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Disruption of Neurogenesis by Hypothalamic Inflammation in Obesity or Aging

Sudarshana Purkayastha and Dongsheng Cai*

Department of Molecular Pharmacology, Diabetes Research Center, Albert Einstein College of Medicine, Bronx, NY 10461

Abstract

Adult neural stem cells contribute to neurogenesis and plasticity of the brain which is essential for central regulation of systemic homeostasis. Damage to these homeostatic components, depending on locations in the brain, poses threat to impaired neurogenesis, neurodegeneration, cognitive loss and energy imbalance. Recent research has identified brain metabolic inflammation via proinflammatory I κ B kinase- β (IKK β) and its downstream nuclear transcription factor NF- κ B pathway as a non-classical linker of metabolic and neurodegenerative disorders. Chronic activation of the pathway results in impairment of energy balance and nutrient metabolism, impediment of neurogenesis, neural stem cell proliferation and differentiation, collectively converging on metabolic and cognitive decline. Hypothalamic IKK β /NF- κ B via inflammatory crosstalk between microglia and neurons has been discovered to direct systemic aging by inhibiting the production of gonadotropin-releasing hormone (GnRH) and inhibition of inflammation or GnRH therapy could revert aging related degenerative symptoms at least in part. This article reviews the crucial role of hypothalamic inflammation in affecting neural stem cells and thus mediates the neurodegenerative mechanisms of causing metabolic derangements as well as aging-associated disorders or diseases.

Keywords

Hypothalamus; inflammation; neural stem cells; obesity; aging; brain; IKK β ; NF- κ B

Introduction

It is now widely accepted that neurogenesis in the adult brain is very much an often-seen case ^{1–6} and not a fictional myth as was believed and refuted several decades ago ⁷. New neuron formation and neuronal stem cells (NSCs) are prevalent in several brain areas ^{8–14}. Very recently, the hypothalamus – the neuroendocrine headquarter of the body was discovered to be a rich NSC niche and a hotspot of neurogenesis ^{15,16}. These hypothalamic NSCs (htNSCs) seem to account for an seminal role of the hypothalamus in neuroendocrine modulation for the whole-body physiology ^{17–20} and even systemic aging ²¹, and in pathophysiology, disruption in the neurogenic function of them through local insults or extrinsic stimuli in this hypothalamic region may have broad impacts on neuronal milieu resulting in neurodegenerative manifestations.

Neuroinflammation has been identified as a primary assaulting candidate for impaired neurogenesis and NSC loss ²². Though acute inflammatory responses are known to provide

*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.

obligatory defensive mechanisms of the body, persistent inflammation impairs neurogenesis, NSC survival and differentiation¹⁶ and promotes aging-related decline²¹ and neurodegenerative diseases^{23–26}. In the hypothalamus, the proinflammatory axis comprising I κ B kinase- β (IKK β) and its downstream nuclear transcription factor NF- κ B (IKK β /NF- κ B signaling) is augmented with aging²¹ or overnutrition^{27,28}. Overnutrition-induced or aging-mediated upregulation of the IKK β /NF- κ B signaling pathway have been found to promote neurodegeneration and cognitive decline²¹, hypothalamic stem cell degeneration¹⁶, in addition to causing obesity and chronic energy imbalance^{19,20,28–33}. Furthermore, evidences and connotations referring to overnutrition-induced neurological diseases such as Alzheimer's (AD) and Parkinson's (PD)^{34–38} further proclaim a link between overnutrition/aging-induced neuroinflammation and neurodegenerative disorders. This current review will outline the neuroinflammatory mechanisms that link overnutrition or aging to the development of neurodegenerative disorders or systemic aging, and also discuss about the related therapeutic potentials and remaining challenges.

Adult neural stem cells and neurogenesis

Disproving the long-held dogma that brain cells are devoid of any regeneration capacity, it has now been established beyond doubt that neurogenesis occurs in discrete regions of the adult brain. Improved scientific and technological advancements have led to the identification and isolation of NSCs in the CNS of adult mammals over the past few decades. Although the earliest evidences of adult neurogenesis were reported in the 1960s^{1,2}, polarized reports claimed that there were no evidences of neurogenesis in adult mammalian brain⁷. It was not until another three decades later, that adult hippocampal neurogenesis was 'rediscovered' in rodents^{3–6} and other mammals^{39,40}. Around the same time in 1990s the "stem-like" properties of these newly generated cells were identified and it was perceived that NSCs were able to autoreplicate and generate different neural lineages including neurons, astrocytes, and oligodendrocytes in adult mammalian brains^{41–43}. Subsequent studies revealed that in the adult CNS, NSCs were prevalent mostly in the subgranular zone (SGZ) of the hippocampal dentate gyrus and the subventricular zone (SVZ) of the lateral ventricles⁴⁴. Considering that neurogenesis in adult mammalian brain was also predominant around these regions, it could be seemingly predicted that in response to intrinsic and extrinsic changes, neurogenesis is initiated by these adult NSCs to maintain functional integrity and plasticity of these brain regions⁴⁵. The turning point in the field of neurogenesis research came when hippocampal neurogenesis was demonstrated in adult human cancer patients injected with bromodeoxyuridine (BrdU) labeling dye⁴⁶. This report inspired extensive investigations in experimental animals^{12,39,47,48} as well as in human samples^{11,49} not just remaining confined to the hippocampus but expanding to other brain regions like olfactory bulb and neocortex^{8–12}. Continued interest prompted researchers to further explore for evidences of adult neurogenesis in broad areas of the brain including the striatum¹³, the amygdala⁹, the substantia nigra¹⁴. Recently, neurogenesis was discovered in the metabolic and neuroendocrine head quarter of the brain, the hypothalamus. Two independent studies^{15,16} published within a very short time window demonstrated the origin of htNSCs, pushing the need for further studies to address the physiological and disease significance of these cells, in particular in human being.

Hypothalamic neural stem cells and neurogenesis

It was recently discovered that adult mouse hypothalamus, in addition to having a rich pool of functionally active newly formed neurons that could integrate into the existing neuronal network^{15,16,50,51}, an area consisting of the mediobasal region of hypothalamus (MBH) and the third ventricle wall is a niche for multipotent NSCs which have the properties of differentiation into astrocytes and oligodendrocytes in addition to new neurons¹⁶, thus

holding the promises of versatile function. The earliest studies concerning adult hypothalamic neurogenesis, identified neural progenitor cells in the ependymal layer of the 3rd ventricle of 8-week-old adult male rats ⁵². In addition to localized re-population, using tracing by recombinant adenoviral infection, the study showed that neuronal progenitors migrated to the hypothalamic parenchyma, the dorso-medial hypothalamus, latero-anterior hypothalamus and ventro-lateral hypothalamus, indicating that these progenitor cells could possibly differentiate into different cell types. Many of these cells lining the 3rd ventricle were identified as glia-like tanycytes which send processes to the arcuate nucleus and ventromedial hypothalamic nucleus and were functionally recognized as glucosensitive and responsive to metabolic stimulation and signaling changes that are relevant to the control of feeding and energy balance ^{16,53–55}. The hypothalamic parenchyma, arcuate nucleus, and ventromedial and dorsomedial nuclei contain neuropeptide Y (NPY) neurons and pro-opiomelanocortin (POMC) neurons, and are primarily engaged in energy-balance have been identified to be significantly neurogenic not only under stimulation but also in basal condition ¹⁵. Some of these newborn cells acquire leptin responsiveness as evidenced from the expression of POMC and STAT3 signal transduction following leptin treatment ¹⁵, signifying that they can integrate in the existing neuronal system to participate in metabolic functioning. Altogether, these evidences suggest the functional importance of hypothalamic NSCs and neurogenesis towards the maintenance of metabolic homeostasis.

Neuroinflammation induces impairment of neurogenesis

Neuroinflammation is a necessary defense response to infections, diseases and injuries of the brain. But, chronic inflammation disrupts the normal protective barriers and propagates the pathogenesis of progressive neurodegenerative and neurological disorders like AD, amyotrophic lateral sclerosis (ALS), depression, epilepsy, Huntington's disease (HD), multiple sclerosis (MS) and PD ^{23–26}. Adult neurogenesis is also modulated in neurological diseases and disorders and negatively impacted during inflammation ⁵⁶. For example, neurogenesis in adult hippocampus has been reported to be impaired by neuroinflammation ²², and blockade of inflammation could restore neurogenesis ⁵⁷. However, the mechanism pertaining to how neurogenesis is modulated during inflammatory processes remains to be fully elucidated. In the CNS, immune cells from both the hematopoietic and nervous systems contribute to the development and progression of neuroinflammation. Intrinsic or extrinsic stimuli induced over-activation of these immune cells further causes release of pro-inflammatory substances like interleukins and nitric oxide, which precipitate neuroinflammation and may underlie the molecular mechanism of neuroinflammatory reactions on affecting neurogenesis ^{58,59}. Since newborn neuronal cells could contribute to neuronal regeneration and plasticity of the nervous system, inflammation-impaired neurogenesis seems to be a significant causal factor for reduced neuroprotection and neuronal repair, and increased neurodegeneration, both leading to neurodegenerative diseases ^{60,61}.

Neurogenesis is significantly attenuated in the hypothalamus of adult mice maintained on prolonged high-fat diet (HFD) feeding ^{16,62}, which could be a consequence of HFD-induced neuroinflammatory responses ¹⁶. On the contrary, hypothalamic neurogenesis can increase in response to short-term HFD feeding, which most likely represents an adaptive reaction of the hypothalamus that attempts to counteract the negative effects of HFD feeding on energy balance ⁵⁴. Thus, only a long-term study along with body weight information would help to decipher the ultimate neurogenic plight in the hypothalamus of HFD-fed mice, and indeed, impairment of neurogenesis can be duly predicted upon long-term HFD feeding, as Li *et al* ¹⁶ have documented that htNSCs-derived from obese mice exhibited impaired proliferation and differentiation. Such contortion ensued from excessive release of inflammatory cytokines such as TNF- and IL-1 which were produced upon NF-κB

activation and are also known to potently activate IKK β /NF- κ B thus triggering a positive feed-forward loop inflammatory axis ¹⁶. In a more direct evidence regarding the deleterious effects of inflammation, the study showed that IKK β /NF- κ B activation markedly decreased *in vitro* htNSC survival, differentiation and neurogenesis, while inhibition of the IKK β /NF- κ B pathway improved survival and differentiation of htNSC and neurogenesis ¹⁶.

The key to the understanding of the functional significance and therapeutic potential of the htNSCs may lie in the process of identifying the underlying regulatory mechanistic events. It was elucidated ¹⁶ that survival, differentiation and neurogenesis of htNSCs were mechanistically mediated by IKK β /NF- κ B-controlled apoptosis and Notch signaling, thus further reinforcing the role of inflammatory machinery in neurogenesis, neuroplasticity and the structural remodeling of the brain.

Metabolic inflammation and impaired neurogenesis in obesity

While hippocampal neurogenesis is known to play an important role in normal hippocampal function, learning and memory ^{63–65}, an obvious apprehension was if the observed hypothalamic neurogenesis would be relevant to metabolic diseases. Two recent studies aptly established that chronic HFD-induced obesity and leptin deficiency in mice reduced adult NSC population and new neuron turnover in the MBH ^{16,62}, particularly affecting the small population of POMC neurons that have important functions of controlling energy balance ¹⁶. Chronic HFD feeding incurs metabolic inflammation in the brain, in particular in the hypothalamus, by triggering several pro-inflammatory cascades including the IKK β /NF- κ B inflammatory axis ^{17,27,66}. Li *et al* demonstrated that chronic HFD feeding in mice led to not only depletion of htNSCs but also neurogenic impairment associated with IKK β /NF κ B activation ¹⁶. The study further demonstrated chronic manifestation of metabolic dysfunctions, including excess calorie intake, glucose intolerance, insulin resistance and overweight in mice that were genetically engineered to deplete the NSCs in the MBH, thus substantially establishing a possible direct link between hypothalamic neurogenesis and metabolic diseases ¹⁶. It remains to be seen if injured adult hypothalamus is amenable to neural repair with stem cell grafting, although a lot more research is needed before stem cell therapy for metabolic disorders can be put to the test in clinic. However, the self-renewing multipotent property of the htNSCs definitely renders them as prime candidates for stem cell based therapy of metabolic disorders in the future.

Neuroinflammatory basis of neurodegeneration and aging

During the course of different neurological and neurodegenerative diseases like PD, AD, HD, brain ischemia and MS, two ubiquitous etiological links are neuroinflammation and mitochondrial impairment ^{25,67–76}. The progression of pathological conditions during neurodegeneration is not just a consequence of inflammation of the neural tissues, but involves inflammatory mediators produced and secreted by different CNS cells, such as microglia, astrocytes and oligodendrocytes ⁷⁷. The secreted inflammatory factors through their paracrine or autocrine actions and dynamic responsiveness lead to intricate crosstalk among these different cell types, and eventually form an etiopathogenic basis of neurodegenerative disorders ⁷⁷. In addition, overnutrition-related environmental factors and neural oxidative stress ^{78–82}, neural ER stress ^{82,83} and neural autophagy defect ^{84–86} all contribute to the etiology of neurodegenerative diseases as well as in aging progression ⁸⁷. Of interest, all these components have also been linked to the activation of central IKK β /NF- κ B inflammatory pathway ^{88–92}, which is a known decisive regulator of metabolic dysfunctions. In line with these observations, metabolic decline has been equated with cognitive decline. It is a common sense that metabolic syndrome and neurodegenerative disorders are chronic, and their prevalence increases exponentially with age. Also, isolated

individual components of metabolic syndrome have been posed to be predisposing risk factors of developing neurodegeneration, dementia and cognitive impairment. In the context of AD, defective central insulin action has been advocated to be labeled as type 3 diabetes⁹³; it has also been shown that chronic HFD-induced obesity decreased certain hypothalamic neuronal populations^{16,62,94} and impaired the proliferation and functional differentiation of hNSCs to mediate a neurodegenerative mechanism of obesity-related diseases¹⁶. Like overnutrition, aging progression can gradually stimulate brain and hypothalamic IKK β /NF- κ B pathway and secretion of related pro-inflammatory factors²¹. Inhibition of these inflammatory changes in the brain or the hypothalamus of mice can provide protection from neurodegeneration under conditions of aging or HFD feeding, further propitiating neuroinflammation-induced neurodegeneration as a common basis of chronic overnutrition and aging as well as their interconnected disease consequences.

Neuroinflammation affects GnRH neurons: potential mechanism of aging

Till date, few studies have looked at the components of the metabolic syndrome and neurodegeneration with a holistic approach, particularly in the context of systemic aging. A very recent report by Zhang *et al*²¹ described how activation of hypothalamic IKK β /NF- κ B significantly expedited cognitive decline, aging and reduced lifespan in mice. With aging, there was significant built-up of hypothalamic microglia with a possible over-stimulation of the NF- κ B pathway. The marked shift in microglial population in the hypothalamus increases the activated NF- κ B, which represents a key mechanistic machinery of aging associated symptoms. Interventional strategies with IKK β /NF- κ B downregulation either in microglia or the MBH neurons effectively slowed down aging retardation and increased lifespan. While NF- κ B is known to play a variety of different roles in stress response and inflammation, this study further elucidated that aging-associated activation of the NF- κ B pathway in the hypothalamic microglia caused progressive decline in levels of gonadotropin-releasing hormone (GnRH), a hypothalamic hormone that is known to play a regulatory role in reproduction and health²¹. Intra-hypothalamic GnRH therapy in adult mice promoted neurogenesis, and systemic treatment with GnRH led to the delay of skin atrophy, bone and muscle decay simultaneously improving cognitive health and lifespan of aging mice²¹. While researchers have attempted to use anti-inflammatory agents for the treatment of neurodegenerative diseases in both animal models^{95–97} and in the clinic^{98–100}, these observations by Zhang *et al*²¹ unravel a new prospect for targeting the effects of the central neuroinflammatory factors to counteract aging and associated neurodegeneration.

Conclusion

Research over past several decades have gradually established the functional significance of neurogenesis in different adult brain areas spanning from the hippocampus, olfactory bulb, neocortex to the recently discovered hypothalamic areas, thus reinforcing functional roles of the newly born neurons in vital homeostatic mechanisms. Continued adult neurogenesis is attainable in healthy condition by virtue of multipotent NCSs which have recently been discovered in the hypothalamus in addition to the earlier known locations such as hippocampus and neocortex. An increasing number of studies indicate that impairment of neurogenesis is mediated through neuroinflammation triggered by various internal or external stimuli such as overnutrition-induced metabolic inflammation, ER and oxidative stress, autophagic defects, all of which are linked to activation of central IKK β /NF- κ B inflammatory signaling cascade, which may form a vicious inflammatory cycle to accrue to neurodegeneration, cognitive decline and aging acceleration. Such chronic onset of neuroinflammation, be it due to aging or external stimuli, is not just restricted to the neurons but was also prevalent in the hypothalamic microglia which negatively impact GnRH production and thus affect overall health. GnRH treatment was found to combat

neuroinflammation and restore neurogenesis and NSCs in aging mice, thus opening up a novel protective and therapeutic option for counteracting aging and aging-related neurodegenerative diseases. Although translating these promising experimental observations to effective bedside therapeutic option still needs a lot more research in diverse models mimicking different complex human disease conditions, the convincing results up to date highly encourage for strategizing neuroinflammation as a therapeutic target of neurodegenerative mechanism to counteract against overnutrition-induced or aging-related problems.

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