HORMONES AND AGING

Vanja Zjačić-Rotkvić[1], Lovro Kavur[2] and Maja Cigrovski-Berković[1]

[1]Department of Endocrinology, Diabetes and Metabolism, Sestre milosrdnice University Hospital; [2]Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY – Since the 19th century, there have been sporadic attempts to attribute the changes of aging to one or another endocrine deficit and efforts to reverse these changes by various replacement therapies. This search for a hormonal 'fountain of youth' continues today.

Key words: *aging, endocrine glands, hormone production, hormone replacement therapies*

Aging is characterized by a progressive loss of coordinated cell and tissue function, so that the body becomes gradually less fit to reproduce and survive. Deterioration of function is heterogeneous among individuals and is detectable first as a loss of reserve capacity and ability to restore homeostasis under stress, and later by altered function at rest. Strehler[1] has suggested five basic criteria best defining aging. It has a characteristic of accumulation, which means that the effect of aging increases over time. Also, it is universal, which implies that all members of a species are showing aging effect. Furthermore, it is intrinsic and alterations occur even when the individual is in optimal external life conditions. Aging is progressive, evolving a series of gradual changes. The last Strehler's component is hurtfulness because normal function is compromised. Today, there are many theories trying to explain aging process but none has succeeded in providing complete answer to the question yet. Do hormones play a role in aging process, how large is their part and is there a possibility that hormones define the rhythm and speed of aging, is being widely considered, and the search for endocrine 'fountain of youth' is ongoing. Dilman[2] and Dilman and Dean[3] have proposed a neuroendocrine theory of aging. The basic hypothesis of neuroendocrine theory advocates the central role of hypothalamus in aging while reduced sensitivity to hormones and other signaling peptides has been demonstrated at this level. This implies that aging could be regulated by hypothalamus and pituitary, which represent the body's internal 'pacemaker' regulating physiological changes over time. To simplify, the loss of hypothalamic sensitivity leads to progressive loss of homeostasis, alterations in hormone concentrations, and reduction of neurotransmitters and signaling molecules (Fig. 1). According to neuroendocrine theory, decreased sensitivity of hypothalamus and peripheral receptors would cause energy misbalance, inadaptability, and weakening of immune and reproductive ability. The theory hypothesizes how metabolic changes, i.e. decreased glucose tolerance and hyperinsulinemia, hyperlipidemia, and especially HDL cholesterol reduction lead to gradual deterioration of health and death[3]. An example of the body decreased capacity of adjustment is cortisol activity. Decreased hypothalamic sensitivity causes weakening of negative feedback of cortisol in hypothalamus and pituitary, and progressively much greater concentrations of cortisol are needed to achieve suppression of corticotropin-releasing hormone (CRH) secretion from the hypothalamus and adrenocorticotropic hormone (ACTH) secretion from the pituitary. Dilman proved this by measuring concentrations of cortisol in female patients of different age groups prior and following different surgical interventions. Results

Correspondence to: *Prof. Vanja Zjačić-Rotkvić, MD, PhD*, Department of Endocrinology, Diabetes and Metabolism, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia

E-mail: ziarot@kbsm.hr

showed much higher concentrations of plasma cortisol in older female patients after surgical procedures, although prior to surgery there were no significant differences in basal cortisol concentrations[2]. His results were confirmed in a study conducted by Mikhailovich *et al*.[4], and they imply that people of older age have a more pronounced and prolonged reaction to stress than younger individuals. Previously mentioned alterations in cortisol concentrations are often variable. It seems they have no immediate effect on the hypothalamus-pituitary-adrenal gland axis, but possibly exert a chronic clinically important influence. It appears they are associated with the lack of sleep in the elderly, reduced memory in women, osteoporosis in older men and an increased risk of fractures in both older men and women. The secretion rate and serum concentrations of aldosterone fall with age and by about age 70 the decreases can be as much as 50 percent. The proximate cause is a decrease in renin secretion. When marked (particularly in patients with renal failure), it can result in hypoaldosteronism, urinary sodium wasting, hyponatremia and hyperkalemia[5,6]. Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) are adrenal gland hormones that are precursors in the synthesis of active androgens and estrogens. Secretion of these steroids significantly decreases with age, so that in 70- to 80-year-old subjects serum concentrations of both are by about 20 percent of those in 20- to 30-year-old subjects. Whether this decrease has a true clinical meaning is still unknown. Many have speculated that DHEA administration might reverse some of the changes in body composition and behavior that occur with aging, but results of placebo-controlled trials in normal older subjects have revealed minimal benefit (small increases in bone density at some sites, small increases in muscle mass) and some harm (androgen effects in women and estrogen effects in men)[7,8]. In older people, serum norepinephrine concentrations are higher than in younger subjects, whereas those of epinephrine are either the same or slightly lower. Norepinephrine levels appear to be a result of higher sympathetic nervous system activity, and not of the adrenal medulla. They are probably compensatory, due to the loss of responsiveness of at least some tissues to norepinephrine[9-12]. The volume of thyroid gland increases slightly with age. There are no age-related changes in serum total or free thyroxine concentrations. Similarly, serum triiodothyronine

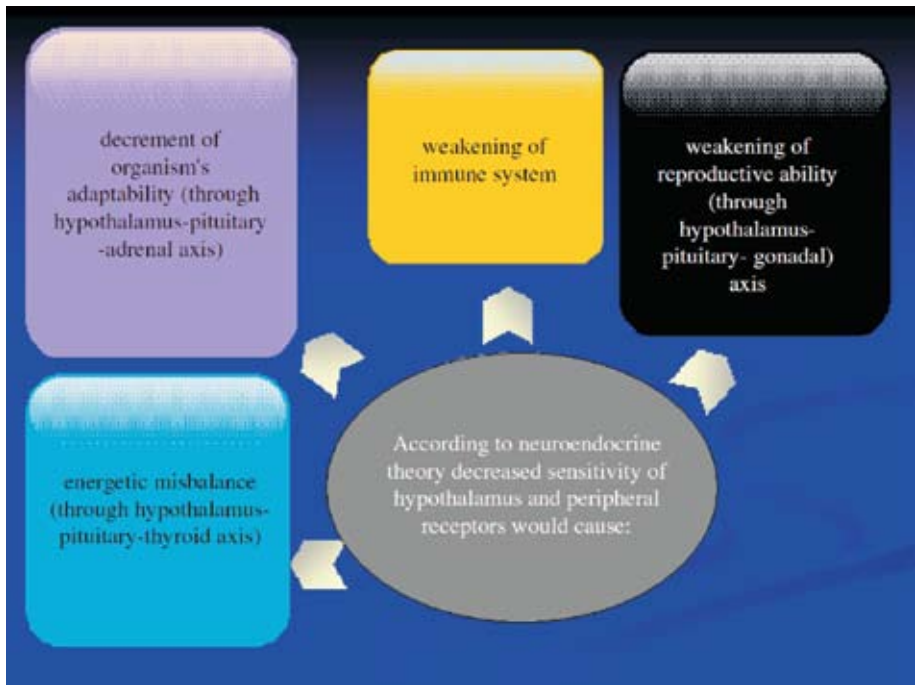

Fig. 1. Neuroendocrine aging theory (from: Dilman V, Dean W. The neuroendocrine theory of aging. Pensacola: The Center for Bio-Gerontology, 1992)[3].

concentrations do not decrease with age significantly. Lower levels of triiodothyronine in some older subjects are probably due to intercurrent nonthyroidal illness that reduces extrathyroidal conversion of thyroxine to triiodothyronine. Serum parathyroid hormone (PTH) concentrations are slightly higher in older as compared with younger subjects. The most likely cause of this increase is a fall in serum calcium concentration due to mild vitamin D deficiency and phosphate retention caused by declining renal function.

The recognition that many older subjects have mild vitamin D deficiency, and the likelihood that it contributes to osteoporosis, falls and fractures in the elderly has led to the recommendation that subjects more than 70 years old should have a dietary vitamin D intake of 800-1000 IU *per* day. The recommended calcium intake is 1500 mg elemental calcium daily[15-17]. Weakening of the immune system, energy misbalance and loss of adaptability are also connected to aging. According to Fabris *et al.*[18], the interaction between neuroendocrine and immune systems exists at two separate levels. First one includes interaction of neuroendocrine system and thymus, whose hormones (proteins and peptides) participate in T-lymphocyte function, regulation and differentiation. Their levels are subject to decrease with age, diminishing the efficacy of defense system. The second level is at the periphery where neuroendocrine signals affect excretion of cell mediators from immune cells (Fig. 2). Decreased reproductive ability is one of the aging components. Neuroendocrine component is crucial for decrement of reproductive ability, and the only endocrine system for which there is a well-defined, abrupt and universal change in function with age is the hypothalamic-pituitary-gonadal axis in women (i.e. menopause)[19]. Wiese *et al.*[20] propose that changes in suprachiasmatic nucleus (Fig. 3) influence cyclic alterations of reproductive function. Granulousa cells are producing less inhibin A and B after age 40, which leads to gradual but progressive growth of follicle-stimulating hormone (FSH) level, while the level of luteinizing hormone (LH) stays unchanged for a few more years. Increased levels of FSH stimulate follicular growth, but ovulation is seldom occurring. Follicles are producing higher concentrations of estradiol (E2), but the level of progesterone is increasingly lower. The new relations of estrogen, progesterone and androgen concentrations are affecting the central nervous system

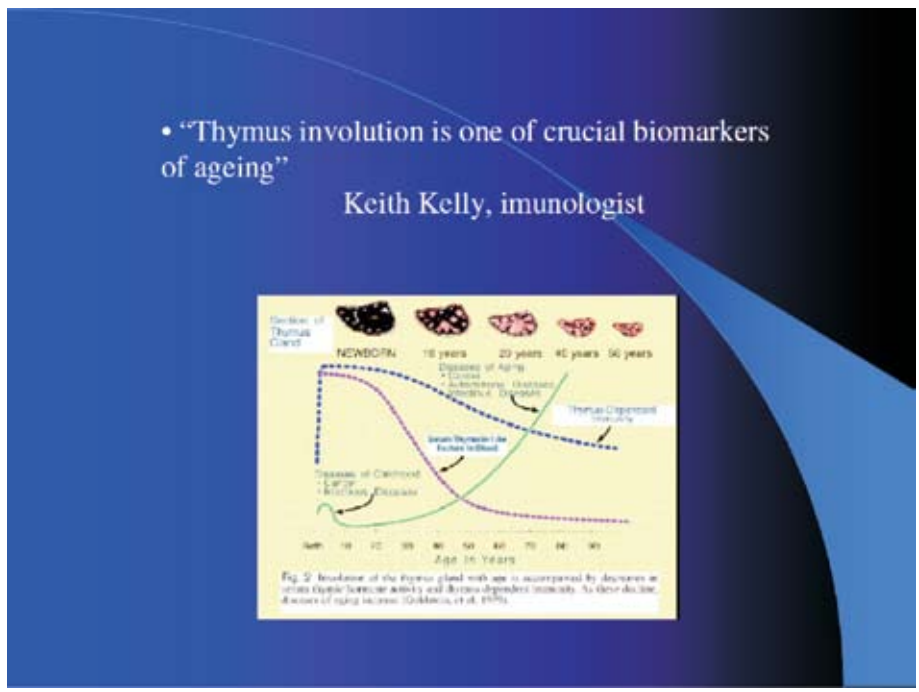

Fig. 2. Thymus involution during the aging process (from: Fabris N, Mocchegiani E, Provinciali M. Plasticity of neuro-endocrine-thymus interactions during aging. Exp Gerontol 1997)[18].

and lead to as yet uninvestigated psycho-neuro-endocrinological syndromes, where the brain and ovary play the main role (Fig. 3). The total testosterone level gradually decreases, but as serum sex hormone-binding globulin concentrations increase with age, older men have a greater decline in serum free testosterone concentrations. This decline is sometimes referred to as 'andropause'. However, unlike menopause, where complete estrogen deficiency with known clinical consequences occurs, the decline in androgens in aging men varies from modest to severe and has unclear clinical consequences. It is of note that more than 70 percent of men over 70 years of age have free T levels consistent with hypogonadism. Spermatogenesis is stable until the age of 70, when it starts to diminish. It is accompanied by tubular fibrosis, testicular shrinkage and modest elevations of FSH[21,22]. Numerous studies tried to answer the question whether hormone replacement therapy could slow down aging process. In 1889, C.E. Brown-Sequard mentioned that in the future negative effects of aging would not only be diminished by hormone replacement, but would lead to rejuvenation[23]. Since then, most studies have investigated the role of growth hormone in such a context, as it was noticed to influence body composition. Rudman *et al.*[24,25] established that healthy men aged over 65 have low levels of plasma IGF-1. It was also noticed that GH replacement significantly increases lean body mass and bone density, while at the same time decreasing body fat and LDL cholesterol levels. Baum *et al.*[26] conclude that replacement therapy in the elderly with growth hormone deficiency improves the results of intelligence tests, but has no overall beneficial effects on cognitive functions or quality of life. Arwert *et al.*[27] showed by using functional MRI that 6-month growth hormone replacement therapy in older peo-

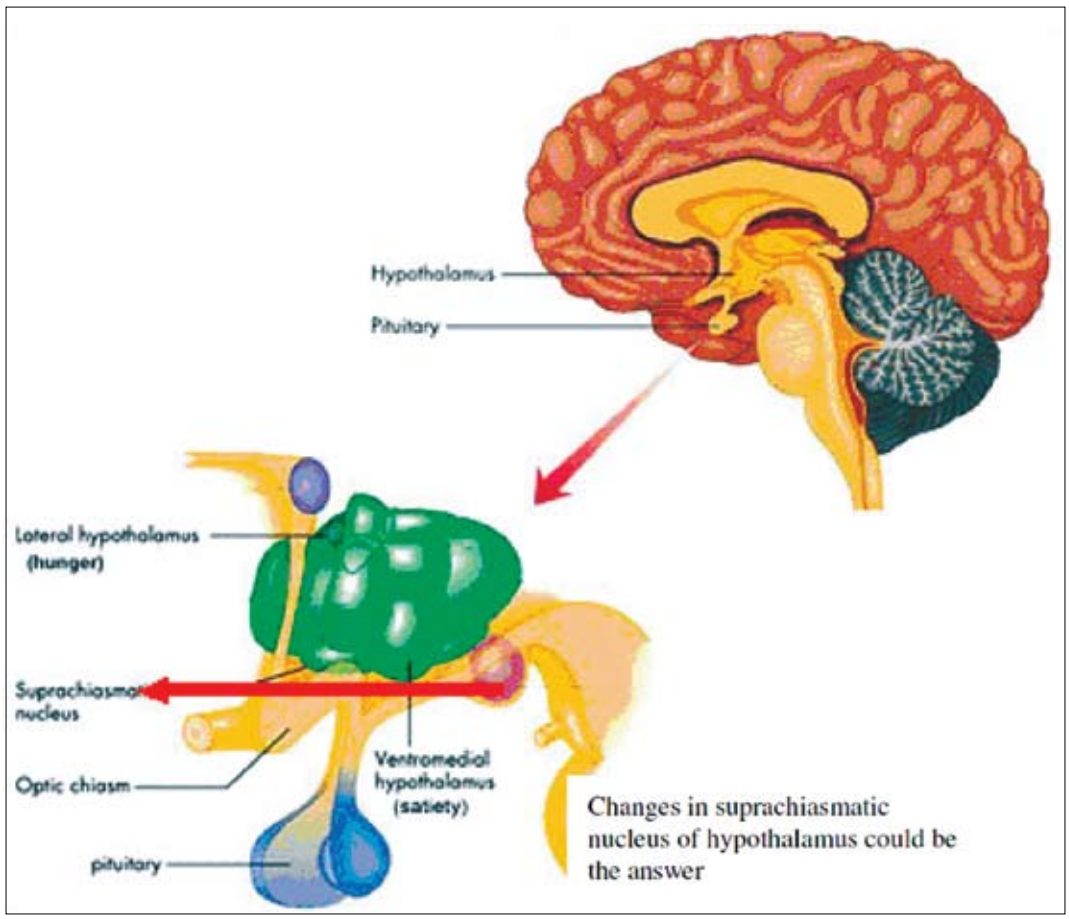

Fig. 3. Suprachiasmatic nucleus of hypothalamus (from: Wise PM, Cohen IR, Weiland NG, London ED. Aging alters the circadian rhythm of glucose utilization in the suprachiasmatic nucleus. Proc Natl Acad Sci U S A 1988)[20].

ple improved long-term and working memory, while Ramsey *et al*.[28] conclude that the same treatment slows down deterioration of cognitive functions. Papadakis *et al*.[29] claim that older people on substitution therapy have a considerably higher capacity of wound healing and higher accumulation of collagen in wound area. Furthermore, when growth hormone replacement is combined with testosterone in older men or estrogen in women, it increases bone density. However, many side effects of such treatment have been observed. They primarily include glucose intolerance and diabetes, and some also consider mitogenic effect. These side effects prompt the need for thoughtful selection of appropriate patient population for replacement GH therapy. Neuroendocrine theory is one of the theories that put the endocrine component in the center of aging process. It is not exclusive and can put additional explanation into other theories. The accuracy of all theories will be evaluated in the future, but it seems likely that hormones would play an important role in final clarification of the aging process[30].

References

1. STREHLER BL. Time, cells and aging. 2nd ed. New York: Academic Press, 1977.
2. DILMAN V. The law of deviation of homeostasis and diseases of aging. Boston: John Wright PSG Inc., 1981.
3. DILMAN V, DEAN W. The neuroendocrine theory of aging. Pensacola: The Center for Bio-Gerontology, 1992.
4. MIKHAILOVICH VA, ZEMTSOVSKII EV, GUSEINOV-OGUZ BA, OSTROUMOVA MN, SHPANSKAIA LS, MIRONOVA NS. Central hemodynamics and hormonal homeostasis during surgical stress in young patients with different levels of physical preparation. Anesteziol Reanimatol 1991;6:22-6.
5. FLOOD C, GHERONDACHE C, PINCUS G, TAIT JR, TAIT SAS, WILLOUGHBY SW. The metabolism and secretion of aldosterone in elderly subjects. J Clin Invest 1967;46:960.
6. BAUER JH. Age-related changes in the renin-aldosterone system. Physiological effects and clinical implications. Drugs Aging 1993;3:238.
7. BARROU Z, CHARRU P, LIDY C. Actions of dehydroepiandrosterone: possible links with aging. Presse Med 1996;25:1885.
8. BAULIEU EE, THOMAS G, LEGRAIN S, LAHLOU N, ROGER M, DEBUIRE B, *et al*. Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: contribution of the DHEAge study to a sociobiomedical issue. Proc Natl Acad Sci U S A 2000;97:4279.
9. MORROW LA, LINARES OA, HILL TJ, SANFIELD JA, SUPIANO MA, ROSEN SG, *et al*. Age differences in the plasma clearance mechanisms for epinephrine and norepinephrine in humans. J Clin Endocrinol Metab 1987;65:508.
10. ESLER M, KAYE D, THOMPSON J, JENNINGS G, COX H, TURNER A, *et al*. Effects of aging on epinephrine secretion and regional release of epinephrine from the human heart. J Clin Endocrinol Metab 1995;80:435.
11. PRINZ PN, VITIELLO MV, SMALLWOOD RG, SCHOENE RB, HALTER JB. Plasma norepinephrine in normal young and aged men: relationship with sleep. J Gerontol 1984;39:561.
12. SCHWARTZ RS, JAEGER LF, VEITH RC. The importance of body composition to the increase in plasma norepinephrine appearance rate in elderly men. J Gerontol 1987;42:546.
13. MARIOTTI S, BARBESINO G, CATUREGLI P, BARTALENA L, SANSONI P, FAGNONI F, *et al*. Complex alteration of thyroid function in healthy centenarians. J Clin Endocrinol Metab 1993;77:1130.
14. MAGRI F, MUZZONI B, CRAVELLO L, FIORAVANTI M, BUSCONI L, CAMOZZI D, *et al*. Thyroid function in physiological aging and in centenarians: possible relationships with some nutritional markers. Metabolism 2002;51:105.
15. SHERMAN SS, HOLLIS BW, TOBIN JD. Vitamin D status and related parameters in a healthy population: the effects of age, sex, and season. J Clin Endocrinol Metab 1990;71:405.
16. MacLAUGHLIN J, HOLICK MF. Aging decreases the capacity of human skin to produce vitamin D3. J Clin Invest 1985;76:1536.
17. PATTANAUNGKUL S, RIGGS BL, YERGEY AL, VIEIRA NE, O'FALLON WM, KHOSLA S. Relationship of intestinal calcium absorption to 1,25-dihydroxyvitamin D [1,25(OH)2D] levels in young *versus* elderly women: evidence for age-related intestinal resistance to 1,25 (OH)2D action. J Clin Endocrinol Metab 2000;85:4023.
18. FABRIS N, MOCCHEGIANI E, PROVINCIALI M. Plasticity of neuro-endocrine-thymus interactions during aging. Exp Gerontol 1997;32:415-29.
19. ŠIMUNIĆ V, CIGLAR S, SUCHANEK E. Ginekologija. Zagreb: Naklada Ljevak, 2001;369-72.
20. WISE PM, COHEN IR, WEILAND NG, LONDON ED. Aging alters the circadian rhythm of glucose utilization in the suprachiasmatic nucleus. Proc Natl Acad Sci U S A 1988;85:5305-9.
21. HARMAN SM, TSITOURAS PD. Reproductive hormones in aging men. I. Measurement of sex steroids, basal luteinizing hormone, and Leydig cell response to human chorionic gonadotropin. J Clin Endocrinol Metab 1980;51:35.
22. MULLIGAN T, IRANMANESH A, KERZNER R, DEMERS LW, VELDHUIS J D. Two-week pulsatile go-

nadotropin releasing hormone infusion unmasks dual (hypothalamic and Leydig cell) defects in the healthy aging male gonadotropic axis. Eur J Endocrinol 1999;141:257.

23. BLACKMAN MR, SORKIN JD, MUNZER T, BELLANTONI MF, BUSBY-WHITEHEAD J, STEVENS TE, *et al*. Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. JAMA 2002;288:2282-92.
24. RUDMAN D, FELLER AG, NAGRAJ HS, GERGANS GA, LALITHA PY, GOLDBERGET AF, *et al*. Effects of human growth hormone in men over 60 years old. N Engl J Med 1990;323:1-6.
25. RUDMAN D, FELLER AG, COHN L, SHETTY KR, *RUDMAN* IW, DRAPER MW. Effects of human growth hormone on body composition in elderly men. Horm Res 1991;36 Suppl 1:73-81.
26. BAUM HB, BILLER BM, KATZNELSON L, OPPENHEIM DS, CLEMMONS DR, CANNISTRARO KB, *et al*. Effects of physiological growth hormone (GH) therapy on cognition and quality of life in patients with adult-onset GH deficiency. J Clin Endocrinol Metab 1998;83:3184-9.
27. ARWERT LI, VELTMAN DJ, DEIJEN JB, van DAM PS, DRENT ML. Effects of growth hormone substitution therapy on cognitive functioning in growth hormone deficient patients: a functional MRI study. Neuroendocrinology 2006;83:12-9.
28. RAMSEY MM, WEINER JL, MOORE TP, CARTER CS, SONNTAG WE. Growth hormone treatment attenuates age-related changes in hippocampal short-term plasticity and spatial learning. Neuroscience 2004;129:119-27.
29. PAPADAKIS MA, GRADY D, BLACK D, TIERNEY MJ, GOODING GA, SCHAMBELAN M, *et al*. Growth hormone replacement in healthy older men improves body composition but not functional ability. Ann Intern Med 1996;124:708-16.
30. MORLEY JE,Van Den BERG L. Endocrinology of aging, Vol. 20. New York: Humana Press, 2000.

Sažetak

HORMONI I STARENJE

V. Zjačić-Rotkvić, L. Kavur i *M. Cigrovski-Berković*

Još od 19. stoljeća bilo je sporadičnih pokušaja da se promjene u starenju pripišu nekom endokrinom deficitu, kao i nastojanja da se utječe na te promjene različitim nadomjesnim terapijama. Ta potraga za hormonskim 'izvorom mladosti' traje do današnjih dana.

Ključne riječi: *starenje, endokrine žlijezde, proizvodnja hormona, hormonske nadomjesne tearpije*