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Neuroinflammation in Overnutrition-induced Diseases

Dongsheng Cai*

Department of Molecular Pharmacology, Institute of Aging, Diabetes Research Center, Albert Einstein College of Medicine, Bronx, New York 10461

Abstract

Inflammation is a biological response mounted by the immune system against dangerous assaults that threaten the integrity and normal physiology of an organism. During the past decades, cross-disciplinary research from immunology and endocrinology has much broadened this knowledge by demonstrating that chronic conditions of nutritional excess constitute an independent category of inflammatory activators, and the resulting chronic and low-grade inflammation is an important characteristic of overnutrition-induced diseases. A large body of research has demonstrated that these diseases are pathogenically associated with the local, negative actions of inflammation in peripheral tissues predominantly including the liver, muscle and fat. In this research background, more recent research has advanced to a new level, with the important discoveries showing that overnutrition-induced inflammation occurs in the brain and thus plays a broad and leadership role in overnutrition-induced diseases. While much more research establishments are expected in this emerging and quickly expanding research, the appreciated understandings have been mainly based on proinflammatory IKKβ/NF-κB pathway and related molecules in the hypothalamus. In this chapter, the author focuses on describing IKKβ/NF-κB-induced neural inflammation in the context of overnutrition-induced metabolic inflammation and especially the central roles of this neural inflammation in the development of a spectrum of overnutrition-related diseases.

Keywords

inflammation; IKKβ; NF-κB; overnutrition; central nervous system; hypothalamus; energy balance; feeding; body weight; obesity; glucose tolerance; insulin resistance; metabolism; diabetes; hypertension; cardiovascular diseases; stroke; neurodegeneration; neural stem cell

I. INTRODUCTION

Inflammation is a biological response mounted by the immune system against dangerous assaults that threaten the integrity and normal physiology of an organism. In response to pathogens or injuries, pattern recognition receptors of the innate immune system are activated, which, in turn, initiates proinflammatory signaling cascades to produce cytokines, chemokines and other inflammatory products in order to eradicate inflammatory insults and perform tissue repair. IκB kinase beta (IKKβ) and its downstream effector nuclear factor

*Address correspondence to: Dongsheng Cai, M.D., Ph.D., Department of Molecular Pharmacology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461, Phone: 718-430-2426, Fax: 718-430-2433, dongsheng.cai@einstein.yu.edu.

kappa B (NF-κB) form a key proinflammatory axis to pivotally mediate a broad network of inflammatory reactions (Baeuerle and Baltimore, 1996; Karin and Lin, 2002; Hayden and Ghosh, 2008). Activation of NF-κB leads to expression of a large battery of inflammatory genes that promote inflammation and also direct proliferation of involved immune cells. Many other inflammatory signaling pathways, such as c-Jun N-terminal kinases (JNKs) and downstream transcription factor activator protein 1 (AP1), can interact with IKKβ/NF-κB pathway to mediate inflammation (Zhang and Kaufman, 2008). In the past decades, cross-disciplinary studies at the interface of immunology and endocrinology have revealed negative relationships between immunity and metabolic regulation. It has been known that overnutrition-induced metabolic diseases and in particular obesity and type 2 diabetes (T2D) are pathogenically associated with immune changes in the circulation as well as metabolic tissues including liver, muscle and fat (Lehrke and Lazar, 2004; Schenk et al., 2008; Shoelson and Goldfine, 2009; Cai, 2009; Cai and Liu, 2011; Lumeng and Saltiel, 2011; Gregor and Hotamisligil, 2011; Cai and Liu, 2012). In contrast to classical inflammation seen in diseases like infections, trauma, cancers and autoimmune diseases, the type of inflammation in obesity and T2D is often devoid of pathogen invasion or physical injuries, but instead primarily results from various metabolic abnormalities. The onset of systemic and tissue inflammation in obesity and T2D is chronically low-grade and atypical in many aspects, and “metabolic inflammation” (Cai, 2009; Cai and Liu, 2011; Cai and Liu, 2012) or “metaflammation” (Gregor and Hotamisligil, 2011) is specifically used to reflect its biological characteristics. In-depth research has revealed that under pro-obesity/T2D conditions, IKKβ/NF-κB pathway can induce metabolic inflammation to mediate insulin resistance and glucose/lipid disorders and thus mechanistically contribute to the development and progression of T2D and relevant metabolic diseases (Shoelson and Goldfine, 2009; Cai, 2009; Cai and Liu, 2011; Cai and Liu, 2012).

More recently, metabolic inflammation was discovered to also significantly exist in the brain and was further identified as a root and baseline cause for many overnutrition-induced diseases (Cai, 2009; Thaler and Schwartz, 2010; Cai and Liu, 2011; Cai and Liu, 2012). In these studies, it was shown that excessive nutrients in the form of glucose and fatty acids can directly activate the innate immune system of the central nervous system (CNS), and the resulting central metabolic inflammation disrupts the central neuroendocrine and neural regulations of metabolic related physiology. Recently, non-neuronal glial cells including astrocytes and microglia have been recognized to be as an integral part of central inflammation (Horvath et al., 2010; Thaler et al., 2012). Molecular research had led to the elucidation that IKKβ/NF-κB in the hypothalamus can be activated by excessive nutrients via receptor-independent intracellular organelle stresses as well as receptor-dependent pathways through such as toll-like receptor (TLR) and cytokine receptors. To date, IKKβ/NF-κB-directed metabolic inflammation in the CNS has been studied mostly in the mediobasal hypothalamus (MBH) – the hypothalamic region containing first-order metabolic sensing neurons which are known to primarily regulate feeding, energy balance and other metabolic activities. Metabolic inflammation in these neurons has been linked to their neuronal dysfunctions leading to energy imbalance and other pre-T2D changes including insulin resistance and glucose intolerance. Furthermore, metabolic inflammation in the MBH was found to interfere with the central control of cardiovascular homeostasis to

mediate the development of obesity-related hypertension (Purkayastha et al., 2011a; Purkayastha et al., 2011b). In addition, although still limitedly studied, central metabolic inflammation is relevant to neurodegeneration which might be a basis for the epidemic correlation between obesity/T2D and neurodegenerative diseases including Alzheimer's disease, Parkinson's disease and Huntington's disease. Very recently, obesity-related neural inflammation was discovered to impair neural stem cells (NSC) to mediate neurodegenerative mechanism of obesity and pre-T2D (Li et al., 2012b). Altogether, stemming from obesity/T2D-associated peripheral inflammation, neural inflammation has now become an emerging topic and an expanding research area in studying various overnutrition-induced diseases and disorders. Herein, in the context of overnutrition-associated inflammation, this chapter will focus on describing the involvement of IKKβ/NF-κB-mediated neural metabolic inflammation in a spectrum of overnutrition-related diseases.

II. IKKβ/NF-κB AND METABOLIC INFLAMMATION

The NF-κB family transcription factors play central roles in immunity and inflammation (Baeuerle and Baltimore, 1996; Karin and Lin, 2002; Hayden and Ghosh, 2008). Mammalian NF-κB family proteins have five members, and they have Rel-homology domain for protein dimerization and DNA binding. Three members including p65/RelA, RelB and cRel have C-terminal transcription activation domain which is required for exerting transcriptional regulation. Two other members, p105 and p100, are inert precursor proteins with C-terminal ankyrin repeats which inhibit DNA binding, and they need proteolytic processing to produce functional proteins p50 and p52. Distinct members of NF-κB proteins can form homo- or hetero-dimeric complexes and bind to κB site of target genes for transcriptional activation. In quiescent state, canonical NF-κB protein activity is inhibited through being maintained in the cytoplasm due to the binding of IκB proteins. Canonical activation of NF-κB pathway is induced through proinflammatory receptors such as TNF receptor members, cytokine receptors and TLRs, and this process is crucially mediated by IKK complex which consists of three subunits, the catalytic IKKα and IKKβ subunits and the regulatory IKKγ subunit. IKKβ is known to be mainly accountable for inflammatory response, while IKKα can be involved in alternative functions of NF-κB such as tissue development. Upon activation of receptors, IKK complex is activated to induce phosphorylation and then ubiqutin-dependent degradation of IκB proteins, leading to NF-κB nuclear translocation for its transcriptional activities. Activated IKKβ/NF-κB induces the expression of a large number of genes, and many of them are involved in inducing and regulating immune reaction, inflammation and related molecular and cellular events.

The IKKβ/NF-κB pathway plays a central role in metabolic inflammation. It has been long appreciated that in chronic obesity and obesity-related diseases, several metabolic tissues including fat, liver and muscle undergo inflammatory changes. In response to metabolic overload, immune cells such as macrophages invade metabolic tissues, and for example, in the case of adipose tissue, infiltration of M1 population of macrophages is proinflammatory (Xu et al., 2003; Weisberg et al., 2003). Within adipose tissue, resident T cells were found to have compositional changes (Nishimura et al., 2009; Winer et al., 2009; Feuerer et al., 2009), where the number of immunosuppressive T regulatory cells decreases and the ratio of $CD8^+$ to $CD4^+$ T cells increases. All these factors coherently produce a proinflammatory

milieu, which also divergently occurs in other types of metabolic tissues. At molecular level, proinflammatory cytokines like tumor necrosis alpha (TNF-α) and interleukins due to IKKβ/NF-κB activity can up-activate IKKβ/NF-κB signaling via TNF-α and interleukin receptors, which leads to the sustained production of proinflammatory cytokines, thus, formulating a feed-forward inflammatory loop to maintain metabolic inflammation in metabolic tissues. Chronically elevated inflammatory molecules in metabolic tissues can substantially impair their physiological functions to promote the development of obesity and T2D. The recent discovery of metabolic inflammation in the hypothalamus is leading metabolic research to a new area. Amongst these new levels of research, IKKβ/NF-κB pathway has been identified as a pivotal mediator for neural metabolic inflammation in overnutrition-induced diseases (Zhang et al., 2008; Milanski et al., 2009; Kleinridders et al., 2009; Posey et al., 2009). In summary, IKKβ/NF-κB is a pivotal mediator of metabolic inflammation in not only peripheral tissues but also the CNS, and because of the brain's leadership position in controlling the whole-body physiology, neural metabolic inflammation has been conceived to play broad and fundamental roles in the development of various overnutrition-induced diseases.

III. MEDIATORS OF BRAIN METABOLC INFLAMMATION

Obesity and T2D-associated inflammation in peripheral tissues has predominantly been studied in terms of cytokine receptor-mediated NF-κB activation. In contrast, nutrient overload in the brain was reported to directly activate IKKβ/NF-κB and induce neural inflammation via receptor-independent intracellular stresses, putting forth a concept that excessive nutrients under pro-obesity/T2D conditions per se represent a class of independent stimuli for brain IKKβ/NF-κB pathway (Zhang et al., 2008; Meng and Cai, 2011; Purkayastha et al., 2011a; Purkayastha et al., 2011b). Along this line, mounting evidences have demonstrated that excessive nutrients in the brain present a type of metabolic stresses to neurons in the hypothalamus or the brain. The intracellular consequences can be multiple, and so far researchers have paid attention to a few organelles including mitochondria, endoplasmic reticulum (ER) and autophagosomes. As revealed, neurons seem to be very sensitive to increased oxidative activities induced by increased amount of nutrient influx, which puts great pressure on intracellular oxidative machinery leading to mitochondrial dysfunction and oxidative stress. At the same time, increased cellular oxidative work load drives cellular protein synthesis to higher levels, and thus promotes unfolded protein response of the ER which can result in ER stress response. While overnutrition-induced cellular oxidative stress and ER stress persist, accumulation of defective macromolecules (e.g., misfolded proteins and dysfunctional mitochondria and ER) can negatively affect macroautophagic protein degradation machineries, and leads to development of overnutrition-induced autophagic defect.

From the molecular signaling perspective, cellular oxidative stress can activate NF-κB via reactive oxygen species (ROS)-induced alternative phosphorylation of IκBα to abolish its inhibitory effect on NF-κB (Schieven et al., 1993; Tanaka et al., 2000; Schoonbroodt et al., 2000) or through oxidative inactivation of IKKβ/NF-κB pathway inhibitors (Lee et al., 2002; Kamata et al., 2002; Herscovitch et al., 2008). Reversely, activation of NF-κB has reinforcing effects on cellular oxidative stress by producing cytotoxic products (Pahl, 1999).

In addition, as established in recent research (Deng et al., 2004; Hu et al., 2006; Yamazaki et al., 2009), ER stress can activate NF-κB via signaling cross talk between IKKβ/NF-κB pathway and three UPR pathways which are mediated by PKR-like ER kinase (PERK), inositol requiring enyzyme-1 (IRE1) and activating transcription factor-6 (ATF6). Under overnutrition, activation of IKKβ/NF-κB and induction of neuronal ER stress indeed promote each other (Zhang et al., 2008; Purkayastha et al., 2011b). Furthermore, prolonged overnutrition can lead to brain autophagy defect which further promotes IKKβ/NF-κB-dependent inflammation in the hypothalamus (Meng and Cai, 2011). The underlying mechanism that links neural autophagic defect to hypothalamic inflammation remains unexplored, but theoretically, it may work at least through NLRP3 inflammasomes (Zhou et al., 2011), as NLRP3 inflammasomes can activate IKKβ/NF-κB pathway through the comprised inflammatory IL-1β and IL-18 release (Strowig et al., 2012).

In addition to intracellular organelle stresses, receptor-dependent signaling pathways can be parallely or secondarily involved in the formation of neural inflammation under chronic conditions of overnutrition. An important candidate is TLR pathway, which was initially found to be involved in obesity/T2D-associated peripheral inflammation. Though classically known as mediators of innate immune defense by recognizing pathogens (Beutler, 2004; Takeuchi and Akira, 2010), researchers found that in models of dietary obesity, high circulating levels of fatty acids can activate TLR2 and TLR4 to induce inflammation in muscle and adipose tissues as well as macrophages (Shi et al., 2006; Caricilli et al., 2008). More recently, researchers discovered that high-fat diet (HFD) feeding or central administration of fatty acids can activate brain TLR4 to induce neural inflammation (Milanski et al., 2009). Consistently, brain-specific inhibition of TLR4 signaling significantly attenuates NF-κB-mediated central metabolic inflammation in mice under chronic HFD feeding (Kleinridders et al., 2009). These findings indicated that TLR pathway is linked to NF-κB activation in the context of metabolic inflammation.

A number of relevant signaling pathways have been significantly related to metabolic inflammation in the brain. JNK pathway is known to be closely interacted with IKKβ/NF-κB, and in terms of metabolic inflammation, JNK pathway can respond to lipid overexposure, ER stress and cellular oxidative stress to mediate systemic inflammation which contributes to the development of insulin resistance and dyslipidemia (Hirosumi et al., 2002; Solinas et al., 2007; Sabio et al., 2008; Vallerie et al., 2008; Sabio et al., 2009; Sabio et al., 2010b). Recent studies demonstrated that JNK-mediated inflammation in the brain can contribute to the development of obesity and insulin resistance under dietary overnutrition (Belgardt et al., 2010; Unger et al., 2010; Sabio et al., 2010a). MyD88, an adaptor protein in IKKβ/NF-κB signaling, has also been investigated in the brain, and it was found that mice with brain-specific MyD88 knockout were protected from developing HFD-induced obesity (Kleinridders et al., 2009). Regarding the downstream molecules of IKKβ/NF-κB, suppressor of cytokine signaling-3 (SOCS3) has been examined, and brain-specific SOCS3 knockout was demonstrated to normalize central regulation despite overnutrition and thus prevent against the induction of obesity by overnutrition (Mori et al., 2004). Moreover, SOCS3 overexpression in the hypothalamus reduces the anti-obesity effect of centrally inhibiting IKKβ/NF-κB, indicating that SOCS3 is a molecular mediator

for the effect of IKKβ/NF-κB-induced central inflammation in obesity and T2D (Zhang et al., 2008).

Non-neuronal glia cells including microglia and astrocytes are also significantly involved in overnutrition-induced central inflammation. Newborn rats that were exposed to HFD feeding at 60-day age showed prominent CNS microglial activation and increased local production of IL-6, followed by hyperleptinemia and weight gain (Tapia-Gonzalez et al., 2011), demonstrating that nutrient overload can lead to central metabolic deregulation via microglial inflammation. In another study, researchers reported that central administration of IL-4 to induce microglial activation resulted in elevated hypothalamic inflammation and weight gain in HFD-fed rats (Oh et al., 2010). In addition to microglia, astrocytes can mediate central metabolic inflammation, which agrees with the observation that astrocytes are susceptible to the influences of various proinflammatory cytokines (Belanger et al., 2011). A recent study found that saturated fatty acids activate inflammatory signaling in astrocytes and trigger astrocyte release of proinflammatory cytokines TNF-α and IL-6 in rats (Gupta et al., 2012). Thus, the crosstalk between neurons and non-neuronal cells is another integral part of central metabolic inflammation.

IV. METABOLIC INFLAMMATION AND NEURAL DYSREGULATION

The CNS's metabolic regulatory functions largely reside in the hypothalamus, a midbrain structure that consists of functionally distinct nuclei and forms extensive neural connections with limbic forebrain and hindbrain structures. The hypothalamus is the "headquarters" for controlling energy and metabolic homeostasis through sensing metabolic signals and accordingly regulating appetite, energy expenditure, and nutrient metabolism (Cone, 2005; Lam et al., 2005; Morton et al., 2006; Flier, 2006; Coll et al., 2007; Sandoval et al., 2008). The hypothalamus exerts its metabolic regulatory functions based on a variety of metabolic signals sent to the brain, which include circulating hormones leptin, insulin, gut hormones as well as nutrients (Kahn et al., 2005; Murphy and Bloom, 2006; Myers et al., 2008; Belgardt and Bruning, 2010; Zhang et al., 2011). The arcuate nucleus in the MBH is the first-order metabolic regulatory center. Agouti-related peptide (AGRP) and proopiomelanocortin (POMC) neurons in the arcuate nucleus receive metabolic signals such as circulating leptin, insulin and nutrient moieties to interpret the body's energy statuses. When energy is in positive balance, increased circulating levels of insulin, leptin and other metabolic clues can activate POMC neurons by promoting gene expression and secretion of two anorexigenic neurpeptides including α-melanocyte-stimulating hormone and cocaine and amphetamine regulated transcript, and on the other hand, these metabolic signals inhibit AGRP neurons through reducing gene expression and release of two orexigenic neuropetides including AGRP and neuropeptide Y (Morton et al., 2006; Myers et al., 2008; Belgardt and Bruning, 2010). The synergistic effects of these neuroendocrine regulations ensure balanced energy intake and expenditure and therefore body weight balance. In parallel, hypothalamic regions such as arcuate nucleus and paraventricular nucleus can use neural pathways to regulate various metabolic physiological activities.

At the pathophysiological level, the neuroendocrine and neural pathways can be both negatively impacted by overnutrition-induced central metabolic inflammation. It has been

shown that metabolic inflammation in first-order metabolic sensing neurons in the MBH interferes with the comprised neuronal leptin and insulin signaling, resulting in central leptin and insulin resistance to cause feeding and energy imbalance (Zhang et al., 2008). In parallel, since these neurons also exert the functions of regulating systemic glucose and blood pressure homeostasis via central-peripheral neuroendocrine axes and neural circuitries, metabolic inflammation can negatively impact these neuroendocrine and neural networks to potentiate the development of diabetes and related complications. For example, monosodium L-glutamate-induced neural inflammation was linked to suppression of hypothalamic-pituitary-thyroid axis and upregulation of hypothalamic-pituitary-adrenal axis to cause metabolic problems (Castrogiovanni et al., 2008). In addition to the hypothalamus-regulated neuroendocrine pathways, the sympathetic nervous system modulated by hypothalamic neurons represents another mechanistic avenue in the central inflammatory mechanism of overnutrition-induced diseases. Recent literature has demonstrated that overnutrition-induced hypothalamic metabolic inflammation can increase the sympathetic outflow into peripheral organs (Purkayastha et al., 2011a; Purkayastha et al., 2011b) and cause obesity-related hypertension and glucose disorders (Romanatto et al., 2007; Muse et al., 2007; Singhal et al., 2007; Arruda et al., 2011; Purkayastha et al., 2011b). Altogether, overnutrition-induced neural inflammation can affect multiple neuroendocrine and neural regulatory functions to comprehensively mediate the development of overnutrition-induced diseases.

V. BRAIN METABOLIC INFLAMMATION AND OBESITY

Obesity is a pathological state of chronic positive energy balance cumulatively resulting from excessive energy intake and/or decreased energy expenditure. According to World Health Organization guideline, the body mass index greater than or equal to 25 is defined as overweight, and if it is greater than or equal to 30, obesity is then diagnosed. Based on this standard, the obesity incidence has reached an alarming rate in today's obesogenic environment, with 300 million women and 200 million men affected worldwide (Word Health Organization, 2011). Obesity is a core and baseline component of metabolic syndrome, and is a major risk factor for many diseases such as T2D, hypertension, stroke, and neurodegenerative diseases. The hypothalamus is the master regulator of whole body energy balance, and hypothalamic metabolic sensing center in the hypothalamus critically governs food intake and energy expenditure via combined neuroendocrine and neural mechanisms. Research to study the neural inflammatory mechanism of obesity has largely focused on identifying inflammatory molecules. Using HFD feeding or intracerebroventricular lipid infusion in rodents to model overnutrition, researchers found that lipid excess can induce metabolic inflammation in the hypothalamus via IKKβ/NF-κB activation (Zhang et al., 2008; Milanski et al., 2009; Kleinridders et al., 2009; Posey et al., 2009), which mechanistically impairs hypothalamic leptin and insulin signaling (Zhang et al., 2008). Brain-specific ablation of IKKβ (Zhang et al., 2008) or MyD88 (Kleinridders et al., 2009), MBH-specific inhibition of autophagy defect (Meng and Cai, 2011), and whole-body deficiency of NF-κB subunit p50 (Gao et al., 2009) all have protective effects against dietary obesity. The role of hypothalamic IKKβ/NF-κB in obesity development is significantly related to ER stress (Zhang et al., 2008), and indeed, central induction of ER

stress via genetic inactivation of X-box binding protein-1 can render mice highly susceptible to central leptin resistance and dietary obesity (Ozcan et al., 2009). Researchers also studied IKKβ/NF-κB-related signaling pathways such as JNK1. It was shown that JNK1-mediated central metabolic inflammation plays a role in the pathogenesis of obesity. Through analyzing different tissue-specific deletion of JNK1, only brain-specific JNK1 deletion exhibited anti-obesity effect (Belgardt et al., 2010; Sabio et al., 2010a) which was similarly seen in the whole-body JNK1 knockout mice (Hirosumi et al., 2002), indicating that JNK1-mediated neural inflammation causes energy imbalance to induce obesity. These mice with brain-specific JNK1 deletion manifested decreased food intake, increased energy expenditure and increased physical activity (Belgardt et al., 2010), all of which are indicative of brain regulatory improvements. SOCS3 (Howard and Flier, 2006; Myers et al., 2008) is a well-established negative regulator of leptin and insulin signaling, and it was found that SOCS3 haploinsufficiency (Howard et al., 2004) or brain-specific SOCS3 knockout (Mori et al., 2004) can enhance central leptin sensitivity and counteract HFD-induced obesity. Research proved that SOCS3 is a key effector downstream of IKKβ/NF-κB in the neural inflammatory mechanism of dietary obesity, as obesity-associated hypothalamic SOCS3 upregulation requires IKKβ/NF-κB signaling, and transgenic overexpression of SOCS3 in the MBH abolishes the anti-obesity effect of central IKKβ inactivation (Zhang et al., 2008). The receptor signaling upstream of IKKβ/NF-κB has also been investigated, and in this regard, mice deficient of TLR2 (Caricilli et al., 2008; Himes and Smith, 2010) or TLR4 (Tsukumo et al., 2007; Milanski et al., 2009) have reduced HFD-induced inflammation and are strongly protected from HFD-induced obesity.

To summarize, metabolic inflammation is a prominent feature of obesity, and central metabolic inflammation forms the pathogenic root of overnutrition-induced obesity. This central inflammatory mechanism of obesity is critically mediated by IKKβ/NF-κB, its upstream and downstream components and related signaling pathways. From the therapeutic perspective, these molecular mediators in the CNS can be potential therapeutic targets for combating obesity.

VI. BRAIN METABOLIC INFLAMMATION AND DIABETES

Diabetes is a medical condition arising from the body’s inability to lower blood sugar to the normal range, and chronic hyperglycemia and related pathophysiological changes can lead to serious, life-threatening complications. Insulin is a hormone produced by pancreatic β cells to be responsible for lowering blood glucose through insulin’s actions in metabolic tissues including liver, muscle and adipocytes. Peripheral insulin resistance in these metabolic tissues is a major etiological basis for the development of T2D. Interestingly, recent research advances have established the role of the brain and especially the hypothalamus in regulation and dysregulation of glucose homeostasis. As elucidated in the literature, the hypothalamus can employ multiple neuroendocrine and neural mechanisms to exert the central control over glucose homeostasis (Elmquist et al., 2005; Plum et al., 2006; Herman and Kahn, 2006; Morton, 2007). Metabolic signals such as circulating insulin, leptin, gut hormones and nutrients are converged in certain types of hypothalamic neurons, and through secreting neuropeptides and/or neurotransmitters, these neurons send metabolic orders to downstream neuroendocrine networks and hindbrain autonomic sites (e.g., dorsal

motor nucleus of the vagus nerve and nucleus tractus solitarius in the brain stem) to regulate peripheral glucose metabolism. Under physiological conditions, central insulin (Obici et al., 2002) and leptin (Asilmaz et al., 2004) signaling have hypoglycemic effects via suppressing hepatic glucose production and promoting peripheral glucose uptake.

It has been long known that obesity-induced inflammation in the peripheral metabolic sites contributes to insulin signaling defect and the development of insulin resistance (Cai, 2009; Hotamisligil, 2010; Lumeng and Saltiel, 2011). Recently, research has begun to demonstrate that obesity-related metabolic inflammation can impact the CNS leading to the central dysregulation of glucose homeostasis. While the molecular mechanism of this central dysregulation still largely remains to be investigated, it includes inflammation-induced central insulin and leptin resistance. The relationship between T2D and obesity-related inflammation, particularly in the CNS, has been considered as a basis for developing novel anti-T2D strategies. Given that ER stress is a critical inducer of obesity-related central metabolic inflammation, ER stress inhibitors can be a class of optional therapeutic targets which can inhibit inflammation in not only peripheral tissue but also the CNS to treat diabetes. Indeed, brain-specific inhibition of hypothalamic ER stress can improve overnutrition-induced systemic insulin resistance and glucose abnormality without involving body weight changes (Purkayastha et al., 2011b). The finding suggested that the anti-diabetic effect of systemically delivered ER stress inhibitors shown in the literature (Ozcan et al., 2006) might involve anti-ER stress/inflammation actions in the CNS. Thus, while anti-ER stress therapeutic strategy is driving new drug discovery efforts to treat T2D (Kim et al., 2008), it is an important research area to investigate the roles of such designs in manipulating neural ER stress and inflammation to treat systemic glucose disorder and insulin resistance in diabetes.

VII. BRAIN METABOLIC INFLAMMATION IN HYPERTENSION AND STROKE

Obesity-related hypertension is a frequent and serious cardiovascular complication of obesity. Due to its prominent role in promoting deleterious CVDs such as atherosclerosis and stroke, obesity-induced hypertension is an important epidemic factor for CVDs. Blood pressure is physiological output of multiple factors such as cardiac output, body fluid and salt balance and vascular compliance, and all of these functions are under the neural control of the CNS. Earlier studies have provided evidences showing that obesity-related inflammation in endothelial cells, smooth muscles and vasculature resident macrophages contribute to the development of obesity-related hypertension (Savoia and Schiffrin, 2006; Harrison et al., 2008; Duan et al., 2009). More recently, obesity-induced central neuroendocrine and neural changes, such as over-activation of the melanocortin system (Rahmouni et al., 2002; Rahmouni et al., 2005) and sympathetic nervous system (Purkayastha et al., 2011a; Purkayastha et al., 2011b), have been identified to underlie the pathogenesis of obesity-related hypertension. In this context, it was discovered that central metabolic inflammation is a critical pathogenic link between obesity and sympathetic upregulation of blood pressure (Purkayastha et al., 2011a; Purkayastha et al., 2011b). In these studies, researchers found that activation of IKKβ/NF-κB pathway by overnutrition in the MBH or more specifically the POMC neurons can upregulate sympathetic nervous activity to cause hypertension. On the other hand, systemic or CNS-targeted anti-

inflammatory interventions have demonstrated antihypertensive therapeutic effects. For example, in experimental rodent models, genetic inactivation of IKKβ/NF-κB pathway in POMC neurons (Purkayastha et al., 2011a) or pharmacological inhibition of brain ER stress upstream of NF-κB activation (Purkayastha et al., 2011b) both significantly intercept the development of obesity-related hypertension. Hence suppression of central metabolic inflammation holds two converging benefits in combating not only obesity but also obesity-related hypertension in an obesity-independent manner. It is also worth mentioning that due to CNS's important role in blood pressure control, NF-κB-induced central inflammation has also been causally involved in many other forms of hypertension such as essential hypertension, spontaneous hypertension, and angiotensin II-induced hypertension (Qadri et al., 2002; Kang et al., 2009; Wu and Schmid-Schonbein, 2011), and it should be an interesting topic to explore if similar central inflammatory mechanism is widely shared between these hypertension and obesity-related hypertension.

Stroke is a devastating cerebrovascular disease featuring rapid loss of brain function(s) due to interruption of cerebral blood supply. World widely, stroke is second only to cardiac ischemia in causing nonaccidental death. Based on the cause of disturbance of brain blood supply, there are ischemic stroke in which brain blood vessels are blocked by such as thrombosis, and hemorrhagic stroke in which brain arteries rupture due to pathological conditions such as hypertension, atheroma and brain aneurysm. Thus, obesity-related disorders such as hypertension, diabetes, dyslipidemia and atherosclerosis all become risk factors of stroke (Donnan et al., 2008). It has been clear that brain inflammation plays critical roles in stroke pathogenesis. Firstly, brain inflammation can generally mediate stroke development through promoting the above mentioned obesity-related metabolic disorders. Secondly, brain inflammation can directly induce ischemic brain damage (Iadecola and Anrather, 2011). In an ischemic event, brain neurons that are at the center of ischemic region quickly die from energy failure-induced degeneration and necrosis. Neurons in the ischemic penumbra, though remain viable, are under severe stress and vulnerable to adverse events such as post-ischemic inflammatory insults. Meanwhile, hypoxia-induced cell death or injury at early post-ischemic stage leads to release of a host of proinflammatory factors to trigger post-ischemic inflammation. This inflammation leads to microvascular occlusions and exacerbated ischemia at the intravascular site, and recruits perivascular macrophages and mast cells to reinforce post-ischemic inflammation and tissue damage at the perivascular site. The signaling mediators of inflammatory activation in stroke can include many molecules, including TLRs which respond to dead or damaged cells, ROS that result from hypoxia, and cytokines and chemokines produced by primary inflammatory response. Brain IKKβ is found to be activated in mouse stroke model, while inhibition of brain IKKβ/NF-κB can protect against stroke (Herrmann et al., 2005; Liu et al., 2009; Cheng et al., 2010; Jiang et al., 2012). In addition to directly inhibiting IKKβ/NF-κB, other relevant anti-inflammation methods have been explored to treat ischemic brain damage and stroke (Wang, 2005). For example, pharmacological anti-inflammatory agents such as granulocyte colony-stimulating factor, tetramethylpyrazine and picroside 2 (Liao et al., 2004; Lu and Xiao, 2007; Guo et al., 2010) or that promote expression of anti-inflammatory cytokines TGFβ and IL-10 (Becker et al., 1997; Cheyuo et al., 2012) all exhibited neuroprotective effects in animal stroke models. Clinically, IL-1 receptor blockade treatment has proven to markedly

decrease neurological impairments in stroke patients (Emsley et al., 2005). On the other hand, while anti-inflammation can effectively reduce ischemic brain lesions, its application in stroke should bear cautions, because stroke is known to be associated with postischemia immune suppression of lymphoid organs and increased risk for opportunistic infections (Meisel et al., 2005). Therefore, selective anti-neuroinflammation without compromising the function of systemic immune system may represent an optimal strategy for treating stroke.

VIII. METABOLIC INFLAMMATION AND NEURODEGENERATION

Neurodegenerative diseases are a group of severe health problems characterized by loss of neurons and neural cells, for example, Parkinson's disease, Alzheimer's disease and Huntington's disease. Though their symptoms differ from each other, these diseases have a common basis in pathology, that is, excessive intracellular accumulation of misfolded proteins such as α-synuclein aggregates in Parkinson's disease, mutant Huntingtin protein aggregates in Huntington's disease, and tau protein aggregates in addition to abnormal formation of extracellular β-amyloid plaques in Alzheimer's disease (Taylor et al., 2002). Accumulation of these toxic proteins is attributed to intracellular changes including organelle membrane damage, oxidative stress, mitochondrial dysfunctions and defective protein degradation machinery, and such cellular proteinopathy can lead to neural cell apoptosis and thus neurodegenerative diseases. In addition to the appreciated genetic etiology, overnutrition-related environmental factors are important for these neurodegenerative diseases. For example, obesity and insulin resistance are known to be two major risk factors of developing neurodegeneration. Along this line, these neurodegenerative diseases have been causally related to neural oxidative stress and mitochondrial dysfunction (Dawson and Dawson, 2003; Cui et al., 2006; Lin and Beal, 2006; DiMauro and Schon, 2008), neural ER stress (Xu et al., 2005; Uehara et al., 2006; Tabas and Ron, 2011) and neural utophagy defect (Komatsu et al., 2006; Martinez-Vicente and Cuervo, 2007; Lee and Gao, 2009), and it should be noted that all these neural stresses can be induced by overnutrition. Also importantly, the interactive relationships between intracellular stresses and neural IKKβ/NF-κB activation have been observed in neurodegenerative diseases, for example, oxidative stress (Lezoualc'h and Behl, 1998; Bazan et al., 2002; Yamashima, 2011), ER stress (Braun and Zischka, 2008; Giraud et al., 2010) and autophagy defect (Lim and Lim, 2011) have all been related to neural NF-κB activation in these diseases. Therapeutically, anti-inflammatory agents were shown to effectively treat animals with neurodegenerative diseases (Zhu and Qian, 2006; Hu et al., 2010; Kawamata and Shimohama, 2011), and moreover, clinical studies have shown promises in testing the potential use of anti-neuroinflammation in treating these diseases in humans (Choi et al., 2009; Dinarello, 2010; Glass et al., 2010). Altogether, based on evidences in literature, metabolic neuroinflammation can be significantly accountable for the susceptibility of developing neurodegenerative diseases under conditions of obesity and T2D.

Very recently, research has begun to appreciate that obesity and T2D also suffer from the problem of neurodegeneration. Most recent publications have interestingly demonstrated that chronic HFD feeding can lead to a reduction of certain hypothalamic neurons (Thaler et al., 2012; McNay et al., 2012; Li et al., 2012b). Based on more in-depth research findings, obesity-related metabolic inflammation is sufficient to disrupt neural stem cells in the brain

and especially in the hypothalamus to mediate a neurodegenerative mechanism of obesity-related diseases (Li et al., 2012b). In this research, it was shown that chronic HFD feeding activates IKKβ/NF-κB pathway in adult neural stem cells, leading to not only dramatic apoptotic depletion of NSCs but also their impaired neuronal differentiation, and over a long period, animals under chronic overnutrition had poor neural regeneration which results in reduced numbers of functional neurons (Li et al., 2012b). Though the focus of this research was on hypothalamic neural stem cells, it is likely that overnutrition and obesity employ the inflammatory mechanism to induce neurodegeneration in other brain regions. Thus, to study the involvement of inflammation in neural regeneration and degeneration will be much required, which may represent an important future research area in order to understand the neural inflammation in overnutrition-induced diseases.

IX. CONCLUSIONS

Research over the past decades has significantly unveiled the pathogenic mechanisms of overnutrition-induced metabolic diseases including obesity, insulin resistance, T2D, CVD and neurodegenerative diseases. A milestone understanding is that chronic overnutrition causes an atypical form of inflammation, namely metabolic inflammation to mediate the development and progression of these diseases. While this type of inflammation occurs in the peripheral sites to locally affect individual metabolic functions, it is significantly induced in the CNS and the hypothalamus, leading to the central dysregulation of metabolic physiology. Because the CNS is in the leadership position in regulating physiology including energy and nutrient metabolism, metabolic inflammation in the brain has widespread involvement in various aspects of metabolic diseases ranging from feeding disorder, energy imbalance, obesity, glucose intolerance, blood pressure increase to neurodegeneration. IKKβ/NF-κB pathway is a major molecular mediator for neural metabolic inflammation, and represents an anti-inflammatory target in order to treat various overnutrition-induced diseases. Despite these understandings, the knowledge on neural inflammation in metabolic diseases is still limited in general, and future research is much needed to delineate the involved molecular and cellular network and complex actions, which will help developing more specific and effective interventional strategies to conquer related diseases.

ABBREVIATIONS

AGRP	agouti-related peptide
CNS	central nervous system
CVD	cardiovascular diseases
ER	endoplasmic reticulum
HFD	high-fat diet
IKKβ	IκB kinase beta
JNK	c-Jun N-terminal kinase
MBH	mediobasal hypothalamus

NF-κB	nuclear factor kappa B
POMC	pro-opiomelanocortin
ROS	reactive oxygen species
SOCS3	suppressor of cytokine signaling-3
T2D	type-2 diabetes
TLR	toll-like receptor
TNF-α	tumor necrosis factor alpha

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