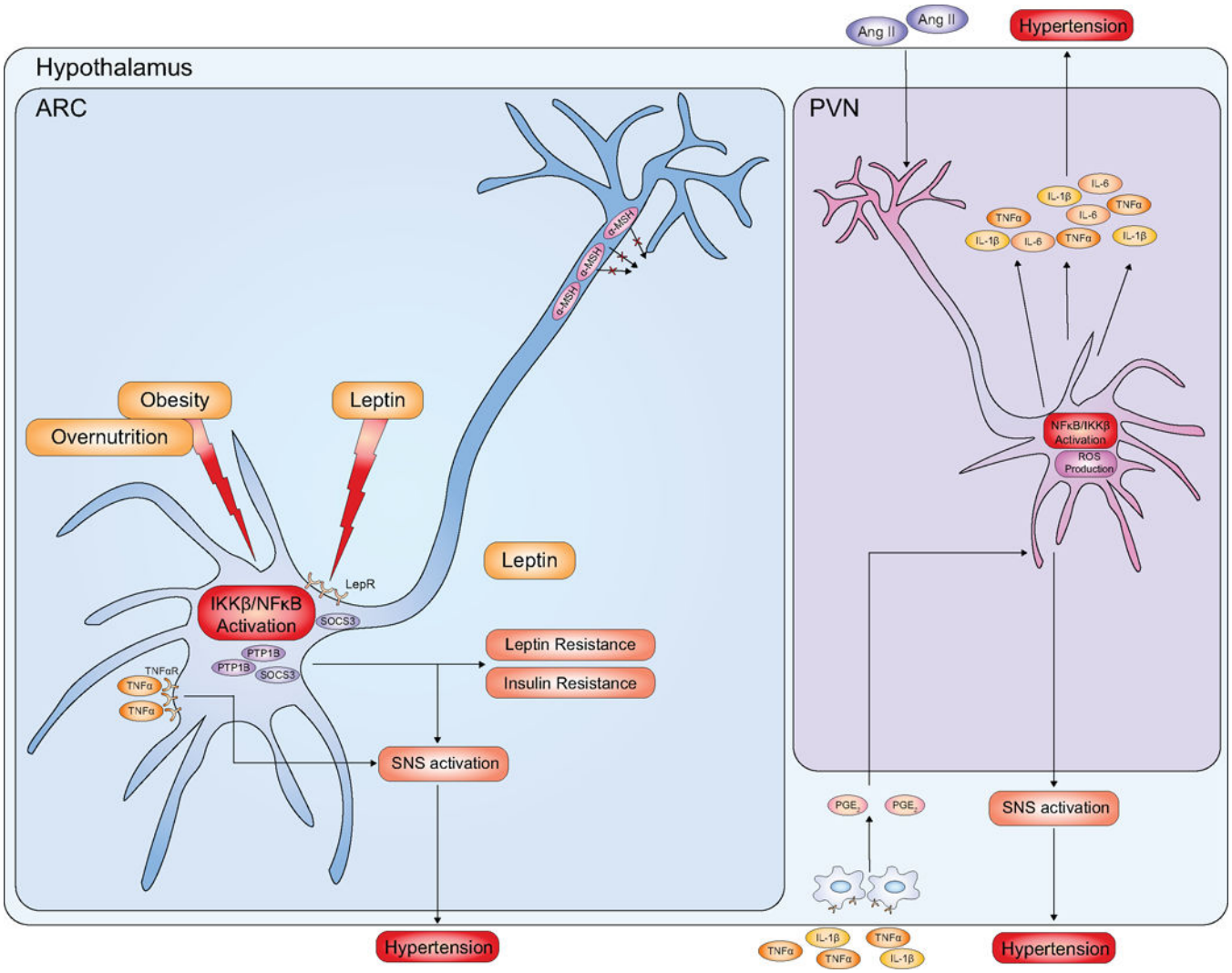

Figure 3. Pro-inflammatory hypertensive signalling in the hypothalamus

In response to overnutrition states, pro-inflammatory signalling including IKKβ/NFκB is activated in certain hypothalamic neurons such as POMC neurons in the ARC. NFκB activation triggers a variety of molecular reactions, such as increased levels of SOCS3 and of PTP1b, contributing to SNS activation and subsequent increased blood pressure. In addition, POMC neurons bind TNFα, which further stimulates SNS activation. Also, TNFα and IL-1β activate perivascular macrophages that produce prostaglandin E2, which signals through the PVN to activate the SNS and subsequent hypertension. Central RAS activation and Ang II production stimulates IKKβ/NFκB activation and ROS production in PVN neurons. Subsequent release of pro-inflammatory cytokines further contributes to ROS production, mitochondrial dysfunction, neuroinflammation and sustained increase in blood pressure leading to pathological hypertension.