INTRODUCTION

Investigation of the peculiarities of neuroendocrine functions under aging and stress is a crucial problem in modern gerontology and geriatrics. First of all, this is caused by pronounced demographic changes with a sharp increase in the number of elderly and senile people in modern society. Secondly, aging of society has an enhanced/premature character which is usually connected with increased psychogenic pressure on the human organism due to progress in science and technology, environmental disturbances, technogenic and military disasters, global problems in social and economic fields, and the threat of terrorism. Thirdly, it is just some neuroendocrine systems, the HPA axis in the first instance, which provide adaptation of the organism to environmental stress factors; that is why it natural to assume that age-related alterations of the HPA axis can define an inadequate response of the aging organism to stress and cause stress- and age-related pathologies.

Therefore, investigation of the main patterns of age-related changes in the HPA axis including its response to stress and the role of age-related dysfunctions of the HPA axis during aging of the organism and pathogenesis of age-related disorders is of current interest. Species differences in functioning of the HPA axis determine the importance of experimental models for studies. Nonhuman primates are the most promising model because of the similarity in physiology and biochemistry of endocrine processes and a range of pathologies similar to humans [2, 4, 6, 18]. This review presents the main results of long-term studies of age-related changes in the HPA axis using two monkey species—hamadryas baboons (*Papio hamadryas*) and rhesus macaques (*Macaca mulatta*).
in monkeys in the morning are original. Furthermore, we were among the first to notice the presence of the above mentioned changes in human adrenal steroidogenesis [7].

A significant decline in the plasma DHEA and DHEAS concentrations during aging results in a sharp increase in the F/DHEA and F/DHEAS molar ratios [1, 2, 4, 6, 17] which has significant physiological importance. Thus, DHEA and DHEAS can act as functional antagonists of glucocorticoids [2, 4, 16, 24]. They are neuropeptide hormones of the hypothalamic paraventricular nucleus which is the central part of the HPA axis [10, 16]. In addition, DHEA and DHEAS are precursors of androgens and estrogens [16, 25]. The age-related increase in the F/DHEA and F/DHEAS molar ratios plays an important role in pathogenesis of a sensitivity decrease of the HPA axis to negative feedback regulation, which is connected with a decrease in the levels of pregnenolone and 17-hydroxy pregnenolone in peripheral blood. It has been shown that pregnenolone and 17-hydroxy pregnenolone are involved in regulation of neuronal activity in the brain [9, 27].

The HPA axis in Primates during Aging under Its Activation by Specific Stimuli

Pronounced age-related changes were revealed in the response of the adrenal cortex to adrenocorticotropic hormone (ACTH) and corticotrophin releasing hormone (CRH) introduced in the morning [4, 17]. Thus, the adrenal cortex response to a single administration of both short-time ACTH and CRH was more pronounced in old female rhesus monkeys compared to young animals. Changes involved mainly the process of restoration of the plasma F level after reaching the peak value. Significant inhibition of glucocorticoid level restoration was observed in old monkeys as compared to young animals. The revealed changes indicate a disturbance in the HPA axis plasticity. The latter can be partially caused by age-related alterations in the negative feedback regulation of the HPA axis [4, 17]. Similar trends were detected in aged people [12].

Age-related changes in the HPA axis response to specific stimuli, which are accompanied by increased production of glucocorticoid hormones, can promote disorders in adaptation of the aging organism to changing environmental conditions and increase in the risk of cardiovascular and neurodegenerative diseases, diabetes, etc. [4, 17].

Circadian Rhythms

Despite the absence of significant age-related differences in F concentrations in nonhuman primates in the morning (9:00 and 10:00 a.m.), a statistically significant increase in the concentration of this hormone was found in old monkeys in the evening (9:00 and 10:00 p.m.) [4, 6, 20]. It was also shown that diurnal dynamics of F secretion in monkeys is opposite to circadian dynamics of melatonin at least in the morning and the evening [4, 6, 20]. While F secretion sharply decreases in young monkeys in the evening as compared to the basal level (at 9:00, 10:00 a.m.), the melatonin concentration on the contrary increases [4, 6, 20]. In contrast to F, the melatonin concentration sharply declined in old monkeys in the evening and at night [4, 6, 20]. Analogous data were obtained for humans [6, 8, 12].

Age-related changes in the circadian rhythm of the HPA axis are likely to be caused by age-related disturbances in AVP-producing neurons in the hypothalamic suprachiasmatic nucleus (SCN), the number of which decreases in laboratory primates and humans in aging [16]. The latter are at least partially caused by an age-related decrease in pineal secretion of melatonin which regulates their activity [4, 6, 20]. In particular, the literature contains data on the presence of melatonin receptors in AVP-producing neurons within the SCN [11]. Moreover, it was shown that a decrease in AVP-producing neurons within the SCN in old animals and people is accompanied by desynchronization of circadian rhythms of the HPA axis function [16, 22]. Age-related changes in the circadian rhythm of F secretion can have negative consequences for functioning of many tissues, organs, and systems that are controlled by the HPA axis [12–14, 21].

STRESS REACTIVITY OF THE HPA AXIS: CIRCADIAN RHYTHMS OF THE HPA AXIS STRESS REACTIVITY

Acute Stress

Acute stress in monkeys was modeled using a psycho-emotional stimulus (restraint—mild immobilization in a metabolic cage for 2 h) which was applied at various times of the day (9:00 a.m. or 3:00 p.m.). Studies were carried out in summer using female rhesus macaques [5, 6, 14–16]. The experiments revealed that stress reactivity of the HPA axis largely depended on the time of day when the stimulus was applied and, consequently, on the initial sensitivity of the HPA axis. Young monkeys demonstrated much higher increases in ACTH and F levels in response to restraint applied