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The Regulation of Slow-Wave Sleep on Growth Hormone Secretion and Homeostatic Aging: A Pure Model in Man

Zi-Jian Cai

CaiFortune TriL Consulting, No. 129, Building 6, Room 404, North Dongwu Road, Suzhou, China
Email: hrsh8@126.com

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Abstract

Introduction: It is complicated for regulation of growth hormone (GH) secretion. Herein, it is considered the effects of slow-wave sleep (SWS) on GH secretion and related homeostatic aging, and their implications to other complicated GH secretions. **Methods:** It was best and most convincing to integratively review the literatures in various fields, especially the relationship among GH, SWS, aging, evolution, etc., and then discuss and summarize to deal with such a complicated topic. **Results and Discussions:** 1) With various pharmacological manipulations of SWS demonstrating the congruent change of GH secretion following SWS in man, it is defined such SWS regulation on GH secretion as pure model. 2) On aging, it is congruent in senescent reduction of both SWS and GH secretion in man. 3) It occurs the complicated GH secretions beyond the period of SWS, notably in woman and depression, rhesus monkeys and dogs. It was shown in woman the estrogen facilitated the endogenous GH release, so was in depression the growth hormone-releasing hormone (GHRH) along with reduced somatostatin before sleep onset. 4) In evolution, it has been suggested the various GH secretions across vertebrates manifest an evolutionary trend for simplification in factors for secretion regulation. **Conclusions:** It is feasible to classify various forms of GH secretion and related aging as either compatible or incompatible with the pure model in man, making it convenient to investigate their underlying mechanisms including satiety, estradiol, etc.

Subject Areas

Neuroscience, Physiology, Geriatrics, Zoology, Evolutionary Studies

Keywords

Growth Hormone, Slow-Wave Sleep, Depression, Homeostatic Aging, Evolution

1. Introduction

Growth hormone (GH) produced from the pituitary somatotrophs is a key endocrine regulator for development, growth and aging, while is also involved in regulation of metabolism, reproduction, physical activity, neuroprotection, immunity, and osmotic pressure in vertebrates [1]-[4]. The regulators of pituitary GH synthesis and secretion are diverse and various. Two major hormones in mammals, the hypothalamic growth hormone-releasing hormone (GHRH) and somatostatin, along with many other hormones such as the glucocorticoids, sex hormones, thyroid hormones, ghrelin, leptin, insulin-like growth factor-I, and so on in vertebrates, all play roles in regulating the secretion of GH [1]-[3]. Also, such neurotransmitters as GABA, acetylcholine, dopamine, serotonin, noradrenaline and so on are likewise important for the regulation of GH secretion [1] [2]. Finally, sleep-wake cycle is furthermore another regulator of GH secretion [5]-[8].

With so diverse and various forms of regulation on GH secretion, it is certainly difficult to demonstrate their intricate and complicated regulative interactions and underlying mechanisms. In this article, it is demonstrated a simple pure model for regulation of GH secretion during slow-wave sleep (SWS) in man and rats, while classifying the diverse and various forms of GH secretion in other situations as either compatible or incompatible with this simple pure model, making it convenient to investigate their underlying mechanisms by comparison, such as food intake, sex hormones, and so on.

2. Material and Methods

To deal with such an important but complicated theme, there was no better and more convincing way than integrative review of all related fields of researches. Meta-analysis fit investigation of a specific topic in a well-studied subfield, while neglected many valid proposals in some papers, such as the 2009 paper of Gahete *et al.* [2]. Besides, many studies on animals, like baboon, monkey, and dog, provided only one or two papers for each animal, insufficient for meta-analysis. Thus, meta-analysis did not fit the complicated studies in this paper. Besides, it was certainly required to analyze and integrate the collected reviews and papers from several fields by classification, comparison and summarization.

Papers were searched out from Pubmed, Europe PMC and Baidu Xueshu. The updated relevant reviews in subfields were given priority to cite. If not available, relevant reviews more than 10 years ago were cited. If still unavailable, the salient and repeated experimental results of original articles in subfields were cited. In this way, it was possible to further classify, compare and summarize them to make achievements in the important complicated theme.

The words and phrases utilized in the search of paper were collected as the followings: "aging", "slow wave sleep", "depression", "growth hormone", "evolution", and so on. Sometimes, two or three of these words and phrases were utilized together to restrict the results in the search, such as "growth hormone slow wave sleep", "slow wave sleep aging", "growth hormone aging", and so on.

3. Results

3.1. The Pure Regulation of SWS on GH Secretion and Homeostatic Senescence

3.1.1. The Pure Regulation of SWS on GH Secretion

In man, GH secretion occurs in SWS in all age stages of life [4]-[6], arguing for the predominant pure nature for the regulation of SWS on GH secretion. Further evidences supporting such pure nature of regulation come from the pharmacological manipulation of SWS. It was reported in men that the weak gamma-aminobutyric acid (GABA) agonist sodium oxybate doubled SWS and the cross-correlation between GH levels and SWS [9], while gamma-hydroxybutyrate, a reliable stimulant of SWS, likewise stimulated the secretion of GH simultaneously [10]. In contrast, The benzodiazepine antagonist flumazenil caused an inhibition in SWS and decrease in plasma GH concentration in male controls [11]. The congruent change in GH following manipulation of SWS strongly supported the unitary pure regulation of SWS on GH secretion in man.

Because of the unitary pure regulation of SWS on GH secretion in man, it is obviously a simple model for regulation of GH secretion, so it is herein defined such unitary SWS regulation of GH secretion in man as a pure model.

Likewise, early studies in rats complied with the unitary SWS regulation of GH secretion in man. Hypothalamic GHRH stimulated the secretion of GH in rats [7] [8], while it also enhanced the SWS concomitantly [7] [8], linking the SWS and GH secretion in rats, compatible with the pure model observed in man.

3.1.2. The Coherent Decrement of SWS and GH Secretion during Aging

It has been well evidenced that SWS decreases continually throughout the process of life toward aging [5] [6] [12] [13]. In consistence with the unitary regulation of SWS on GH secretion in man, the GH secretion also decreases [4]-[6] coherently in parallel to the decrement of SWS in aging [5] [6] [12] [13].

3.2. SWS and Complicated Growth Hormone Secretions

3.2.1. The Complicated GH Secretions in Woman and Depression

Even though the studies in man and rats have supported the unitary regulation of GH secretion by SWS, the GH secretion in woman deviates this pure model, so does in depression, making it complicated.

For woman, it has been reviewed that, in contrast to the sleep-onset-associated pulse as the major or even the only daily episode of active GH secretion in man, awake GH secretory pulses are frequent in woman [14] [15]. It has further been reported that the temporal relationship between GH and SWS may become even weaker after menopause [15].

For depression, because shorter SWS duration has been frequently associated with depression [16]-[18], GH secretion may dissociate with SWS in depression. Indeed, it was reported that GH was hypersecreted during wakefulness, with a major pulse before rather than after sleep onset [19] [20].

Even though the GH secretion in woman and depression deviates from the unitary regulation of GH secretion by SWS in man, the complicated GH secretion in woman and depression also differs with each other. Although daytime GH secretory pulses are frequent in woman, substantial GH secretion is normal in SWS [14] [15], while shorter SWS duration are frequently associated with depression [16]-[18] with GH hypersecreted mainly before sleep onset [19] [20].

In all these respects, it is thereby feasible to classify GH secretions as either pure under the unitary regulation of SWS or complicated beyond the period of SWS.

3.2.2. Different Mechanisms for Complicated GH Secretions in Woman and Depression

It is certainly necessary to reveal the factors influencing the complicated secretions in woman and depression.

For woman, a few studies have revealed that estradiol could be responsible for stimulating the pulsatile GH secretion in postmenopausal woman via the release and/or action of hypothalamic GHRH rather than somatostatin [21] [22]. As estradiol is a sex hormone, such mechanism in woman would not affect the SWS regulation of GH secretion in man, which also occurs in woman [14] [15].

For depression, because of the shorter SWS duration [16]-[18], it may be insufficient for SWS to secrete sufficient GH for basic homeostasis. Hypersecretion of GH before sleep may be the physiological shift resulting from the shortage of SWS for GH secretion, with overall high levels of cortisol [19] [20] and deficits in somatostatin-positive GABA interneuron [23]. Furthermore, in a stress-induced rat model of depression, it was demonstrated that the hypersecretion of GH could synergically result from GHRH before sleep and reduced content of somatostatin in depressed rats [24].

Accordingly, the complicated GH secretions in woman and depression beyond SWS involve different mechanisms. The woman may resort to estradiol to stimulate the pulsatile GH secretion via GHRH [21] [22], while the depression adopt GHRH before sleep and reduced content of somatostatin to synergically enhance GH secretion [24].

Table 1 outlines the pure and complicated GH secretions with regard to SWS regulation.

Table 1. The pure and complicated GH secretions with regard to SWS regulation.

GH Secretion	Man	Woman	Depression
Classification	Pure	Complicated	Complicated
Association with SWS	Almost only SWS enhances substantial GH secretion	Although substantial GH secretion occurs in SWS, pulsatile GH secretion also occurs in waking frequently	With SWS shortened, hypersecretion of GH occurs with a major pulse before rather than after sleep onset
Physiological Mechanisms	GHRH enhances both SWS and GH secretion, while GH secretion still follows SWS changes even by drug manipulation	Estradiol additionally stimulates the pulsatile GH secretion via GHRH during waking	GHRH before sleep and reduced somatostatin synergically enhances GH secretion

Abbreviation Notes: GH growth hormone; GHRH growth hormone-releasing hormone; SWS slow wave sleep.

3.3. The Growth Hormone Secretion in Various Other Animals

3.3.1. The GH Secretions and SWS in Animals

The association of GH secretion with SWS also occurs in animals. In baboon, it was reported that GH secretion occurred in sleep as in humans [25]. Besides, in rats, as mentioned above, it was early demonstrated that GHRH enhanced both GH secretion and SWS concomitantly [7] [8], associating the SWS and GH secretion.

However, exceptions occur in some animals. In rhesus monkeys, it was reported that, in contrast to man, sleep and SWS were not associated with the 24-h GH pattern [26]. In dogs, it was demonstrated that, in undisturbed condition, the episodic GH secretion had no apparent relationship with sleep or the light-dark cycle [27], while after sleep deprivation, the incidence of sleep-onset GH peaks and GH secretion during the first hour of recovery sleep significantly increased [27].

Together, the substantial GH secretion occurring only during SWS in man [4]-[6] also occurs in some animals, such as baboon [25] and rats [7] [8], while not in some others, such as rhesus monkeys [26] and dogs [27].

3.3.2. The Factors Governing GH Secretion in Evolution

In mammals, GHRH and somatostatin are the two major hormones directly controlling the secretion of GH [1]-[3], with GHRH stimulatory and somatostatin inhibitory.

Whereas, besides these two major hormones, many other hormones or factors affect, either stimulate or inhibit, the secretion of GH in vertebrates, such as the common glucocorticoids, sex hormones, thyroid hormones, ghrelin, leptin, insulin-like growth factor-I, fibroblast growth factors, and the seldom mentioned adropin, klotho, nucleobindin-encoded peptides, and so on [1] [2]. Meanwhile, many neurotransmitters like GABA, acetylcholine, dopamine, serotonin, noradrenaline and so on also participate the regulation of GH secretion [1] [2].

With so many various factors to regulate the secretion of GH, some authors suggested that GH production be differentially regulated across vertebrates with an apparent evolutionary trend for simplification, especially in the number of stimulatory factors governing substantial GH release [2].

3.4. The Importance of Pure Regulation of SWS on GH Secretion to Aging

As mentioned in Section 3.1.2, SWS decreases continually throughout the lifespan toward aging [5] [6] [12] [13], while the GH secretion also follows to decrease coherently during aging [4]-[6], resulting from the unitary regulation of SWS on GH secretion in man [9]-[11].

As per the unitary regulation of SWS on GH secretion in man [9]-[11] and rats [7] [8], the mechanisms causing the senescent reduction of SWS can as well explain the decrease in GH secretion during aging [4]-[6]. This would extend the application of pure model for SWS regulation of GH secretion in man to comprehension of aging mechanisms related to GH.

Recently, it was hypothesized by Cai that continual skin aging reduce both electrodermal activities and emotional responses/memories, and in turn cause the senescent reduction of SWS [28] [29], with the major supports as the followings:

1) Constant exposure to sunshine [30] [31] and oxygen [32] [33], plus genetic shortening the length of telomeres [34], resulted in continual skin aging.

2) It was demonstrated that fear [35] was associated with an increase in electrodermal activities, while the measures to reduce stress resulted in decrease in electrodermal activities [36] [37].

3) The electrodermal activities decreased in the older subjects than younger [38] [39], opposite to that of fear [35] and stress [36] [37]. In other words, skin aging reduced electrodermal activities and the physiological effects of aversive emotional responses and memories in aging.

4) SWS played indispensable function to adjust the emotional balance disrupted by the accumulated aversive emotional memories [40] [41]. The reduction in physiological effects of aversive emotional memories in aging required less SWS to balance, resulting in the continual reduction of SWS toward aging, as evidenced by many observations [5] [6] [12] [13].

5) In brain, the hypothalamic suprachiasmatic nucleus (SCN) controlled the circadian rhythm and alteration of sympathetic/parasympathetic activities [42] [43]. The reduced requirement for SWS in aging would decrease the requirement for SCN regulation onto SWS, and result in partial degeneration of SCN [28] [29]. In parallel, the senescent reduction of SWS as well decreased the GH secretion during aging [4]-[6].

In all in man, continual skin aging from constant exposure to sunshine [30] [31] and oxygen [32] [33], plus genetic shortening the length of telomeres [34], decreased the electrodermal activities [38] [39] and physiological effects of aversive emotional responses and memories in aging, which in turn required less SWS to balance and caused continual reduction of SWS in aging. The senescent reduction of SWS decreased: 1) the requirement for SCN regulation onto SWS, causing partial degeneration of SCN [28] [29], and 2) the SWS-related GH secretion during aging [4]-[6].

4. Discussion

In this article, it is classified the secretion of GH as either pure, under the unitary regulation of SWS in man [4]-[6] and rats [7] [8], or complicated beyond the period of SWS in woman [14] [15] and in depression [19] [20]. Various pharmacological manipulations of SWS demonstrated the secretion of GH in man congruent following the occurrence of SWS [9]-[11], making the unitary secretion of GH suitable as a stable pure model.

In woman, in addition to the SWS-associated GH secretion, GH secretory pulses are also frequent in waking [14] [15]. The GH secretion in SWS of woman is compatible with the SWS-regulated GH secretion, whereas the GH secretory pulses of woman in waking are complicated GH secretion. Whether the daytime complicated GH secretion in woman contributes significantly to homeostatic anti-aging, and, if yes, how it contributes to homeostatic anti-aging would require more investigations.

In depression, GH secretion is also complicated, hypersecreted during wakefulness with a major pulse before rather than after sleep onset [19] [20], different from that in woman [14] [15]. As depressed patients are subject to stress or helplessness, it is speculated that such complicated GH secretion in patients might contribute compensatorily to homeostatic anti-aging, which requires further investigation.

In human aging, because of the continual decrease of SWS toward aging [5] [6] [12] [13], the GH secretion also decreases in aging [4]-[6] coherently by the unitary regulation of SWS on GH secretion in man [9]-[11]. Recently, it was proposed by Cai that the continual skin aging would decrease SWS via reduction of emotional responses and memories [28] [29], hence herein it accomplishes the link from continual skin aging to homeostatic aging via SWS and GH. Whereas, complicated GH secretions are various, and need to be considered from case to case.

GH secretions in animals are various in manifestations. Unitary SWS regulation of GH secretion occurs in baboon [25] and rats [7] [8], while complicated GH secretions are present in rhesus monkeys [26] and dogs [27].

It is certainly convenient to classify the GH secretions in animals as either compatible or incompatible with the unitary SWS regulation of GH secretion. For the GH secretion under the unitary regulation by SWS in man, the homeostatic aging via decrement of SWS and GH would fit as the corresponding aging mechanism of homeostasis. For the complicated GH secretions in animals beyond SWS, the homeostatic aging via SWS and GH would not fit, so that it is necessary to investigate whether such complicated GH secretions could contribute to anti-aging from case to case.

Some authors suggested that GH production be differentially regulated across vertebrates with an apparent evolutionary trend for simplification, especially in the number of stimulatory factors governing substantial GH release [2]. Many factors such as SWS [4]-[6], satiety from food intake [3], sex hormones [21] [22], and so on may influence GH release. Among them, the circadian immobile SWS under the regulation of hypothalamic SCN favors sympathetic deactivation and bodily restitution in contrast to active sympathetic status in waking [42] [43], which is obvious the evolutionarily most suitable and advanced status for GH secretion and functions, so is the pure model for regulation of GH secretion in man. Therefore, in other vertebrates of diverse stimulatory factors for GH release, it is perspective to apply the classification of GH secretions as either compatible or incompatible with this pure model, and investigate their underlying mechanisms, such as satiety from food intake [3], sex hormones [21] [22], and so on.

Table 2 outlines the pure/complicated regulation of GH secretions and homeostatic aging via SWS and GH.

Table 2. Pure/complicated regulation of GH secretions and homeostatic aging.

	Pure regulation of GH secretion	Complicated regulation of GH secretions
SWS	Under SWS regulation only	Beyond SWS at least partially
GH-related homeostatic aging	Under SWS regulation only	Beyond SWS at least partially

Abbreviation Notes: GH-Growth Hormone; SWS-Slow Wave Sleep.

5. Conclusion

In this article, based on the tight congruent occurrence of SWS and GH secretion in man by various pharmacological manipulations, it defines the GH secretion during SWS in man as a pure model. In aging, SWS decrement reduces its unitary regulation of GH secretion in man. Whereas, it occurs the complicated regulation of GH secretions beyond the period of SWS, notably in woman and depression, as well as in rhesus monkeys and dogs. Because of the evolutionary trend to simplify the number of stimulatory factors for GH secretions in vertebrates, it is advanced in evolution for immobile SWS with sympathetic deactivation to regulate the substantial GH secretion in man, which is advantageous for the pure model of GH secretion and homeostatic aging. Other GH secretions and homeostatic aging mechanisms can be classified as either compatible or incompatible with this simple pure model. It is expected that such classification could benefit to future researches to investigate the various related underlying mechanisms, such as satiety from food intake, sex hormones, and so on.

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Availability of Data and Materials

The data and materials in this work are available in the relevant cited references.

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