REVIEWS

Age-Associated Endocrine Dysfunctions and Approaches to Their Correction

N. D. Goncharova, B. A. Lapin, and V. Kh. Khavinson*

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 134, No. 11, pp. 484-489, November, 2002
Original article submitted May 27, 2002

This review discusses age-specific functional changes in different components of the endocrine system (pituitary, epiphysis, adrenals, and gonads), their role in aging and age-specific diseases, and possible approaches to correction of endocrine disorders and prevention of accelerated aging.

Key Words: *aging; endocrine functions; geroprotectors; monkeys*

The endocrine system is an important regulatory system of the organism participating in organization of complex forms of behavior, adaptation to exo- and endogenous extreme factors, regulation of reproduction, homeostasis, thermoregulation, immune status, and higher nervous activity, *i.e.* the processes most often disturbed during aging. It can be expected that age-specific disorders in endocrine regulation caused primarily by age-specific changes in the functioning of the endocrine system underlie age-specific disturbances in various functions. Considerable rejuvenation of some age-related diseases in modern society characterized by wide spectrum of stress factors indicates the important role of endocrine disorders in the pathogenesis of accelerated aging.

Therefore the study of the basic regularities of age-specific disorders of endocrine functions and their role in aging and in the pathogenesis of age-associated diseases acquires special importance, as well as the search for approaches to correction of endocrine disorders and prevention of accelerated aging. Species-specific differences in the functioning of the endocrine system components make the choice of experimental model for such studies a particularly important problem. By the physiology and biochemistry of endocrine processes and the spectrum of pathological processes monkeys seem to be the most perspective model [1,4, 38,42].

This review discusses the results of many-year studies of the hypothalamic-pituitary-adrenal system (HPAS), hypothalamic-pituitary-testicular system (HPTS), and pineal gland functioning in the course of aging and investigation of approaches to correction of age-specific endocrine disorders in two monkey species (*Papio hamadryas* and *Macaca mulatta*), carried out at Institute of Medical Primatology and previously at Institute of Experimental Pathology and Therapy of the USSR Academy of Medical Sciences in Sukhumi.

Function of the Hypothalamic-Pituitary-Adrenal System

The concentration of hydrocortisone, the main glucocorticoid hormone in primates, little varies with age [1,4,5,13,15,27,28,30], while the content of its early precursors (pregnenolone and 17-hudroxypregnenolone) and adrenal androgens (dehydroepiandrosterone, DHEA, and dehydroepiandrosterone sulfate, DHEAS) decreases with age reaching a minimum in monkeys

Institute of Medical Primatology, Russian Academy of Medical Sciences, Sochi; *St. Petersburg Institute of Bioregulation and Gerontology, North-Western Division of Russian Academy of Medical Sciences.
Address for correspondence: iprim@sochi.net. Goncharova N. D.

0007-4888/02/1345-0417$27.00

aged 20-27 years [1,3-5,13,15,27,28,30]. Similar picture age-specific changes in corticosteroid level were observed in humans [1,4,5,43,44,52].

A pronounced decrease in plasma DHEA and DHEAS levels during aging leads to a considerable increase in hydrocortisone/DHEA and hydrocortisone/DHEAS ratios, which can be physiologically significant. It is known that hydrocortisone and DHEA (DHEAS) act as antagonists in some physiological systems, for example the immune and nervous systems [19,22,39]. Therefore, the age-related increase in hydrocortisone/DHEA (DHEAS) ratio can determine decreased HPAS sensitivity to glucocorticoid regulation by the negative feedback mechanism. The latter phenomenon was demonstrated in old female macaques using dexamethasone tolerance test in monkeys of different age. In old monkeys (20-27 years), suppression of hydrocortisone secretion in response to both low and high doses of dexamethasone was less pronounced than in young animals (6-8 years) [15, 27,30]. Relative resistance of HPAS to dexamethasone was observed in old monkeys of other species [46], in other animals [47], and in humans [26]. In old rats similar disorders were induced by the toxic effect of glucocorticoids on the hippocampal glucocorticoid-sensitive neurons [47]. On the other hand, an inhibitory tonic effect of the hippocampus on the production of corticotropin releasing factor (CRF) by specific hypothalamic nuclei not only in rats, but in other animals, including monkeys, and in humans was demonstrated [21,49]. According to some data, injection of DHEA (DHEAS) prevents destructive effects of stress on the brain structures, specifically on the hippocampus [23,39].

Pronounced age-specific changes were detected in the adrenocortical reaction to specific stimuli (corticotropin, ACTH, and CRF) [30]. The reaction of the adrenal cortex of old rhesus macaques to a single injection of short-acting ACTH and to CRF was more pronounced than in young animals. The disorders were observed mainly in normalization of plasma hydrocortisone level after it reached the peak. In old monkeys normalization of the glucocorticoid level was notably slower than in young animals. For example, in old females injected with ACTH 1-39 the concentration of hydrocortisone in the blood remained maximal 1 h after it reached the peak, while in young animals it rapidly dropped. Age-associated changes in recovery of HPAS function in response to specific stimuli indicate impaired plasticity of this system. This can be partially due to age-associated dysregulation of the hypothalamic-pituitary component of HPAS by the feedback mechanism [27,30]. More pronounced activation of hydrocortisone secretion in response to CRF and ACTH was observed in old humans [20,44].

Unlike hydrocortisone, the increase of DHEA (DHEAS) concentration in response to CRF and ACTH was less pronounced in old animals. On the other hand, the increase in DHEA (DHEAS) level in comparison with its initial concentration in the older age group was more pronounced than in the younger group [30]. Presumably, in old monkeys increased intensity of biosynthetic processes in adrenocorticocytes in response to stimulation cannot compensate decreased production of DHEA (DHEAS). Age-dependent loss of adrenocortical reticular zone cells in monkeys cannot be excluded [33]. It is also possible that a progressive decrease of DHEA (DHEAS) secretion with age is caused by decreased utilization of cholesterol and/or pregnenolone production by adrenocortical cells in aged monkeys. The latter hypothesis is confirmed by simultaneous decrease of plasma concentrations of DHEA, DHEAS, pregnenolone, and 17-hydoxypregnenolone in old monkeys [1,4,5,13,15,27,28,30] and by a pronounced decrease of lipid content in the reticular and bundle zones of the adrenal cortex [30]. The maintenance of hydrocortisone secretion at a high level under these conditions is presumably due to switch over of the biosynthetic processes from the production of adrenal androgens to glucocorticoid production. The results of functional test with long-acting ACTH indicate that in old monkeys the adrenocortical reserve is preserved for hydrocortisone and notably decreased for DHEA and DHEAS [30].

Circadian Rhythms

Despite the absence of appreciable age-associated differences in hydrocortisone concentrations at 9.00, statistically significant differences in hormone secretion in monkeys were detected at 21.00. In old animals hydrocortisone concentration at 21.00 was 80-90% of its level at 9.00, while in young animals hydrocortisone level at 21.00 was 2-fold lower than at 9.00 [16,36]. Disorders in the circadian rhythm of hydrocortisone secretion can have negative consequences for some tissues, organs, systems, and the organism, as daily rhythms of glucocorticoids largely determine biological rhythms of the immune system components, mitotic activity of bone marrow cells, blood cells, *etc.*

Disorders in HPAS functioning observed during aging indicate its dysfunction progressing with age.

Melatonin concentrations in the blood of old monkeys markedly decreased in comparison with young animals. In both young and old animals melatonin concentration was higher at 21.00 than at 9.00. It is noteworthy that circadian changes in melatonin secretion in monkeys are opposite to the circadian rhythm of hydrocortisone, at least at 9.00 and 21.00. In young

monkeys hydrocortisone concentration at 21.00 drops in comparison with its basal level (at 9.00), while melatonin concentration increases at 21.00 [16,36]. Similar picture was observed in humans [45,51].

Pineal gland is one of the main brain structures involved in the organization of circadian rhythms of the major systems (nervous, endocrine, cardiovascular, immune, *etc.*) [45,51], which suggests the involvement of the pineal gland in organization of the circadian rhythm of glucocorticoid secretion as well. That is why the detected disorders in hydrocortisone secretion at 21.00 in old animals can be explained by age-associated decrease of melatonin secretion.

Hypothalamo-Pituitary-Testicular System Functioning

The concentration of bioactive fraction of luteinizing hormone (LH) in old (20-26 years) male *Papio hamadryas* is higher than in the majority of young (6-8 years) and adult (10-15 years) male baboons. Testosterone levels are slightly lower in the majority of animals aged 20-26 years in comparison with the mean concentrations in animals aged 6-9 and 10-15 years [1,5,13,28,29].

The opposite age-specific changes in testosterone and LH concentrations indicate the development of degenerative changes in the gonads of aging monkeys. This hypothesis is confirmed by decreased volume of the testicles in old animals, oligo- and azoospermia or the absence of ejaculatory response to electrostimulation in old monkeys [1,28,29]. Histological findings are in line with these data [38]. Similar endocrine and morphological changes in the gonads were detected in humans [40].

Pronounced age-associated differences in HPTS function in response to LH releasing factor (LHRF) and LHRF stimulatory analogs (LHRF agonists — aLHRF) were detected. Like age-associated changes in HPAS function in response to specific stimuli, the normalization of LH and testosterone secretion after their concentrations reached the peaks in response to a single injection of LHRF was slow [1,5,13,28,29]. Decreased sensitivity of HPTS to inhibitory effect of a prolonged course of aLHRF (busereline, Hoechst A. G.) was observed in the oldest (26 years) male [1,5,13,28, 29]. Disorders in the adenohypophyseal and testicular response to LHRF in old men were described [25,50].

Despite pronounced age-associated changes in HPTS function, testicular reserves of testosterone seem are preserved in old baboons, because the results of functional test with human chorionic gonadotropin (HCG) were similar in old and young animals [1,5, 13,28,29]. High concentrations of testosterone in old males injected with HCG persist for a long time due to some adaptive mechanisms maintaining testosterone concentration at the optimal level. A possible mechanism is stimulation of synthesis of sulfated testosterone precursors and their transformation into testosterone. In one of the oldest males (26 years) with testicular hypotrophy and absence of ejaculatory response to electrostimulation an increase of DHEAS level in the blood correlated with activation of testosterone secretion in response to LHRF, aLHRF, and HCG [1,3,28,29]. The possibility of testosterone biosynthesis from sulfated precursors, for example DHEAS, and activation of this process after stimulation with HCG were also described in humans [24,37].

Estradiol concentration did not essentially change in old animals, but the estradiol/testosterone ratio increased in comparison with that in young males [1]. A similar regularity was detected in humans [1].

Hence, function of endocrine components, primarily HPAS, HPTS, and the pineal gland change with age in monkeys, and these changes are similar to age-associated endocrine disorders in humans. These changes lead to pronounced hormone imbalance in the peripheral blood: decreased concentrations of adrenal and testicular androgens, precursors of steroid hormones (pregnenolone, 17-hydroxypregnenolone), and melatonin, the concentrations of hydrocortisone and estradiol remaining unchanged and the levels of gonadotropic hormones increasing. This imbalance plays an important role in impairment of the hormone regulation of many body functions and in development of age-associated diseases, for example neurodegenerative diseases, atherosclerosis, increased insulin tolerance, reproductive dysfunctions, higher incidence of tumors, *etc.*

A progressive decrease of DHEA and DHEAS levels plays an important role in the realization of negative aftereffects of hormone imbalance. Modern demonstrated the role of DHEA (DHEAS) in the regulation of immune status, lipid and carbohydrate metabolism, cell growth, neuron activity, *etc.* [19,22, 23,39,41,48,52].

Age-associated changes in HPAS reaction to specific stimuli manifesting in deceleration of the pituitary-adrenal axis recovery and paralleled by increased production of glucocorticoid hormones lead to disorders in adaptation of the aging organism to changing environmental conditions and increase the risk of cardiovascular and neurodegenerative diseases, diabetes mellitus, *etc.* [30,49].

The imbalance of androgenic and estrogenic fractions of sex steroid hormones creates the pathophysiological base for age-associated diseases of the reproductive system (hypogonadism, prostatic hypertrophy and cancer, *etc.*) and, presumably, for some other disorders caused by dysfunctions of tissues and organs

sensitive to testicular hormones (myasthenia, changes in erythropoiesis, fatty metabolism disorders, *etc.*). Experimental and clinical studies showed an important role of increased estrogen/androgen ratio in the pathogenesis of prostatic hypertrophy [32].

It should be emphasized that similar hormonal disorders were observed in humans and monkeys under conditions of chronic stress induced by hemoblastosis [1,4,8,9]. More pronounced disorders in the adrenocortical and gonadal functions were observed in young patients and animals with hemoblastosis [1,4,8,9]. Similar adrenocortical and gonadal dysfunctions were observed in patients with non-oncological and other than oncological chronic diseases and in monkeys under conditions of prolonged stress exposure [9].

Decreased secretion of melatonin, one of the most important components of the antioxidant defense system involved in the organization of biological rhythms of the body, during aging seems to be a pathogenetic factor of many mental and somatic diseases, which is confirmed by experimental and clinical findings. Injection of melatonin prevented the development of symptoms of many neurodegenerative diseases simulated in animals [45], and melatonin treatment of elderly patients with insomnia improved the quality and efficiency of sleeping [33].

Approaches to Correction of Age-Associated Disorders

A possible was to correction of age-associated disorders in HPAS, HPTS, and epiphyseal functions and hence, to prevent accelerated aging, is an increase in DHEA, DHEAS, testicular androgen, and melatonin levels and normalization of circadian rhythm of hydrocortisone secretion. Our studies were aimed at the search for agents increasing the level of natural melatonin in the body (as exogenous melatonin is fraught with the risk of neoplastic growth [35]) and restoring the circadian rhythms of glucocorticoid hormone secretion and increasing androgen production. One of the most promising approaches to stimulation of melatonin secretion is treatment with epiphyseal peptide preparations developed at St. Petersburg Institute of Bioregulation and Gerontology. The production of physiologically active peptides in organs and tissues decreases with age, and injection of peptides originating from the corresponding organ as a rule repaired tissue homeostasis primarily of the maternal organ [17]. We therefore can expect that peptide preparations of the pineal gland can produce topical effects primarily on the epiphysis, and this possibility was confirmed experimentally [2].

We investigated the effects of a pharmacopoeian drug Epithalamin (bioactive peptide extract of cattle pineal gland) and a new synthetic peptide epithalone (Ala-Glu-Asp-Gly, designed on the basis of analysis of epithalamin amino acid composition) on the production of melatonin. Epithalon (10 μg intramuscularly daily for 10 days) 3-fold increased melatonin level in the peripheral blood at 21.00 in old monkeys, but did not change melatonin level in young monkeys [16,36]. Similar results were observed for Epithalamin injected in a daily dose of 5 mg for 10 days. The selective stimulatory effect of epithalone and epithalamine on melatonin production in old animals can be due to stimulatory effect of pineal peptides on the number and/or affinity of β-adrenergic receptors to norepinephrine on pinealocyte membranes. As we know, adrenergic innervation of the pineal gland plays the priority role in the regulation of melatonin secretion [45,51], and the sensitivity of pineal β-adrenoreceptors is reduced in aging rodents [31]. Along with the stimulation of melatonin secretion, the pineal peptides regulate hydrocortisone secretion in old animals, which manifests in recovery of daily rhythm of hydrocortisone secretion and its increase to the level characteristic of young animals [16,36]. The normalizing effect of Epithalon and Epithalamin on circadian rhythms of hydrocortisone secretion seems to be mediated by normalization of melatonin production. It is confirmed by the data on the negative correlation between hydrocortisone and melatonin levels in the peripheral blood in young monkeys at 9.00 and 21.00 [16,36].

One more trend of research is evaluation of the possibility of using LHRF agonists for correction of age-associated gonadal dysfunctions. A single intravenous or intramuscular injection of a low dose of aLHRF (busereline, Hoechst A. G.) or surfagone (Russia) in doses of 50-500 ng/kg to male *Papio hamadryas* induced a pronounced prolonged (8-24 h) activation of gonadotropin and androgen production [1, 6,29]. Treatment with aLHRF for 1-2 weeks resulted, in addition to activation of LH and testosterone production, in stimulation of the germinative processes (total concentration of spermatozoa and number of their mobile forms) [1,6,7,10-12]. Therefore, injections of aLHRF in low doses (e.g. surfagon) can be useful in the treatment of hypogonadotropic hypogonadism in some elderly patients or in patients with accelerated aging. Clinical improvement in male patients with hypogonadotropic hypogonadism after treatment with some aLHRF confirms this conclusion [18].

In contrast to a short course of low-dose aLHRF, prolonged treatment with busereline and surfagon in high doses can inhibit gonadotropin and testicular androgen production [1,7,10-12,14,29]. These effects of aLHRF are used in the treatment of some age-associated tumors of the reproductive system, for example prostatic cancer and hypertrophy [42].

Hence, aging involves pronounced changes in the functions of HPAS, HPTS, and pineal gland. These deviations can be pathophysiologically significant for age-associated dysfunctions of hormone-competent cells, tissues, and organs, and for the development of age-associated diseases. Young individuals exposed to chronic stress also can develop these hormonal disturbances, therefore we hypothesize that prolonged severe stress accelerates aging. Early correction of endocrine disorders can become an important component in therapy of age-associated diseases and in prevention of rapid aging. Pineal peptides (Epithalon, Epithalamin) and stimulatory LHRF analogs can be used for this purpose.

REFERENCES

1. N. D. Antsiferova, *The Function of Steroid-Producing Glands in Aging, Chronic Stress, and the Correction of Reproductive Disorders*, Abstract of Doct. Med. Sci. Dissertation, Novosibirsk (1997).
2. L. A. Bondarenko and V. N. Anisimov, *Byull. Eksp. Biol. Med.*, **113**, No. 2, 194-195 (1992).
3. N. D. Goncharova, *Ibid.*, **116**, No. 12, 598-601 (1993).
4. N. D. Goncharova, *Ibid.*, **124**, No. 8, 207-210 (1997).
5. N. D. Goncharova, *Zh. Evolyuts. Biokhim. Fiziol.*, **33**, No. 1, 44-51 (1997).
6. N. D. Goncharova, *Probl. Endokrin.*, **43**, No. 12, 43-45 (1997).
7. N. D. Goncharova, E. G. Belova, and V. M. Gorlushkin, *Ibid.*, **38**, No. 3, 55-58 (1992).
8. N. D. Goncharova and N. P. Goncharov, *Eksp. Onkol.*, **7**, No. 3, 47-50 (1985).
9. N. D. Goncharova and N. P. Goncharov, *Probl. Endokrinol.*, **34**, No. 6, 27-31 (1988).
10. N. D. Goncharova and N. P. Goncharov, *Ibid.*, **35**, No. 2, 62-67 (1989).
11. N. D. Goncharova and N. P. Goncharov, *Ibid.*, **35**, No. 5, 68-72 (1989).
12. N. D. Goncharova and L. A. Mkhitarova, *Ibid.*, **38**, No. 1, 51-54 (1993).
13. N. D. Goncharova and L. A. Mkhitarova, *Ibid.*, No. 2, 37-41 (1996).
14. N. D. Goncharova, L. A. Mkhitarova, and E. M. Gogiladze, *Ibid.*, **37**, No. 3, 45-48 (1991).
15. N. D. Goncharova, T. E. Oganyan, and A. G. Taranov, *Ibid.*, **45**, No. 5, 39-42 (1999).
16. N. D. Goncharova, V. Kh. Khavinson, and B. A. Lapin, *Byull. Eksp. Biol. Med.*, **131**, No. 4, 466-468 (2001).
17. V. Kh. Khavinson and V. V. Malinin, *Ibid.*, **133**, No. 1, 4-10 (2002).
18. W. Aulitrky, J. Frick, and G. Galvan, *Fertil. Steril.*, **50**, 480-486 (1988).
19. K. L. Blauer, M. Roth, W. M. Rogers, *et al.*, *Endocrinology*, **29**, 3174-3179 (1991).
20. M. Blichert-Toft, *Geriatric Endocrinology. Aging*, Vol. 5, Ed. R. B. Greenblatt, New York (1978), pp. 81-104.
21. S. M. Brook, A. M. de Haas-Johnson, J. R. Kaplan, *et al.*, *Neuroendocrinology*, **60**, No. 2, 134-140 (1994).
22. R. A. Daynes, D. J. Dudley, B. A. Araneo, *Eur. J. Immunol.*, **2**, 793-801 (1990).
23. D. M. Diamond, B. J. Branch, M. Fleshner, and G. M. Rose, *Ann. NY Acad. Sci.*, **774**, 304-307 (1995).
24. R. Dixon, V. Vincent, and N. Kase, *Steroids*, **6**, 757-769 (1965).
25. E. M. T. Erfurth and L. E. Hagmar, *Eur. J. Endocrinol.*, **132**, No. 6, 663-667 (1995).
26. E. Ferrari, F. Magri, D. Dori, *et al.*, *Neuroendocrinology*, **61**, No. 4, 464-470 (1995).
27. N. D. Goncharova and B. A. Lapin, *Baltic J. Lab. Anim. Sci.*, **9**, No. 2, 80-85 (1999).
28. N. D. Goncharova and B. A. Lapin, *J. Med. Primatol.*, **29**, No. 1, 26-35 (2000).
29. N. D. Goncharova and B. A. Lapin, *Baltic J. Lab. Anim. Sci.*, **11**, No. 2, 87-97 (2001).
30. N. D. Goncharova and B. A. Lapin, *Mech. Ageing Dev.*, **123**, No. 8, 1191-1201 (2002).
31. L. H. Greenberg and B. Weiss, *Science*, **201**, No. 1, 61-63 (1978).
32. U.-F. Habenicht, U. W. Tunn, Th. Senge *et al.*, *J. Steroid. Mol. Biol.*, **44**, No. 4-6, 557-563 (1993).
33. I. Haimov, P. Lavie, M. Laudon, *et al.*, *Sleep*, **18**, 598-603 (1995).
34. P. J. Hornsby, *Ann. NY Acad. Sci.*, **774**, 29-46 (1995).
35. V. Kh. Khavinson, D. M. Ismailov, L. K. Obukhova, V. Malinin, *Mech. Ageing Dev.*, **120**, No. 2, 141-149 (2000).
36. V. Kh. Khavinson, N. D. Goncharova, B. A. Lapin, *Neuroendocrinol. Lett.*, **22**, No. 4, 251-254 (2001).
37. T. Laatikainen, E. A. Laatinen, and R. Vihko, *J. Clin. Endocrinol. Metab.*, **32**, No. 1, 59-64 (1971).
38. B. A. Lapin, R. I. Krilova, E. M. Cherkovich, and N. S. Asanov, *Aging in Nonhuman Primates*, ed. D.M.Bowden, New York (1979), pp. 14-37.
39. M. D. Majewska, *Ann. NY Acad. Sci.*, **774**, 111-120 (1995).
40. W. B. Neaves, L. Johnson, amd C. S. Petty, *Biol. Reprod.*, **33**, No. 1, 259-356 (1985).
41. J. E. Nestler, J. N. Clore, and W. G. Blackard, *J. Steroid Biochem. Mol. Biol.*, **40**, No. 4-6, 599-605 (1991).
42. E. Nieschlag, G. F. Weinbauer, and H. M. Behre, *Contraception*, **46**, 189-192 (1992).
43. N. Orentreich, J. L. Brind, J. H. Vogelman, *et al.*, *J. Clin. Endocrinol. Metab.*, **75**, 1002-1004 (1992).
44. E. P. Pavlov, S. M. Harman, G. P. Chrousos, *et al.*, *Ibid.*, **62**, No. 4, 767-772 (1986).
45. R. J. Reiter and J. Robinson, *Melatonin*, New York (1995).
46. R. Sapolsky and J. Altman, *Biol. Psychiatry*, **30**, 1008-1013 (1991).
47. P. M. Sapolsky, L. C. Krey, and B. S. McEwen, *Endocrine Rev.*, **7**, No. 3, 284-301 (1986).
48. A. G. Schwartz and L. L. Pashko, *Ann. NY Acad. Sci.*, **774**, 180-186 (1995).
49. T. E. Seeman and R. J. Robbins, *Endocrine Rev.*, **15**, No. 3, 233-260 (1994).
50. P. J. Snyder, J. F. Reitano, and R. D. Utiger, *J. Clin. Endocrinol. Metab.*, **41**, 938-945 (1975).
51. Y. V. Touitou and E. H. Haus, *Chronobiol. Int.*, **17**, No. 3, 369-390 (2000).
52. A. Vermeulen, *Ann. NY Acad. Sci.*, **774**, 121-127 (1995).