БИОГЕРОНТОЛОГИЯ

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ONTOGENETIC ROLE OF SOMATOLACTOGENS AND RELATED PEPTIDES AS ANTISTRESS HORMONES

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Earlier we have described the role of glucocorticoids in ontogenetic regulation. Present paper reviewed the literature data on possible participation of glucocorticoid interactions with somatolactogens (growth hormone, prolactin) and related peptides (insulin-like growth factor-I, oxytocin) in ontogeny, especially in aging. The bibliographic analysis included also evaluation of these hormones as antistress or anticatabolic factors. It was concluded that such important bioactivities of somatolactogens and related peptides are necessary for optimizing immune defense and survival, in spite of the observed negative influences on life expectancy of at least some of them. It appears also that more complex hormonal interactions should be considered for interpretation of these paradoxical data.

Key words: somatolactogens, oxytocin, IGF-I, glucocorticoids, ontogeny.

ОНТОГЕНЕТИЧЕСКАЯ РОЛЬ СОМАТОЛАКТОГЕНОВ И РОДСТВЕННЫХ ПЕПТИДОВ В КАЧЕСТВЕ АНТИСТРЕССОРНЫХ ГОРМОНОВ

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Ранее мы описали роль глюкокортикоидов при старении и в патогенезе возрастзависимых заболеваний. В настоящей работе был проведен обзор данных литературы относительно возможного участия взаимодействий глюкокортикоидов с соматолактогенами (соматотропным гормоном, пролактином) и родственными пептидами (сходным с инсулином ростовым фактором типа I, окситоцином) в онтогенезе, особенно при старении. Библиографический анализ включил в себя также оценку этих гормонов в качестве антистрессорных или антикатаболических факторов. Было сделано заключение о том, что такие важные биоактивности соматолактогенов и родственных пептидов необходимы для оптимизации иммунной защиты и выживания, несмотря на наличие наблюдений о негативном влиянии, по крайней мере некоторых из них, на продолжительность жизни. Похоже на то, что для интерпретации этих парадоксальных данных следует учитывать более сложные гормональные взаимодействия.

Ключевые слова: соматолактогены, окситоцин, сходный с инсулином ростовой фактор типа I, глюкокортикоиды, онтогенез.

Introduction. Recent evidence implicated glucocorticoids in the mechanisms of ontogenetic bioregulation [16]. Therefore, the question emerged: is it possible to counteract adverse actions of glucocorticoids? Our work presented here aimed at considering somatolactogens and related peptides for this counteraction.

Since the seminal works of Walter Cannon and Hans Selye in the first half of 20th century, glucocorticoids and catecholamines (noradrenaline and adrenaline) were considered as principal hormonal mediators of stress. Therefore, antistress hormones should be at least functional antagonists of glucocorticoids.

Basically, we need to discuss, as referred to stress and its mediators, the activities of principal somatolactogenic proteins: growth hormone (GH) and prolactin, as well as insulin-like growth factor of type I (IGF-I) and oxytocin, i.e. peptide regulators related to growth and lactation respectively.

Growth hormone and insulin-like growth factor-i.

Hans Selye was the first to demonstrate in 1952 that GH could counteract growth-inhibitory action of cortisone acetate in rats [37]. Since that moment, a lot of studies have confirmed and extended this data. For example, GH prevented prednisolone-induced increase in functional hepatic nitrogen clearance in humans [50]. In addition, IGF-I had a potential to counteract the decrease in nitrogen balance induced by dexamethasone in rats [25].

GH and IGF-I promoted protein deposition and body growth in dexamethasone-treated piglets [47]. In addition, GH or IGF-I prevented glucocorticoid-induced muscular atrophy in rats [20]. The GH secretagogue ipamorelin counteracted methylprednisolone-induced decrease in bone formation and muscle strength in rats [3]. On the other hand, IGF-I increased total gut weight in dexamethasone-treated rats [33].

However, not always GH was able to counteract glucocorticoid effects. For example, combined administration of GH with cortisone acetate could not prevent the decrease in somatomedin activity in glucocorticoid-treated rats [5]. Besides, IGF-I did not prevent dexamethasone-induced apoptosis of thymocytes, although it slightly reduced cell death in the spleen of rats [19].

These data indicated that it is important to evaluate also the effects of glucocorticoids on GH / IGF-I axis. In this sense, both stimulatory and inhibitory effects of glucocorticoids on GH secretion were demonstrated. In fact, dexamethasone enhanced GH release in male volunteers. Probably, glucocorticoids may initially enhance GH release by augmenting GH-releasing hormone (GHRH) receptor function. In addition, they may diminish the sensitivity of somatotropes to somatostatin and IGF-I [42].

However, high doses of glucocorticoids inhibit GH secretion in rats and humans, probably by stimulating somatostatin release from the hypothalamus [43]. Acute and sustained hypercortisolism decreased GH secretion induced by GHRH in acromegaly, probably by enhancing somatostatin tone also [14]. The response of GH secretion to GHRH and GH-releasing peptide-6 was significantly less in dexamethasone-treated rats [46].

In vitro low concentrations of corticosterone increased GHRH production by cultured fetal rat hypothalamic cells, whereas high concentrations decreased it; besides, corticosterone increased somatostatin production [11]. Cortisol inhibited GHRH-stimulated GH release in sheep pituitary cell culture [36].

The data concerning IGF-I and its binding proteins (IGFBP) are quite heterogeneous. For example, long-term prednisone treatment suppressed GH levels and increased IGF-I in humans [32]. In normal male volunteers dexamethasone enhanced serum immunoreactive IGF-I level, but it decreased IGFBP-1 and IGFBP-2 levels and IGF-I bioactivity [26]. In rats methylprednisolone dose-dependently decreased free serum IGF-I, what correlated with body weight changes [40].

Finally, there are some data involving glucocorticoid-induced changes of receptors and sensitivity to the action of GH and IGF-I. It seems that glucocorticoids diminish sensitivity of chondrocytes to GH and IGF-I [39]. In rats glucocorticoids decreased GH receptor expression and binding activity in the liver [35].

What for aging, Hertoghe [18] suggested that elderly persons are considerably more depleted in anabolic hormones, including GH, than in cortisol. The resulting imbalance with predominance of catabolism may trigger or accelerate pathological aging. Besides, it was

proposed that age-related changes in body composition are the result of age-dependent decrease of GH / cortisol ratio at the level of adipose tissue [27].

In fact, GH is able to inhibit the activity of 11beta-hydroxysteroid dehydrogenase of type I, therefore GH deficiency in the elderly provokes local reactivation of glucocorticoids in target tissues (liver and adipose), what can be responsible, at least in part, for the pathogenesis of central obesity, adverse metabolic profile (increased body metabolic index and fat mass, decreased lean body mass, dyslipidemia, insulin resistance and glucose intolerance) and osteoporosis [41].

Prolactin and oxytocin.

Oxytocin is considered as antistress hormone having anxiolytic and relaxing effects [15]. Prolactin can reduce the activity of HPA axis, whereas oxytocin can inhibit adrenocorticotropic hormone (ACTH) and cortisol release in both men and women, following corticotropin-releasing hormone (CRH) or exercise [6].

According to Arumugam et al. [4], prolactin and glucocorticoids have opposing effects on a number of pancreatic beta-cell genes. Besides, prolactin induces beta-cell replication and inhibits beta-cell apoptosis, whereas glucocorticoids provoke the opposite. In addition, lactogens appear to preserve beta-cell function during fasting, stress or states of glucocorticoid excess.

There are several studies confirming oxytocin and prolactin actions on HPA axis activity. For example, central oxytocin administration decreased stress-induced corticosterone release in rats [48]. Besides, central oxytocin attenuated the activation of specific forebrain regions associated with modulation of HPA activity during the stress reaction [49]. This oxytocin action is considered as manifestation of its antistress influence.

Elevated prolactin antagonized apoptosis in murine thymocytes exposed to glucocorticoids in vivo [23]. It was suggested that prolactin may function as antistress mediator under conditions of elevated glucocorticoid levels in vivo. Prolactin prevented restraint stress-induced gastric erosions and ulcers, as well as hypocalcemia in rats [12].

Centrally administered prolactin decreased stress-induced ACTH secretion and therefore, was considered as antistress factor [44]. In vivo prolactin protected neurogenesis in the dentate gyrus of chronically stressed mice from adverse glucocorticoid action [45].

Oxytocin reduced salivary cortisol during the couple conflict in humans [7]. This neuropeptide appears to have an important mediating role in stress-buffering effects of

positive social interactions. Besides, human volunteers treated with a combination of oxytocin and social support, exhibited the lowest salivary cortisol during the stress reaction [17].

If prolactin and oxytocin affect HPA axis activity, then stress and its mediators like glucocorticoids may influence their secretion. In fact, acute stress increases a release of prolactin which in turn can augment glucocorticoid secretion [34]. Serum prolactin increased after ether stress and decreased following dexamethasone treatment in rats [31]. Corticosterone inhibited prolactin release from rat pituitaries incubated in vitro. Moreover, corticosterone decreased prolactin levels in hypophysectomized rats with pituitary grafts [24]. For evaluation of the role of glucocorticoid interactions with lactogens in late postnatal ontogeny and aging, it is important to mention that prolactin, together with GH, IGF-I and thyroid hormones, is considered as antistress and immunoprotective factor, since primary role of these hormones appears to counteract the effects of negative immunoregulatory factors, such as glucocorticoids, especially during the stress situations [9].

Important advances in this sense were obtained principally in hypopituitary dwarf mice. In fact, earlier works have already demonstrated that immunodeficiency of these animals and precocious aging-like alterations could be overcome by GH and thyroxine [10, 30]. In subsequent studies it was shown that a combination of thyroxine with GH and prolactin corrected the defects in numbers of various types of splenocytes in dwarf mice [13]. Besides, GH3 pituitary adenoma cells, producing GH and prolactin, could reverse thymic aging, when transplanted into rats [22]. Nevertheless, the role of glucocorticoid interactions with prolactin and GH in aging is all far from clear.

Although GH / IGF-I axis and insulin were implicated by genetic studies in negative influences on life expectancy [1, 21], caution is suggested against the tendency to translate results in simple postmitotic organisms like worms and flies to large mammals in which somatic organs are regulated by stem cell compartment. In fact, restoration of IGF-I levels in the elderly may have significant health benefits due to preventive IGF-I effects against skeletal muscle atrophy and cardiomyocyte loss as a function of age [2].

On the other hand, data in rodents indicate that there is an optimal level of GH / IGF-I axis activity to maximize survival in mammals [38]. Strains of mice and rats used as controls may have increased frequency of some tumors in advanced age, for example, those of pituitary gland [21]. However, the severly attenuated GH / IGF-I axis in dwarf mice might also promote tumorigenesis by reducing immune function, particularly NK cell activity [38].

Finally, the retardation or apparent acceleration of aging induced by changes of GH levels in mutant mice may be a consequence of compensatory changes in insulin levels [8]. In any case, the GH / insulin ratio should be considered for evaluating the effects of anti-aging procedures like caloric restriction [29].

Concluding remarks.

Although stress peptide hormones may be subdivided into 3 subgroups: stress-, euphoria- and coping-related peptides [28], and it seems that at least, coping and perhaps, euphoria peptides could be considered as antistress factors, nevertheless, the overlapping nature of hormonal proteins and peptides complicates such subdivision, therefore, even CRH and glucocorticoids may paradoxically have antistress activity inhibiting gastric ulcers in rats [12]. The picture tends to become even more complicated, if to consider multiple hormonal interactions. Here we tried to create stress- and principally glucocorticoid-centered schemes involving somatolactogenic hormones and related peptides. However, many future research efforts are necessary yet (probably, with the use of systems biology and medicine), in order to make these schemes and integral picture more clear.

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