БИОГЕРОНТОЛОГИЯ

УДК 612.67

ONTOGENETIC ROLE OF MELATONIN AND NEUROACTIVE STEROIDS AS ANTISTRESS HORMONES

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Earlier we have discribed the role of glucocorticoids in aging and age-related diseases. In present paper the proposal was analysed for possible counteraction of glucocorticoid ontogenetic influence by melatonin and neuroactive steroids. At first, the data are discussed on antistress or antiglucocorticoid actions of these hormones. Thereafter, the evidence is evaluated for contributions of melatonin and neuroactive steroids to ontogenetic bioregulation, especially in aging. It is concluded that ontogenetic approach may be of great value for estimating the physiopathologic role of hormonal interactions. However, due to complexity of such interactions, the employment of systems biology and medicine will be urgently needed in future studies.

Key words: melatonin, neuroactive steroids, glucocorticoids, ontogeny.

ОНТОГЕНЕТИЧЕСКАЯ РОЛЬ МЕЛАТОНИНА И НЕЙРОАКТИВНЫХ СТЕРОИДОВ В КАЧЕСТВЕ АНТИСТРЕССОРНЫХ ГОРМОНОВ

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Ранее мы описали роль глюкокортикоидов в возраст-зависимых заболеваниях и при старении. В настоящей работе проведен анализ предположения о возможном противодействии онтогенетическому влиянию глюкокортикоидов посредством мелатонина и нейроактивных стероидов. Вначале обсуждаются данные об антистрессорных или антиглюкокортикоидных эффектах этих гормонов. Затем осуществлена оценка сведений о вкладе мелатонина и нейроактивных стероидов в онтогенетическую биорегуляцию, особенно при старении. Сделано заключение о том, что онтогенетический подход может иметь большое значение для выяснения физиопатологической роли гормональных взаимодействий. Однако, из-за сложности таких взаимодействий, в будущих исследованиях может оказаться весьма необходимым применение системной биологии и медицины.

Ключевые слова: мелатонин, нейроактивные стероиды, глюкокортикоиды, онтогенез.

Introduction. Earlier we have discussed the role of stress and glucocorticoids in aging and age-related diseases [17, 18]. Therefore, the question emerged: how to counteract the adverse influence of these hormones? In present article we discuss the idea that melatonin and neuroactive steroids having antistress properties may be involved in ontogenetic regulation and therefore, these hormones should be considered as candidates for counteraction of glucocorticoid effects.

At first, we describe the available evidence for antiglucocorticoid or antistress actions of melatonin and neuroactive steroids in adults. Thereafter, their roles in mechanisms of aging and age-related diseases are considered. The relative novelty of our approach is ontogenetic evaluation of the contribution of various hormones and their interactions to bioregulation.

Interactions of melatonin with glucocorticoids.

Melatonin is the only secretory product identified in pineal gland till the present moment. It is considered as important hormonal mediator in the mechanisms of both circadian and seasonal biorhythms that depend on photoperiod duration [40].

Earlier data have already suggested antiglucocorticoid and antistress actions of melatonin. In fact, exogenous melatonin counteracted the effect of acute restraint stress or corticosterone on thymus weight and antibody response to sheep red blood cells in mice. The antistress activity was abolished by naltrexone, suggesting opiatergic mechanism of melatonin action [27].

Later it was shown that melatonin prevented glucocorticoid-induced apoptosis of mouse thymocytes [21] and impaired glucocorticoid receptor (GR) translocation from cytosol to the nucleus in these cells [38]. Melatonin was able also to down-regulate GR mRNA in rat thymocytes [43]. Besides, melatonin suppressed dexamethasone-induced activation of GR in MCF7 human breast tumor cells [24].

Melatonin decreased neurotoxic effects of dexamethasone in the rat hippocampus [15]. In hippocampal HT22 cell line melatonin prevented dexamethasone-induced inhibition of cell proliferation, and it reduced the toxicity caused by glucocorticoid. Furthermore, melatonin decreased GR translocation from cytosol to the nucleus in these cells also [39].

Whereas dexamethasone caused significant pro-oxidant changes including the increase in serum malonedialdehyde levels, and produced DNA fragmentation in brain tissue of young adult rats, melatonin pretreatment was found to reverse all dexamethasone-induced alterations. Melatonin showed slightly more pronounced antioxidant and neuroprotective influence than acetyl-L-carnitine [2].

On the other hand, melatonin (0,1-10 nM) inhibited cortisol production stimulated by 100 nM corticotropin in cultures of cells or explants of capuchin monkey adrenal gland [48]. Besides, melatonin attenuated the response to stress in rats, according to serum levels of corticosterone and corticotropin [25], and it normalized most of the symptoms of impaired hypothalamo-pituitary-adrenal regulation caused by exposure to dexamethasone, including corticotropin release in vitro [26].

Stress and glucocorticoids are able to influence melatonin production. As a matter of fact, chronic stress increased plasma melatonin concentrations in rats [11]. Moreover, corticosterone potentiated noradrenaline-induced melatonin production by cultured rat pineal gland in a bell-shaped manner [13].

Finally, an imbalance between the anti-inflammatory effects of cortisol and the proinflammatory effects of melatonin seems evident in patients affected by rheumatoid arthritis [10].

Interactions of neuroactive steroids with glucocorticoids.

Excitatory neuroactive steroids (with $GABA_A$ receptor antagonist action) include sulfated derivatives of pregnenolone and dehydroepiandrosterone (DHEA), as well as the 3α, 5α- and 3α, 5β-reduced metabolites of cortisol, whereas inhibitory neuroactive steroids (with $GABA_A$ receptor agonist effects) include 3α, 5α- and 3α, 5β-reduced metabolites of progesterone and deoxycorticosterone, DHEA and testosterone [34]. It is important to note that neuroactive steroids as allosteric modulators may influence, besides $GABA_A$, various other neurotransmitter receptors including σ1, cholinergic and NMDA [28].

At present, it is well known that neuroactive steroids like progesterone and its derivatives, DHEA and estrogens exert a variety of neuroprotective effects. Furthermore,

pregnenolone sulfate, allopregnanolone and DHEA may be involved in regulation of neuroprogenitor cell functions [32].

For understanding the antistress action, it is important to consider that neuroactive steroids with agonistic GABAergic action inhibit corticoliberin, corticotropin and glucocorticoid release in response to stress [34]. On the other hand, stress was shown to induce tetrahydrodeoxycorticosterone (THDOC) to levels that can activate $GABA_A$ receptors [32]. Besides, rats exposed to a stress condition, showed a rapid increase in serum and brain levels of allopregnanolone [5].

In rodents both corticoliberin and corticotropin elevate the brain and plasma levels of 5α, 3α-tetrahydroprogesterone (THPROG). Similarly, in humans plasma levels of this neurosteroid were elevated following corticoliberin administration. Probably, the rapid elevation of neurosteroid levels that occurs during stress may act as a brake upon hypothalamo-pituitary-adrenal axis activity by enhancing the GABAergic inhibition exerted upon the paraventricular nucleus, the main site of corticoliberin production [19].

From all neuroactive steroids, DHEA and its sulfated ester (DHEAS) have received the principal attention, perhaps, because of their anti-aging action (see the section on aging). DHEA was shown to reverse stress-induced inhibition of body weight gain, adrenal weight, GR levels in the liver, thymus and spleen, and lipid peroxidation levels in liver and heart of rats [22]. Furthermore, DHEA appeared to act as functional antiglucocorticoid in behavioral tests of learning and memory in rats [14].

In general, DHEA and cortisol have opposing actions on immune system, promoting Th1 and Th2 cytokine production respectively [7]. On the other hand, DHEAS counteracted decremental effects of corticosterone on dentate gyrus long-term potentiation in rats [23]. However, the effects of DHEA on memory and attention after stress exposure seemed to be heterogenous in elderly humans: while memory appeared to be impaired, attention was enhanced [49].

Progesterone prevented glucocorticoid-induced apoptosis of thymocytes in vitro and in vivo in mice [31]. Besides, testosterone administered with prednisolone, prevented the loss in body weight and partially attenuated the loss in diaphragm weight in rats [12]. However, in this case only anabolic action of testosterone was considered and not its putative neurotropic action.

According to Goodyer et al. [16], the focus on cortisol as the only steroid of importance is too narrow for understanding pathogenetic mechanisms of depression, since a

higher evening cortisol / DHEA ratio may be a better predictor of depressive state. On the other hand, emotional self-management program decreased cortisol levels, but it enhanced DHEA(S) levels in healthy adults [30].

Melatonin and neuroactive steroids in aging.

First of all, both melatonin and DHEA levels demonstrate significant reduction during the aging process. According to various studies reviewed by Poeggeler [37], the amplitude of diurnal rhythm of melatonin is reduced in old age, and in some neurodegenerative diseases such as Alzheimer's disease it is almost abolished. It was suggested earlier by Reiter [41] that by means of protecting macromolecules against free radical attack, melatonin could be a major factor in determining the rate at which organisms age. Moreover, if melatonin preferentially affords antioxidant protection to the brain, it could be a major player in delaying aging and age-related diseases. Besides, the protection afforded by melatonin to DNA would also reduce the likelihood of cancer.

Another research groups reported previously that both melatonin treatment and pineal graft into thymus prolonged survival of aging mice and preserved aspects of their youthful state, as well as corrected the reduced thymic endocrine activity and increased the weight of thymus and its cellularity [33, 36].

The decline in production of hormones such as melatonin has been proposed to play a significant role in contributing to immunosenescence. In fact, the age-related impairment of the immune system in humans appears around 60 years of age, coinciding with the decrease in plasma melatonin concentration [45]. Besides, regression of thymus in laboratory animals can be induced by pinealectomy and conversely, the process of regression can be reversed by melatonin administration [46]. It is important to note that melatonin may be considered not only as hormone, but also as antioxidant vitamin and therefore, it can be used in the form of dietary supplement [47]. Moreover, melatonin has the properties of geroprotector and anticarcinogen [1].

Concerning melatonin and glucocorticoid interactions, it was shown that melatonin levels decreased, and cortisol serum concentrations increased at night in patients with coronary heart disease [6]. On the other hand, administration of prolonged-release melatonin was able to rectify the cortisol diurnal rhythm in the elderly patients with insomnia. The authors suggested that the clinical benefit of such melatonin therapy may be beyond the improvement of sleep and mood and provide better control of blood pressure and metabolism also [50].

As was hypothesised previously, if pineal gland hypoplasia associated with intrauterine growth restriction extends into adulthood, then the chronic deficiency of melatonin could provoke higher lipid peroxidation with resultant increase in the incidence of stroke and coronary heart disease [29].

What for neuroactive steroids, about 60% decreases were observed in the levels of some of them in the brain of aged mice as compared to young adults [28]. And again, the principal attention was attracted to DHEA, since this steroid is increasingly used for its supposed anti-aging effects [20]. In fact, low levels of DHEA are associated with aging process and age-related diseases [9].

The age-associated increase in cortisol / DHEA ratio may be a major determinant of immunosenescence [3, 4]. It seems also that age-related increase in the cortisol / DHEA(S) ratio synergizes with elevated cortisol during stress to reduce immunity in the elderly [8].

Conclusion.

For a long time, the attention of many researchers was attracted to only one class of hormones contributing to ontogenetic bioregulation (e.g., glucocorticoids) [17]. Surely, focusing on only one class of hormones helps in constructing quite reasonable discussion, without immersing into enormous depth of sometimes very complex hormonal profiles. However, the necessity of finding the means of counteracting the effects of glucocorticoids has forced us to begin not so easy analysis of glucocorticoid interactions with other hormones. This analysis may have both physiological and pharmacological aspects. In fact, since melatonin and glucocorticoids appear to regulate immunity in opposite directions, some authors hypothesise that winter stressors and concomitant augment of glucocorticoid production may counteract short-day enhancement of immune function mediated by melatonin [35]. On the other hand, the natural corticotropin-stimulated secretion by adrenal cortex of DHEA with glucocorticoid probably enables the latter to protect the body from ill-effects of stress without exerting their deleterious potency. Nevertheless, exogenous glucocorticoid administration in the elderly may result in further DHEA deficiency, by means of inhibition of corticotropin release and consequent adrenal cortex involution, especially significant in females [42].

Of course, at present there exist a number of poorly investigated topics concerning interactions of glucocorticoids with melatonin, neuroactive steroids and other hormones in ontogenetic bioregulation. On our opinion, the next difficult step may be considering not only pair-wise, but also triple and even more complex hormonal interactions. Probably, systems

biology and medicine may help in treating adequately these challenging new fields of complexity.

And finally, the emerging discovery of neurosteroids and immunosteroids synthesized locally in the brain and immune system strongly complicates rather “simple” picture based on evaluation of the levels of various hormones only in systemic blood circulation [44]. Nevertheless, we hope that the data analysed in this article allow us to affirm that melatonin and at least, some neuroactive steroids may be considered as candidates for counteracting glucocorticoid effects. Obviously, such hypothesis needs to await the confirmation by forthcoming experimental and clinical data. In any case, the idea of considering hormonal interactions proves to be quite promising and should involve other bioregulators in our future studies.

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