Review

Neuroinflammation and neurodegeneration in overnutrition-induced diseases

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Overnutrition-induced diseases such as obesity and type 2 diabetes (T2D) involve neural dysregulation of metabolic physiology. Recently, interdisciplinary research in neuroscience and immunology has linked overnutrition to a non-classical onset of inflammation in the brain, particularly in the hypothalamus. This neuroinflammation impairs central regulatory pathways of energy balance and nutrient metabolism, and leads to obesity, diabetes, and cardiovascular complications. This review describes recent findings on the roles of overnutrition-induced hypothalamic inflammation in neurodegeneration and defective adult neurogenesis, as well as in impaired neural stem cell regeneration, and their relevance to obesity and related diseases. In addition, commonalities in terms of neuroinflammation between neurodegenerative diseases and overnutrition-induced metabolic diseases are discussed. Targeting neuroinflammation and neurodegeneration will provide promising approaches for treating obesity and other overnutrition-related diseases.

Overnutrition-induced diseases and neuroinflammation

Metabolic syndrome refers to a collection of interconnected disorders such as obesity, insulin resistance, glucose intolerance, hyperlipidemia, and hypertension, and the explosion of these problems has become a global health concern. Obesity is a driver of metabolic syndrome and a well-recognized risk factor for the development of T2D and related cardiovascular diseases (CVDs). Known as a chronic and pathologic outcome of excessive caloric intake and storage, obesity development is significantly attributed to overeating and insufficient physical activity; therefore, lifestyle interventions such as diet and exercise remain two useful non-medical methods for controlling or limiting obesity development. However, despite this awareness and practice, obesity and obesity-related complications continue to spread. One difficulty may be related to the complexity of its etiology and pathogenesis. Indeed, recent advances have disproven the principle that obesity is a simple equation of caloric intake and expenditure, but instead is a complex neurological process involving neurohormonal and even neurotransmitter dysregulation (see Glossary) of physiology [1–9].

Research in neuroendocrinology and immunology over the past several years reveals that overnutrition-induced neuroinflammation is an important pathologic component, leading to a range of dysfunctions in the central nervous system (CNS) in obesity and in related metabolic diseases [10–14]. In addition to its negative impacts on neurohormonal signaling of hypothalamic neurons, as reviewed elsewhere [10–14], overnutrition-induced inflammation contributes to neurodegeneration [15–18] and disruption of hypothalamic neural stem cells [16], and proinflammatory molecules in the nuclear factor κB (NF-κB)/IκB kinase β (IKKβ) pathway are mechanistically accountable for this neurodegenerative disorder [16]. The newly established

Glossary

Hypothalamic inflammation: diverse types of molecular and cellular changes in the hypothalamus which may differ when responding to different inflammatory stimuli ranging from externally-induced local injuries such as infections, trauma, and stroke to systemic physiological changes such as metabolic abnormalities and aging.

Metabolic inflammation: chronic and low-grade inflammatory changes in overnutrition-induced metabolic diseases (such as obesity and T2D) which are displayed primarily in the form of inflammatory signaling and molecular products, but without evident onset of histological abnormalities or symptoms that are typically seen in infection- or cancer-induced inflammation.

Neurodegeneration: a general term indicating the progressive loss of structure or function of neurons, including neuronal death, and can include ER stress, protein misfolding and degradation, defects in autophagy, mitochondrial dysfunction, and apoptosis.

Neurogenesis: a process of generating neurons and other terminal neural cells from neural stem cells and/or progenitor cells; the process is active typically during prenatal brain development but recent research has shown that limited neurogenesis in several brain regions continues into adulthood.

Neurohormonal dysregulation: abnormal regulation arising from altered synthesis, release, signaling, or actions of neurohormones – hormonal substances released by neurons in the brain and in particular in the hypothalamus.

Neuroinflammation: a diverse range of molecular and cellular changes in the brain that may differentially take place in response to different inflammatory stimuli ranging from externally-induced brain injuries, such as infections, trauma, and stroke, to systemic changes including metabolic abnormalities and aging.

Neurotransmitter dysfunction: abnormal regulation arising from altered synthesis, release, signaling, or actions of neurotransmitters, the chemicals that transmit signals from a neuron to a target cell across a synapse, which can lead to induction of an action potential in the postsynaptic cell.

Overnutrition: persistent and prolonged exposure to excessive amounts of calorie-rich nutrients, often presented in the form of excessive lipids and carbohydrates.

Proopiomelanocortin (POMC) neurons: a group of neurons that synthesize and cleave POMC leading to the release of peptidyl hormone α-MSH, which plays an important role in regulating appetite, energy expenditure, body weight, and other metabolic parameters.

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link between obesity-related inflammation and neurodegeneration, although much still remains to be uncovered, enlarges the picture of obesity and related diseases. In addition, a mechanistic hint seems to be emerging which underlies the close relationship between overnutrition-induced metabolic diseases and neurodegenerative diseases such as Alzheimer's and Parkinson's [19–23]. Herein we review findings in overnutrition-related neuroinflammation, and the role of neuroinflammation in neural degeneration and regeneration in the context of overnutrition-induced obesity and related metabolic diseases.

Neuroinflammation in the hypothalamus

Research during the past decades has focused on examining peripheral tissues relevant to the pathogenesis of obesity and related diseases, such as skeletal muscle, liver, and fat, because they represent the metabolic sites which are predominantly responsible for nutrient utilization and storage. One significant discovery is that many metabolic dysfunctions in peripheral tissues are causally related to local inflammation [12,24–30]. Indeed, evidence derived from epidemiology, clinical medicine, and experimental research demonstrates that obesity and related diseases are associated with chronic low-grade inflammation in peripheral tissues and the circulation [12,24–30]. Inflammation in several peripheral tissues is mounted by the immune system, as well as by non-immune cells, and is critically mediated by the proinflammatory IKKβ/NF-κB pathway [12,28]. Recently, chronic overnutrition was shown to induce IKKβ/NF-κB-dependent inflammation in the CNS and particularly in the hypothalamus, a change that might contribute to the development of various overnutrition-related diseases [10–13].

The concept of overnutrition-induced hypothalamic inflammation

The hypothalamus is the master regulator of energy balance, governing physiological processes including feeding, energy expenditure, body weight, and glucose metabolism [31–36]. The mediobasal hypothalamus (MBH) senses circulating metabolic signals, such as leptin, insulin, gut hormones, and nutrients, and commands the downstream neurohormonal networks to control various aspects of metabolic physiology. In addition, hypothalamic neurons can project to the autonomic sites in the brain to modulate the sympathetic and parasympathetic nervous systems that control metabolic activities. From the perspective of pathophysiology, central neurohormonal and neurotransmitter dysregulations represent a critical neural basis for the development of metabolic diseases [1–5]. Along these lines, overnutrition-driven inflammation, also termed 'metabolic inflammation' [10–13], has been found to occur in the hypothalamus in the context of obesity and related metabolic diseases [37]. This type of hypothalamic inflammation has many features that differ from classical inflammation seen in diseases such as infectious diseases and cancers, and which can exert central anorexic actions to cause cachexia and sickness syndrome (reviewed in [11]). As observed in different types of research models with chronic or acute overnutrition [38–43], overnutrition-induced hypothalamic inflammation is in general manifested in modest magnitude, and often primarily in the form of molecular changes instead of morphological abnormalities, agreeing with the characteristic 'low-grade' inflammation in obesity and T2D.

Disease relevance of overnutrition-induced hypothalamic inflammation

With the emerging recognition of overnutrition-mediated hypothalamic inflammation, recent research has demonstrated that it is involved in the development of an increasing range of metabolic diseases, and most of these findings have been based on experimental models targeting the IKKβ/NF-κB pathway. Hypothalamic inflammation was initially revealed to link environmental nutritional excess to overeating, with the latter further sustaining the body overnutrition, leading to chronic energy imbalance that causes overweight and obesity [37–40,42,43]. In parallel, IKKβ/NF-κB-driven hypothalamic inflammation was shown to use a body-weight-independent mechanism to cause diabetic changes, including glucose intolerance, hepatic insulin resistance, and impaired insulin secretion [40,43–45]. More recently, it was discovered that the proinflammatory IKKβ/NF-κB pathway in the hypothalamus represents a pathogenic point that couples obesity with hypertension [46], thus further expanding the disease relevance of hypothalamic inflammation in the context of overnutrition. In addition, the disease significance of IKKβ/NF-κB-related signaling molecules, such as myeloid differentiation primary response gene 88 (MyD88) and the c-Jun N-terminal kinase JNK1, has also been investigated. For example, brain-specific knockout of MyD88, a downstream effector of toll-like receptor 4 (TLR-4) and an inducer of the NF-κB pathway, was shown to prevent leptin resistance and dietary obesity, and this protective effect was related to hypothalamic IKKβ suppression [39]. Also, high-fat diet (HFD) feeding can activate JNK1 in the hypothalamus [47], possibly in an IKKβ/NF-κB-dependent manner. Consistently, mice with brain-specific JNK1 deletion are protected from HFD-induced energy imbalance [48] or weight gain [47,48] as well as from systemic glucose and insulin disorders [47,48]. Together, hypothalamic inflammation in the CNS, that involves IKKβ/NF-κB and related molecules, is now emerging as an important contributor to an increasing range of overnutrition-induced diseases.

IKKβ/NF-κB signaling in overnutrition-induced neuroinflammation

Cellular pathways converging on central NF-κB activation

It is well-established that the NF-κB transcriptional program is a crucial regulator of immunity and inflammation [49–51]. Canonical NF-κB activation is induced predominately by the serine/threonine kinase IKKβ that phosphorylates and degrades IκB proteins, thus liberating NF-κB to enter the nucleus and induce transcription of many inflammatory genes. During the classical immune response and inflammation, IKKβ/NF-κB activation is induced by a number of cell-membrane receptors including TLRs. Recently, with the increasing recognition of TLR-mediated peripheral inflammation in obesity and T2D [52], TLRs have been shown to mediate the induction of obesity-related

neuroinflammation [38]. Cytokine receptors such as receptors for tumor necrosis factor α (TNF-α) have also been shown to mediate neuroinflammation in the context of obesity, and loss-of-function approaches showed that TNF-α receptor knockout [45,53] or brain-directed TNF-α receptor inhibition [54] reduced dietary obesity and prediabetes in mice. However, cytokines in the CNS can have diverse metabolic consequences, ranging from positive energy balance in obesity to negative energy balance in cachectic diseases such as chronic infections and cancers (reviewed in [11]). The different outcomes depend on multiple factors such as the sources and intensity of inflammatory stimuli, the affected cell types, and potentially other so far unidentified factors (reviewed in [11,55]). In addition to TLRs and certain cytokine receptors, overnutrition-induced neuroinflammation is mediated, perhaps in a primary manner, by receptor-independent intracellular organelle stresses and disturbances involving the endoplasmic reticulum (ER) [37,44], oxidative stress [56], and defects in autophagy [43]. Recent research has shown that ER stress [37,44] and autophagy defects [43] can converge on IKKβ/NF-κB to induce hypothalamic inflammation, providing a new scope in understanding the causes of overnutrition-induced neuroinflammation.

Compared to dividing cells in peripheral tissues, neurons in the brain are highly sensitive to intracellular stresses [57–59], including the metabolic stresses induced by chronic overnutrition [37,38,43,60–66]. The MBH in the hypothalamus is in a vulnerable anatomic position because of the partially leaky blood–brain barrier (BBB) in the MBH and, as a result, MBH neurons are exposed to excessive amounts of circulating nutrients which drive increased mitochondrial oxidation. When exposure to excess nutrients is prolonged, oxidative stress and mitochondrial dysfunction in these neurons can occur perhaps even prior to their induction in other cells [67]. Although detailed experimental studies are still needed, it is known that mitochondrial dysfunction and oxidative stress lead to inflammation, and potential mediators are intracellular NLRP3 inflammasomes [56] which can directly activate IKKβ/NF-κB [68]. At the same time, increased oxidative workload demands higher levels of ER activity, such as protein synthesis, which causes ER stress and which can also be potentiated by HFD-induced TLR4 activation [38]. Of note, hypothalamic ER stress has been shown to activate IKKβ/NF-κB in the hypothalamus [37,44]. In addition, overnutrition-induced cytosolic changes, such as dysfunctional mitochondria and ER, can lead to autophagy defects. Recent research demonstrated that autophagy defect is a late-onset intracellular factor that mediates overnutrition-induced brain IKKβ/NF-κB activation [43]. Importantly, whereas various intracellular organelle stresses promote inflammatory reactions [37,43,44], inflammation can reciprocally render cells more prone to the induction of intracellular stresses, including ER stress [38,69–71] and autophagy defects [72–74]. From a therapeutic perspective, central inhibition of ER stress [37,44,60,75] or central improvement of autophagic function [43] can both attenuate the detrimental effects of overnutrition through inhibiting NF-κB, further supporting the stress–inflammation connection in the neural mechanisms underlying these diseases.

Neuroinflammation inducers downstream of NF-κB

A question that arises is how neuroinflammation leads to metabolic diseases. Although one can deduce that the functions of inflamed neurons are generally compromised, leading to neuronal dysregulation of physiology, it is also of interest to understand the molecular events downstream of IKKβ/NF-κB that induce disease outcomes. However, this research is still in early stage, and to date few molecules have specifically been related to the pro-obesity and diabetic effects of neural IKKβ/NF-κB. One such molecule is suppressor of cytokine signaling-3 (SOCS3), an inhibitory signaling protein that inhibits both leptin and insulin signaling [76]. Studies have shown that overnutrition-induced IKKβ/NF-κB activation can cause upregulation of hypothalamic SOCS3 gene expression to induce hypothalamic leptin and insulin resistance [37]. Genetic mouse models have shown that SOCS3 knockout in hypothalamic neurons can improve central leptin signaling and reduce obesity [77–79], as does central IKKβ knockout [37], and overexpression of SOCS3 in the MBH can diminish the obesity-reducing effects of neural IKKβ inhibition [37]. Protein tyrosine phosphatase 1B (PTP1B) is another protein which, similarly to SOCS3, inhibits insulin and leptin signaling and, interestingly, PTP1B has been implicated in the IKKβ/NF-κB inflammatory pathway. For example, TNF-α, an activator of and also transcriptional target of IKKβ/NF-κB, can increase hypothalamic PTP1B expression [80], and neural PTP1B inhibition counteracts overnutrition-induced leptin resistance, obesity, and glucose disorders [81–83]. Of interest, brain PTP1B was recently linked to Alzheimer's disease in genetic mouse models [84], and thus may represent a connection between neurodegeneration and central mechanism of metabolic diseases. It is also noted that additional tyrosine phosphatases in the brain with functions relevant to obesity and related diseases were identified, such as T-cell protein tyrosine phosphatase (Tcptp) [85], suggesting that the molecular relationship between inflammation and tyrosine phosphatases warrants further investigation.

Neurodegeneration in obesity and related diseases

The importance of the hypothalamus in regulating bodyweight homeostasis was historically shown by lesion studies in animals [86]; indeed, ablation of some ventral hypothalamic regions causes overeating and obesity, whereas disruption of the lateral hypothalamus leads to anorexia and weight loss. However, based on the classical dogma that adult neurons do not undergo turnover, these studies mostly suggested the physiological importance of the hypothalamus, but barely addressed the etiology or pathophysiology of obesity and T2D. Recent research has shown a link between neurodegenerative mechanisms and the development of metabolic diseases such as obesity and related T2D [15–17]. First, chronic overnutrition during an 8-month period of HFD-feeding induced a modest but measurable reduction in the number of proopiomelanocortin (POMC) neurons in adult mice [15,16]. Second, chronic overnutrition was shown to increase the apoptosis of mature neurons [15,87], newborn neurons or dividing cells [17], or neural stem cells [16] in the hypothalamus, and caloric restriction can reverse some of these defects [17].

These findings align well with the finding from studies on postnatal hypothalamic development that neurons in the arcuate nucleus undergo postnatal turnover even in adult ages [17], and such postnatal neurogenesis occurs under physiological or experimental conditions [17,18]. On the other hand, the disease relevance of these observations remains to be tested; nevertheless, it was recently shown that long-term outcomes of overnutrition-induced neurodegeneration included the development of obesity and prediabetic changes [16]. In conjunction with these findings, hypothalamic neurodegeneration, independently of overnutrition, was found to lead to the development of adult-onset obesity in several genetic models [88–90]. Based on a few recent studies, hypothalamic inflammation can mediate obesity-related hypothalamic neurodegeneration [15,16,87], and this fits within the context that neuroinflammation is a common background shared by obesity/T2D and neurodegenerative diseases. Molecular research in this line has further revealed that IKKβ/NF-κB pathway is critically responsible for the neurodegenerative mechanism in the development of obesity and T2D. Taken together, overnutrition-induced hypothalamic neurodegeneration via inflammation represents an emerging and intriguing research paradigm in studying the central mechanism of obesity, T2D, and related diseases.

Disruption of neural stem cells by neuroinflammation in obesity and T2D

Adult hypothalamic neurogenesis and neural stem cells in mice

It has been known since the 1990s that adult mammalian brains contain multipotent neural stem cells able to generate different neural lineages including neurons, astrocytes, and oligodendrocytes [91,92]. The biological functions of adult neural stem cells might be to mediate adult neurogenesis, a process needed by the brain to maintain its plasticity in response to intrinsic and extrinsic changes [93]. Mammalian adult neural stem cells predominantly exist in the subventricular zone of the forebrain lateral ventricle and in the subgranular zone of the hippocampal dentate gyrus [94]. Not long ago, the hypothalamus of adult mice was found to have neurogenic activities in stimulated [95] or basal [96] conditions. It was also reported that, in a mouse model with genetically-induced AGRP neuron degeneration, *de novo* hypothalamic neurogenesis led to new cells which differentiated into leptin-responsive AGRP neurons [18]. A recent study further demonstrated that the arcuate nucleus in adult mice undergoes physiological neuronal remodeling via neurogenesis-mediated neuronal turnover [17]. Related to these findings, a fundamental question is whether the hypothalamic neurogenesis observed in these studies can be attributed to neural stem cells in this brain region. In answering this question, a recent study showed that tanycytes in the median eminence can function as neural stem cells, and induce postnatal hypothalamic neurogenesis in newborn pups or pre-adult young mice [97]. Li *et al.* reported that, in addition to the third ventricle walls, the MBH contains a significant number of neural stem cells in adult mice and, importantly, these cells are multipotent and can differentiate into neurons, astrocytes, and oligodendrocytes under both *in vivo* and *in vitro* conditions [16]. As presented in Figure 1, these recent stimulating findings can potentially direct hypothalamic research in a new and interesting direction.

The role of hypothalamic neurogenesis and neural stem cells in metabolic disease

The consistent observation of hypothalamic neurogenesis in adult mice leads to another key question, namely whether hypothalamic neurogenesis is relevant to metabolic diseases. Indeed, dietary obesity and leptin deficiency-induced obesity are both associated with reduced arcuate neurogenesis, with the arcuate nucleus containing fewer new neurons but more old neurons [17]. In the study by Li *et al.* [16] it was shown that chronic HFD feeding markedly impaired adult neural stem cells in the MBH, leading to a fractional (~10%) loss of POMC neurons in the MBH. To explore a potential causal role of impaired hypothalamic neurogenesis in metabolic diseases, this study further revealed that mice genetically engineered to deplete neural stem cells in the MBH chronically developed metabolic disorders, including overeating, glucose disorder, insulin resistance, and obesity [16]. Therefore, hypothalamic neurodegeneration in obesity can result from neuronal loss and reduced neural regeneration arising from impaired neural stem cells (Figure 1). Of note, such neurodegeneration requires a long duration of overnutrition [16], which agrees with the slow progression of neurodegenerative disease. Additionally, it seems that only certain types of neurons are susceptible to such injury, and this mechanism may result in only a modest loss of neurons, which might be insufficient to affect many classical neurological functions; however, the modest changes in certain neurons such as POMC neurons, which have small populations by nature but have important metabolic regulatory functions, can be significant and causally lead to the development of metabolic disease.

As mentioned above, Li *et al.* demonstrated that IKKβ/NF-κB-mediated inflammation has an important role in obesity-associated hypothalamic neurodegeneration [16]. Earlier research showed that NF-κB-mediated inflammation, via activation of TLR4 or MyD88 pathways [98] or the interleukin (IL)-1 receptor [99], can impair hippocampal neurogenesis in the disease context of memory loss or mood disorders. Along these lines, Li *et al.* found that chronic overnutrition led to IKKβ/NF-κB overactivation in hypothalamic neural stem cells in adult mice. Mechanistically, obesity-related neurodegeneration was attributed to excessive production of IKKβ/NF-κB-dependent cytokines such as TNF-α and IL-1β from microglial cells, which sustained an inflammatory state through the paracrine actions of these cytokines. Microglia-specific IKKβ ablation showed that breaking the inflammatory crosstalk between microglia and neural stem cells can promote hypothalamic neural stem cell survival and neurogenesis [16]. In this research, the authors further discovered that IKKβ/NF-κB activation employed the apoptotic program to impair the survival of hypothalamic neural stem cells, and the Notch signaling pathway to inhibit the neuronal differentiation of these cells [16]. Taken together, IKKβ/NF-κB-mediated neural inflammation not only affects the neurohormonal

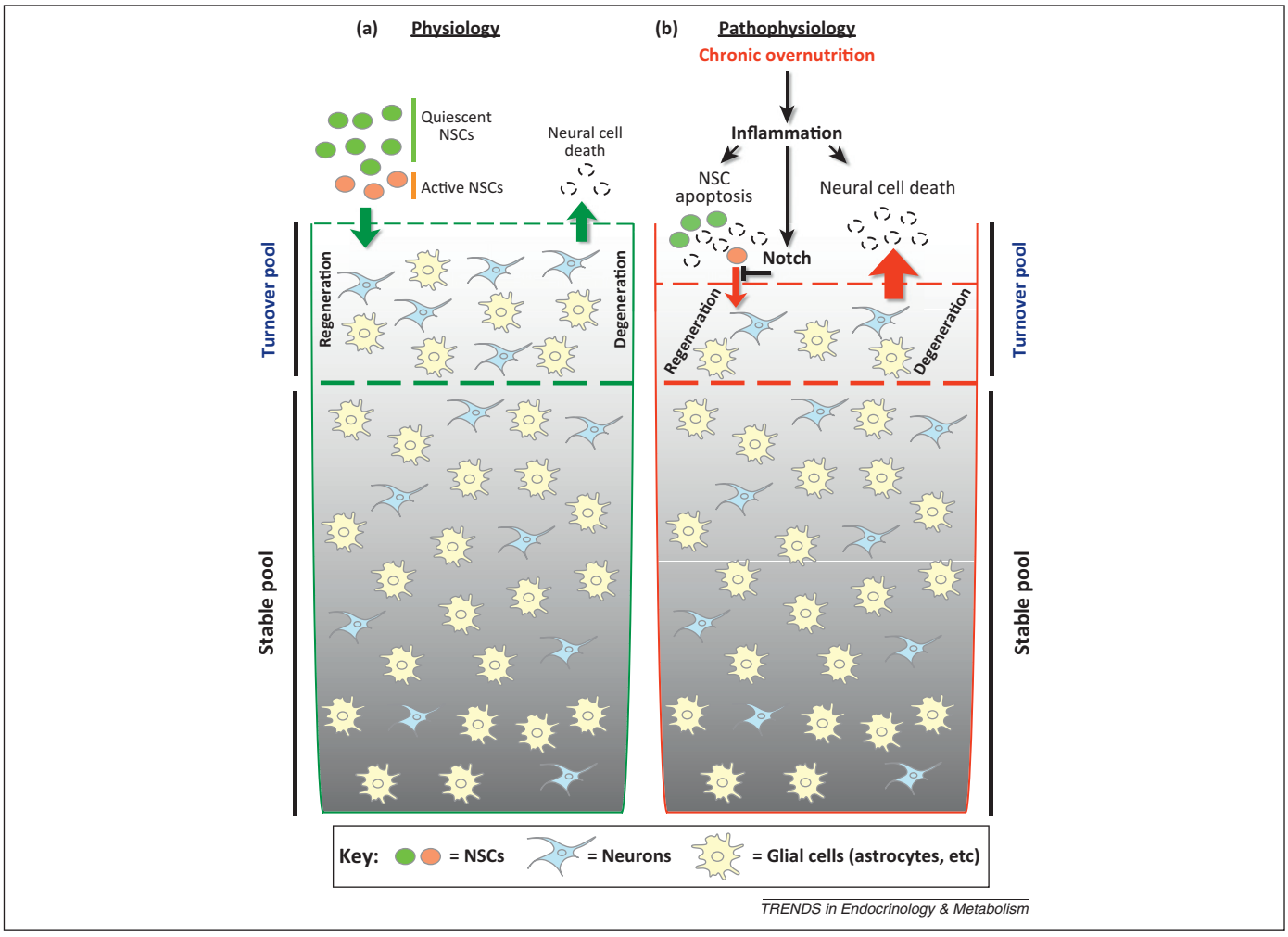

Figure 1. Inflammation-mediated neurodegeneration in overnutrition-related diseases. **(a)** Although the majority of neurons in the adult mammalian brain are terminally stable, a pool of neural cells including neurons undergoes slow turnover in normal physiology, and this process requires neurogenesis induced by adult neural stem cells (NSCs) including hypothalamic NSCs, a small number of multipotent cells residing in several brain regions including the mediobasal hypothalamus. Although NSC-directed neurogenesis in physiological conditions is rather slow and also region-specific, recent research suggests that it may have important roles in maintaining brain control of life-long physiological homeostasis. **(b)** Under pathophysiological conditions, such as long-term overnutrition and probably aging, the resulting neuroinflammation affects the turnover pool of neural cells in adult brain. This process involves the inhibitory action of neuroinflammation on survival and differentiation of NSCs, mediated by NF-κB-directed apoptosis and Notch signaling. The neurodegenerative change under these conditions is slow and modest; however, when it affects certain neuronal types which by nature have small populations but critical functions, it can produce severe disease outcome. For example, impairment of NSCs in the mediobasal hypothalamus can lead to a factional reduction of hypothalamic POMC neurons over a long period, and mediate the late-onset development of obesity and pre-diabetes.

signaling of hypothalamic neurons in the regulation of body and metabolic physiology, but also hinders neurogenesis, leading to neurodegeneration and the development of metabolic diseases. A schematic in Figure 2 is used to summarize the neuroinflammation-induced mechanisms of signaling defects, as well as neurodegeneration, which are both important for the development of overnutrition-induced disease.

Links between neuroinflammation seen in obesity/T2D and neurodegenerative diseases

Epidemiological and clinical studies suggest that obesity, T2D, and their related lifestyles (e.g., physical inactivity) are highly associated with Alzheimer's diseases and Parkinson's disease [20–23]. Conversely, therapeutic interventions of metabolic diseases have often been shown to protect against neurodegenerative disorders as well [100,101], suggesting that obesity and diabetes contribute to the development of neural degeneration and neurodegenerative diseases. The potential causal relationship between obesity/T2D and neurodegenerative diseases has also been suggested by several experimental animal models. For example, overnutrition can directly promote dopaminergic neurodegeneration in a mouse model of Parkinson disease [102]. Brain insulin-signaling changes in diabetes were reported to cause neuronal oxidative stress and mitochondrial dysfunction, and promote Huntington disease [103]. PTEN-induced putative kinase-1 (PINK1), a genetic locus responsible for familial Parkinson disease via neuronal apoptosis [104], was demonstrated to undergo altered regulation in obesity and T2D [105]. In addition, obesity- and T2D-driven neurodegenerative diseases depend on neuroinflammation, and an important inflammatory mediator is the IKKβ/NF-κB pathway which controls cell survival and apoptosis. For example, interleukin-6, a cytokine which is overproduced in obesity and diabetes, was shown to mediate degeneration of forebrain GABAergic interneurons, and this neurodegenerative effect was attributed to neuronal NF-κB activation and the subsequent induction of neurotoxic inflammatory products

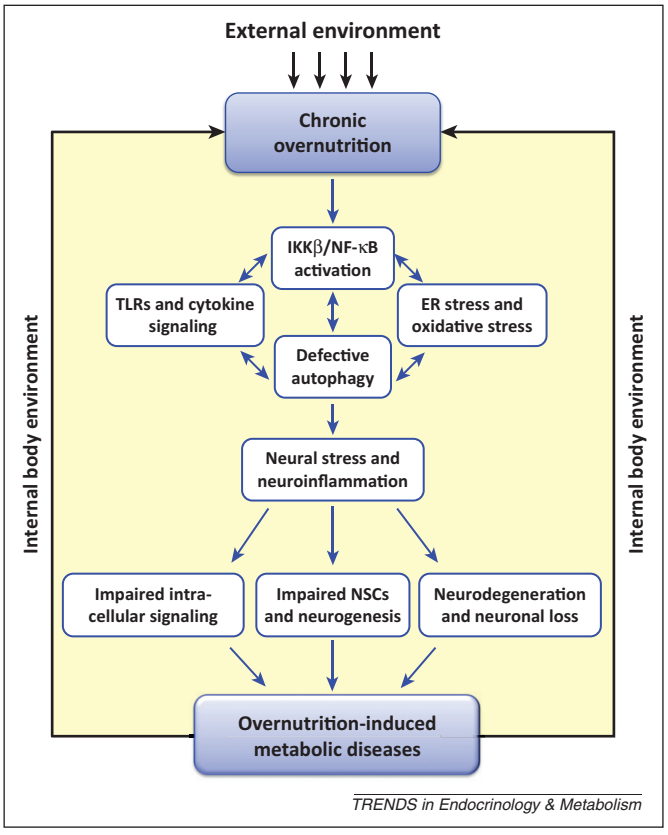

Figure 2. Role of neuroinflammation in overnutrition-induced diseases. Under conditions of chronic overnutrition, the mediobasal hypothalamus (MBH) is affected by chronic overnutrition, a prolonged nutritional change which primarily arises from environmental and sociobehavioral factors such as a Western diet, sedentary lifestyle, and disrupted diurnal rhythmicity. These lead to the IKKβ/NF-κB-directed inflammatory response and intracellular organelle stress in the MBH. Many of these cellular and molecular components promote each other, resulting in overnutrition-related neuroinflammation. Such neuroinflammation impairs intracellular hormonal signaling of regulatory neurons and disrupts neurogenesis through depletion of neural stem cells (NSCs). The progression of overnutrition-related diseases such as obesity and diabetes, characterized by hyperlipidemia and hyperglycemia, secondarily leads to pathophysiological overnutrition in the internal environment of the body, which exacerbates neuroinflammation. In summary, neuroinflammation employs multiple pathways, including hormonal signaling dysfunction and neurodegeneration, to link overnutrition to overnutrition-related diseases such as obesity, diabetes, and related complications. Abbreviation: TLRs, toll-like receptors.

[106]. Furthermore, whereas obesity and T2D are associated with metabolic overload and neuronal insulin resistance, both of these changes render neurons vulnerable to cell death through neural stress and inflammation [107,108]. Overall, neuroinflammation-induced neurodegeneration may be a common basis for not only metabolic diseases, such as obesity and T2D, but also for neurodegenerative diseases, and future research in this direction will broaden our understanding of both categories of disease.

Concluding remarks

Research during the past decade has demonstrated that obesity and its comorbidities are not only disorders of peripheral tissues but also fundamentally involve neurological changes that result in neural dysregulation and altered metabolic physiology. Recently, interdisciplinary research in neuroscience and immunology has linked overnutrition to IKKβ/NF-κB-directed inflammation in the brain, and particularly in the hypothalamus. This neuroinflammation was shown to impair the neurohormonal as well as autonomic regulations of energy balance and nutrient metabolism, leading to obesity, diabetes, and related cardiovascular diseases. As depicted in Figure 2, obesity-related neuroinflammation is induced in the brain by multiple processes and, although some underlying mechanisms may remain to be discovered, it is now clear that intracellular disturbances and stresses, including ER stress, oxidative stress, and autophagic defects, are important mediators. In the context of obesity and comorbidities, neuroinflammation-induced pathologic changes are also multifold, including loss of regulatory neurons and impaired neural regeneration resulting from neural stem cell defects. Collectively, all these pathologic changes contribute to a battery of central dysregulation that underlies the induction of overnutrition-induced diseases. The neurodegenerative mechanism of these diseases represents the most recent research advance, and the involvement of adult neural stem cell-directed neural regeneration is particularly attractive. On the other hand, because this is an emerging area of research, many unsolved questions remain (Box 1), but the clinical significance and possible avenues for targeting neuroinflammation and neurodegeneration to treat obesity and comorbidities warrant our attention.

Box 1. Outstanding questions

- What are the dynamic interactive upstream and downstream network pathways of overnutrition-induced neuroinflammation?
- What are the mechanistic aspects of the glia–neuron interaction in overnutrition-induced neuroinflammation?
- How important is the role of adult neural stem cells in the hypothalamus in metabolic physiology and diseases?
- How does neuroinflammation disrupt neural cell generation?
- Could neural stem cells be therapeutic targets for treating neuroinflammation and relevant diseases?
- Is neuroinflammation casually responsible for the relationship between classical neurodegenerative disease and overnutrition-induced metabolic disease?

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