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Hypothalamic Micro-inflammation: A Common Basis of Metabolic Syndrome and Aging

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Abstract

Chronic micro-inflammation is a hallmark of many aging-related neurodegenerative diseases as well as metabolic syndrome-driven diseases. Recent research indicates chronic caloric excess can lead to hypothalamic micro-inflammation, which in turn participates in the development and progression of metabolic syndrome disorders such as obesity, glucose intolerance and hypertension. Additionally, it was recently shown that age increase since young adulthood can, independently of nutritional status, cause hypothalamic microinflammation to mediate a central mechanism of systemic aging. Taken together, these findings suggest that the hypothalamus has a fundamental role, via hypothalamic microinflammation, in translating overnutrition and aging into complex outcomes. Here, we summarize recent work and suggest a conceptual model that hypothalamic microinflammation is a common mediator of metabolic syndrome and aging.

1. Co-basis of metabolic syndrome and aging: hypothalamic micro-inflammation

Metabolic syndrome, defined as a family of interrelated pathophysiological consequences of metabolic dysfunctions, in particular including obesity, hyperglycemia, insulin resistance, hyperlipidemia and hypertension, represents a pathogenic soil for the development of debilitating chronic diseases such as type-2 diabetes (T2D) and cardiovascular disease (CVD). Also importantly, metabolic syndrome is frequently associated with aging^{1,2}, and moreover, it can participate in the development of other aging-related diseases, for example, Alzheimer disease (AD), Parkinson's disease (PD) and some types of cancers^{3–6}. Conversely, caloric restriction (CR), a nutritional manipulation which effectively improves metabolic homeostasis, is known to counteract aging and aging-related disorders^{7,8}. Following from this close relationship between metabolic syndrome and aging, a major question is: could nutritional change and age increase engage a common mechanism in the

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progression to their interconnected disease outcomes and, if so, which organ(s) in the body play a leading role in this process?

The hypothalamus is a key neuroendocrine system known to regulate energy homeostasis via the orchestrated actions of neural pathways and neuroendocrine hormones which regulate energy balance and nutrient homeostasis^{9–16}. Nutritional status exerts important effects on various types of hypothalamic signaling, such as insulin and leptin pathways, and hypothalamic dysfunction is a critical cause of metabolic syndrome and its related diseases^{17–24}. For example, recent research has shown that chronic overnutrition induces inflammation-like changes in the hypothalamus^{25–35}, mediated by a low-degree activation of pro-inflammatory nuclear factor κ B (NF- κ B) and its upstream I κ B kinase β (IKK β)^{25–27,31–33,36–40}. These atypical neural inflammatory changes comprise hundreds of inflammatory genes, including classical inflammatory molecules such as tumor necrosis factor- α (TNF- α) and interleukins (ILs), which are dynamically induced during disease development, although many aspects of which still remain to be characterized. In general, these molecular inflammatory changes in the hypothalamus are often a result of hypothalamic low-level NF- κ B activation, and henceforth are termed “hypothalamic micro-inflammation”. This overnutrition-triggered, NF- κ B-dependent hypothalamic micro-inflammation can interrupt the central regulation of energy balance, glucose homeostasis and blood pressure, and mediate the core features of metabolic syndrome including obesity, glucose intolerance, and hypertension^{25–27,31–33,36,37,39–41}.

It should be noted that low-grade inflammation is also a hallmark of aging; the systemic level of inflammation is negatively correlated with human longevity^{42–45}. Studies using rodent models have shown that certain pro-inflammatory signaling pathways mediated by such as NF- κ B are activated in a variety of tissues during the development of aging^{46–48}. In accordance with the ‘free radical’ theory of aging⁴⁹ (see Glossary), chronic inflammation is known to damage cellular functions, and the relationship between inflammation and oxidative stress may have a critical role in aging development. In the central nervous system (CNS), neural inflammation is a feature of aging-related neurodegenerative diseases⁵⁰, and anti-aging effects of CR correlate with enhanced synaptic plasticity, neurogenesis and related protection against neurodegeneration in AD, PD, Huntington’s disease (HD) and stroke^{51–53}. Interestingly, much like chronic overnutrition, age increase since young adulthood can cause hypothalamic micro-inflammatory changes, albeit in a manner which can be independent of nutritional status. Recently, studies have shown that hypothalamic micro-inflammation promotes the development of systemic aging^{36,37,54}. This work is in agreement with various rodent models (Table 1) which have linked neural, endocrine or metabolic signals to the influences on aging and/or longevity. Therefore, NF- κ B-dependent hypothalamic micro-inflammation represents a shared means through which the conditions of overnutrition and aging can mediate the consequent development of metabolic and aging-related diseases. In the following sections, we will discuss the molecular and cellular mechanisms and physiological relevance of hypothalamic micro-inflammation comparatively in the context of overnutrition or aging.

2. Hypothalamic micro-inflammation via mitochondrial and ER dysfunctions

Unlike classical inflammation manifested in disease conditions like infections, trauma and certain cancers, overnutrition/aging-related inflammation is often related to an unbalanced nutrient influx which challenges intracellular organelles such as mitochondria and endoplasmic reticulum (ER). It has been appreciated that mitochondrial oxidative stress, at least through the chronic excess of reactive oxygen species (ROS), generates damage to cells and is implicated in the pathophysiology of metabolic syndrome as well as aging-related diseases^{55,56}. For example, overexpression of the antioxidant genes superoxide dismutases (SODs), catalase, or thioredoxin-1 was shown to delay aging-related physiological impairments or protect against aging-associated diseases in mice⁵⁷ and, conversely, knockout of an antioxidant gene such as SODs, methionine sulfoxide reductases or thioredoxin 2 in mice shortens lifespan and predisposes animals to deficits in normal aging or age-related diseases^{57,58}. On the other hand, it was recently shown that ROS production, presumably at physiological levels, can have biological actions, including metabolic functions^{59–61}. Along these lines, a few studies have reported that the aging process did not accelerate in *Sod2*^{+/-} mice⁶², *Sod3*^{-/-} mice^{63,64}, or *sod* mutant worms⁶⁵. Despite that oxidative stress was not clearly elevated in these animals with defective SODs^{63,65–67} – perhaps due to activation of stress resistance pathways⁶⁸, this literature should provoke us to assess other alterations in mitochondrial stress. Indeed, besides the elevated production of ROS, aging is associated with a wide spectrum of changes in mitochondria, including disorganization of mitochondrial structure, accumulation of mitochondrial DNA mutation, and functional decline in mitochondrial oxidative phosphorylation – all of which compromise normal cellular functions^{69–74}. Of the many mechanisms involved, inflammation is likely a significant link between dysfunctional mitochondria and organismal aging⁷⁵. Defective mitochondria can directly drive the production of proinflammatory cytokines and, reciprocally, inflammation can disrupt mitochondrial homeostasis, thus leading to an intracellular vicious cycle which should eventually compromise cellular functions. Therefore, although the contribution of ROS to aging remains to be elucidated, the connection between dysfunctional mitochondria and inflammation seems to play a role in the development of aging and aging-related diseases.

ER stress is a local, intracellular stress response that is prototypically reactive to the unfolded protein response (UPR) of the ER. When activated, UPR downstream cascades can interact with inflammatory molecules, including IKK β /NF- κ B and JNK-API pathways as well as oxidative stress pathways, all of which are known to influence metabolism⁷⁶. Research has demonstrated that ER stress can be formed in various peripheral tissues under overnutrition to participate in the mechanisms of metabolic syndrome⁷⁶. More recently, it was revealed that ER stress is induced in the hypothalamus under overnutrition^{27,77} to promote hypothalamic NF- κ B inflammation²⁷, and this hypothalamic interaction between ER stress and inflammation is sufficient to cause central insulin and leptin resistance²⁷. Consistent with these results, brain-specific deletion of X-box binding protein 1 (XBP1), which results in loss of ER function which led to ER stress in the hypothalamus, was reported to lead to leptin resistance and obesity⁷⁷. Furthermore, ER stress-promoted

hypothalamic inflammation causes sympathetic upregulation to induce glucose intolerance and hypertension³². In addition to metabolic diseases, ER stress may also play a role in aging. For example, in aging-related neurodegenerative diseases such as HD, AD, amyotrophic lateral sclerosis and PD, abnormal protein degradation along with ER stress has been proposed to be mechanistically important^{78–81}. Altogether, brain ER stress can contribute to certain aspects of hypothalamic micro-inflammation, although it is unclear whether this mechanism is early enough to initiate inflammation. Also, it remains to be addressed if ER stress in the brain is critical for normal aging as opposed to aging-related brain diseases.

3. Hypothalamic micro-inflammation via RNA stress response

RNA stress response and its associated formation of stress granules in the cytoplasm of cells regulate eukaryotic mRNA translation and decay in response to environmental dynamics⁸². RNA stress granules and its pathological accumulation have been implicated in the development of several degenerative diseases⁸³. Recently, it was shown that obesity- and aging-associated RNA stress response leads to an acceleration in I κ B α mRNA decay and therefore activation of proinflammatory NF- κ B signaling in the hypothalamus, therefore contributing to hypothalamic inflammation-induced prediabetic changes⁸⁴. Detailed investigation revealed that the loss of I κ B α mRNA and resultant activation of NF- κ B-mediated inflammation in the hypothalamus is induced by excessive production of TGF- β from astrocytes in obesity or aging⁸². It is worth noting that, unlike classical NF- κ B activation that requires membrane receptor-activated kinases such as IKK and TAK1, TGF- β modulates this machinery of mRNA quality control to discharge I κ B α which would otherwise bind and inhibit NF- κ B. These findings identified a new molecular mechanism of NF- κ B activation and a potentially early mediator of inflammatory changes in the hypothalamus, and also indicate that cross-talk between astrocytes and neurons plays a role in mediating obesity- and aging-associated hypothalamic NF- κ B activation and inflammation.

4. Hypothalamic micro-inflammation via autophagy dysfunction

Autophagy is a conserved mechanism of intracellular quality controls, a process that is mediated through the lysosomal pathways of protein degradation and is critical for development and cellular homeostasis of organs. A growing body of evidence now suggests that alteration or dysfunction of autophagy causes accumulation of abnormal proteins and/or damaged organelles, thereby leading to neurodegenerative disease. Autophagy-mediated cellular quality control is particularly important for neurons, because neurons do not undergo cell division and thus cannot redistribute abnormal proteins or damaged organelles through cell passaging. Also, autophagy is important for maintaining a healthy neuronal environment as well as the polarized morphology and protein trafficking of neurons. Autophagic decline has been recently implicated as a driving force in neurodegeneration in mice⁸⁵, and decline of autophagy is observed during the course of normal aging as well as in the development of aging-related diseases in human and rodent organs, including the brain^{86,87}. Genetic studies demonstrated that inhibition of brain autophagy by knockout of either autophagy-related protein Atg7 or Atg5 disrupts neural function and leads to

neurodegeneration^{88–90}, and may contribute to the development of neurodegenerative diseases⁹¹. Also, autophagy can reduce toxic protein aggregation in neurons to counteract neurodegenerative disease^{89,90}, and this effect can lead to lifespan increase in *Drosophila* or mice^{92–95}. Independent of aging, chronic overnutrition was recently shown to impair autophagic function in the hypothalamus³¹. Compared to the induction of hypothalamic inflammation by ER stress or RNA stress granules²⁷, autophagy dysfunction is a late event in the development of hypothalamic micro-inflammation³¹. Inhibition of autophagy in the mediobasal hypothalamus can promote hypothalamic NF- κ B-dependent inflammation and greatly accelerate the development of diet-induced obesity, while inhibition of NF- κ B in the brain significantly reduces the disease outcomes of hypothalamic autophagy decline³¹. Thus, chronic overnutrition-mediated hypothalamic autophagy defect is a key cause of hypothalamic dysregulation that leads to energy imbalance and related metabolic disorders. This defect may participate in the hypothalamic mechanism of aging, given the recently revealed role of hypothalamic NF- κ B in the control of systemic aging³⁶. Future research is much needed to detail the effects of neuronal autophagy in the development of aging and aging-related disease.

5. Cellular diversity in mediating hypothalamic micro-inflammation

Glial cells, which comprise astrocytes, oligodendrocytes and microglia, are non-neuronal cells that constitute neural microenvironment, form myelin, and provide support and protection for neurons. In addition to these structural, metabolic and supportive functions, glial cells were recently shown to have gliotransmission^{96,97} and also mediate the neuroinflammatory response⁹⁸. For example, in this last case, astrocytes have been identified to work as an important source of inflammation in the brain via activation of gp130, NF- κ B, MAPK and Jak1/Stat1 pathways^{99,100}. Hypothalamic astrocytes are also responsible for producing excess TGF- β in obesity and aging conditions, causing the decay of I κ B α mRNA and atypical activation of proinflammatory NF- κ B in the hypothalamus, and subsequent pro-diabetic development⁸⁴. Microglial cells, which are the resident macrophages of the brain, are critically involved in response to neural injuries – partly through the release of inflammatory cytokines, can, however, aggravate pathophysiology in the context of metabolic or neurodegenerative diseases^{101–105}. Recently, it was shown that hypothalamic microglia-neuron crosstalk via NF- κ B-directed inflammation is causally important for aging development³⁶. In addition to these glial cells, the vasculature and the blood-brain barrier (BBB) provide the foundation of brain functional integrity, and are subject to aging-associated functional and structural decline, characterized by loss or deterioration of capillary endothelium and supporting cells and an increase in BBB permeability. Indeed, brain vasculature is altered under conditions of aging¹⁰⁶, which is further damaged in diseases such as cerebrovascular ischemia and stroke as well as hypertension, which promotes renal damage, vascular inflammation and oxidative stress, leading to increased BBB permeability. In general, brain vascular and endothelial dysfunctions in either aging or metabolic diseases are both related to oxidative stress and inflammation, including systemic stress and pro-inflammatory signals which can activate brain microglia^{107,108}. Along this line, the importance of anti-inflammatory actions by peroxisome proliferator-activated receptors (PPARs) in vascular cells has been of great

interest. For example, PPAR γ activation was shown to protect the cerebral vasculature via its anti-inflammatory mechanism^{109,110}. Moreover, the vascular endothelial niche is important for neurogenesis¹¹¹, and given that neural inflammation mediates neurodegeneration, the complex interactions among brain endothelial cells, neural stem cells and inflammation might be crucial for the brain mechanism of metabolic syndrome and aging.

6. Hypothalamic micro-inflammation affects neural stem cells and neurogenesis

Neural stem cells (NSCs) are characterized by the abilities to undergo self-renewal and to differentiate into three types of neural cells, i.e., neurons, astrocytes, and oligodendrocytes. Adult NSCs are found mainly in the subgranular zone (SGZ) of the hippocampal dentate gyrus and in the ventricular-subventricular zone (SVZ). Neurogenesis in these regions throughout the lifespan is essential for olfactory and cognitive functions in rodents¹¹². Recently, two independent studies revealed that the hypothalamus of adult mice contains hypothalamic NSCs^{39,113}. Li *et al*³⁹ discovered that there are *bona fide* hypothalamic NSCs (namely htNSCs) predominantly in the mediobasal hypothalamus and the wall of the third ventricle. Consistent with these results, Lee *et al*¹¹³ found that radial tanycytes in the median eminence of the hypothalamus have stem cell-like properties and can give rise to neurons. Long-term overnutrition via high-fat diet feeding can impair htNSCs at least through microglial NF- κ B inflammation³⁹, and this effect was shown to be a basis of the neurodegenerative mechanism in diet-induced obesity and pre-diabetes³⁹. Very recently, the physiological and therapeutic relevance of htNSCs were demonstrated in mice⁴⁰. In this study, Li *et al*⁴⁰ showed that partial ablation of htNSCs caused weight gain and glucose intolerance, while implantation of survival-improved htNSCs, on the other hand, counteracted obesity and glucose disorder. With regard to aging, there is a progressive decline in neurogenesis and prevalence of adult NSCs with concomitant deterioration in cognitive functions¹¹⁴, and this impairment is mediated at least by hypothalamic NF- κ B activation which reduces gonadotropin-releasing hormone (GnRH)-mediated neurogenesis³⁶. Therapeutically, GnRH treatment can prevent the negative effect of neuroinflammation on neurogenesis and therefore might protect against aging physiology³⁶. Although, further research is much warranted, these recent findings suggest the potential of targeting the hypothalamus via NSC therapy to treat complex disease.

7. Induction of metabolic syndrome by hypothalamic micro-inflammation

With an increasing appreciation of overnutrition-induced hypothalamic micro-inflammation, some research has sought to understand if such atypical inflammatory changes in the hypothalamus are pathologically important for overnutrition-related diseases. A focus of these studies has been on two neuronal subpopulations in the mediobasal hypothalamus which act as the first-order regulation of metabolic balance, i.e., anorexigenic neurons expressing proopiomelanocortin (POMC) and orexigenic neurons expressing agouti-related peptide (AgRP). In response to feeding or physiological fat gain, increased secretion of insulin from pancreatic beta cells and leptin from fat tissue are known to inhibit AgRP neurons and activate POMC neurons, leading to decreased energy intake and increased

energy expenditure and therefore body weight homeostasis. This mechanism is, however, compromised during the development of obesity, partially due to chronic nutritional challenge-inflicted reduction in leptin and insulin signaling in the hypothalamus. It was reported that activation of NF- κ B-dependent inflammatory changes in the mediobasal hypothalamus is responsible for the loss of leptin and insulin signaling and, of note, hypothalamic AgRP neuron-specific IKK β ablation provided protective effects against hyperphagia, obesity and glucose intolerance²⁷. In addition to targeting NF- κ B signaling, several upstream and downstream molecules, including MyD88, SOCS3 and ER stress mediators, have been studied. Inhibition of any of these molecules in the CNS was sufficient to provide an anti-obesity effect in mice^{29,77,115}, although it remains unexplored whether AgRP neurons are crucial. In contrast to AgRP neurons, inhibition of IKK β in POMC neurons was insufficient to affect obesity³³. However, prolonged overnutrition impairs neurogenesis of htNSCs and, as a result, it led to a fractional loss of POMC neurons which might participate in this neurodegenerative mechanism of obesity-T2D syndrome^{35,39,116}. Therefore, the anti-obesity effect of inhibiting hypothalamic micro-inflammation for the long run seems to involve a counter-neurodegenerative action and thus the maintenance of POMC neuronal population in the hypothalamus.

In addition to its effects on feeding and body weight, hypothalamic micro-inflammation impinges on multiple components of metabolic syndrome ranging from glucose intolerance to hypertension. For example, ER stress-mediated inflammation in the hypothalamus was reported to set off glucose intolerance and a rise in blood pressure, and these effects can occur independently of body weight change, while inhibiting ER stress or NF- κ B could attenuate these alterations³². Mechanistically, these effects are mediated by hypothalamic inflammation-induced upregulation of the sympathetic pathway³². Of interest, IKK β /NF- κ B inflammatory cascade in POMC neurons has a direct role in obesity-related hypertension, as suggested by the finding that inhibition of this pathway in POMC neurons is able to reduce the magnitude of hypertension³³. Of course, there are many other types of hypothalamic neurons playing important regulatory or supporting roles in the central control of physiology and, in pre-diabetic or aging conditions, these cells might not be spared from the effects of hypothalamic micro-inflammation. Exposure of these hypothalamic neurons to inflammatory changes, including those mediated by activation of the pro-inflammatory IKK β /NF- κ B pathway, could lead to various onsets of neuronal injuries and dysfunctions, which can have a wide range of negative impacts on normal physiology and thus contribute to diverse outcomes in relation with metabolic syndrome. While many details remain to be unveiled, recent research has formulated a basis for concluding that hypothalamic micro-inflammation is a mechanistic link between overnutrition and metabolic syndrome.

8. Induction of aging pathology by hypothalamic micro-inflammation

In general, chronic inflammation is closely associated with aging, a phenomenon known as “inflammaging” (Glossary). In recent work using mouse models, it was reported that molecular inflammation in the hypothalamus via activation of pro-inflammatory NF- κ B pathway in hypothalamic microglia hindered neurogenesis, accelerated cognitive decline and aging, and reduced lifespan³⁶. However, it remains largely unclear how inflammation is initially triggered in aging, although it was recently shown that intracellular RNA stress

response⁸⁴ and TNF- α -mediated inflammatory crosstalk between hypothalamic microglia and neurons³⁶ are involved. It is also conceivable that tissue changes during aging development, such as adiposity and immune dysfunction, secondarily provide contributions to inflammaging. Regardless of insufficient understanding as to its primary causes, such inflammatory changes in the hypothalamus were recently demonstrated to inhibit GnRH-directed neurogenesis, and GnRH therapy was shown to slow down aging in mice³⁶. In addition to GnRH neurons, other hypothalamic neurons such as AgRP neurons and POMC neurons could be relevant to aging development, too. For example, damage in AgRP neurons was linked to neurodegenerative disease and aging-related functional deteriorations^{117,118}. Aging and aging-associated neurodegenerative diseases are also associated with neuronal oxidative stress and mitochondrial dysfunction, leading to neuronal dysfunction or death^{119–122}, including in AgRP neurons and other hypothalamic neurons^{117,118}. Adult POMC neurons are sensitive to damage induced through chronic overnutrition-impaired neurogenesis, resulting in a fractional loss of POMC neurons. These changes have been known to cause metabolic derangements^{35,39}, perhaps representing a mechanistic link between aging and aging-associated metabolic diseases. Finally, it also has been shown that hypothalamic POMC neurons, via an IKK β /NF- κ B inflammatory mechanism, mediate illness-induced anorexia¹²³ (a problem characterized by weight loss and muscle atrophy), which is also seen in advanced aging. Recently, Satoh *et al*¹²⁴ showed that brain-specific overexpression of Sirt1, the mammalian Sir2 ortholog, can extend lifespan in mice via activation of dorsomedial and lateral hypothalamic nuclei. Of interest, Sirt1 has been known to inhibit NF- κ B signaling and act as an inflammatory suppressor in mice^{125,126}. Sirt6, another sirtuin in mammals, also inhibits NF- κ B signaling by deacetylating the H3K9 at NF- κ B target loci¹²⁷. Further studies are needed to test if Sirt6 can act in the hypothalamus to affect aging. In addition, using *C. elegans* and *Drosophila*, several types of neurons have been shown to mediate longevity^{128–134}, while it remains unexplored what the mammalian counterparts of these neurons are, and if manipulations of these neurons in mammals have roles in slowing down aging and promoting longevity.

Concluding remarks

Research in the last few years has greatly advanced our understandings on the role of the brain in the development of overnutrition- and aging-associated diseases. The pathogenesis of these diseases involves dysregulation of a number of neural signaling pathways and neural cell types, including signaling and cells that are responsible for adaptation to energy status and for resistance to stress. Chronic presence of micro-inflammation is one core feature shared by all these health problems, and is exhibited broadly across different organs, including the brain. As outlined in this review, chronic micro-inflammation in the hypothalamus is detrimental to tissue homeostasis and is, at least in part, the brain basis for a number of disease phenotypes under conditions of chronic overnutrition or aging. One important piece of this puzzle, as highlighted in this review, is that chronic micro-inflammation impairs hypothalamic regulatory functions, and disrupts its neural and neuroendocrine controls over a wide range of physiological processes. For that reason, the alterations in diverse neural cells during the course of overnutrition-induced or aging-associated diseases are not merely accompanying events, but play causative roles and significantly contribute to aging or disease progression (Fig. 1). While recent studies in

mouse models have provided some initial evidence to support this notion, a thorough, comparative analysis of cell types and their interaction for initiating and propagating the inflammation has yet to be conducted, and physiological and disease relevance of hypothalamic micro-inflammation still needs to be studied in detail (see Outstanding Questions).

Glossary

‘Free radical’ theory of aging	also referred to as the ‘oxidative stress’ theory of aging, argues that accumulation of free radical damage causes the aging of an organism. Free radicals are molecules or atoms with unpaired electrons and are generated by intracellular redox reactions or from exogenous sources such as ionizing radiation. Highly reactive free radicals can oxidize other molecules and cause damage to biological structures, such as causing DNA cross-linking, that in turn leads to many biological changes during aging
Overnutrition	chronic uptake (weeks to months in rodents and longer duration in humans) of excessive amounts of calories, for example, through overeating of calorie-rich food such as high-fat diet
Pre-diabetes	a pro-diabetic metabolic condition which often features glucose intolerance, insulin resistance, hyperlipidemia, and obesity, and a few others, which reflects an early therapeutic window to prevent the development of T2D
Inflammaging	aging-associated changes in inflammatory networks, characterized by chronic, low-grade pro-inflammatory cellular status or microenvironment. The initial causes may include various intracellular stresses such as ER stress, RNA stress and mitochondrial dysfunction. It also refers to promotion of aging process by these inflammatory changes

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Outstanding questions

- How might hypothalamic micro-inflammation differ in normal aging versus aging-related chronic diseases? What causes these differences, and at what stage could they be reversible?
- How are the functions of other brain regions affected by hypothalamic micro-inflammation, which may further contribute to the progression of metabolic syndrome and aging?
- What are the relationships between hypothalamic inflammation and peripheral inflammation, which is also induced by chronic overnutrition and during aging?
- What interventional targets and methods can be practically developed to reduce human hypothalamic micro-inflammation, and therefore counteract metabolic syndrome-driven and aging-related diseases in patients?

Highlights

- Introducing the concept of hypothalamic micro-inflammation;
- Discussing intracellular and cellular mediators of hypothalamic micro-inflammation;
- Discussing the role of hypothalamic micro-inflammation in metabolic syndrome;
- Discussing the role of hypothalamic micro-inflammation in aging.

Figure 1. Intracellular and cellular networks of hypothalamic micro-inflammation under chronic overnutrition or aging

Overnutrition and aging trigger several cellular and mechanistic stressor factors that precipitate hypothalamic micro-inflammation. Activated neuroinflammatory axis and related proinflammatory cytokines through neuronal interactions, glia-glia and neuron-glia crosstalk impede hypothalamic regulatory functions as well as hypothalamic neural stem cell (NSC)-directed neurogenesis, and therefore collectively mediate and propagate the development of metabolic dysfunctions and aging related disorders.

Table 1

Effects of manipulating neuroendocrine pathways on longevity.

Animals	Sex	Gene of Target	Manipulation	Medium or mean lifespan	Maximum lifespan	Comments	Ref
Mouse C57BL/6	Male Female	IGF1R	Brain-specific heterozygous	↑	No change	Delayed growth, increased adiposity	135
Mouse C57BL/6	Male Female	IGF1R	Brain-specific knockout	No change	No change	Severe growth retardation	135
Mouse C57BL/6	Male Female	IRS2	Brain-specific hetero- or homozygous knockout	↑	↑	Obesity, glucose intolerance	136
Mouse C57BL/6	Male Female	IRS2	Brain-specific heterozygous knockout	No change	No change		137
Mouse C3H	Male Female	Klotho	Transgenic overexpression	↑	↑	Aging retardation	138
Mouse (Ames)	Male Female	Prop-1	Mutation	↑	↑	Deficiency of GH and other pituitary hormones	139
Mouse (Snell) C3H/HeJ × DW/1	Male Female	Pit1	Mutation	↑	↑	Deficiency of GH and other pituitary hormones	140
Mouse (Laron) 129Ola × BALB/c and C57BL/6	Male Female	GHR/BP	Knockout	↑	↑	Reduced plasma IGF-1 and IGFBP-3	141,142
Mouse C57BL/6 and Ola-BALB/cJ	Male Female	GHR	Knockout	↑	↑	Decreased body weight, insulin and IGF-1 levels	142
Mouse (C57BL/6 × 129SV)	Male Female	GHRH	Knockout	↑	↑	Increased activity, body fat, sensitivity to insulin	143
Mouse (Little) C57BL/6	Male Female	GHRHR	Mutation	↑	↑	GH deficiency and reduced IGF-1	140
Mouse C57BL/6	Male	IKKβ	Mediobasal hypothalamic overexpression	↓	↓	Aging acceleration	36
Mouse C57BL/6	Male	IκBα	Mediobasal hypothalamic overexpression	↑	↑	Aging retardation	36
Mouse C57BL/6	Male	IKKβ	Brain-specific knockout	↑	↑	Aging retardation	36
Mouse C57BL/6	Male	SIRT1	Brain-specific overexpression	↑	↑	Reduced mortality rate and cancer, youthful physiology	124
Mouse C57BL/6	Male Female	UCP2	Overexpression in hypocretin neurons	↑	Unknown	Elevated hypothalamic temperature, reduced core body temperature	144
Mouse FVB/N	Female	uPA	CNS-specific overexpression	↑	Unknown	Reduced food intake, body weight and size	145

Animals	Sex	Gene of Target	Manipulation	Medium or mean lifespan	Maximum lifespan	Comments	Ref
Mouse UM-HET3	Male Female		Acarbose	↑	↑	Improved liver function	146
Mouse UM-HET3	Male		17- α -estradiol	↑	No change	No lifespan change on female	146
Mouse C57BL/6 and B6C3F1	Male		Metformin, oral	↑	↑	High dose of metformin is toxic	147
Mouse UM-HET3	Male Female		Rapamycin, oral	↑	↑		148
Rat Sprague-Dawley		AGT	Astrocyte-specific knockdown	↑	↑	Improved cardiovascular function and locomotion	149,150

Abbreviations: GH: growth hormone; AGT: angiotensinogen; GHR: growth hormone receptor; Pit1: Pituitary-specific transcription factor 1; Prop-1: Homeobox protein prophet of Pit-1; UCP2: uncoupling protein 2; uPA: urokinase-type plasminogen activator; ↑: increase; ↓: decrease.