CALL FOR PAPERS | CNS Control of Metabolism

Neuroinflammatory and autonomic mechanisms in diabetes and hypertension

Cheng Han, Matthew W. Rice, and Dongsheng Cai
Department of Molecular Pharmacology, Diabetes Research Center, Institute of Aging, Albert Einstein College of Medicine, Bronx, New York

Submitted 15 January 2016; accepted in final form 3 May 2016

Han C, Rice MW, Cai D. Neuroinflammatory and autonomic mechanisms in diabetes and hypertension. Am J Physiol Endocrinol Metab 311: E32–E41, 2016. First published May 10, 2016; doi:10.1152/ajpendo.00012.2016.—Interdisciplinary studies in the research fields of endocrinology and immunology show that obesity-associated overnutrition leads to neuroinflammatory molecular changes, in particular in the hypothalamus, chronically causing various disorders known as elements of metabolic syndrome. In this process, neural or hypothalamic inflammation impairs the neuroendocrine and autonomic regulation of the brain over blood pressure and glucose homeostasis as well as insulin secretion, and elevated sympathetic activation has been appreciated as a critical mediator. This review describes the involved physiology and mechanisms, with a focus on glucose and blood pressure balance, and suggests that neuroinflammation employs the autonomic nervous system to mediate the development of diabetes and hypertension.

autonomic nervous system; hypothalamus; inflammation
The liver is a critical organ in the regulation of homeostasis of the body. The hypothalamus, in particular, plays a role in controlling hepatic glucose output and therefore glucose homeostasis. Recent findings indicate that the hypothalamic and cardiovascular systems are interconnected through autonomic and neuroendocrine pathways, which contribute to glucose and blood pressure disorders. Dysfunctions resulting from hypothalamic inflammation that contribute to glucose and blood pressure disorders have been noted.

**Table 1. Hypothalamic connections with autonomic control regions in regulating glucose and BP balance**

<table>
<thead>
<tr>
<th>Hypothalamic Nucleus</th>
<th>Downstream Autonomic Control Regions</th>
<th>Target Organs</th>
<th>Physiological Effects</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVN</td>
<td>DMV, RVLM, NTS, IML</td>
<td>Liver, kidney, CVS</td>
<td>Glucose production, BP homeostasis, food intake</td>
<td>129</td>
</tr>
<tr>
<td>DMH</td>
<td>PVN, DMV, NTS</td>
<td>CVS</td>
<td>BP homeostasis</td>
<td>129</td>
</tr>
<tr>
<td>LHA</td>
<td>DMV, NTS, IML, VMH, ARC</td>
<td>Liver, BAT</td>
<td>Hepatic function, BAT activation, food intake</td>
<td>129</td>
</tr>
<tr>
<td>ARC, VMH (MBH)</td>
<td>PVN, DMV, NTS</td>
<td>Liver, skeletal muscle, BAT, pancreas</td>
<td>Hepatic function, skeletal muscle glucose uptake, BAT activation, pancreatic insulin secretion, food intake</td>
<td>119</td>
</tr>
</tbody>
</table>

**Cardiovascular disorders (100, 102).** Herein, this review will focus on summarizing recent findings on the hypothalamic and autonomic basis of glucose and blood pressure regulation as well as dysfunctions resulting from hypothalamic inflammation that contribute to glucose and blood pressure disorders.

**Autonomic and hypothalamic control of hepatic glucose production.** The liver is a critical organ in the regulation of glucose homeostasis, serving as the principal site for glycogen storage and acting to regulate levels of circulating glucose. For example, in response to increasing levels of blood glucose, the liver reduces hepatic glucose production; conversely, low levels of blood glucose lead to increases in hepatic glucose production (104). Regarding neuroendocrine regulation of hepatic glucose production, the arcuate nucleus and PVN of the hypothalamus respond to circulating levels of regulatory hormones to modulate glucose homeostasis. Experimental evidence demonstrates that restoration of leptin signaling in leptin receptor-deficient mice normalizes blood glucose concentrations (28, 56). These effects can also be achieved through restoring leptin receptor specifically in POMC neurons of mice that are genetically deficient in leptin receptor (40, 56). Other studies demonstrate the role of AgRP neurons in leptin’s actions on glucose homeostasis (40, 44). Intracerebral ventricular administration of neuropeptide Y was shown to elevate hepatic glucose production due to an impairment in hepatic insulin sensitivity, and both of these effects were shown to be mediated by sympathetic activity in the autonomic nervous system (131). Additionally, glucocorticoid signaling in the arcuate nucleus was recently demonstrated to impair insulin sensitivity (141). Altogether, these findings signify the importance of the mediobasal hypothalamus in glucose homeostasis.

The central nervous system (CNS) innervates the liver through both the sympathetic and parasympathetic nervous systems (38, 142). Sympathetic efferent pathways from the intermediolateral nucleus of the spinal cord reach the liver to regulate hepatic functions, while parasympathetic efferent signals for the liver are generated significantly from the dorsal vagal complex (142). Several hypothalamic areas are also responsible in regulating autonomic signals to the liver, including the ventral medial nucleus, which participates in sympathetic function, the lateral hypothalamus in parasympathetic function, and the PVN, which integrates signals from several hypothalamic regions to affect the autonomic function (129). The PVN is anatomically connected to the arcuate nucleus and the ventral medial nucleus, functioning to convey information from these hypothalamic nuclei to the brain regions that employ the autonomic nervous system to regulate liver glucose production (131). Also, there is evidence suggesting that the PVN plays a role in regulating the biological clock, which is primarily controlled by the suprachiasmatic nucleus and thus contributes to circadian rhythms of blood glucose changes (62). This effect has been shown to be mediated through the actions of GABAergic and other neurons in the PVN (62). Furthermore, recent studies have linked the PVN to glucose intolerance induced by excess thyroid hormone. An administration of thyroid hormone in the PVN was shown to increase blood glucose levels and hepatic glucose production via hepatic sympathetic activation (38). Sympathetic regulation of hepatic glucose production is known to involve the ventral hypothalamus, since studies demonstrated that stimulation of the ventral hypothalamic region increases the activity of gluconeogenic enzyme phosphoenolpyruvate carboxykinase in the liver (118). Parasympathetic regulation of the liver is closely related to the lateral regions of the hypothalamus, with studies having shown that stimulation of these areas promotes glycolysis in the liver, an effect that is associated with decreased levels in hepatic phosphoenolpyruvate carboxykinase gene expression (118). Also, it was reported that activation of orexin-expressing neurons, which are densely localized in the lateral hypothalamus, can increase the autonomic outflow to the liver (143). In summary, in addition to neuroendocrine pathways, the autonomic outflow regulated by the hypothalamus, involving both parasympathetic and sympathetic innervations of the liver, clearly plays an important role in controlling hepatic glucose output and therefore glucose homeostasis of the body.

**Table 1. Hypothalamic connections with autonomic control regions in regulating glucose and BP balance**

<table>
<thead>
<tr>
<th>Hypothalamic Nucleus</th>
<th>Downstream Autonomic Control Regions</th>
<th>Target Organs</th>
<th>Physiological Effects</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVN</td>
<td>DMV, RVLM, NTS, IML</td>
<td>Liver, kidney, CVS</td>
<td>Glucose production, BP homeostasis, food intake</td>
<td>129</td>
</tr>
<tr>
<td>DMH</td>
<td>PVN, DMV, NTS</td>
<td>CVS</td>
<td>BP homeostasis</td>
<td>129</td>
</tr>
<tr>
<td>LHA</td>
<td>DMV, NTS, IML, VMH, ARC</td>
<td>Liver, BAT</td>
<td>Hepatic function, BAT activation, food intake</td>
<td>129</td>
</tr>
<tr>
<td>ARC, VMH (MBH)</td>
<td>PVN, DMV, NTS</td>
<td>Liver, skeletal muscle, BAT, pancreas</td>
<td>Hepatic function, skeletal muscle glucose uptake, BAT activation, pancreatic insulin secretion, food intake</td>
<td>119</td>
</tr>
</tbody>
</table>

**Table 1. Hypothalamic connections with autonomic control regions in regulating glucose and BP balance**

<table>
<thead>
<tr>
<th>Hypothalamic Nucleus</th>
<th>Downstream Autonomic Control Regions</th>
<th>Target Organs</th>
<th>Physiological Effects</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVN</td>
<td>DMV, RVLM, NTS, IML</td>
<td>Liver, kidney, CVS</td>
<td>Glucose production, BP homeostasis, food intake</td>
<td>129</td>
</tr>
<tr>
<td>DMH</td>
<td>PVN, DMV, NTS</td>
<td>CVS</td>
<td>BP homeostasis</td>
<td>129</td>
</tr>
<tr>
<td>LHA</td>
<td>DMV, NTS, IML, VMH, ARC</td>
<td>Liver, BAT</td>
<td>Hepatic function, BAT activation, food intake</td>
<td>129</td>
</tr>
<tr>
<td>ARC, VMH (MBH)</td>
<td>PVN, DMV, NTS</td>
<td>Liver, skeletal muscle, BAT, pancreas</td>
<td>Hepatic function, skeletal muscle glucose uptake, BAT activation, pancreatic insulin secretion, food intake</td>
<td>119</td>
</tr>
</tbody>
</table>

ARC, arcuate nucleus, BAT, brown adipose tissue, BP, blood pressure, CVS, cardiovascular system, DMH, dorsal medial hypothalamus, DMV, dorsal motor nucleus of the vagus, IML, intermediolateral nucleus of the spinal cord, LHA, lateral hypothalamic area, MBH, mediobasal hypothalamus, NTS, nucleus of the solitary tract, PVN, paraventricular nucleus, RVLM, rostral ventrolateral medulla, VMH, ventromedial hypothalamus.
Autonomic and hypothalamic modulation of glucose uptake in skeletal muscle. Skeletal muscle is a critical tissue responsible for insulin-stimulated glucose uptake in response to feeding. Under normal conditions, hyperglycemia triggers insulin secretion and increases glucose uptake in skeletal muscle; however, this ability is markedly impaired in the condition of insulin resistance, which is characteristically displayed in type 2 diabetes and also frequently seen in obesity (61, 76). The hypothalamus plays a significant role in affecting glucose update of skeletal muscle via the sympathetic nervous system and probably through insulin-independent pathways (86, 115). For instance, the intracerebral ventricular injection of leptin in the hypothalamic third ventricle leads to an increase in muscle glucose uptake, and this effect was shown to be dependent on β-adrenergic activation (81) and mediated through an insulin-independent mechanism (49). Furthermore, electrical stimulation of the ventromedial hypothalamus resulted in the increased uptake of glucose by skeletal muscle through sympathetic action, with this result also being independent of insulin signaling (119). In addition, injection of orexin-A in the ventral hypothalamic region was found to cause sympathetic excitation, leading to an increase in muscle glucose uptake (120). Finally, much of the sympathetic activation that regulates skeletal muscle glucose uptake appears to be regulated through norepinephrine signaling (86). To summarize, the hypothalamus has effects on glucose uptake and utilization in skeletal muscles through insulin-independent autonomic activation, and this effect might provide an appreciable contribution to the control of glucose homeostasis under certain physiological conditions.

Autonomic and hypothalamic control of glucose utilization in brown fat. Thermogenic brown adipose tissue is known to be heavily innervated by sympathetic nerve fibers, although the role of the parasympathetic nervous system in brown fat is less well known (43). Brown adipose tissue is activated by the sympathetic nervous system through the stimulation of β-adrenergic receptors (6, 46, 93, 128, 136). For example, mice deficient in β1-adrenergic receptor showed a lower basal metabolic rate and defective cold tolerance (128). Consistently, blockade of β1- and β2-adrenergic receptors can reduce brown adipose tissue activity, as determined by imaging in mice as well as patients (93, 136). Interestingly, administration of a β2-adrenergic receptor agonist increased energy expenditure, mainly through white adipose tissue, rather than direct activation of brown adipose tissue (46). In recent years, specific neuronal types in the hypothalamus have been identified for the regulation on brown adipose tissue, for example, POMC neurons in the arcuate nucleus are present in the neural pathways that project to brown fat, whereas brown fat-innervating neurons in the lateral hypothalamus were found to express neuropeptides such as orexins and melanin-concentrating hormone (89). In addition, it has been demonstrated that brown adipose activation is associated with metabolism in relation to circadian rhythm or cold exposure (7, 127), and, in connection with this physiology, central administration of fibroblast growth factor-21 was shown to enhance the sympathetic mechanism of energy expenditure and weight loss (91). Treatment of type 2 diabetes with glucagon-like peptide-1 analog tiraglutide has been shown to activate brown fat and to induce the browning of white adipose tissue through sympathetic activation (74). Additionally, glucagon-like peptide-1 activation through the use of dipeptyl peptidase inhibitors has been demonstrated to activate brown fat, lower adiposity, and improve glucose metabolism (63, 117). Compared with brown adipose tissue, the neural control of white adipose tissue has been less well studied, despite white adipose tissue being the primary means of lipid energy storage. Of note, a recent study by Zeng et al. shows that induction of sympathetic activity induces lipolysis in white adipose tissue, suggesting that white adipose tissue is under similar neuronal control compared with brown adipose tissue (145). Moreover, the CNS has been recognized as an activator of the sympathetic innervation of white adipose tissue and is potentially a mediator in the control of peripheral lipid storage in this tissue (84). Despite this research progress, the role of the hypothalamus in the control of white adipose tissue has yet to be fully explored.

Autonomic and hypothalamic control of β-cell function. The pancreas, including islets, is richly innervated by both the sympathetic and parasympathetic nervous systems (115), with sympathetic nerves innervating pancreatic α-cells, while the parasympathetic system innervates pancreatic α- and β-cells (108, 115). Sympathetic efferents to the pancreas are produced by neurons in the spinal cord that are connected to preganglionic neurons in the brain stem and peripheral preganglionic neurons in the pancreas (17). In addition, several hypothalamic and extrahypothalamic (e.g., the dorsal vagal complex) sites have been identified that regulate the autonomic output to the pancreas (59, 60, 92, 97). The ventral hypothalamic region plays a critical role in the hypothalamic regulation of glucose response, in part because this region is important for glucose-induced pancreatic glucagon secretion (13, 14). The underlying mechanism of the ventral hypothalamus in modulating pancreatic function has been demonstrated by targeting propylendopeptidase, an enzyme that regulates neuropeptide production (65). Mice with propylendopeptidase gene knockdown developed pancreatic endocrine changes, including increased blood glucagon and decreased blood insulin in basal and glucose-stimulated conditions, and these changes were accompanied by increased sympathetic outflow to the pancreas (65). Stimulation of the dorsal motor nucleus of the vagus, either electrically or chemically, was demonstrated to activate not only endocrine but also exocrine functions, and vagotomy can block these effects (83, 134). Also, glucose-induced insulin secretion can be increased through the local injection of a chemical that antagonizes GABA to activate the dorsal motor nucleus of the vagus, and this effect can be suppressed by administration of a chemical that antagonizes muscarinic receptors (82). Furthermore, glucagon-like peptide-1 can depolarize neurons in the dorsal motor nucleus of the vagus that project to the pancreas, indicating that the effect of glucagon-like peptide-1 in modulating insulin secretion is mediated, at least in part, through the neural control of the pancreas (133, 134).

Autonomic and hypothalamic control of blood pressure. Circumventricular organs, the hypothalamus, and the brain stem perform important functions in processing and integrating various stimuli from the periphery to maintain blood pressure and fluid homeostasis through influencing the sympathetic tone and the renin-angiotensin system (47, 51, 73, 75, 77, 96). Circumventricular organs, for example, the subfornical organ, organum vasculosum lamina terminalis, and median eminence,
do not have a complete blood-brain barrier, and, of importance, angiotensin receptors are highly expressed in these brain areas (78). Hence, both circulating and locally produced angiotensin can activate these areas (57, 90), leading to the prediction that angiotensin in the CNS mediates the sympathetic upregulation and blood pressure elevation. In addition, these brain areas send projections to the paraventricular hypothalamus and the sympathetic center RVL (57, 90). Activation of the circumventricular organs, the PVN and the RVL, is important for angiotensin receptor activation, being one of the crucial neural mechanisms of hypertension (47, 57, 90, 96). Other brain sites, for example, the median preoptic nucleus, which receive neural signals from the subfornical organ or organum vasculosum lamina terminalis, are also responsible for angiotensin-induced blood pressure increase (90). Furthermore, angiotensin receptors and glutamatergic receptors in the RVL have been related to hypertension in animals (58). In addition, leptin is also known to mediate increases in blood pressure via the sympathetic nervous system (2, 48, 121, 122). Furthermore, this effect of leptin on blood pressure was shown to be facilitated through neuronal circuits in the dorsal hypothalamus (48). To summarize, the brain renin-angiotensin system, as well as leptin, is known to play a substantial role in the central regulation of blood pressure through the mechanism of sympathetic activation, and the hypothalamus plays a significant role in this process.

**Obesity-induced hypothalamic inflammation and autonomic dysfunction.** Obesity is associated with a set of chronic inflammatory changes in the hypothalamus (21, 100, 125, 148), with subsequent disease progression being promoted and sustained by dynamic effects of inflammatory signaling pathways. Molecules that interact with the IKKβ/NF-κB signaling cascade, such as MyD88 or JNK1, have been demonstrated to contribute to the development of hypothalamic inflammation (66). The cellular mediators for hypothalamic inflammation include microglia, which can spread inflammatory molecules to surrounding cells (33, 41, 88, 130, 146). Astrocytes have also been proposed to mediate the hypothalamic inflammation (55, 140). Cytokine receptors, such as TNF-α receptor, appeared to mediate obesity-related neural and hypothalamic inflammation (5, 109). In addition, intracellular endoplasmic reticulum stress has been associated with the induction of neural and hypothalamic inflammation (102). In general, while it remains to be determined how high-fat diet feeding causes endoplasmic reticulum stress and inflammation in the brain, the responsible mediators can include, at least, alterations in calcium homeostasis, production of toxic metabolites, upregulation of proinflammatory cytokines, and fatty acid-mediated reactive oxygen species (25, 64). More recently, hypothalamic RNA stress response was found to promote iκBα mRNA degradation and rapidly activate the NF-κB pathway, representing another mediator of neural inflammation in the prediabetic high-fat diet condition (140).

Among various outcomes of hypothalamic inflammation, one important one seems to be upregulation in sympathetic excitation. In 2011, Purkayastha et al. demonstrated that the acute induction of hypothalamic endoplasmic reticulum stress led to increased spontaneous renal sympathetic activity and hemodynamic changes, indicating cardiovascular sympathetic activation (102). In parallel, inhibition of inflammation in the mediobasal hypothalamus was shown to reverse the sympathetic effects caused by hypothalamic endoplasmic reticulum stress (102). Further research demonstrated that intracerebroventricular injection of TNF-α could lead to sympathetic upregulation and sympathetic hemodynamic changes (101), with these actions being reversible through anti-inflammatory treatment in the hypothalamus (116). Despite these understandings, therapeutic options of directly inhibiting NF-κB might have pitfalls such as altered response to bacterial infections (8, 45), calling for alternative approaches of suppressing hypothalamic inflammation. Interestingly, while excess hypothalamic TGF-β was recently found to affect hepatic glucose production potentially through the sympathetic nervous system (140), it should be noted that suppression of TGF-β already shows clinical promise in the treatment of cancers (50, 72, 105), and these medications were considered generally safe (3, 106). Because it is still early to therapeutically predict, it holds promise that practical and safe anti-inflammatory approaches of targeting the brain should exist and will be identified through future research.

**Glucose intolerance by hypothalamic inflammation and autonomic dysfunction.** Recent studies using experimental mouse models of hypothalamic inflammation have revealed that these animals manifest diabetic or prediabetic symptoms (102, 125). Purkayastha et al. demonstrated that short-term endoplasmic reticulum stress in hypothalamus upregulates the proinflammatory NF-κB pathway to cause hepatic glucose disorder, a metabolic effect that was associated with increased levels of gluconeogenic enzymes in the liver (102). In agreement, site-specific NF-κB inhibition in the hypothalamic arcuate nucleus was revealed to attenuate the induction of glucose intolerance by high-fat diet feeding or brain endoplasmic reticulum stress (102). Yan et al. found that hypothalamic TGF-β production under conditions of aging or obesity is higher than normal and that administration of TGF-β to the hypothalamus led to glucose intolerance, which was independent of feeding or body weight (140). Mechanistically, this effect of hypothalamic TGF-β excess was induced through hypothalamic NF-κB (140). Consistent with this conceptual model, oxidative stress has been demonstrated to be related with inflammation in the hypothalamus. Researchers found that the intracerebroventricular injection of apelin (an endogenous ligand for G protein-coupled apelin receptor that affects diverse biological functions, including fluid homeostasis, cardiovascular function, and insulin secretion) induced hypothalamic overproduction of reactive oxygen species and increased expression of inflammatory factors leading to hyperglycemia in mice. This impairment in systemic glucose homeostasis caused by hypothalamic apelin was attributed to the enhanced sympathetic activity that increased glucose production from the liver (32). Interestingly, an intracerebroventricular injection of an antioxidant before apelin injection was found to prevent the establishment of hyperglycemia in a body weight-independent manner (32). Furthermore, Burgos-Ramos et al. demonstrated that diabetic insulin receptor substrate 2 (IRS2)-deficient mice displayed greater amounts of hypothalamic inflammation than prediabetic IRS2-deficient mice, being the result of NF-κB and JNK activation (19). In summation, numerous studies have demonstrated a strong association between hypothalamic inflammation and glucose intolerance, supporting the concept of the hypothalamus as being a crucial central regulator for glucose homeostasis.
Insulin resistance and β-cell dysfunction by hypothalamic inflammation. As described previously, studies have demonstrated that hypothalamic inflammation via endoplasmic reticulum stress activates the proinflammatory NF-κB pathway leading to glucose intolerance, with this metabolic disorder being partly attributed to insulin resistance (102). Indeed, injection of endoplasmic reticulum stress suppressor in the hypothalamus improved systemic glucose tolerance and peripheral insulin signaling (102). Despite these observations, it should be noted that endoplasmic reticulum stress is not the only cause of hypothalamic inflammation in affecting insulin resistance. For instance, increased redox signaling and reactive oxygen species in the hypothalamus were also observed to be associated with NF-κB activation, leading to hyperglycemia, hyperinsulinemia, and insulin resistance in mice (32). Furthermore, an intracerebral ventricular injection of antioxidant chemical trolox (a water-soluble analog of vitamin E) before the induction of reactive oxygen species in the hypothalamus inhibits the development of diabetic characteristics (32). Besides, long-term overnutrition can impair hypothalamic autophagic function, also contributing to chronic hypothalamic inflammation, which causes not only obesity but also systemic insulin resistance (66). The proinflammatory TNF-α pathway was also studied, showing that obesity and insulin resistance can both be abrogated in mice that lack either TNF-α pathway was also studied, showing that obesity and insulin resistance can both be abrogated in mice that lack either TNF-α or TNF-α receptor (52, 132). Resistin, another proinflammatory cytokine that is produced mainly from the fat, was found to induce hepatic insulin resistance via neural actions (1). Recently, it was revealed that central TGF-β excess employs an RNA metabolism-dependent mechanism to activate proinflammatory NF-κB in the hypothalamus, leading to a rapid manifestation of systemic and hepatic insulin resistance (140). In addition, and in line with the fact that pancreatic β-cell function is, at least in part, under the control of the autonomic system, it was shown that hypothalamic inflammation led to the loss of first-phase insulin secretion, with this loss being restored following sympathectomy (115). Altogether, hypothalamic inflammation and associated autonomic changes have a significant role in impairing insulin sensitivity, as well as insulin secretion, contributing to the development of type 2 diabetes.

Hypothalamic inflammation links aging to diabetes development. Obesity, type 2 diabetes, and their related complications increase in prevalence with aging and with aging-related diseases such as Alzheimer’s disease and Parkinson’s disease (11, 70). In addition, therapeutic interventions for metabolic diseases (e.g., diabetes) are known to counteract symptoms related to neurodegeneration-associated disorders, suggesting that metabolic and age-related diseases share several mechanistic pathways (31, 112). Indeed, studies with the use of animal models have frequently demonstrated the causal relationships between diabetes and neurodegenerative diseases. For instance, degeneration of dopaminergic neurons in a mouse model of Parkinson’s disease can be significantly promoted by overnutrition (15). Also, while diabetes-associated brain insulin-signaling changes can cause neuronal oxidative stress and mitochondrial dysfunction, these changes in the brain were also shown to mediate Huntington’s disease (111). Furthermore, obesity and diabetes are known to alter the functioning of phosphatase and tensin homolog-induced putative kinase-1, which mediates neuronal apoptosis and is causally related to familial Parkinson’s disease (113). IL-6 is a classical NF-κB product and is overproduced in obesity and diabetic conditions. This cytokine has been reported to mediate GABAergic neuronal degeneration in the forebrain, with this neurodegenerative outcome induced through neuronal NF-κB activation (34). Conceptually, it has been suggested that metabolic overload and neuronal insulin resistance in obesity and diabetes render neurons more susceptible to neural inflammation and neuronal death (16, 30). Recent studies have also implicated that glial cells in the brain play roles in the etiology of diabetes symptoms. For instance, hyperglycemia is associated with a reduction in the expression level of glucose transporter-1 in hypothalamic glial cells (26), and reduced levels of glucose transporter-1 were shown to impair the hypothalamic regulation of hepatic glucose production, while this impairment can be prevented by restoring glucose transporter-1 in hypothalamic glial cells (26). In addition, glucose transporter-2 in astrocytes and tanyocytes has been suggested to contribute to glucose sensing of the brain (42, 71).

Hypertensive effect by hypothalamic inflammation and autonomic dysfunction. Evidence from both neuroendocrinology and neuroimmunology studies indicates that chronic overnutrition is an independent environmental factor in the pathogenesis of obesity-related hypertension (100, 125). As discussed earlier, overnutrition is known to lead to hypothalamic inflammation, and several studies have eluded to the chronic activation of proinflammatory pathways within both central and peripheral tissues as being associated with obesity-induced hypertension (135). Within the CNS, NF-κB-driven hypothalamic inflammation employs an obesity-dissociable mechanism to induce the loss of blood pressure homeostasis, likely in parallel to producing glucose intolerance and insulin resistance, acting as an uncoupling point between hypertension and obesity-associated metabolic diseases (5, 98, 101, 102). Increased proinflammatory cytokines in the hypothalamus are closely related to the condition of hypertension, and recent literature highlighted the relationship between the renin-angiotensin system and inflammation in understanding the neural mechanism of hypertension (103). For example, blocking NF-κB activation in the brain can significantly attenuate angiotensin-induced hypertension (23). Within the hypothalamus, TNF-α and IL-1β stimulation in the PVN was shown to augment adrenocorticotropic hormone release, enhance cardiac sympathetic afferent reflex, and increase sympathetic outflow, all of which belong to important factors for the development of hypertension (36, 37). Furthermore, angiotensin-induced prohypertensive mechanisms may be significantly attenuated by PVN-specific blockade of TNF-α (23, 36). The key role of TNF-α was also recognized for angiotensin-stimulated inflammation, which may involve cross talk between this inflammatory cytokine and reactive oxygen species signals, given that central administration of reactive oxygen species scavenger tempol is able to decrease angiotensin-induced IL-1β in the PVN, further decreasing sympathetic activity and blood pressure (124). Angiotensin and prorenin both increase proinflammatory cytokine expression, such as TNF-α and IL-β, in the
nucleus tractus solitarius via the NF-κB complex (150). Purokayastha et al. further showed that TNF-α stimulates the IKKβ and NF-κB pathway in POMC neurons, leading to elevated blood pressure via a central mechanism involving sympathetic nervous system activation (101). Although it is clear that inflammatory cytokines are directly or indirectly induced by angiotensin stimulation, studies are needed to address which molecules and processes work to initiate and mediate this inflammatory response.

It is also worth noting that circulating angiotensin can send signals to the nucleus tractus solitarius neuronal networks leading to an increase in the blood-brain barrier permeability (94, 147). Because of this change, circulating factors including angiotensin have better access to brain areas such as the PVN, the RVLM, and the nucleus tractus solitaries, which are important for the autonomic control of blood pressure (12). Inflammatory cytokines IL-1β, TNF-α, and IL-6 can dysregulate adherens and tight junctions, further increasing the blood-brain barrier permeability (68). In addition, inflammatory cytokines are also produced by astroglia and microglia, which might also contribute to the development of hypertension (29, 33, 41, 88, 110, 130, 137), given that these glial cells play a particular role for the induction of hypothalamic inflammation in diet-induced obesity (24, 55, 69, 126, 135). Anti-inflammatory cytokines, such as IL-10, inhibit microglia activation and lead to reduced blood pressure levels in animals (116), but it remains to be studied if this effect on microglia was mechanistically involved in the decrease in blood pressure. Taken together, angiotensin and its associated inflammatory pathways interact closely in the hypothalamus and the rest of the brain to mediate the development of hypertension and, in particular, obesity-related hypertension.

Concluding remarks. Multiple lines of evidence indicate that the CNS is a mediating factor in the pathogenesis of diabetes and hypertension, rather than these ailments simply being disorders of peripheral tissues. Within the CNS, the hypothalamus lies at the intersection of the neuroendocrine and autonomic systems, and is a central component in the regulation of glucose and blood pressure homeostasis. As summarized in Fig. 1, provocative evidence has recently emerged to indicate that hypothalamic inflammation is a major contributor to the central dysregulation of glucose and blood pressure homeostasis. Although the cause of hypothalamic inflammation is not fully understood, this condition is closely associated with endoplasmic reticulum stress, RNA stress, oxidative damage, and autophagy defects, all of which can trigger or promote proinflammatory NF-κB activation. The amelioration of hypertensive and diabetic symptoms following administration of anti-inflammatory agents (39, 53) or targeting inflammatory molecular pathways (50, 72, 105) indicates therapeutic possibilities of reducing hypothalamic inflammation to control these epidemic diseases and related complications. While the pathogenic basis of neural and hypothalamic inflammation is formed dynamically through multiple processes, many of them still need further investigation. Regardless, recent findings have made it safe to conclude that neural inflammation, especially in the hypothalamus, alters the autonomic system to contribute to the development of diabetes and hypertension.

ACKNOWLEDGMENTS

We thank the members of the laboratory of D. Cai for contributions to projects that were related to this review.

GRANTS

These projects were supported by National Institutes of Health Grants R01-DK-078750, R01-AG-031774, R01-HL-113180, and R01-DK-099136 (all awarded to D. Cai).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.
REFERENCES


AUTHOR CONTRIBUTIONS

C.H. drafted manuscript; M.W.R. prepared figures; M.W.R. and D.C. edited and revised manuscript; D.C. conception and design of research; D.C. approved final version of manuscript.


