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Age-related differences in stress responsiveness of the hypothalamic-pituitary-adrenal axis of nonhuman primates with various types of adaptive behavior

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ABSTRACT

Aging is characterized by disturbances in the functioning of the hypothalamic-pituitary-adrenal (HPA) axis, associated with disturbances in the adaptation processes and increase of the probability of the onset of post-stress syndrome. However, the individual features of age-related disorders stress reactivity of HPA axis have not been studied. *The purpose* was to study individual characteristics of the HPA axis responsiveness to acute psycho-emotional stress exposure (restraint, ASE) at different age periods on the model of the young adult and old physically healthy female rhesus monkeys that differ in their behavioral responses to stress, i.e., with depression-like and anxiety-like behavior (DAB) on the one hand and healthy standard (control) adaptive behavior (SB) on the other hand. No significant intergroup differences were observed in HPA axis responses to ASE in young animals. During aging the monkeys with SB showed reduced ACTH response to the ASE, whereas the monkeys with DAB demonstrated its increase. The old animals with DAB in response to ASE demonstrated the most pronounced HPA axis disorders, such as the highest levels of corticotrophin (ACTH), the lowest levels of dehydroepiandrosterone sulfate (DHEAS), reduced cortisol (F) levels and the highest values of the F/DHEAS molar ratio. The ratio F/DHEAS positively correlates with the malondialdehyde concentration in erythrocytes that is considered as the biomarker of oxidative stress. Thus, these data allow us to consider the old monkeys with DAB as individuals with higher vulnerability to the adverse effects of ASE. In addition, depression-like and anxiety-like behavior of aged primates under mild/moderate stress along with reduced DHEAS plasma concentration and increased values of F/DHEAS ratio can be used to identify individuals with increased vulnerability to ASE and accelerated aging.

1. Introduction

The hypothalamic-pituitary-adrenal (HPA) axis is a key adaptive neuroendocrine system essential for adequate stress responsiveness and health. Disruption of corticosteroid regulation due to severe stress is associated with pathological states such as psychiatric disorders, metabolic syndrome, cardiovascular disorders, immunopathologies, diabetes, osteopenia and others (for example Howlett and Stein, 2016; Kassi and Crousos, 2013; Levy and Tasker, 2012; Risch et al., 2009). The probability of the onset of post-stress syndrome is sharply increased with aging (Alves de Rezende et al., 2009; Howlett and Stein, 2016; Pradeep and Sutin, 2014; Risch et al., 2009). However, the same stressful event can cause various symptoms/severity or even lack of symptoms of stress-related disorder in different individuals, including the elderly. In this regard, considerable interest is the elucidation of individual characteristics of the HPA axis responsiveness to acute psycho-emotional stressor at different age periods, as well as the search for biomarkers to identify individuals with an increased vulnerability and/or resistance to stress. One of the promising approaches in this direction is to study the HPA axis stress responsiveness of individuals, which differ in their features of higher nervous activity, in particular in behavioral reactions under mild/moderate stress.

Indeed there is evidence that links behavioral features of the individual with peculiarities in their HPA axis function in humans and animals. So, there are a number of publications that reflect the peculiarities of HPA axis in individuals, which differ according to the type of adaptive behavior in basal conditions or during functional tests. For example, hyperactivation of the HPA axis occurs in persons who exhibit increased anxiety, in those with some forms of depression (Beluche et al., 2009; Belvederi Murri et al.,

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2014; Burke et al., 2005; Hatzinger et al., 2002; Vreeburg et al., 2009) as well as in animals with depression-like and anxiety-like behavior (Boyle et al., 2006; Dirks et al., 2003; Goncharova et al., 2010). Moreover, there are data showing a decline in dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) secretion in depressed persons (Genazzani and Pluchino, 2010; Maninger et al., 2009; Micheal, 2000) and in monkeys with depression-like and anxiety-like adaptive behavior (Goncharova, 2013; Goncharova et al., 2010).

However, while in the literature there are a number of papers that reflect the relationship between characteristics of HPA axis functioning and behavioral characteristics of the individual in the basal conditions or performing diagnostic tests, much less publications on the relationship between HPA axis response to stress exposure and the characteristics of individual adaptive behavior. Earlier in experiments on female rhesus monkeys, we found a higher corticotrophin (ACTH) response and smaller reaction of cortisol (F) and DHEAS to acute stress exposure (two hours restraint, ASE) in old monkeys with depression-like and anxiety-like behavior (DAB) compared to old monkeys with healthy standard (control) adaptive behavior (SB) (Goncharova et al., 2015a). At the same time, there were no significant between-group differences in HPA axis response to similar ASE in young female rhesus monkeys with the SB and DAB (Goncharova et al., 2017). Marked dysfunctions of HPA axis similar to those identified in nonhuman primates were found in elderly male patients with depression (Belvederi Murri et al., 2014) and among healthy adult individuals that characterized by smaller and higher trait anxiety ratings (Alexander et al., 2010; Petrides et al. 1997). However, the mechanisms of differential HPA axis vulnerability to stress and aging, both in monkeys with maladaptive behavior and in persons with depression and anxiety are not clear. Meanwhile, it is important to identify them, as they have pathophysiological importance in the development of many psychiatric disorders, including depression and anxiety, the probability of which increases in the elderly (Ferrari et al., 2013; Hidaka, 2012).

However, there is very little information on the individual specificity of the age-related changes within the HPA axis, namely data on how the stress responsiveness of HPA axis varies through aging in individuals with different types of adaptive behavior (Goncharova et al., 2010; Gupta and Morley, 2014). For example, we have previously presented the data on age-related changes HPA axis stress reactivity in female rhesus monkeys with different types of adaptive behavior, but they are concerned only F response but not ACTH and DHEAS response (Goncharova et al., 2010). At the same time it is important to study for understanding the mechanisms that underlie individual differences in stress reactivity of HPA axis, developing with aging, and the significance of the features of these age-related changes for accelerated aging and development of age-related pathology. Since there are more data on the regulatory influence of HPA axis on the activity of free radical processes in the organism, the intensification of which is characteristic for the aging processes (Goncharova et al., 2008a,b; Haider et al., 2014; Stark et al., 2014), the study of oxidative stress biomarkers (e.g., malondialdehyde) together with indicators of the HPA axis stress reactivity in individuals with different adaptive behavior is of great interest.

Monkeys are the preferable model for this type of research. Indeed, nonhuman primates and humans are similar in their diurnal pattern of the HPA axis activity, i.e. high activity during daylight hours and low activity during the night. Furthermore, primates are essentially different from rodents according to the characteristics of adrenal steroidogenesis as well as by age-related character of its changes. While the F is the main glucocorticoid hormone of humans and monkeys, and secretion of adrenal androgens (DHEA, DHEAS) are drastic decreased with aging, the adrenals of adult rats synthetize predominantly corticosterone along with extremely low secretion of adrenal androgens (Goncharova, 1997; Goncharova and Lapin, 2002; Guillemette et al., 1996; Lane et al., 1997; Muehlenbein et al., 2003; Yen and Laughlin, 1998). Moreover, unlike rodents, nonhuman primates demonstrate the psycho-emotional reactions and adaptive behavior more similar to those in humans (Boccia et al., 1995; Hennessy et al., 2014; McKinney et al., 1984).

The purpose was to study individual characteristics of HPA axis responsiveness to acute psycho-emotional stress at different age periods on the model of the young adult and old physically healthy female rhesus monkeys that differ in their behavioral responses to stress, i.e., with depression-like and anxiety-like behavior (DAB) on the one hand and healthy standard (control) adaptive behavior (SB) on the other hand. We have found, for the first time that aging of nonhuman primates is accompanied by opposite changes in the reaction of the anterior pituitary (ACTH) to ASE associated with features of adaptive behavior of animals (reduced in individuals with SB and increased in individuals with DAB) and leading to the most severe age-related damage of HPA axis stress reactivity in old animals with DAB.

2. Material and methods

2.1. Animals

Fourteen young adult (5–8 years) and fourteen old (21–30 years) healthy female rhesus monkeys (*Macaca mulatta*) were used in the experiments. The monkeys originated from the Adler monkey colony (Research Institute of Medical Primatology, Sochi, Russia). The animals were housed in open enclosures (size 250 $m^2 \times 5$ m and 650 $m^2 \times 5$ m, housing 10–15 and 40–50 individuals of various age, including newborns and elderly animals, respectively) or cages designed for group housing (size 10 $m^2 \times 2.75$ m, housing 3–5 individuals). Lighting, humidity, and temperature were as per the ambient environment, though each enclosure featured small closed sections, which are heated in winter, where animals can hide in adverse weather conditions.

During the observation period the animals were moved into individual metabolic cages ($80 \times 80 \times 80$ cm) in a separate room with narrow windows, natural illumination and ambient surrounding temperature. All experiments were carried out in the period of June-August when ovarian cycles are not typical for female rhesus monkeys. Natural illumination during this period was monitored approximately from 06.00 to 18.00. Surrounding temperature varied from 20 °C to 28 °C. Additional artificial illumination could be switched on as required, for example when taking blood samples in the evening, in which case soft illumination was switched on for 10–20 min.

The state of health of the animals was monitored by noninvasive methods (assessment of mobility, condition of a hair cover, condition of stool and urine, microbiological evaluation of rectal smears, surveying for signs of ovarian cycles – color and a degree of swelling of a "sexual skin") and also with use of biochemical analysis of blood and blood counts (Lapin et al., 1987). The animals were fed pellets prepared in the Institute according to the technique of Altromin Spezialfutter GmbH & Co. KG (Lage, Germany). The pellet diet was complemented with bread, boiled eggs, and fresh vegetables and fruit. Water was available *ad libitum*.

Before the experiments, the animals were adapted to living in metabolic cages and to the procedure of bleeding for 4 wk. During this period the animals were attended by the same keepers and researchers. The animals were subjected to blood sampling followed by food reinforcement (fruit, sweets) once or twice weekly. It was established previously that this period of time is sufficient

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