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The Adipose Cause of Senescence of Male Hypothalamic Preoptic Nucleus: An European View

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Review Article

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ABSTRACT

Recently, it was hypothesized by Cai that, from skin senescence to slow wave sleep, it be completed a new degenerative aging pathway to explain the hypothalamic chronological sequence of aging on suprachiasmatic nucleus. In parallel, it was likewise supposed by many European people in television an additional senescent pathway for male reproduction analogously resulting in the degeneration of hypothalamic preoptic area by the common knowledge of adipose accumulation in middle age/early old age and reduction of sperm production on that age, while the senescence of female reproduction resulting also from ovary menopause. It was earlier pointed out by Cohen that, as male aging progressed there relatively increased the body fat which was associated with the increase in enzyme aromatase converting testosterone to estradiol, leading to diminished testosterone levels. In this article, it is integratively reviewed the relevant evidence to support the view of the European people in television for the degeneration of male hypothalamic preoptic sexually dimorphic nucleus additionally from adipose accumulation, which was even present earlier in evolution than the appearance of forebrain slow wave in sleep.

HIGHLIGHTS

1. The genetic increase and redistribution of fat tissue in male middle age.
2. The expression of aromatase in adipose tissue converting testosterone to estradiol.
3. The disturbance on male reproductive system from adipose and aromatase in aging.
4. The neuronal degeneration in male preoptic sexually dimorphic nucleus after aging.
5. The preservation of aromatase in regulating sex in all vertebrates including fishes.

INTRODUCTION

Aging is complicated with many biochemical, cellular and physiological changes mainly characterized as senescent degeneration. The underlying mechanisms are very diverse for senescence, include the accumulation of intracellular oxidized metabolites [1-4], telomere length-shortening [5,6], chronological senescent changes in hypothalamic neuroendocrine control of hormones [7,8], thymic involution [9,10], brain amyloid-beta accumulations [11,12], and so on.

Among the various mechanisms of senescence, the senescent hypothalamic neuroendocrine change [7,8] determines the chronological sequence of aging in vertebrates including mammals. However, the mechanisms underlying the chronological manifestation of hypothalamic aging are unknown, and need to be elucidated. It should be pointed out that, not all aging processes are controlled by the hypothalamic neuroendocrine system in vertebrates. Those senescent processes such as skin exposure to sunshine and oxygen, brain senescence [11,12], as well as thymic involution [9,10] are all beyond the influence of hypothalamic neuroendocrine control. Recently, Cai suggested that, from skin senescence to slow wave sleep(SWS), there could form a new degenerative aging pathway to explain the chronological sequence of hypothalamic aging of suprachiasmatic nucleus(SCN) [13].

Following this clue of thought, in parallel on July 4, 2016, many European people in television, such as the European congressmen in English channel and European sportsmen in sport channel in China Central Television Station(CCTV), likewise supposed that there might be an additional senescent pathway for male reproduction analogously resulting in the degeneration of hypothalamic preoptic area(POA) by the common knowledge of adipose accumulation in middle age or early old age and reduction of spermatogenesis on that age [13], while the senescence of female reproduction likewise resulting from the ovary menopause.

In this review article, it is attempted to review the relevant evidence to support this view of the European people in television that the degeneration of male hypothalamic preoptic area(POA) resulted additionally from the adipose accumulation [13].

SENESCENT HETEROGENEITY OF HYPOTHALAMIC NUCLEI AND HYPOTHETICAL CAUSES

Heterogeneity of Hypothalamic Nuclei in Aging

The hypothalamic nuclei manifest variation in degeneration during aging [7,14-17]. The paraventricular nucleus (PVN) is responsible for stress response and is functional throughout the lifespan, maintaining its neuron number during aging [7,14]. In contrast, the number of neurons is decreased in the suprachiasmatic nucleus (SCN) as the main controller of circadian rhythm in the process of aging [7,14,16]. Moreover, the sexually dimorphic nucleus in preoptic area (SDN-POA) declines sharply in cell number after aging [7,14,15,17]. This nucleus is twice as large in men as in women [7], manifesting its functional differentiation in sex. In short, the hypothalamic nuclei manifest differentiation in degeneration corresponding to their functions in aging, with useful preserved while useless degenerated.

Amyloid-beta and Brain Aging

The hypothalamus is in turn controlled by many higher brain structures, so that the aging brain, which is characterized as the accumulation of amyloid-beta [4,11], is also a plausible cause of hypothalamic senescence. However, recently it was reported that sleep helped biophysical clearance of amyloid-beta from the adult brain [12,18], implicating that the neurons of brain were homogeneously subject to the aging toxicity of amyloid-beta, including the hypothalamic nuclei.

Investigation on hypothalamic change during aging revealed that each cell group of the hypothalamic nuclei had their own specific pattern of aging, some decreasing while others maintaining their volume during aging [7,14-17]. Since the biophysical homogeneity in toxicity of amyloid-beta from forebrain [12,18] would cause homogeneous degeneration of all hypothalamic nuclei, the heterogeneity in degeneration of hypothalamic nuclei [7-17] indicated that the hypothalamic aging would result from the aging mechanisms other than the toxicity of amyloid-beta from forebrain.

The Hypothetical Peripheral Causes of Senescent Heterogeneity of Hypothalamic Nuclei

Recently, Cai suggested a new hypothesis to explain the chronological sequence of hypothalamic aging on suprachiasmatic nucleus(SCN) [13]. The skin underwent aging from exposure to environmental sunshine and oxygen as well as from genetic shortening of telomere [13]. The skin senescence was reported repeatedly to result in reduction in electrodermal activities [13], which would in turn reduce the emotional responses and memories manifested by the electrodermal activities [13]. Therefore, due to such reduction in emotional responses and memories in aging brain, it would further reduce the requirement for slow wave sleep (SWS) to regulate the emotional balance and memories [13,19-21], as demonstrated by many observations as the continuous decrement in duration of SWS in the process of aging [13,22-24]. The senescent decrement in duration of SWS [13,22-24] would in turn cause continuous functional degeneration of SCN in hypothalamus during aging [13]. In this regard, from skin senescence to SWS, it was formulated a new degenerative aging pathway to explain the chronological sequence of hypothalamic aging on SCN [13].

The aging-related disorganization in expression of core clock genes in various brain regions supports this hypothetical pathway. It is common knowledge that the hippocampus plays a big role in learning and memory [25]. It was demonstrated that the expression of Clock, Bmal1 and Per2 genes in hippocampus lost their circadian rhythm earlier than those in hypothalamic SCN [26,27], implicating that the hippocampal circadian rhythm relevant to sleep and memory actually decreased earlier in response to reduction of emotional responses, while such dysfunctions later began to affect the hypothalamic SCN [13].

This mechanism also provides a clue to understand how other hypothalamic nuclei undergo degeneration during aging in similarity. In parallel, on July 4, 2016, the European people in television speculated that there was an additional senescent pathway for male reproduction from the common knowledge of accumulation of adipose and reduction of spermatogenesis in middle age/early old age to analogously elicit the degeneration of hypothalamic preoptic area (POA) [13], while the senescence of female reproduction likewise resulting from the ovary menopause. Because the senescent degeneration of hypothalamic SCN from skin senescence via SWS would as well affect the reproductive system of animals, this pathway from adipose accumulation would provide an additional cause for degeneration of hypothalamic preoptic area(POA) [13], making it degenerate sharply in the course of senescence as observed [7,14-17].

THE EVIDENCE IN SUPPORT OF THE EUROPEAN VIEW OF HYPOTHALAMIC AGING OF PREOPTIC AREA

The Genetic Increase and Redistribution of Fat Tissue in Middle Age

The European view on the hypothalamic aging of preoptic area from adipose accumulation [13] implicated the premise that it was the intrinsic aging process genetically set in development and growth. In this regard, it is necessary to consider the hormonal regulation on the initiation of adipose accumulation in middle age.

The developmental morphogenesis in animals are controlled by both induction and termination [28]. Induction initiates the developmental morphogenesis while termination controls the final shape of the generated organ during morphogenesis [28]. Many animal models can demonstrate the induction and termination as key developmental control, such as the sexual dimorphism in mammary glands, the epidermal scale in reptiles, the tail metamorphosis in amphibians, the variation in limb digits in vertebrates, and so on [28].

In vertebrates, fat depot sizes reach a peak by middle age or early old age, followed by a substantial decline in advanced old age [29]. Fat tissue growth occurs by increase in size and number of fat cells. Beginning at middle age, the subcutaneous fat loses earlier and consequently the intra-abdominal fat increases relatively in the course toward aging [29], resulting in insulin resistance and increased risk of atherosclerosis and diabetes, even in lean subjects [29]. Nutrients, hormonal effectors such as insulin, leptin, IGF-1, glucocorticoids, and so on are responsible for the regulation of adipose size and redistribution in development and aging [29,30].

The Special Role of Enzyme Aromatase Converting Testosterone to Estradiol

The enzyme aromatase in vertebrates converts the testosterone to estradiol and decreases the testosterone levels [31,32]. The aromatase is expressed in the differentiated adipose cells [31]. Accordingly, Cohen suggested earlier that the increase in adipose tissue in middle age be associated with an increase in the enzyme aromatase and lead to diminished testosterone levels during male aging [32].

It seems not convincing to overemphasize the special role of only one enzyme as aromatase in disturbing the male reproductive functions in aging. However, aromatase is really a remarkable enzyme and even plays more dramatic roles in sex determination. Aromatase is an evolutionary conserved enzyme present in amphioxus [33], fishes [34,35], amphibians [36], reptiles [37], and mammals including humans [31,32]. It is suggested as the key enzyme even in the epigenetic determination of sex as male or female during the ontogeny of some species of vertebrates [38], as demonstrated in African cichlid fishes [35], Japanese frog Rana rugosa [36] and some reptiles [37].

In this regard, due to the significant effects of aromatase demonstrated in sex determination in many vertebrates, it is obvious that the increase in aromatase from increment of fat size in middle age is sufficient to significantly disturb the male reproductive system via converting the testosterone to estradiol.

The Disturbance on Male Reproductive System from Adipose and Aromatase in Aging

The disturbance on male reproductive system from adipose and aromatase in aging can even be assayed *in vivo*. In one report, it was demonstrated that the free and bioavailable estradiol levels decreased modestly with age as did the ratio of free testosterone to free estradiol, the latter testifying to the age-related increase in aromatization of testosterone [39]. The estradiol levels were highly, significantly and positively related to the body fat mass [39]. In another paper comparing BMI in relation to sperm count, it was shown that the overweight and obesity were associated with an increased prevalence of azoospermia or oligozoospermia [40].

Neuronal Degeneration within Preoptic Sexually Dimorphic Nucleus by Sex Hormones in Aging

Due to the disturbance on male reproductive function from adipose accumulation and the consequent decrease in bodily sexual drive in the course of aging, the sexually dimorphic nucleus in preoptic area (SDN-POA) would decrease in use from the reduction in bodily driven male sexual behaviors, undergoing degeneration and manifesting as useful preserved while useless degenerated. As mentioned above, it was indeed observed that the sexually dimorphic nucleus in preoptic area (SDN-POA) declined in cell number after aging [7,14-17]. Besides, it was even shown that the higher estradiol resulted in neuron loss in SDN-POA in male rats in aging [15], while the testosterone reversed the neuronal degeneration within SDN-POA in aging male rats [17], demonstrating that the hormonal outcomes of adipose accumulation during male aging [31,32,39] directly resulted in the neuronal degeneration within SDN-POA.

Because the degeneration of suprachiasmatic nucleus(SCN) from skin aging via slow wave sleep(SWS) would also affect the function of reproduction, the cause from adipose accumulation for SDN-POA degeneration would make an additional contribution to its senescent degeneration, so that make its cells decline sharply after aging as observed [7,14,15,17] in response to decrease in bodily sexual drive.

Section Summary

In this section, it is demonstrated the supporting evidence to the European view as followings: (1) The genetic increase and redistribution of fat tissue in male middle age; (2) The expression of aromatase in adipose tissue converting the testosterone to estradiol; (3) The ability of aromatase to determine sex differentiation in vertebrates; (4) The disturbance on male reproductive system from increment of adipose and aromatase in aging; (5) and in response to the hormonal outcomes from the rise in adipose and aromatase, the neuronal degeneration within the sexually dimorphic nucleus in preoptic area (SDN-POA) after male aging.

DISCUSSION

The new theory for the aging pathway from adipose accumulation to degeneration of hypothalamic preoptic sexually dimorphic nucleus (SDN-POA) is significant. It provides an explanation to account for the chronological aging of male hypothalamic SDN-POA with the intrinsic aging process genetically set in development and growth as adipose accumulation beginning in the male middle age. In parallel, it resembles the new theory of Cai to explain the chronological aging of hypothalamic SCN by the cellular senescent processes of skin via SWS. These two theories are similar in mechanism with peripheral causes to understand how the hypothalamic nuclei undergo degeneration heterogeneously during aging. There is only the paraventricular nucleus (PVN) in hypothalamus left waiting for clarification of its relative stability without change in aging.

It is even possible to compare these two newly hypothesized degenerative mechanisms addressing to two hypothalamic nuclei during aging. In phylogeny, forebrain slow wave in sleep is only present in vertebrates more advanced than reptiles [19,20], so that the senescent pathway from skin senescence to slow wave sleep(SWS) to degeneration of suprachiasmatic nucleus (SCN) [13] would be applicable only to the advanced vertebrates. Whereas, because aromatase is present in all vertebrates including fishes, amphibians, reptiles and mammals, the aging pathway from adipose accumulation to degeneration of hypothalamic preoptic sexually dimorphic nucleus(SDN-POA) would be applicable to all vertebrates, more ancient and conserved in evolution than the SCN degeneration from slow wave sleep.

On the other hand, it also provides a useful theory to guide the therapeutic efforts against male reproductive aging in future. With regard to SDN-POA degeneration during aging, the therapeutic anti-aging efforts should be more devoted to control of energy intake, exercise to reduce adipose and so on. In these regards, this new theory would be important to biomedical sciences.

CONCLUSION

In this article, it is reviewed the relevant progressions to support the view of the European people in television for the degeneration of male hypothalamic preoptic sexually dimorphic nucleus (SDN-POA) from the common knowledge of adipose accumulation in middle age, including the genetic increase and redistribution of fat tissue in male middle age; the expression of aromatase in adipose tissue converting the testosterone to estradiol; the ability of aromatase to even determine the sex differentiation in vertebrates; the disturbance on male reproductive system from increase of adipose and aromatase in aging; and finally the neuronal degeneration within the hypothalamic preoptic sexually dimorphic nucleus (SDN-POA) after male aging due to the hormonal outcomes from rise in adipose and aromatase.

Because the degeneration of suprachiasmatic nucleus(SCN) from skin senescence via slow wave sleep(SWS) would also affect the function of male reproductive system, the adipose accumulation causing SDN-POA degeneration would make an additional contribution to its degeneration, making its cells decline sharply after aging as observed.

Because aromatase is present in all vertebrates including fishes, the aging pathway from adipose accumulation to degeneration of hypothalamic preoptic sexually dimorphic nucleus(SDN-POA) would be more ancient and conserved in evolution than the SCN degeneration from slow wave sleep.

CONFLICT OF INTEREST

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