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Stress in Different Periods of Ontogeny: Consequences and Peculiarities

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Abstract- The peculiarities and consequences of exposure to stress were described in various periods of pre- and postnatal ontogeny, in the intermediate age groups and in senescence. Principal focus was made on the actions of glucocorticoids (GC), important stress mediators and also used as pharmaceutical agents. Caution was proposed for the treatment with these drugs, especially in perinatal period.

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I. Introduction

In our previous works the role of stress was characterized in the etiopathogeny of various diseases, including metabolic, neuropsychiatric and cardiovascular disorders (Goudochnikov, 2018 a, b, 2020). In addition, the importance of physiologic and cellular mediators was outlined in different mechanisms of stress and in their interactions (Goudochnikov, 2015). Finally, the contribution of stress and its mediators was described for the phenomena of programming/ imprinting and biological embedding in the framework of DOHaD – developmental origins of health and disease (Goudochnikov, 2018 c). The present study aimed at evaluation of peculiarities and consequences of stress in different periods of pre- and postnatal ontogeny, in order to elaborate the ontopathogenic model in more detailed form.

II. Stress and Related Processes

First of all, we should underline that stress is rather wide concept, what results in its overlaying with such processes as infection, malnutrition, hypoxia / ischemia, trauma (including associated with surgery), exaggerated physical activity and even drug abuse (Sullivan et al., 2006; Raff et al., 2007). Obviously, each of these processes has its own peculiarities and mediators involved. For example, the infections are characterized generally by augment of the production of pro-inflammatory cytokines (principally, interleukin-1beta, tumor necrosis factor-alfa and interleukin-6) that in turn provoke the activation of hypothalamo-pituitary-adrenal (HPA) axis. On the other hand, there exist highly complex aspects, such as socio-economic status and allostatic load characterizing more the chronic stress and its consequences.

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III. Stress and its Mediators in Gestation and in Perinatal Period

In the first place, it should be mentioned that at present the stress during pregnancy is much more frequent than previously, due to elevated number of women executing important functions and jobs (Knackstedt et al., 2005). Nevertheless, it could be thought that the fetus in humans and in animals is influenced by stress only at the end of gestation, when its HPA axis is already mature enough. However, maternal stress and related processes (infections, malnutrition, etc.) are able to influence the fetus indirectly via placenta and its hormones. One of more important aspects is the capacity of maternal cortisol to provoke the paradoxical augment of the production of corticotropin-releasing factor (CRF) by placenta, what results in the mechanism of positive feedback, with gradual elevation of cortisol levels in maternal and fetal circulation till the end of gestation (Mulder et al., 2002). If a pregnant woman suffers from exaggerated stress, then it can provoke intrauterine growth restriction or prematurity. Both of these outcomes can have adverse consequences in the long term (Hobel & Culhan, 2003; Davis & Sandman, 2006).

In physiologic situation the augment of cortisol levels at the end of pregnancy is important for causing the maturation of fetal tissues, preparing the body of newborn to live in extra-uterine environment. However, in the cases of prematurity there exists a necessity of accelerating such maturation in artificial mode, by means of administering synthetic GC (usually betamethasone or dexamethasone) to pregnant woman and / or infant. Although such treatment literally saves the lives of some newborns that otherwise cannot even breath because of pulmonary immaturity, its consequences in the long term can be quite unfavorable, affecting not only respiratory system, but also other organs and systems, including the brain (Velisek, 2005). Unfortunately, in at least one third of all the cases there occurs fetal exposure to exogenous GC in unnecessary mode (Whittle et al., 2001).

It is extremely important that both stress and exposure to GC in excess can provoke alterations of regulatory set-points in fetal HPA axis, with notable tendency to its hyperactivity in postnatal ontogeny, probably via diminution of the content of GC receptors and the consequent decrease in the efficacy of negative

feedback centrally (Maccari et al, 2003). On the other hand, such tendency, due to gradual deterioration of hippocampus in aging can result in premature appearance of age-related diseases, both cardiometabolic (hypertension, diabetes mellitus) and neuropsychiatric (depression, dementia) (Matthews et al., 2002).

It is worth to note also that infants, especially in the case of prematurity, possess low amounts of energetic and plastic reserves and moreover, must redirect a great part of them for somatic growth. Therefore, some stressors, such as surgical one, and other invasive medical procedures can have particularly adverse impact in these cases (Anand, 1990; Schmelly & Coran, 1990).

IV. Stress and Related Processes in Children

It is estimated that a half of all the children in the world suffer from exaggerated stress, as well as related processes (infections, malnutrition, etc.) (Fenoglio et al., 2006). Especially adverse is the impact of abuse or neglect in the family, with consequences in the long term (Kaufman et al., 2000). In this regard, besides CRF and GC as stress mediators, the important role in the mechanisms of such consequences belongs to glutamatergic neurotransmission and its NMDA receptors in central nervous system. The parental neglect results in the insufficient activation of such receptors, whereas physical or sexual abuse cause their hyperactivation, with the consequent predisposition to psychopathologies in posterior life (Anand & Scalzo, 2000). In addition, according to the hypothesis of "double hit", the stress in early postnatal ontogeny augments the individual vulnerability to stress in future life, already in adult state (Cirulli et al., 2009). Obviously, the children can suffer from various diseases where synthetic GCare used, but it appears that considerable adverse impact can be provoked by these drugs in the treatment of leukemias.

V. Stress and Related Processes in Advanced Age Groups

The differentiation of intermediate age groups and senescence emerged on the basis of epidemiologic analysis of morbidity and mortality rates (Goudochnikov, 2009). On the other hand, it appears that in feminine gender there occurs an acceleration of aging with the onset of menopause at the age of approximately 50 years. Probably, such acceleration is provoked by the decrease in levels of estrogens that possess neuroprotective and anti-stress actions (Goudochnikov & Prokhorov, 2012). In addition, in both genders a diminution of the levels of other anti-stress hormones, such as melatonin and neuroactive steroids, somatotropin (growth hormone) and related peptides can also contribute to greater impact of stress in advanced age groups (Goudochnikov & Prokhorov, 2014; Prokhorov & Goudochnikov, 2014).

What for synthetic GC, their use by elderly persons was studied quite scarsely in pharmacoepidemiologic and drug surveillance studies. However, it can be anticipated a priori that exaggerated GC use in advanced age groups is capable to provoke more severe forms of age-related disorders, with the impact that deserves more preoccupation in osteoporosis and the resultant bone fractures.

VI. Final Comments

Bibliographic analyses performed allow to suggest the terms of pharmacotoxicologic programming /imprinting and embedding, being applied principally to the use of GC in excess (Goudochnikov, 2018 c). On the other hand, the exaggerated stress can also cause adverse effects, with consequences in the long term. On our opinion, these aspects can be quite useful for the ontopathogenic model in DOHaD paradigm.

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