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Central Positions of Glucocorticoids and Stress in the Phenomena of Hormonal and Metabolic Programming / Imprinting

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Abstract

The review is presented about contribution of glucocorticoids and stress to programming / imprinting phenomena. After their definition, possible mechanisms of such phenomena are described, including the role of glucocorticoids in ontopathogenic model, as well as the ways of diminishing adverse effects of these hormones. It is outlined that health professionals should participate in educational campaigns for decreasing adverse actions of stress and glucocorticoids, especially in perinatal period. Moreover, DOHaD concept should be introduced to the contents of university courses in biomedical sciences.

Abbreviations

ACTH – adrenocorticotropic hormone

AVP – arginine vasopressin

CRF / CRH – corticotropin-releasing factor / hormone

DM – dexamethasone

DHEA(S) – dehydroepiandrosterone (sulfate)

DOHaD – developmental origins of health and disease

GC – glucocorticoids

HPA – hypothalamo-pituitary-adrenal (axis)

IUGR – intrauterine growth restriction

MP – methylprednisolone

Introduction

At first, we should remember briefly, what is the physiological significance of glucocorticoids (GC) in the body. As many other hormones, GC possess pleiotropic actions, i.e., they execute multiple activities at the same time. The most known are immunosuppressive and anti-inflammatory ones, according to principal uses of GC in clinics[1]. However, the proper name indicates another important action of GC on metabolism of glucose, although their influence on other types of metabolism, e.g., that of aminoacids, is also essential[2].

Nevertheless, natural GC, cortisol in humans and corticosterone in rats possess significant mineralocorticoid activity, i.e., they regulate the homeostasis of sodium and potassium. In addition, many GC actions are permissive ones, potentiating, for example, vasoconstrictive influence of catecholamines and some other

bioregulators. Quite important also is catabolic action of GC that is revealed by somatic growth retardation as one of the most notable adverse effects in pediatrics[3,4].

Together with catecholamines, epinephrine and norepinephrine, GC are important mediators of stress. These steroids execute such function, taking part of hypothalamo-pituitary-adrenal (HPA) axis that includes also corticoliberin or corticotropin-releasing factor / hormone (CRF / CRH) of hypothalamic paraventricular nucleus and adrenocorticotropic hormone (ACTH), or simply corticotropin secreted by corticotrophs of anterior pituitary. However, regulation of stress is highly complex, involving various feedforward and feedback relations and many other bioregulators, among which we shall mention here only arginine vasopressin (AVP), due to its essential role of stimulating ACTH release, especially during chronic stress[5]. In addition, quite important is neural regulation of HPA axis, in particular by splanchnic nerve controlling GC release in the adrenals[6].

Methodology of Bibliographic Search

In our long, 45-year experience of scientific investigations we have used already various methods of literature search. Approximately before the year 2000 we employed some paper-based sources: mainly "Current Contents – Life Sciences" and "Index Medicus", but thereafter we began to use several online databases: Ebsco, Lilacs – Bireme (Literatura Latino-Americana & Caribes – Biblioteca Regional de Medicina, São Paulo), Scielo (Scientific Electronic Library Online) and others.

However, during the last 15 years we have employed preferably the search engine Scholar Google (especially in the title of the articles), using various key words, including "glucocorticoids", "stress", "programming", "imprinting" and their combinations, almost exclusively in English and during, at least, the last 2-3 decades. For more details on bibliographic search, the reader is addressed to the section "Notes added in proof".

Phenomena of Programming / Imprinting

At the end of the last century research team of English epidemiologist David Barker has performed a series of studies showing that low birthweight of neonates serves as indicator of higher risk of cardiometabolic disorders in later life. This is especially so if accompanied by subsequent catch-up growth in childhood[7-9]. Usually, low birthweight is the result of intrauterine growth restriction (IUGR). At present, approximately 25 years after these seminal studies, it is already clear that there are many causes of IUGR. In developed countries the principal one is placental insufficiency, thus limiting the passage of nutrients and oxygen from maternal side to the fetus[10]. However, in developing countries one of the main causes of IUGR is malnutrition, especially as a result of low protein diet in pregnancy[11-13]. In addition, consumption during gestation of drugs of abuse, in particular cocaine and amphetamines, can also lead to IUGR.

Both malnutrition in the case of low protein diet and several drugs of abuse provoke IUGR, probably by means of endogenous GC in excess[14-23]. Moreover, synthetic GC used during gestation for treating congenital adrenal hyperplasia, severe autoimmune diseases or preventing transplant rejection and in the cases of prematurity can also result in IUGR[24-28].

In the cases of maternal infections the leading mechanism of IUGR appears to be related to higher levels of pro-inflammatory cytokines that in turn can stimulate the activity of HPA axis[29,30]. Several other factors, including maternal anemia, Zn deficiency, gestation in adolescence, Cd^{2+} toxicity, chronic maternal diseases such as bronchial asthma, hypertension, diabetes and renal disorders, physical activity in excess, use of assisted reproduction technology procedures, anxiety disorders and even low socio-economic status, can also provoke IUGR and low birthweight[31-40].

David Barker and other researchers used the terms of biological programming / imprinting, in order to describe the phenomena that occur, when some adverse factors acting usually in critical perinatal period, provoke long-term consequences, resulting in higher risk of several diseases in later life. However, it seems to us that Swedish biochemist Jan-Ake Gustafsson was the first to use the term of biological programming in 1972-1973, in order to describe the organizational effects of sex steroid hormones on metabolism of GC. Nevertheless, Lucas was the first to apply the term "programming" to early postnatal malnutrition[41]. Moreover, long before David Barker, German researcher Gunter Dorner has already performed pioneering studies on sexual brain differentiation in the framework close to developmental origins of health and disease – DOHaD. Nevertheless, only after seminal epidemiologic investigations of David Barker and his colleagues, the concept of DOHaD was firmly established in a world-wide mode, since the confirmation of its principal aspects occurred in many countries on various continents[42].

Shortly after these epidemiologic studies, it became clear that the mechanisms of programming / imprinting phenomena can be explored almost exclusively in experimental models on laboratory animals, because of severe bioethical restrictions for invasive procedures, especially in pregnant women and newborn infants. Among all the animal species available for experimentation, in particular rodents (rats and mice) are especially suitable for such studies, because of shorter periods of ontogeny in these species that allow for good logistics in both time and

cost. However, rats are more suitable for pediatric modeling till adult state, whereas mice (or hamsters) appear to be better for geriatric modeling, because of the differences in body and organ sizes of these rodents.

Mechanisms of Programming / Imprinting Phenomena

There are several mechanisms of these phenomena on different levels of organization. On molecular level the most important mechanisms appear to be epigenetic ones, with alterations of DNA methylation, histone acetylation and some RNAs regulating gene transcription. On the level of cells one of mechanisms may be related to alterations of mitochondria. On the level of tissues and organs the possible mechanisms may include changes in the number of cells and in tissue vascularization or innervation. And on the level of whole organism such mechanisms may involve the alterations of bioregulatory set-points, e.g., for circulating concentrations of GC[43-47].

What for the role of GC in these phenomena, it appears that such hormones can provoke premature maturation of various tissues and organs during perinatal period, by means of decreasing cell proliferation and promoting cell differentiation[48]. In relation to cardiometabolic disorders, three most important mechanisms are the following:

1. GC can interfere in maturation of kidneys, resulting in lower number of nephrons. In subsequent ontogeny this provokes renal hyperfiltration and accelerated wear-and-tear, especially in the cases of obesity[49,50].
2. GC cause the disruption of heart maturation, provoking a tendency to cardiac hypertrophy and subsequent decrease in functional reserve, thus elevating the risk of heart insufficiency[51,52].
3. GC can diminish the number of beta-cells in pancreatic islets of Langerhans, thus resulting in relative glucose overload, insulin resistance and higher risk of type 2 diabetes mellitus[53,54].

Several mechanisms favor the participation of GC in programming / imprinting phenomena. First of all, although in adults the hormones including GC cause in many cases down-regulation or desensitization events resulting in lower response to long-lasting hormonal stimulus, nevertheless in early ontogeny such mechanism is not active and therefore, the same hormones can provoke permanent alterations, characteristic to programming / imprinting phenomena[55,56]. In addition, P-glycoprotein transporting GC across blood-brain barrier is too low in early ontogeny, therefore dexamethasone is able to access central nervous system in this critical period, what is not possible in adults with mature level of P-glycoprotein[57]. On the other hand, 11 beta-hydroxysteroid dehydrogenase type 2, the enzyme inactivating GC in placenta, is inhibited in the cases of hypoxemia, thus resulting in higher fetal exposure to maternal GC[58].

Role of Glucocorticoids in the Ontopathogenic Model

Earlier we began to elaborate the ontopathogenic model that describes the etiopathogenic mechanisms along the whole scale of ontogeny (or at least its main part), including pre- and postnatal development till adult state and continuing through middle age and the period of senescence. The question emerges: how GC could be involved in the ontopathogeny of various diseases? Here we should consider that prenatal stress or exogenous GC are able to provoke increased levels of GC in postnatal period[59-61]. On the other hand, these excessive levels of GC are probably responsible for higher risk of several age-related disorders including systemic arterial hypertension, type 2 diabetes mellitus, depression, osteoporosis, sarcopenia etc.[62,63]. Of course, we must mention here the triple hit concept that considers together genetic predisposition (the first hit), prenatal stress (second hit) and postnatal stress (third hit) (see discussion in ref.64).

In addition, we must be aware that in order to produce significant adverse effects, acute stress types should be toxic or traumatic, like those occurring after so called life events (environmental accidents, loss of the 1st degree relatives etc.). Another type of high-impact stress is chronic one that occurs during prolonged influence of even moderate stress factors (chronic disease, caring of the 1st degree relatives etc.) and can be described by the concept of allostatic load and overload corresponding to pre-disease and manifested disorder respectively.

In middle age and senescence the sequential decrease of some natural, endogenous anti-stress hormones, such as melatonin, growth hormone and weak adrenal androgens like DHEA/ DHEAS can favor the adverse effects of elevated GC levels. We should consider also that one of principal ontopathogenic mechanisms may be neurotoxic GC influence on hippocampal region pertaining to brain areas responsible for negative feedback in the HPA axis[65-67]. This can result in prolonged reactions to stressors, increasing in this way the exposure (concentration multiplied by the time) to endogenous GC[68].

The age-dependent inflamaging, accompanied by increase in the levels of pro-inflammatory cytokines that cause GC resistance may provoke a tendency to parallel increase in both cytokines and GC concentrations, thus mutually potentiating adverse effects of these bioregulators, like higher risk of osteoporosis, depression etc.

On the other hand, elderly patients are the dominant population treated with exogenous GC[69,70], and such

treatment results in higher blood levels of these pharmacotherapeutic agents for longer time, because of the age-related decrease in their metabolism and clearance[71]. Here we should outline that unfortunately, pharmacoepidemiologic and drug surveillance studies of GC utilization and adverse GC effects in senescence period are rare even in developed countries. What for some developing countries, the low knowledge of a great part of the population in relation to drug treatment, together with the tendency to automedication can increase the exposure to elevated levels of highly potent synthetic GC. This is valid also for immigrants in developed countries, for example some Mexican people in the USA[72].

The ways of decreasing Adverse Glucocorticoid and Stress Actions

Earlier we have already discussed this topic, outlining the ability of several bioregulators to decrease the unwanted effects of GC. Among them, several antioxidants like vitamins C and E, melatonin and neuroactive steroids, somatolactogens and related peptides were mentioned[73-75]. Here we shall update the list of compounds with anti-GC or antistress actions (see the Tables 1 and 2).

The mechanisms of these actions may be various ones. For example, long-chain polyunsaturated fatty acids like ethyl eicosapentaenoic acid are able to do this, since GC inhibit the activity of enzymes involved in their synthesis: Δ^5- and Δ^6-desaturases[76,77]. However, in many cases such mechanisms are not clear yet.

Final Comments

In conclusion, both toxic or traumatic acute stress, as well as chronic stress should be avoided or prevented from the very beginning of human life, especially in pregnant women and newborn infants. On the other hand, GC pharmacotherapy must be executed by highly skilled practitioners, particularly in perinatal period. However, all health professionals and first of all, specialists in medicine, nursing and pharmacy, but also psychologists and others should participate in educational campaigns for lay population, as referred to stress and GC use in clinical practice.

Notes added in Proof

Although we study GC and stress for more than 30 years, both in experimental and theoretical investigations,

Table 1: Updating the possibilities for counteracting adverse effects of glucocorticoids (GC): dexamethasone (DM), methylprednisolone (MP) and others in experimental studies.

Anti-GC agents	Type of GC and period / animal	GC-induced adverse effects	References
L-carnitine	DM, neonatal rat	Renal lesions	78
Melatonin	DM, neonatal rat	Hypertension	79
Melatonin	DM, prenatal rat	Hypertension	80
Melatonin	DM, prenatal rat	Liver steatosis	81
Pravastatin	DM, neonatal rat	Brain alterations	82
Ginseng extract	DM, prenatal rat	Defect in testosterone synthesis by Leydig cells	83
Vitamin D	DM, neonatal rat	Decrease in bone mineral content	84
L-thyroxine	DM in the young mice	Body growth retardation	85
Conjugated linoleic acid or creatine monohydrate	MP in the young mice	Body growth retardation	86, 87
L-glutamine	Cortisol acetate, adult rats	Skeletal muscle and body weight loss	88
Pyridoxine and some others	GC in general	Adverse actions in general	89, 90
Alpha-ketoglutarate	DM, prenatal pigs	Osteolytic action, growth retardation	91, 92
Nandrolone decanoate	DM, local action in mouse skin	Mitosis inhibition	93
Ethyl eicosapentaenoic acid	Corticosterone augmented by interleukin-1 beta in rats	Memory defect, behavioral alterations	94, 95
Resveratrol or tempol	DM, in culture of osteocyte-like cells	Apoptosis	96

Table 2: Updating the possibilities for counteracting adverse effects of stress.

Antistress agents	Type of stress and period / species	Stress-induced adverse effects	References
Docosahexaenoic acid	Stress, prenatal in rats	Memory and learning defects	97
Ladostigil (MAO inhibitor)	Stress, prenatal in rats	Anxiety	98
Amitriptiline	Stress, prenatal in rats	Anxiety	99
CRF antagonist, diazepam, antidepressants, allopregnanolone	Stress, prenatal in general	Anxiety, depression	100
Imipramine, tianeptin, agomelatin	Stress, prenatal in general	Various alterations	101
Ketoconazol, mifepristone, aminoglutetimide, RU-486	Human adults in general	Depression	102

unfortunately we cannot affirm that our mini-review article presented here is a comprehensive one, simply because the "ocean" of scientific information becomes too deep for each individual to be sure of search completeness. Some time ago we have made an effort to evaluate the number of articles retrieved by us using Scholar Google and other search engines in bibliometric exploration, and its results have clearly shown almost exponential increase in scientific productions during at least the last 3 decades, approximately since the onset of Internet functioning in amplified mode and with greater velocity[103].

Nevertheless, our aim to focus the attention almost exclusively on the role of GC and stress in programming / imprinting phenomena was supported by our participation in Latin-American chapter of International Society for DOHaD (2009-2020) and especially, in its Council (2011-2019), since these activities have allowed us to identify the principal investigators in this vast area in a world-wide mode.

What for the role of health professionals in promoting educational campaigns, recently we have suggested to include the principal results of DOHaD paradigm to the contents of biomedical disciplines at the universities[104], but it appears that till the present moment this has not happened yet, at least in Brazil, probably because it will take some (perhaps rather long) time for accepting the ontopathogenic model based on DOHaD concept that previously was named simply as "Barker's hypothesis".

In our work presented here we could not discuss all the important themes related to endocrinology, but in order to obtain a lot of of full-length citations, we strongly recommend the interested readers to retrieve at least some of our numerous, previous and quite recent articles (like ref.105), published in their majority in the open access journals and freely available on our personal pages on ResearchGate and Academia websites.

Conflict of Interest

The author affirms that conflict of interest does not exist.

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