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Role of hypothalamus in aging and its underlying cellular mechanisms

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ABSTRACT

Aging is characterized by a progressive loss of several physiological functions that can cause various age-related disorders. Several factors have been identified as causes of aging to elucidate the decline in functions. Various aspects of physiological deterioration are controlled by the hypothalamus, a critical brain region that connects the neuroendocrine system to physiological functions. In addition, functional alterations in a set of agouti-related peptide/neuropeptide Y (AgRP/NPY) and pro-opiomelanocortin (POMC) neurons, a set of growth hormone-releasing hormone (GHRH) and somatostatin (SST) neurons, a set of arginine vasopressin (AVP) and vasoactive intestinal peptide (VIP) neurons, and a set of gonadotropin-releasing hormone (GnRH) and kisspeptin/neurokinin B/dynorphin (KNDy) neurons contribute to age-related physiological decline in energy metabolism, hormone regulation, circadian rhythm, and reproduction, respectively. The underlying cellular mechanism for the hypothalamus-mediated aging progression comprises dysregulation of nutrient sensing, altered intercellular communication, stem cell exhaustion, loss of proteostasis, and epigenetic alterations. Furthermore, mammalian target of rapamycin (mTOR), NF-kB, hypothalamic stem cell, autophagy, and SIRT1 have been recognized as critical factors or pathways mediating the mechanism. Perhaps, further dissection of these pathways or components could provide the potential for developing a therapeutic intervention for age-related diseases or the extension of healthy lifespan.

1. Introduction

Aging is characterized by a progressive loss in several physiological functions and increased susceptibility to various age-related disorders. Even healthy aged people are known to often experience a decline in several physiological functions including metabolism, hormonal regulation, circadian rhythm, reproduction, and cognition. Interestingly, a majority of physiological functions that decline with aging are broadly governed by the hypothalamus, a brain region controlling development, metabolism, reproduction, circadian rhythm, and homeostasis. In addition, the hypothalamus is poised to connect the brain and the body so that the environmental information affecting aging can be transmitted through the hypothalamus to affect the systematic aging of the peripheral organs. Thus, the hypothalamus is hypothesized to be a primary regulator of the process of aging of the entire body. This review aims to assess the contribution of hypothalamic aging to the age-related decline in body functions, particularly from the perspective of energy homeostasis, hormonal balance, circadian rhythm, and reproduction, and to highlight its underlying cellular mechanisms with a focus on nutrient sensing, inflammation, loss of stem cell, loss of proteostasis, and epigenetic alterations. Therefore, we intend to provide supporting evidence for the hypothesis that the hypothalamus is a master regulator for the systematic aging and that cellular mechanisms operating in the hypothalamus are a target for the possible development of anti-aging and aging-control technologies.

2. Energy homeostasis

The shift in energy homeostasis is one of the hallmarks of the physiological changes during aging. As consistently demonstrated in a cross-sectional (Hildrum et al., 2007) and longitudinal analyses (Lim et al., 2010), the prevalence of metabolic syndromes significantly increases with aging. Even in healthy aged people without a degenerative disease, a variation in the metabolic activity and body composition often results in sarcopenic obesity, which is characterized by an increase in the fat mass due to loss of muscles in the body composition. Paradoxically, a loss of appetite is also observed in the elderly (Wolden-Hanson et al., 2004), resulting in an imbalance between nutrition and energy metabolism. Hence, elucidation of the neurobiological and cellular mechanism of aging-associated changes will significantly contribute to understanding the aging process and the development of aging-control technologies.

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Presumably, the hypothalamus plays a critical role in maintaining energy homeostasis of an individual (Dietrich and Horvath, 2013). In the hypothalamus, intensive intra-hypothalamic neural network among the arcuate nucleus (Arc), dorsomedial hypothalamus (DMH), ventromedial hypothalamus (VMH), paraventricular nucleus (PVN), and lateral hypothalamus (LH) critically govern the neuronal and hormonal control over the feeding behavior and energy expenditure. In the Arc, an antagonistic interaction between neurons expressing agouti-related peptide (AgRP) and neuropeptide Y (NPY) and neurons expressing proopiomelanocortin (POMC) constitute the central metabolic controlling axis. The AgRP/NPY neurons activate orexigenic behaviors through its neuronal projection to the LH and PVN (Betley et al., 2013). In addition, the Argp/NPY neurons participate in the control of energy expenditure by inhibiting thermogenesis of the brown adipose tissue (Shi et al., 2013). The POMC neurons exert its anorexigenic effect through its connection to the PVN, LH, and VMH and by releasing α-melanocyte-stimulating hormone (α-MSH), a processed protein product of POMC, to activates MC4R in the target cells.

Assumedly, the age-dependent changes in the hypothalamic neurons controlling metabolism, especially the POMC and AgRP/NPY neurons, underlie the imbalance of energy homeostasis with aging. Reportedly, the activity of anorexigenic POMC neurons significantly decreases in the Arc in aged mice (Yang et al., 2012). The messenger level of POMC in the Arc did not alter substantially between young and middle-aged animals, although the POMC mRNA level in old animals was not assessed in the study (Burke et al., 2014). Interestingly, reversal of the decreased POMC tone by infecting adeno-associated virus expressing POMC in the basomedial hypothalamus of aged rats reversed age-dependent changes in metabolic measures, such as food intake, weight gain, and peripheral fat mass (Li et al., 2005). Despite changes in POMC neurons critical in age-dependent obesity, the response to α-MSH, a final product of POMC transcript, might be sensitized with age. Furthermore, the central α-MSH application induced more body weight loss and prolonged decrease in the food intake in aged rats than in young rats (Petervari et al., 2011).

Paradoxically, the NPY protein level in the Arc decreases in aged rats (Kowalski et al., 1992). Although the AgRP mRNA level did not change with aging in normally fed rats, it exhibited a significant blunting in its induction in response to fasting (Wolden-Hanson et al., 2004). In aged rats, autoradiography revealed that the NPY receptor level decreased in the brain (Veyrat-Durebex et al., 2013); especially the decrease in NPY Y1 receptor-like signal in aged rats was observed in the hippocampus and mediodorsal thalamic nuclei. In addition, a decline in NPY Y2 receptor-like signal in aged rats was observed in the hippocampus and anterior hypothalamic area. These findings suggest that age-related changes in the NPY neurons and its receptor might differentially affect the energy metabolism dependent upon the feeding status.

Thus, although the level and activity of hypothalamic regulator neurons of energy metabolism changes with aging, the previously reported data regarding the anorexigenic and orexigenic neurons might not be sufficient to illustrate the aging-related shift in energy homeostasis. Hence, further studies are warranted to investigate the balance between activities of those neurons in aged animals and elucidate the role of the hypothalamus in the aging-related metabolic imbalance.

3. Growth hormone imbalance

One of the primary functions of the hypothalamus is to produce and release hypothalamic hormones into the portal vessel to stimulate the release of pituitary hormones into the systemic circulation. Among hypothalamic hormones, growth hormone-releasing hormone (GHRH) and somatostatin (SST) are affected by the aging process, which, in turn, affect several age-related changes.

The GHRH neurons, cell bodies of which are located in the Arc, and SST neurons, cell bodies of which are located in the ventromedial nucleus (VMN) of the hypothalamus, project their axonal terminal into the median eminence for its access to the portal vessel. As the GHRH activates, the SST inhibits the production and secretion of the growth hormone (GH) from the anterior pituitary gland. The target of GH is broadly distributed across the entire body, including the brain, liver, and muscle, to mediate the effects of upstream hormones. In addition, the blood levels of GH and insulin-like growth factor 1 (IGF-1) are highest during the adolescence and gradually decrease to become barely detectable in the elderly (Ashpole et al., 2015; Corpas et al., 1993). Based on the metabolism-enhancing role of the GH, the age-associated decline in the GH and IGF-1 might contribute to the sarcopenic obesity in the aged. In fact, the GH treatment of older adults with a low plasma IGF-1 level increased the lean body mass, decreased the adipose tissue mass, and increased the bone density (Rudman et al., 1990). However, genetic studies using a mouse model overexpressing or lacking the GH suggested an intriguing role of the GH in aging and longevity. Transgenic mice lines overexpression of the GH, which are higher than control wild-types, consistently exhibited a shorter lifespan (Bartke, 2003). In addition, a mutation of the *Pit1* gene, a transcription factor critical for the development of the anterior pituitary where somatotrophs reside, prevents the GH production, prolonging the lifespan of mutant mice (Flurkey et al., 2001). Thus, timely control of the GH level along with the postnatal development might be critical in proper aging.

To date, the upstream mechanism of the age-associated decline in GH and IGF-1 levels remains unclear. Although how the upstream elements in the GHRH/SST-GH-IGF-1 axis changes along with aging remains partially investigated, the alterations of expression of GHRH/SST and the response of somatotrophs to GHRH and SST in aged rats has been reported previously. Sonntag et al. (1990) reported that the gene expression of SST in the hypothalamus decreases with aging in rats. Immunohistochemically, the same group revealed that the GHRH level in the median eminence (ME) reduced in aged rats, whereas either the SST level in the ME or the GHRH and SST levels in their soma did not change (Spik and Sonntag, 1989). Notably, the SST-induced inhibition of GHRH-responsive GH induction was sensitized in aged rats (Morimoto et al., 1988), suggesting a possible clue for the age-dependent decrease in the plasma GH levels.

4. Circadian rhythm and sleep

A majority of physiological processes are controlled by the circadian rhythm, which implies endogenous biological rhythm with an approximately 24-h period. The circadian rhythm machinery regulates the sleep–wake cycle as well as daily oscillation of metabolism and hormonal rhythm. In addition, the circadian rhythm of an individual synchronizes hierarchically from the master clock residing in the suprachiasmatic nucleus (SCN) of the hypothalamus to the peripheral clocks in the almost every extra-SCN tissues. In the SCN, two major types of neurons forming a synchronized neuronal network to maintain 24-h oscillation are the arginine vasopressin (AVP)–positive neurons in the dorsolateral shell region and the vasoactive intestinal peptide (VIP) neurons in the ventromedial core region. Besides the neuronal network of the SCN, the molecular clockwork comprising the transcriptional–-translational feedback loop governs the molecular circadian oscillation of cellular transcriptome.

The circadian rhythm of an individual undergoes several age-related changes with aging (Dijk et al., 2000; Hood and Amir, 2017). Chronotype, a behavioral manifestation to wake up earlier than average and stay more active in the morning than in the evening (morningness) or stay awake later than average and feel more active in the evening than in the morning (eveningness), shifts toward morningness with aging (Roenneberg et al., 2007). Reportedly, the adjustment capacity of the circadian phase in response to the external time cue is often impaired in the elderly, especially when advancement in the circadian phase is required (Monk et al., 2000). In addition, the aged exhibit a fragmented

Table 1
Summary of cellular substrates in aging.

Cellular substrate	Hypothalamic region/neuron	Levels in old	Related physiological effect	Ref.
mTOR	POMC neurons	Increased activity	Obesity, food intake, glucose tolerance	Yang et al. (2012)
	POMC neurons	Not determined	Obesity, food intake, leptin level	Mori et al. (2009)
NF-κB	MBH	Increased activity	Longevity, cognition, and muscle endurance	Zhang et al. (2013)
htNSC	MBH	Decreased number	Longevity, cognition, and muscle endurance	Zhang et al. (2017)
Autophagy	POMC neurons	Decreased activity	Obesity, glucose tolerance, insulin tolerance	Kaushik et al. (2012)
SIRT1	SCN	Decrease	Circadian rhythm	Chang and Guarente (2013)
	DMH, LH	Transgenic overexpression	Longevity, circadian rhythm	Satoh et al. (2013)

sleep pattern with earlier awakening (Dijk et al., 2000), possibly contributing to the lack of wakefulness and cognitive problems in them.

Perhaps, aging-related changes in circadian rhythms could be attributed to several age-associated changes in synchronization, maintenance, and output pathway of the circadian rhythm. Here, we primarily focus on age-related signatures in hypothalamic neurons residing in the master clock, as other aspects of aging-associated changes of the circadian rhythm are reviewed elsewhere (Mattis and Sehgal, 2016; Paschos and FitzGerald, 2017). The SCN comprises two major neuronal populations, AVP and VIP neurons. Reportedly, the number of AVP-positive neurons in the SCN and the volume of the SCN decreases in aged rats per an immunohistochemical analysis (Roozendaal et al., 1987; Wu et al., 2007). To the best of our knowledge, limited research has been conducted on the VIP-positive neurons in the SCN with aging. Notably, the synchronized electric activity generated from the SCN, which is mediated by the coordinated activity of the AVP and VIP neurons (Mohawk et al., 2012), decreases with aging (Nakamura et al., 2011; Satinoff et al., 1993). In addition, as the synchronized output from the SCN is pivotal in the maintenance of coherent master oscillator, it is imperative to investigate whether the dampened neuronal population activity of the SCN is attributable to age-related variations in the circadian rhythm and whether age-dependent cellular changes in the AVP and VIP neurons underlie the age-associated desynchronization of the master clock.

5. Reproduction and sexual behavior

In mammals, hypothalamus–pituitary–gonad axis (HPG axis) plays an essential role in the regulation of mammalian reproduction. Gonadotropin-releasing hormone (GnRH) neurons located in the preoptic area of the hypothalamus project to the median eminence and release GnRH into the portal vessel in a pulsatile manner (Herbison, 2006). Secreted GnRH activates gonadotropes in the pituitary to synthesize and release luteinizing hormone (LH) and follicle stimulation hormone (FSH) to control the function of gonads. Therefore, biological machinery driving pulsatile GnRH release, the so-called GnRH pulse generator, has long been conceived as a master regulator of mammalian reproductive function (Knobil, 1980; Maeda et al., 2010). In addition, in the last 15 years, kisspeptin neurons have been included in the neural network of GnRH pulse generator as an upstream regulator of GnRH neuron (Lehman et al., 2010; Maeda et al., 2010; Murakawa et al., 2016; Navarro, 2012). Kisspeptin neurons are located in ARC and anteroventral periventricular region (AVPV). Interestingly, kisspeptin neurons in ARC co-express the positive regulator neurokinin B and the negative regulator dynorphin A (together called KNDy neurons), possibly forming self-regulatory feedback loop to drive GnRH pulse generator.

With age, reproductive functions including fertility and sex hormone status naturally decline in both female and male. In human, female reproductive aging is characterized by menopause that includes a dramatic reproductive and endocrinological shift as well as the cessation of menstrual cycle (Hale et al., 2014). Although laboratory rodent models do not exhibit human-like dichotomic transition in reproductive aging, they gradually become acyclic with the impairment of gonadotropin surge (Finch, 2014). Both human and rodent male experience aging-associated decline in the levels of reproductive activity, testosterone, gonadotropins, and gonadotropin-releasing hormone, while preserving their fertility to some extent (Hermann et al., 2000). Importantly, the activities of GnRH pulse generator, as reflected in the pulsatility of LH, are markedly reduced in aged animal in both female and male (Scarbrough and Wise, 1990; Steiner et al., 1984; Wise et al., 1988), suggesting the notion that GnRH pulse generator, the uppermost regulator of the reproductive system, may be a crucial mediator of reproductive aging. Consistent with the aforementioned finding, Kunimura et al. (2017) recently reported that the number of KNDy neurons constituting putative regulatory feedback loop upstream of GnRH pulse generator decreases with age in both female and male rats, while the number of GnRH neurons does not alter. This finding suggests that age-dependent change in a set of hypothalamic neurons constituting GnRH pulse generator and its regulators contribute to the reproductive aging of an individual. Notably, decreases in sex hormone level and its pulsatility are associated with other aging phenotypes, such as metabolic disturbance and cognitive impairment (Veldhuis, 2000).

6. Underlying cellular mechanisms

Here, we review and discuss findings that focus on age-related variations in the cellular function and their contribution to hypothalamus-mediated aging. Lopez-Otin et al. (2013) determined the relevance of the cellular mechanisms based on nine hallmarks of aging; five identified hallmarks of hypothalamus-mediated cellular mechanisms include deregulated nutrient sensing, altered intercellular communication, stem cell exhaustion, proteostasis loss, and epigenetic alterations. Given below is the detailed description of factors or pathways that directly affect these mechanisms (Table 1).

6.1. Deregulation of nutrient sensing: mTOR

The mammalian target of rapamycin (mTOR) is a crucial coordinator of metabolic regulation and exists in two different complex forms, mTORC1 and mTORC2 (Cota et al., 2006; Martínez de Morentin et al., 2014). mTOR1 primarily controls the feeding behavior and body weight through leptin and ghrelin signaling and peripherally regulates adipogenesis and gluconeogenesis in various tissues (Martínez de Morentin et al., 2014). In contrast, mTORC2 controls the number, size, and morphology of neuronal cells and provides the hypothalamus with the regulation of energy balance. Studies have shown an increase in the mTOR activity in the POMC neurons of aged mice (Yang et al., 2012). The elevation of mTOR signaling causes enlarged POMC neuronal soma and decreases the neurite projection to PVN, contributing to age-dependent obesity (Mori et al., 2009). In addition, intracerebral injection of rapamycin, an inhibitor of mTOR, causes the POMC neuronal excitability and neurite projection, thereby leading to the decreased food intake and body weight. Reportedly, feeding starting at the late stage (600 days of age) with rapamycin significantly extends the median and maximal lifespan in both genders of mice (Harrison et al., 2009). Furthermore, the inhibition of mTOR signaling might offer therapeutic

interventions for delaying aging and improving healthy lifespan in humans because the mTOR pathway is a major accelerator of aging.

6.2. Intercellular communication: NF-κB

Research has revealed that the microglial cells are highly sensitive to perturbation in homeostatic imbalances in the brain, and their increased activation is apparent as a sign of inflammation response (Arvin et al., 1996). The microglia cells communicate with the hypothalamic neurons through pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) (Tannahill et al., 2013). The prolonged chronic activation of this pathway causes signal resistance and loss of hypothalamic homeostatic regulation (Blagosklonny, 2012; Dilman and Anisimov, 1979).

Using several interventional mouse models, Cai and colleagues provided direct evidence that the hypothalamus serves as a control center for the whole-body aging in mice (Zhang et al., 2013). They reported that the age-associated inflammation increase is mediated by IκB kinase-β (IKK-β) and nuclear factor κB (NF-κB) in the microglia and, subsequently, nearby neurons through the microglia–neuron interaction in the mediobasal hypothalamus. Apparently, blocking the hypothalamic or brain IKK-β or NF-κB activation causes delayed aging phenotype and improved lifespan. Aging correlates with a decline in the hypothalamic GnRH expression in mice and, mechanistically, activated IKK-β and NF-κB significantly downregulates the GnRH transcription. Notably, GnRH therapy through either hypothalamic third ventricular or subcutaneous injection leads to a significant recovery of neurogenesis in the hypothalamus and hippocampus and a noticeable improvement of age-related phenotype in the skin thickness, bone density, and muscle strength when applied in middle-aged mice. Reportedly, this central dysregulation is associated with systemic aging and the accelerated development of aging-related metabolic syndromes, obesity, type 2 diabetes, and reproductive dysfunctions (Schwartz and Porte, 2005).

6.3. Loss of neural stem cells: hypothalamic neural stem cells

One of the physiological changes in the aging brain is decreased neurogenesis, which is caused by the reduced generation of functional neurons from neural stem cells in adults (Seib and Martin-Villalba, 2015). Evidence suggests that neural stem cells exist in the hypothalamus and are directly associated with the energy balance regulation (Kokoeva et al., 2005). Some of these hypothalamic neural stem cells (htNSC) exhibit functionally relevant phenotypes, including leptin-induced activation of signal transducer and activator of transcription 3 (STAT3) in the hypothalamus to facilitate long-term body weight control in adult mice. Zhang et al. (2017) explained the role of htNSC in systemic aging using several sophisticated animal models. First, they observed that the number of htNSCs decreases significantly during aging. Then, they generated two separate mouse models by the specific removal of these stem cells by injecting into the hypothalamus with two different lentiviruses facilitating the depletion of Bmi1- and Sox2-positive stem cells, respectively, to address a causal role of stem cells in aging. The $Bmi1^+$ cell–depleted mice exhibited a significant decline in physiological functions, including decreases in muscle endurance, cognition, coordination, sociality, and spatial memory. In addition, $Sox2^+$ cell–depleted mice exhibited a reduced lifespan. Perhaps, a delay of these age-associated physiological decline and enhancement of lifespan could be attained when new htNSCs derived from new-born mice are replenished into the mediobasal hypothalamus of middle-aged mice. These stem cells secreted microRNA-containing exosomes that delay physiological deficits with aging when they were exogenously implanted into the hypothalamus. Furthermore, microRNAs secreted from stem cell exosomes might suppress the activation of NF-kB in neurons and restores GnRH secretion. Thus, the loss of htNSCs during aging might contribute to inflammation and systemic physiological changes that accompany aging.

6.4. Loss of proteostasis: autophagy

Autophagy is a highly controlled process that regulates the turnover of cellular components and the maintenance of cellular homeostasis (Levine and Klionsky, 2004). Apparently, basal autophagy activity declines with aging, and autophagy impairment contributes to various aging phenotype and age-related diseases (Cuervo, 2008). NPY, one of the major neuropeptides present in the hypothalamus, exhibited declined expression levels in aged mice hypothalamus (Aveleira et al., 2015). In addition, autophagy was promoted by an increased expression of NPY in both hypothalamic neuronal cells and mice overexpressing NPY in the hypothalamus; this NPY-dependent autophagy stimulation was mediated by NPY Y1 and Y5 receptors through the action of the PI3K, MAPK/ERK, and PKA pathways. Reportedly, normally aged mice exhibit defective autophagy in the hypothalamus (Kaushik et al., 2012), and aging in the hypothalamus reduces ATG7 and LC3-II levels and autophagy flux rate, suggesting the decreased autophagy activity. A noticeable accumulation of p62 in the POMC neurons suggests that the POMC neurons exhibit an increased sensitivity to age-associated reduced autophagy, which in aged mice leads to increased hypothalamic POMC preproprotein levels and decreased α-MSH. Furthermore, aged mice exhibit similar defects in adiposity and lipolysis as observed in ATG7 knockout mice, as evidenced by increases in the body weight, fat amount, and decreases in serum free fatty acids, and glycerol compared to young mice. Thus, POMC neuronal autophagy is essential for the maintenance of energy balance through the generation of α-MSH, and reduced autophagy in the POMC contributes to metabolic complications often observed with aging. Perhaps, modulating hypothalamic autophagy could provide clues to developing new therapeutic interventions for delaying aging.

6.5. Epigenetic alterations: sirtuin 1

SIRT1 is a NAD-dependent deacetylase that regulates diverse physiological pathways. Brain-specific SIRT1-overexpressing (BRASTO) transgenic mice exhibited a significantly extended median and maximal lifespan in both males and females (Satoh et al., 2013). In line with delayed aging, aged BRASTO mice displayed enhanced physiological phenotypes in physical activity, body temperature, oxygen consumption, and sleep quality compared to the wild-type control. Apparently, these phenotypes are attributed to the enhancement of the neural activity in the dorsomedial and lateral hypothalamic nuclei (DMH and LH, respectively), through the augmented expression of orexin type 2 receptor (Ox2r) by SRT1 and its partner NKX2.1. Notably, DMH-specific SIRT1 overexpression in aged wild-type mice improves age-related decline in the physical activity and body temperature to levels of young mice.

In the hypothalamus, SIRT1 controls the circadian rhythm through the activation of two critical circadian regulators, BMAL1 and CLOCK (Chang and Guarente, 2013). Notably, Sirt1 and NAD^+, a molecule responsible for cellular aging, play a role in the operation of the circadian molecular clock (Imai and Guarente, 2014). Sirt1-NAD^+ regulates the transcriptional driving force in the molecular clockwork by affecting the transcription of Bmal1 and Clock, the CLOCK-mediated transcription and the deacetylation of PER2 (Asher et al., 2008; Chang and Guarente, 2013; Nakahata et al., 2008). Based on these regulations, Sirt1 amplifies the amplitude of the molecular clock machinery. Reportedly, the expression level of SIRT1 in the SCN has been shown to decrease during aging (Chang and Guarente, 2013). In addition, the disruption of the *Sirt1* gene in the brain of young mice phenocopies age-related variations of the circadian rhythm, which can be reversed by the brain-specific overexpression of SIRT1 (Chang and Guarente, 2013). Consistently, enhancing the SIRT1 activity by calorie restriction reprogrammed the age-related weakening of the circadian clock (Sato

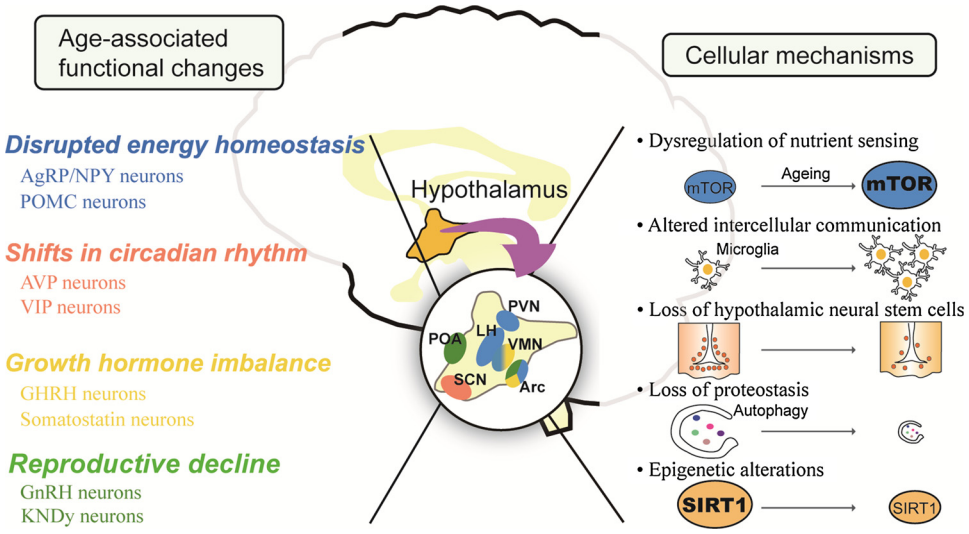

Fig. 1. The hypothalamus as a regulator of systemic aging. We propose a working model that the hypothalamus controls several aspects of systemic aging. Here, an age-dependent decline in physiological functions, including disruption of energy homeostasis, shifts in the circadian rhythm, imbalance in GH levels, and decline in reproduction, is mediated through age-associated changes in the master regulatory neurons, such as the AgRP/NPY, POMC, AVP, VIP, GHRH, SST, GnRH, and KNDy neurons. Notably, the hypothalamus is also a region where a majority of molecular pathways implicated in aging, such as nutrient sensing, inflammation, neural stem cell, proteostasis, and epigenetic regulation, are altered with aging.

et al., 2017).

7. Conclusions

Here, we discussed evidence supporting the idea that the hypothalamus governs systemic aging by the mediation of energy homeostasis, hormonal regulation, circadian rhythm, and reproductive functions through aging-related changes in key neuronal regulators (Fig. 1). Despite identifying several pathways or factors as critical regulators of the hypothalamus-mediated aging progression, detailed mechanisms are unclear. For example, what is the neural substrate of inflammation controlling the progression of the aging? What is the molecular downstream of exosomal miRNA, which can mediate htNSC-driven amelioration of age-associated functional decline? What are the impacts of the age-dependent decrease in autophagy in the regulation of circadian rhythm or hormonal balance? Thus, further studies investigating the interaction among factors involved in the key neuronal regulators might provide clues to these exciting questions that are fundamental to the understanding of systemic aging control from the point of intrinsic hypothalamic regulation of aging.

Growing evidence suggests that age-related hypothalamic inflammation and stem cell loss are associated with cognitive decline, which is another hallmark of aging (Zhang et al., 2013: Zhang et al., 2017). For example, age-dependent cognitive decline may be caused by a complex interaction among hypothalamic neuronal factors, such as GnRH, or a set of miRNAs that could influence cognitive function directly or indirectly. In addition, compromised neural network interaction between the hypothalamus and the main cognition center including the hippocampus and cortices may contribute to the age-associated decline in high level cognitive function. Therefore, future studies should aim at understanding how the dysregulation of hypothalamic neuronal factors and network leads to the impairment of cognitive function and memory in aged population.

Perhaps, understanding the contribution of molecular aging in the hypothalamus provides an insight into the anti-aging and longevity extension technologies. Considering the multifaceted role of molecular targets implicated in the aging process, determining the site of action of the molecule will be instrumental in designing a specific approach to the artificial regulation of aging. For example, rapamycin is under investigation in several clinical trials to determine whether it ameliorates age-associated diseases such as cancer, ALS, and other degenerative diseases. Hence, comprehensive understanding of other critical components involved in hypothalamus-mediated cellular mechanisms for aging might provide excellent clues for the development of therapy for anti-aging and healthy lifespan.

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References

Arvin, B., Neville, L.F., Barone, F.C., Feuerstein, G.Z., 1996. The role of inflammation and cytokines in brain injury. Neurosci. Biobehav. Rev. 20, 445–452.
Asher, G., Gatfield, D., Stratmann, M., Reinke, H., Dibner, C., Kreppel, F., Mostoslavsky, R., Alt, F.W., Schibler, U., 2008. SIRT1 regulates circadian clock gene expression through PER2 deacetylation. Cell 134, 317–328.
Ashpole, N.M., Sanders, J.E., Hodges, E.L., Yan, H., Sonntag, W.E., 2015. Growth hormone, insulin-like growth factor-1 and the aging brain. Exp. Gerontol. 68, 76–81.
Aveleira, C.A., Botelho, M., Carmo-Silva, S., Pascoal, J.F., Ferreira-Marques, M., Nobrega, C., Cortes, L., Valero, J., Sousa-Ferreira, L., Alvaro, A.R., Santana, M., Kugler, S., Pereira de Almeida, L., Cavadas, C., 2015. Neuropeptide Y stimulates autophagy in hypothalamic neurons. Proc. Natl. Acad. Sci. U. S. A. 112 (2015), E1642–E1651.
Bartke, A., 2003. Can growth hormone (GH) accelerate aging? Evidence from GH-transgenic mice. Neuroendocrinology 78, 210–216.
Betley, J.N., Cao, Z.F., Ritola, K.D., Sternson, S.M., 2013. Parallel, redundant circuit organization for homeostatic control of feeding behavior. Cell 155, 1337–1350.
Blagosklonny, M.V., 2012. Answering the ultimate question "what is the proximal cause of aging?". Aging 4, 861–877.
Burke, L.K., Doslikova, B., D'Agostino, G., Garfield, A.S., Farooq, G., Burdakov, D., Low, M.J., Rubinstein, M., Evans, M.L., Billups, B., Heisler, L.K., 2014. 5-HT obesity medication efficacy via POMC activation is maintained during aging. Endocrinology 155, 3732–3738.
Chang, H.C., Guarente, L., 2013. SIRT1 mediates central circadian control in the SCN by a mechanism that decays with aging. Cell 153, 1448–1460.
Corpas, E., Harman, S.M., Pineyro, M.A., Roberson, R., Blackman, M.R., 1993. Continuous subcutaneous infusions of growth hormone (GH) releasing hormone 1-44 for 14 days increase GH and insulin-like growth factor-I levels in old men. J. Clin. Endocrinol. Metab. 76, 134–138.
Cota, D., Proulx, K., Smith, K.A., Kozma, S.C., Thomas, G., Woods, S.C., Seeley, R.J., 2006. Hypothalamic mTOR signaling regulates food intake. Science 312, 927–930.
Cuervo, A.M., 2008. Autophagy and aging: keeping that old broom working. Trends Genet. 24, 604–612.
Dietrich, M.O., Horvath, T.L., 2013. Hypothalamic control of energy balance: insights into the role of synaptic plasticity. Trends Neurosci. 36, 65–73.
Dilman, V.M., Anisimov, V.N., 1979. Hypothalamic mechanisms of ageing and of specific age pathology – I. Sensitivity threshold of hypothalamo-pituitary complex to homeostatic stimuli in the reproductive system. Exp. Gerontol. 14, 161–174.
Dijk, D.J., Duffy, J.F., Czeisler, C.A., 2000. Contribution of circadian physiology and sleep homeostasis to age-related changes in human sleep. Chronobiol Int. 17, 285–311.
Finch, C.E., 2014. The menopause and aging, a comparative perspective. J. Steroid

Biochem. Mol. Biol. 142, 132–141.
Flurkey, K., Papaconstantinou, J., Miller, R.A., Harrison, D.E., 2001. Lifespan extension and delayed immune and collagen aging in mutant mice with defects in growth hormone production. Proc. Natl. Acad. Sci. U. S. A. 98, 6736–6741.
Hale, G.E., Robertson, D.M., Burger, H.G., 2014. The perimenopausal woman: endocrinology and management. J. Steroid Biochem. Mol. Biol. 142, 121–131.
Harrison, D.E., Strong, R., Sharp, Z.D., Nelson, J.F., Astle, C.M., Flurkey, K., Nadon, N.L., Wilkinson, J.E., Frenkel, K., Carter, C.S., Pahor, M., Javors, M.A., Fernandez, E., Miller, R.A., 2009. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature 460, 392–395.
Herbison, A.E., 2006. Physiology of the GnRH neuronal network. In: Neill, J.D. (Ed.), Knobil and Neill'S Physiology of Reproduction, 3rd ed. Academic Press, San Diego, pp. 1415–1482.
Hermann, M., Untergasser, G., Rumpold, H., Berger, P., 2000. Aging of the male reproductive system. Exp. Gerontol. 35, 1267–1279.
Hildrum, B., Mykletun, A., Hole, T., Midthjell, K., Dahl, A.A., 2007. Age-specific prevalence of the metabolic syndrome defined by the International Diabetes Federation and the National Cholesterol Education Program: the Norwegian HUNT 2 study. BMC Public Health. 7, 220.
Hood, S., Amir, S., 2017. The aging clock: circadian rhythms and later life. J. Clin. Invest. 127, 437–446.
Imai, S., Guarente, L., 2014. NAD+ and sirtuins in aging and disease. Trends Cell. Biol. 24, 464–471.
Levine, B., Klionsky, D.J., 2004. Development by self-digestion: molecular mechanisms and biological functions of autophagy. Dev. Cell. 6, 463–477.
Kaushik, S., Arias, E., Kwon, H., Lopez, N.M., Athonvarangkul, D., Sahu, S., Schwartz, G.J., Pessin, J.E., Singh, R., 2012. Loss of autophagy in hypothalamic POMC neurons impairs lipolysis. EMBO Rep. 13, 258–265.
Knobil, E., 1980. The neuroendocrine control of the menstrual cycle. Recent Prog. Horm. Res. 36, 53–88.
Kokoeva, M.V., Yin, H., Flier, J.S., 2005. Neurogenesis in the hypothalamus of adult mice: potential role in energy balance. Science 310, 679–683.
Kowalski, C., Micheau, J., Corder, R., Gaillard, R., Conte-Devolx, B., 1992. Age-related changes in cortico-releasing factor, somatostatin, neuropeptide Y, methionine enkephalin and beta-endorphin in specific rat brain areas. Brain Res. 582, 38–46.
Kunimura, Y., Iwata, K., Ishigami, A., Ozawa, H., 2017. Age-related alterations in hypothalamic kisspeptin, neurokinin B, and dynorphin neurons and in pulsatile LH release in female and male rats. Neurobiol. Aging 50, 30–38.
Lehman, M.N., Coolen, L.M., Goodman, R.L., 2010. Minireview: kisspeptin/neurokinin B/dynorphin (KNDy) cells of the arcuate nucleus: a central node in the control of gonadotropin-releasing hormone secretion. Endocrinology 151, 3479–3489.
Li, G., Zhang, Y., Wilsey, J.T., Scarpace, P.J., 2005. Hypothalamic pro-opiomelanocortin gene delivery ameliorates obesity and glucose intolerance in aged rats. Diabetologia. 48, 2376–2385.
Lim, S., Kim, J.H., Yoon, J.W., Kang, S.M., Choi, S.H., Park, Y.J., Kim, K.W., Lim, J.Y., Park, K.S., Jang, H.C., 2010. Sarcopenic obesity: prevalence and association with metabolic syndrome in the Korean longitudinal study on health and aging (KLoSHA). Diabetes Care 33, 1652–1654.
Lopez-Otin, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. Cell 153, 1194–1217.
Maeda, K., Ohkura, S., Uenoyama, Y., Wakabayashi, Y., Oka, Y., Tsukamura, H., Okamura, H., 2010. Neurobiological mechanisms underlying GnRH pulse generation by the hypothalamus. Brain Res. 1364, 103–115.
Martínez de Morentin, P.B., Martinez-Sanchez, N., Roa, J., Ferno, J., Nogueiras, R., Tena-Sempere, M., Dieguez, C., Lopez, M., 2014. Hypothalamic mTOR: the rookie energy sensor. Curr. Mol. Med. 14, 3–21.
Mattis, J., Sehgal, A., 2016. Circadian rhythms, sleep, and disorders of aging. Trends Endocrinol. Metab. 27, 192–203.
Mohawk, J.A., Green, C.B., Takahashi, J.S., 2012. Central and peripheral circadian clocks in mammals. Annu Rev. Neurosci. 35, 445–462.
Monk, T.H., Buysse, D.J., Carrier, J., Kupfer, D.J., 2000. Inducing jet-lag in older people: directional asymmetry. J. Sleep. Res. 9, 101–116.
Mori, H., Inoki, K., Munzberg, H., Opland, D., Faouzi, M., Villanueva, E.C., Ikenoue, T., Kwiatkowski, D., MacDougald, D.A., Myers, M.G., Guan, K.L., 2009. Critical role for hypothalamic mTOR activity in energy balance. Cell. Metab. 9, 362–374.
Morimoto, N., Kawakami, F., Makino, S., Chihara, K., Hasegawa, M., Ibata, Y., 1988. Age-related changes in growth hormone releasing factor and somatostatin in the rat hypothalamus. Neuroendocrinology 47, 459–464.
Murakawa, H., Iwata, K., Takeshita, T., Ozawa, H., 2016. Immunoelectron microscopic observation of the subcellular localization of kisspeptin, neurokinin B and dynorphin A in KNDy neurons in the arcuate nucleus of the female rat. Neurosci. Lett. 612, 161–166.
Nakahata, Y., Kaluzova, M., Grimaldi, B., Sahar, S., Hirayama, J., Chen, D., Guarente, L.P., Sassone-Corsi, P., 2008. The NAD+-dependent deacetylase SIRT1 modulates CLOCK-mediated chromatin remodeling and circadian control. Cell 134, 329–340.
Nakamura, T.J., Nakamura, W., Yamazaki, S., Kudo, T., Cutler, T., Colwell, C.S., Block, G.D., 2011. Age-related decline in circadian output. J. Neurosci. 31, 10201–10205.
Navarro, V.M., 2012. New insights into the control of pulsatile GnRH release: the role of Kiss1/neurokinin B neurons. Front. Endocrinol. (Lausanne) 3, 48.
Paschos, G.K., FitzGerald, G.A., 2017. Circadian clocks and metabolism: implications for microbiome and aging. Trends Genet. 33, 760–769.
Petervari, E., Szabad, A.O., Soos, S., Garami, A., Szekely, M., Balasko, M., 2011. Central alpha-MSH infusion in rats: disparate anorexic vs. metabolic changes with aging. Regul. Pept. 166, 105–111.
Roenneberg, T., Kuehnle, T., Juda, M., Kantermann, T., Allebrandt, K., Gordijn, M., Merrow, M., 2007. Epidemiology of the human circadian clock. Sleep Med. Rev. 11, 429–438.
Roozendaal, B., van Gool, W.A., Swaab, D.F., Hoogendijk, J.E., Mirmiran, M., 1987. Changes in vasopressin cells of the rat suprachiasmatic nucleus with aging. Brain Res. 409, 259–264.
Rudman, D., Feller, A.G., Nagraj, H.S., Gergans, G.A., Lalitha, P.Y., Goldberg, A.F., Schlenker, R.A., Cohn, L., Rudman, I.W., Mattson, D.E., 1990. Effects of human growth hormone in men over 60 years old. N. Engl. J. Med. 323, 1–6.
Satinoff, E., Li, H., Tcheng, T.K., Liu, C., McArthur, A.J., Medanic, M., Gillette, M.U., 1993. Do the suprachiasmatic nuclei oscillate in old rats as they do in young ones? Am. J. Physiol. 265, R1216–R1222.
Sato, S., Solanas, G., Peixoto, F.O., Bee, L., Symeonidi, A., Schmidt, M.S., Brenner, C., Masri, S., Benitah, S.A., Sassone-Corsi, P., 2017. Circadian reprogramming in the liver identifies metabolic pathways of. Aging Cell. 170, 664–677 e11.
Satoh, A., Brace, C.S., Rensing, N., Cliften, P., Wozniak, D.F., Herzog, E.D., Yamada, K.A., Imai, S., 2013. Sirt1 extends life span and delays aging in mice through the regulation of Nk2 homeobox 1 in the DMH and LH. Cell. Metab. 18, 416–430.
Scarbrough, K., Wise, P.M., 1990. Age-related changes in pulsatile luteinizing hormone release precede the transition to estrous acyclicity and depend upon estrous cycle history. Endocrinology 126, 884–890.
Schwartz, M.W., Porte Jr., D., 2005. Diabetes, obesity, and the brain. Science 307, 375–910.
Seib, D.R., Martin-Villalba, A., 2015. Neurogenesis in the normal ageing hippocampus: a mini-review. Gerontology 61, 327–335.
Shi, Y.C., Lau, J., Lin, Z., Zhang, H., Zhai, L., Sperk, G., Heilbronn, R., Mietzsch, M., Weger, S., Huang, X.F., Enriquez, R.F., Baldock, P.A., Zhang, L., Sainsbury, A., Herzog, H., Lin, S., 2013. Arcuate NPY controls sympathetic output and BAT function via a relay of tyrosine hydroxylase neurons in the PVN. Cell. Metab. 17, 236–248.
Sonntag, W.E., Boyd, R.L., Booze, R.M., 1990. Somatostatin gene expression in hypothalamus and cortex of aging male rats. Neurobiol Aging. 11, 409–416.
Spik, K., Sonntag, W.E., 1989. Increased pituitary response to somatostatin in aging male rats: relationship to somatostatin receptor number and affinity. Neuroendocrinology 50, 489–494.
Steiner, R.A., Bremner, W.J., Clifton, D.K., Dorsa, D.M., 1984. Reduced pulsatile luteinizing hormone and testosterone secretion with aging in the male rat. Biol Reprod. 31, 251–258.
Tannahill, G.M., Curtis, A.M., Adamik, J., Palsson-McDermott, E.M., McGettrick, A.F., Goel, G., Frezza, C., Bernard, N.J., Kelly, B., Foley, N.H., Zheng, L., Gardet, A., Tong, Z., Jany, S.S., Corr, S.C., Haneklaus, M., Caffrey, B.E., Pierce, K., Walmsley, S., Beasley, F.C., Cummins, E., Nizet, V., Whyte, M., Taylor, C.T., Lin, H., Masters, S.L., Gottlieb, E., Kelly, V.P., Clish, C., Auron, P.E., Xavier, R.J., O'Neill, L.A., 2013. Succinate is an inflammatory signal that induces IL-1β through HIF-1α. Nature 496, 238–242.
Veldhuis, J.D., 2000. Recent neuroendocrine facets of male reproductive aging. Exp. Gerontol. 35, 1281–1308.
Veyrat-Durebex, C., Quirion, R., Ferland, G., Dumont, Y., Gaudreau, P., 2013. Aging and long-term caloric restriction regulate neuropeptide Y receptor subtype densities in the rat brain. Neuropeptides 47, 163–169.
Wise, P.M., Dueker, E., Wuttke, W., 1988. Age-related alterations in pulsatile luteinizing hormone release: effects of long-term ovariectomy, repeated pregnancies and naloxone. Biol Reprod. 39, 1060–1066.
Wolden-Hanson, T., Marck, B.T., Matsumoto, A.M., 2004. Blunted hypothalamic neuropeptide gene expression in response to fasting, but preservation of feeding responses to AgRP in aging male Brown Norway rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 287, R138–46.
Wu, Y.H., Zhou, J.N., Van Heerikhuize, J., Jockers, R., Swaab, D.F., 2007. Decreased MT1 melatonin receptor expression in the suprachiasmatic nucleus in aging and Alzheimer's disease. Neurobiol. Aging 28, 1239–1247.
Yang, S.B., Tien, A.C., Boddupalli, G., Xu, A.W., Jan, Y.N., Jan, L.Y., 2012. Rapamycin ameliorates age-dependent obesity associated with increased mTOR signaling in hypothalamic POMC neurons. Neuron 75, 425–436.
Zhang, G., Li, J., Purkayastha, S., Tang, Y., Zhang, H., Yin, Y., Li, B., Liu, G., Cai, D., 2013. Hypothalamic programming of systemic ageing involving IKK-beta, NF-kappaB and GnRH. Nature 497, 211–216.
Zhang, Y., Kim, M.S., Jia, B., Yan, J., Zuniga-Hertz, J.P., Han, C., Cai, D., 2017. Hypothalamic stem cells control ageing speed partly through exosomal miRNAs. Nature 548, 52–57.