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Review Article

THERAPEUTIC METHODS AGAINST AGING

Abstract

Since 80s we know that growth hormone (GH) secretion declines with age. However, in July 1990, Rudman and colleagues reported for the first time, rejuvenation in persons over 61 years of age following the administration of GH. Since then and to date, four therapeutic methods are used against aging: 1) administration of exogenous GH; 2) administration of exogenous growth hormone-releasing hormone (GHRH); 3) administration of secretagogue products, and finally, 4) hypothalamic revascularization. With all of them, rejuvenation is evident, but in different degrees. Therefore, the aging process is a disease, which is initiated in the arcuate nucleus of the hypothalamus secondary to ischemia by atherosclerosis in supraclinoid carotids.

Key Words: Aged; Arcuate nucleus/pathology; Hypothalamus/pathology; Omentum/transplantation.

Derleme

YAŞLANMAYA KARŞI TEDAVİ YÖNTEMLERİ

Öz

Büyüme hormonu (GH) sekresyonunda yaşla birlikte azalma olduğunu 80'lerden bu yana biliyoruz. Ancak, 61 yaş üzeri kişilerde GH uygulanmasından sonra gençleşme olduğunu, Temmuz 1990'da ilk kez Rudman ve meslektaşları bildirmişlerdir. O tarihten bu yana, yaşlanmaya karşı dört tedavi yöntemi kullanılmıştır: 1) eksojen GH uygulanması; 2) eksojen büyüme hormonu salgılayıcı hormon (GHRH) uygulanması; 3) sekretagog ürünleri uygulanması ve son olarak 4) hipotalamus revaskülarizasyonu. Hepsinin kullanımıyla, gençleşme açıkça gözlenmektedir ancak farklı derecelerdedir. Yaşlanma süreci, hipotalamusun arkuat nükleusunda, supraklinoid karotis aterosklerozuna bağlı iskemi nedeniyle başlayan bir hastalıktır.

Anahtar Sözcükler: Yaşlı; Arkuat nukleus/patoloji; Hipotalamus/patoloji; Omentum/transplantasyon.

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INTRODUCTION

Biological aging is a process opposed to growth and development, which produce important anatomical and physiological changes with age, due to a gradual loss of cells from all parts of the body. In 1981, Rudman and associates (1) reported a direct correlation between decreasing growth hormone (GH) levels and effects of aging, especially in persons over 30 years of age. Later on, other authors (2,3) reported that GH replacement therapy in GH deficient young people and adults has a role in the regulation of body composition: muscle volume of the thigh increases and by contrast, the adipose tissue decreases.

In July 1990, Rudman, et al. (4) published for the first time their clinical discovery about rejuvenation following subcutaneous administration of biosynthetic human GH for six months to 12 healthy men from 61 to 81 years old. Since then and to date, several authors have confirmed this clinical observation, and all of them conclude that the aging process is characterized by a progressive reduction in the daily spontaneous GH secretion associated with declining levels of the insulin-like growth factor-I (IGF-I) also known as somatomedin C. However, the **primary cause** of this progressive deficiency with increasing age, is little known. Thereby, in this review article, I will analyse the implicated structures in the regulation of the GH secretion.

Vascularization of The Hypothalamus

A diencephalic structure, the hypothalamus, has a mean height of 10-mm and a mean anteroposterior diameter of 15-mm (5) and weighs about 4-gr in the average adult human brain (6). It is a neuroendocrine structure very vascularized and with many afferent and efferent projections.

Normally the anterior part (constituted by suprachiasmatic, supraoptic, preoptic, anterior, perifornical and paraventricular nuclei) obtains its blood supply from anterior perforating arteries (APAs) originating from the supraclinoid carotids (C4 segments) and anterior half of the circle of Willis (7,8).The middle part (arcuate nucleus and ventromedial, dorsomedial and lateral nuclei) receives its blood supply from the APAs derived from the posterior communicating arteries (PCoAs) (7,9). The posterior part (mamillary bodies, tuberal and posterior nuclei) are supplied by posterior perforating arteries (PPAs) arising from the distal end of the basilar artery and posterior half of the circle of Willis (5,7,10). In most cases, this vascular standard has anatomical variations in relation to number, caliber and distribution of these perforating arteries.

In the hypothalamic parenchyma, the number of capillaries is influenced by the demand of parenchymal elements (glia and neurons) from the bloodstream (11-13). There are not end-arteries, but on the contrary, their terminal branches have anastomoses with branches of another origin as APAs, PPAs or medial lenticuloestriate arteries. The capillary walls in these highly vascularized nuclei are fused with the membranes of neuronal perikaya and process (14,15). In these areas of contact, there is no evidence of glial interposition between the neuronal and vascular elements (neuronal-vascular relationships). Such neuronal-vascular contacts are evident in the supraoptic and paraventricular nuclei (11,14,15).

Therefore, the function and number of hypothalamic neurons is related with the degree of vascularization, since before and during the first years of life.

Hypothalamic Dysfunction and Ischemia

Atherosclerosis is a chronic inflammatory disease (16) that initiates in the aortic arch and progresses in the aorta and its main branches (17,18). It is detected in the first decades of life (fetal life and childhood) in both sexes with equal frequency in men and women, due essentially to mechanical stresses (primary factor) generated by blood flow, which provoke a reactive biological response in the intima, i.e., atherosclerotic changes in children; in adolescents and adults, due to primary and secondary factors (or risk factors) which accelerate the development of atherosclerosis (17,19).

Between 25 and 30 years of age, changes occur in the human brain related with cerebral blood flow (CBF) and neuroendocrinological disorders. **First**, the CBF declines progressively to mean values of adults (50 to 55 ml/100gr/min) until about 55 years of age (17,20), and then CBF is reduced a little more with age (21,22). **Second**, arteriographic (23) and autopsy (24) studies have revealed atherosclerotic changes at the supraclinoid carotids in 4.3% of the cases and at the distal end of the basilar artery in 8%. Later on, these atheromatous lesions increase with age. Thus, the atherosclerotic plaques located at the mouths of the APAs originated from the C4 segments and circle of Willis can cause stenosis or occlusion and therefore, progressive hypoperfusion and hypometabolism in the hypothalamic nuclei. **Third**, GH secretion by the adenohypophysis tends to decline with age (1,25) and on practically every person after 30 years, there is a direct correlation between decreasing GH levels and effects of aging. In other words, the aging process appears about the age of 30. **Fourth**, the dehydroepiandrosterone (DHEA), main precursor of the testosterone and estrogens, declines rap-

idly and markedly after the age of 25 years (26), due to a decreasing secretion of luteinizing hormone, which acts on Leydig testis cells (27). Thus, a reduced concentration of serum testosterone can cause visceral obesity, decreased libido, erectile dysfunction and decreased volume of semen, and moreover, the hypotestosteronemia is a risk factor for the development of atherosclerosis (28,29). **Fifth**, the arcuate nucleus, ventromedial nuclei, tuber cinereum and the preoptic nuclei are the producing hypothalamic nuclei of growth hormone-releasing homone (GHRH) and luteinizing hormone-releasing hormone (LHRH) (30,31), which receive vascularization from several arterioles and capillaries originating from the collateral branches of the C4 segments and circle of Willis (7,9). Through the hypophyseal portal system in the median eminence, both hormones (GHRH and LHRH) conclude in the adenohypophysis and then, GH secreted by the pituitary acts on the liver to stimulate the production of somatomedins (sulphation factors), especially of somatomedin C. Therefore, normal vascularization of the producing hypothalamic nuclei of GHRH is essential for the synthesis and secretion of GHRH (9,23). **Sixth**, the total number of neurons in the arcuate nucleus decrease with age (33). This finding suggests that in the mature brain, the neurogenesis starting from undifferentiated cells (stem cells) (34,35) located in the walls of the third ventricle (subventricular zone) decline with age and disappear (36).That is, about the age of 30, stem cells located in this hypothalamic region are scarce or do not exist, and in contrast, there is a progressive deterioration of adult cell groups in the arcuate nucleus, especially of GHRH and neuropeptide Y (NPY) neurons.

In conclusion, these above-mentioned findings indicate that the aging process **is initiated** in the producing hypothalamic nuclei of GHRH, especially in the arcuate nucleus; due to a progressive hypoperfusion and hypometabolism in this nuclei provoked by atherosclerotic plaques located at the mouths of the PCoAs and superior hypophyseal arteries originating from the C4 segments. For these reasons, I believe that aging is not a normal biological process but a disease (39).

Treatments to Increase The GH Levels

Since 1990 and to date, four therapeutic methods have been used against aging (Figure 1) and the purpose is to reverse the decline in GH secretion that occurs during the aging process.

Treatment with GH. Exogenous GH administration is effective because it increases the GH and somatomedin C levels in bloodstream, and in a conventional replacement dose, can provoke rejuvenation in several tissues of the body, especially in the skin (4,40,41). Many of the target effects of GH are

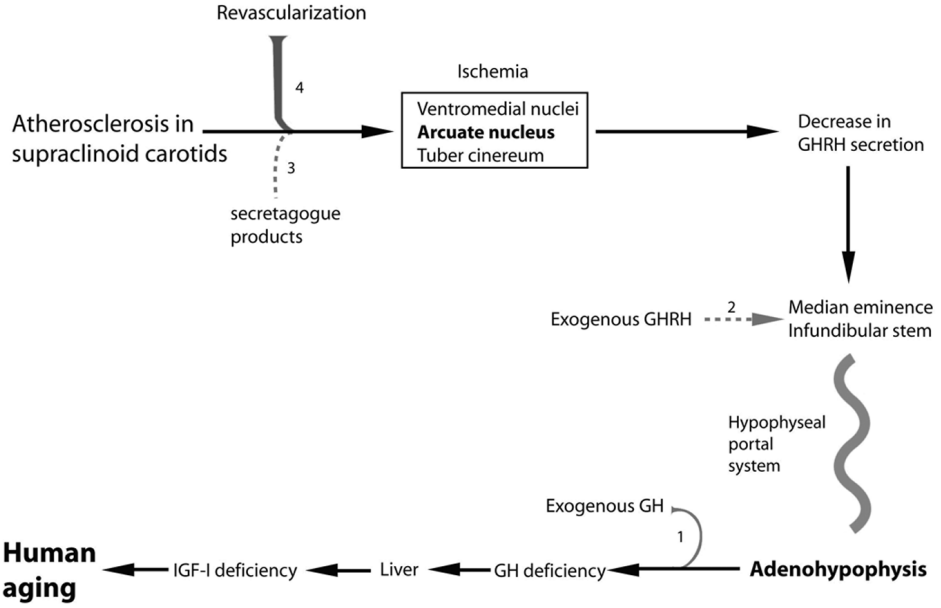

Figure 1— Schematic representation of the aging process and its treatment. GH, growth hormone; GHRH, growth hormone-releasing hormone; IGFI, insulin-like growth factor I. The revascularization favours the synthesis and secretion of endogenous GHRH and GH.

mediated by somatomedin C, which is predominantly produced in the liver. The secretion of somatomedin C is regulated by GH and through the IGF-I exert many biological effects such as 1) incorporation of sulfates in the cartilage in the form of chondroitin sulfate; 2) transformation of amino acids in proteins, especially in the synthesis of insulin, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), and 3) favouring the conversion of proline in hydroxyproline in the cartilage (13). Likewise, GH associated with insulin and thyroxine are necessary requirements for growth and proliferation of cells in the entire body and in the encephalon. The absence of changes in bone density reported by some authors (4,40) could be due to a vascular impairment in bone and cartilage (13) and thus, GH does not terminate in these tissues. However, its use as an anti-aging therapy has not been approved by the Food and Drug Administration in the United States. Some authors (42) reported that exogenous GH in the healthy elderly is associated only with small changes in body composition and therefore, can not be recommended as an anti-aging therapy. On the contrary, other authors (43,44) reported that the GH replacement therapy is safe and there is no evidence that this treatment increases **de novo** malignancies or tumor re-growth in patients. In my opinion, this anti-aging therapy is only palliative or substitutive.

Treatment with GHRH. A physiological means for increasing endogenous GH levels is through the administration of GHRH (45,46). Daily subcutaneous injection of GHRH in elderly men and postmenopausal women for 4 months increased pulsatile GH secretion and serum somatomedin C levels without any adverse side effects (47). Nevertheless, this therapeutic method may fail in persons over 70 years of age, because the degree of atherosclerosis in the supraclinoid carotids is moderate or severe (9,21,48) and the exogenous GHRH does not reach the median eminence and/or adenohypophysis.

Treatment with secretagogue products. Oral or nasal administration of secretagogue products (also known as GH secretagogues) is another method to increase the GH secretion. These secretagogue products are chemically formed by a combination of amino acids, peptides, vitamins and minerals (40,49-51), which act on receptors in the arcuate nucleus and pituitary gland to stimulate the secretion of GH secretion. Oral administration of ghrelin (or MK-677) in healthy older adults may produce increased pulsatile GH secretion and some patients show clinical data of rejuvenation (51,52), due possibly to the activation of neuroendocrine neurons in the arcuate nucleus (38,50,53). However, like the administration of GHRH, these GH secretagogues are uniformly less effective in older men and women than the use of exogenous GH. Because the components (amino-acids, peptides, vitamins and minerals, among others) in these secretagogue products do not terminate in the producing hypothalamic nuclei of GHRH, due to severe atherosclerosis in the C4 segments (9,21,23). In other words, the blood flow in the arcuate nucleus of elderly people is scarce.

Hypothalamic revascularization. The fourth therapeutic method against aging lies in to increase the blood flow in the hypothalamic nuclei and surrounding areas (48,54-56) to improve the function and survival of the residual arcuate nucleus, which is constituted normally by dopamine, GHRH and NPY neurons, as well as ependymal cells and tanycytes (37,38). In reality, it is a physiological method which can reverse the decline in GH secretion, i.e., this method favours the synthesis and secretion of GHRH.

1. Omental transplantation. Since January 2004, and to date, 8 patients (between 61 to 82 years of age) have been operated with this surgical technique. All of them received omental transplantation on the optic chiasma, carotid bifurcation and the anterior perforated space, due to hemiparesis, dysphasia or sensory disorders caused by essential arterial hypertension (EAH) and/or type 2 diabetes mellitus (DM). Preoperative CTscans showed stenosis in the supraclinoid carotids or in its terminal branches. The surgery was performed to improve the stroke. During the surgery we found: 1) moderate or severe atherosclerosis in the supraclinoid carotids and its terminal branches; 2) several exsanguinated and collapsed APAs, and 3) other collateral branches with residual blood flow centripetal to the origin of these vessels. Neurological improvement as well as EAH and the levels of circulating blood glucose were normalized since the first days after surgery (9,54,57). About 1 to 4 months after operation, the patients experienced some changes of progressive rejuvenation. These postoperative observations were findings and the pre-and postoperative pictures are recorded in videotapes. The first patient (9), a 82-year-old man experienced rejuvenation 4 months after omental transplantation. Two years later, he presented with decreased wrinkles, thick and humid skin, new hair growth black-coloured and thereby, his white-hair was reduced to 50%, good elasticity of skin, increased muscle volume, the visceral obesity decreased, and had a sex life with orgasm 3

or 4 times a month. The pre-and postoperative picture was recorded on 4 videotapes. For these reasons, I believe that these results are due, essentially, to **revascularization** of the producing hypothalamic nuclei of GHRH and LHRH. Because the omentum, is the best tissue for development of vascular connections with underlying and adjacent zones and, through omental neovessels, the residual arcuate nucleus received an increase in blood flow, oxygen, neurotransmitters, neurotrophic factors, cytokines and omental stem cells (36,58,59). Therefore, appearance of neurogenesis in the hypothalamus through the omental stem cells is very probable. Thereby, this therapeutic method gives essentially nutrition, oxygen, and neurotropic factors since the first days after surgery (54-56). Thus, the function of neurons in ischemia and ischemic penumbra can improve, due to neuronal regeneration and/or neurogenesis.

2. Influence of aspirin. Recent clinical evidences suggest that the regular use of aspirin reduce the risk for myocardial infarction and stroke (60,61), as well as can improve or normalize EAH and hyperglycemia in patients with type 2 DM (62-64). High-dose aspirin (250 to 500 mg per day) against EAH and type 2 DM should be associated with 1 to 2 mg of clonazepam at night to reduce stress and/or sleep disorders (62,65). I think that these results are due to the anti-thrombotic and anti-inflammatory effects of aspirin (61,66) against atherosclerotic plaques located at the mouths of the APAs originated from the supraclinoid carotids and circle of Willis. Thus, the blood flow in the hypothalamic nuclei may be increased by **recanalization**. Moreover, we have also observed some clinical data of rejuvenation in the skin texture, muscle strength, body fat loss, black hair, and improvement of osteoarthritis in the spine and hands (unpublished observations)

Conclusions

Based on the above-mentioned factors and rejuvenation observed after hormonal replacement therapy or by means of hypothalamic revascularization, there is no doubt that aging is not a "normal phenomenon" but a disease, which is initiated (about 25 to 30 years of age) in the producing hypothalamic nuclei of GHRH by progressive ischemia, due to atherosclerotic plaques located at the mouths of the PCoAs and/or superior hypophyseal arteries. Moreover, the same ischemic process around the arcuate nucleus may also affect to other nuclei of the anterior and posterior hypothalamus and cause type 2 DM or EAH. For these reasons, we must struggle against the pathogenesis of atherosclerosis to prolong the longevity.

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