REVIEW

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Prenatal glucocorticoids can programme postnatal development

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Abstract

Endogenous steroid hormones play a fundamental role in the prenatal development of important vital systems, but when their concentration is long-time enhanced they have a negative impact on the postnatal physiological processes. Prenatal programming is widely used in the context of the permanent alteration of foetal physiological processes. These are caused by factors acting during a critical period of development called the window of the development. Different factors may programme foetal maturity and enhance survival ability after the birth, and may result in disadvantageous consequences in postnatal life. Many studies have shown a relationship between alterations induced by the impact of the mother during pregnancy on the embryo or foetal development, and many consequences which are observed in their offspring. Synthetic glucocorticoids (GCs) given to pregnant females (experimentally or therapeutically), and the increase of endogenous GCs caused by different stressors, lead to identical changes in the process of foetus development. This review focuses on the impact of the prenatal overload with synthetic glucocorticoids on the postnatal development of both humans and experimental animals. It is not known whether these alterations are transient or permanent after the birth, or if they persist, and the extent to which they may be reversed therapeutically.

Key words

prenatal programming, glucocorticoids, dexamethasone, bones

INTRODUCTION

Adaptive, functional, structural and metabolic changes appearing during prenatal development as an effect of interaction between genes and environmental factors, as well as under the influence of the excess of synthetic or endogenous glucocorticoids originating from the mother and placenta, play a dual function. They enhance the chance of survival of newborns under suboptimal conditions during prenatal time, and in later life induce some diseases with prenatal origins [1-4]. Changes in the physiological processes of the prenatal development influence postnatal growth and adaptive possibilities of organism. Developmental anomalies depend on the phase of development, genetic sensitivity of the embryo, and the condition of the pregnant mother, and are a common problem in human and animals [5, 6]. The moment of the action of harmful factors determines the type of anomaly, because each organ has its own critical period when its development may be disturbed. Interferences with placental function or uterine blood flow, release of maternal hypoxia, temperature and light changes, maternal nutrient or protein restrictions, starvation, over-feeding, and either psychological or physical stress of the pregnant mother, as well as glucocorticoids (GCs) overload, are used in studies related to prenatal programming – permanent changes in homeostasis of the regulatory physiological mechanisms [5, 7].

Many experimental researches and clinical statistics confirm the hypothesis of the prenatal origin of many diseases in adults, such as obesity, dyslipidaemia, hyperleptinemia, hyperinsulinemia, glucose intolerance, insulin resistance, type 2 diabetes, hypertension, cardiovascular disease, coronary heart disease, ischaemic heart disease, osteoporosis and hormone-dependent cancer, as well as some allergies. All these events are independent of adult lifestyle [4-6].

Physiological, neuroendocrine and metabolic adaptation of the foetus to suboptimal intrauterine conditions result in a permanent programming of the developmental pattern of tissue and organs and pathological consequences later in life. Further clarification is needed, not only of the molecular or cellular mechanisms underpinning prenatal programming, but as a consequence of the physiological adaptation of foetuses to an altered intrauterine environment.

This review summarizes the understanding of the nature and consequences of foetal programming by several factors, and shows that similar programming has been reported for endogenously-derived glucocorticoids occurring either during prenatal stress or after foetal exposure to an excess of glucocorticoids after therapeutic administration to pregnant mothers.

Prenatal development of hypothalamic-pituitary-adrenal axis. Development of the adrenal gland in vertebrates starts at an early embryonic stage. The fascicular zone forms first, followed by the reticular zone, and finally, at the end of foetal life the glomerular zone of the adrenal cortex. Foetal adrenal glands represent about 0.2 % body weight, and are proportionally about 20 times bigger than in adults. The sdrenal glands regulate foeto-placental steroidogenesis. Cortisol, as natural GC, appears in humans and many species of mammals [2]. It is detectable during the first weeks of foetal life [8]. Human foetal adrenal glands synthesize not only cortisol but also dehydroepiandrosterone (DHEA) and

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aldosterone from halfway through the pregnancy to the end. Cells of the sympathetic nervous system appear in the primary cortex in the embryonic phase, and catecholamines are also present in the early foetal phase. The hypothalamus of the human foetus secretes corticotropin-releasing hormone (CRH) from the 12th week of pregnancy [2]. CRH stimulates the synthesis of the adrenocortocotrophic hormone (ACTH), which regulates production and secretion of GC.

Hypothalamic-pituitary-adrenal (HPA) axis activated at this time regulates the development of the vital organs and foetal stress response. However, a progressive increase of cortisol in foetal blood caused by activation of HPA appears between 3 weeks and 1 week before term, and in humans and farm animals depends on the length of pregnancy. Hormones produced by the adrenal glands play a key role during the embryonic and foetal periods in organogenesis and development. First of all, the prenatal increase of GCs plays an important role in the development of foetal lung and reflects mother's and foetal preparation to term [1-3]. Glucocorticoids inhibit or stimulate signals of the limbic system to the hypothalamus, decrease the secretion of CRH to prevent elevated level of GCs and regulate the stress induced by the response of HPA axis [9].

Glucocorticoid receptors (GRs). GRs are necessary as a hormonal control mechanism for proper neuromotor, psychomotor and endocrinological development characteristic for each species. These prenatal events include neural induction, neurulation, proliferation, migration, axon and dendrite formation and outgrowth, synaptogenesis, differentiation and apoptosis [10]. The function of different structures such as the hippocampus, nucleus amygdales, hypothalamus and pituitary, is linked with the development steroid receptors [3, 11]. There are two types of receptors: type I receptors, called mineralocorticoid receptors (MRs), with a high affinity for corticosterone/cortisol, and type II receptors, called glucocorticoid receptors (GRs) which have the highest affinity for DEX, and about a 10 times lower affinity for corticosterone in comparison with MRs [11]. The presence of GRs is identified in the early human embryo, but specific expression of GRs and MRs in the brain occurs after the first half of pregnancy. Therefore, the impact of foetal GCs exposure is dependent on the expression of receptors in the foetal brain, and it differs between male and female offspring of the same litter. Moreover, there is still no information concerning developmental changes in GRs expression in the human and animals foetus in later gestation [11].

Adrenal hormones. The long loop of feedback includes the inhibition of CRH through glucocorticoids, and the short loop of feedback through ACTH. The changes of the level of ACTH influence not only the production of glucocorticoids, but all the hormones secreted through the adrenal gland.

Mineralocorticoids secreted through the glomerular zone, glucocorticoids through the fascicular zone, and androgens through the reticular zone, belong to the steroid adrenal hormones. There are also secreted other sex hormones, such as dehydroepiandrostenone and androstedione. The adrenal glands are the only place in females where androgens are secreted. Cortisol, as a natural and endogenous glucocorticoid, appears in humans and many species of mammals, whereas corticosterone is typical for rats, amphibia and birds. Cortisol and its rodent counterpart, corticosterone, are synthesized from cholesterol in cells of the zona fasciculata of the adrenal cortex [12]. Cortisol occurs in dynamic equilibrium with cortisone and forms after its oxidation; similarly, corticosterone remains in equilibrium with dehydrocorticosterone, its dehydrogenated derivatives. Cortisol shows about 3-5 times, and cortisone 2-3 times higher activity in comparison with corticosterone or 11-dehydrocortycosterone [13].

The placenta is an additional source of CRH during foetal life, which is subject to the control of glucocorticoids in positive feedback. Placental CRH simultaneously influences the mother (hypercortisolemia without the increase of ACTH on the mothers' side) and foetus, as well as regulates the synthesis of dehydroepiandrosterone sulphate (DHEA-S) in the foetal adrenal glands, the place where foetal estrogens are mainly synthesized [14].

Catecholamines. Glucocorticoids also regulate the synthesis of adrenaline (A), noradrenalin (NA) and dopamine – catecholamines synthesized in the adrenal medulla. The dopaminergic system is especially sensitive to the influence of glucocorticoids in early foetal life [10]. Adrenaline is the results of metylation of NA in the adrenal gland. The enzyme that catalyzes this reaction is present in the adrenal medulla, and its induction is stimulated by glucocorticoids. Because of the existence of the vascular cortical-medullar connection, functional regulation of the synthesis of adrenaline depends on the activity of the adrenal cortex. The adrenal medulla has sympathetic neuration, and additionally, it is indirectly stimulated by the central nervous system. Acetylcholine secreted through the preganglionic part of the sympathetic system stimulates medullar cells to release catecholamine from granules in exocytose. The secretion of catecholamine is present during starvation, hypoxia, pain, cold, fever, dehydration, transport and strong emotional feeling, by the indirect influence of the limbic system. In stress reaction after defective action of catecholamine, when there is a lack of glucocorticoids, circulatory collapse occurs, and when stress reaction is very long and the level of glucocorticoids is still enhanced, blood pressure may be increased, leading to heart diseases [13].

Aim of the use of GCs. The maturity of the vital organs of a foetus is dependent on natural GCs, but they may also pass under the influence of pharmacological doses of synthetic GCs, and occur in clinical intervention if there is a risk of preterm delivery in humans in order to reduce neonatal morbidity and mortality. More and more GCs are commonly given to asthmatic pregnant women in order to stop allergic reaction, or in the therapy of prevention against congenital adrenal hyperplasia (CAH) or rheumatoid arthritis [7,15]. The biological effect depends on daily and cumulative doses, the manner and duration of application. Observations show that changes evoked by prenatal excess of synthetic GCs are the same as these found in the newborns of mothers treated for a different form of stress during pregnancy. Moreover, the treatment with synthetic GCs leads to negative effects similar to these caused by an enhanced level of natural endogenous GCs during prenatal life, caused by changes in the activity of placental 11β-HSD-2.

Effects of GCs maternal overload. There is much information concerning the elevated level of GCs in mothers

with stress condition transferring to the placenta and reaching the foetus, thereby changing its pattern of development to better adaptation for life after the birth according to prenatal programming. The influence of prenatal overload with synthetic GCs was examined with the use of monkey *Rhesus*, rabbits, rats, mouse, sheep, pigs and guinea pigs [16]. Dexamethasone (DEX) as a synthetic GC is used commonly in a wide scope because it is an unsuitable substrate for 11β-HSD-2 [5]. This hormonal programming is also called endocrinization, and occurs in the species-specific profile depending on the development of the expression of GRs and MRs in the foetal brain, as noted above [1, 10, 12]. The study performed on prenatally DEX-exposed rats revealed windows of development for the prenatally inducing negative effects observed after the birth [7, 10]. The excess of GCs induced by prolonged social stress in pregnant monkeys, especially during the third trimester, leads to damage of pyramidal neurons in the hippocampus in both mother and foetus, whose hippocampus decreased in the size of by about 20-30% [11]. Maternal anxiety has a programming effect on the foetus, and this reflected in a range of persistent behavioural abnormalities in the offspring, such as increased immobility and hypoactivity in a new environment, in humans as well as animals [17]. Finally, weakened learning, memory formation, altered behaviour and emotional response, and inhibited psychomotor development were observed. Lowered intelligence quotient and enhanced predisposition to schizophrenia later in life were additionally observed in humans [3,11]. In rats, the prenatal influence of DEX leads to the increase of hypothalamic and medullary serotonin (5-hydrohytryptamine, 5-HT) concentration in offspring, and reduces hipocampal serotonin turnover, one of the modulators of the HPA axis. The changes of prenatal metabolism of 5-HT results in the altered behavior and stress response by serotonergic presynaptic function and receptor activity, since presynaptic membranes are rich in GRs and are regulated by both circulating hormone levels and serotonergic neuronal activity [18]. Serotonin shows the neurotrophic role and regulates axonogenesis, synaptogenesis and gliogenesis occurring in late gestation, and he changed activity of tryptophan hydrolase reduces th serotonin level and neurogenesis. These events underlie the mechanisms of GCs-induced postnatal neurobehavioral alteration. Inhibited neurogenesis reduces the NA level, the rate of dopamine turnover and increases cholinergic hyperactivity of hippocampus. Depression as a result of the disturbances of circadian rhythm and thermogenesis is observed after the birth [17]. An excess of GCs during prenatal time induces co-temporary changes in the developmental dopaminergic system, increasing the risk of schizophrenia, schizoid or antisocial personality, and depression in humans [10].

During the prenatal time, glucocorticoids cause inhibition of the expression of neuropeptide Y (NPY) genes D in the brain, and limitation of convulsive attacks post-natally [19]. Neuropeptide Y, a physiological antagonist of CRH, is stored in the nerve endings of the sympathetic system; it activates the HPA axis, inhibits the hypothalamus-pituitary-gonads axis, and is released with NA as the result of stimulation of this system in stress, depending on the feedback of CRF and ACTH [20]. Prenatal expression of NPY genes in the brain causes the increase of its level in stress without dependence on the intensity of the stimulus. Inhibiting the release of glutamic acid, NPY causes convulsive attacks. Cortisol and DEX show anticonvulsive and anxiolitic action as non-competitive agonists and join to a specific place on one of the GABAegric receptors connecting the neurosteroid. Activation of these receptors by gamma-amino butyric acid, inhibiter neurotransmitter of CNS or synthetic GCs, releases fast synaptic inhibition [19].

Postnatal treatment of rats with an excess of synthetic or natural endogenous glucocorticoids in the upper physiological range is equivalent to that seen after major stressors or chronic stress, induce the loss of pyramidal neurons, with more damage in the CA3 and CA1 regions of the hippocampus [11]. Alteration in the CA3 region is a result of selective block of glutaminergic NMDA receptors (N-methyl-D-aspartate), and the inhibition of steroid biosynthesis, prevented stress-induced atrophy of CA3 pyramidal neurons. Glucocorticoids decreased glucose uptake by the hippocampal cells, and may be the mechanism by which glucocorticoids induce their damaging effect on pyramidal neurons, especially in the CA1 area of the hippocampus. Activation of the CA1 area of the hippocampus results in an increases of the reactivity of HPA axis and a higher release of corticosterone in rats. Low doses of glucocorticoids rapidly and reversibly suppressed the voltage-gated Ca currents in the hippocampus, additionally inducing the reduction of synaptic junction of neurons [3].

The prenatal influence of natural or synthetic GCs on the HPA axis results in the interaction of the HPA axis with another neurohormonal system – hypothalamus-pituitary-gonads. The concentration of CRF, ACTH, and all the hormones synthesized by the cortex of the adrenal glands, including androgens, is reduced. This has a special implication in males before the start of hormonal activity of the testis. Testosterone inhibits the release of CRF from the hypothalamus, and in humans protects male foetuses against GCs influence in the third trimester [14]. The abnormal way of hormonal determination of sex in the prenatal time, induced by natural or synthetic GCs action, alters sexual behavior later in life, caused by the influence on the structures in the anterior hypothalamus associated with sex dimorphism. A similar effect was induced by GCs administered neonatally [18].

Intrauterine growth retardation and catch-up. Exposure to an excess of GCs during prenatal life leads additionally to intrauterine growth retardation (IUGR), related with low birth weight and lowered brain size of newborns. IUGR is a common problem in humans and animals and increases the risk of mortality of newborns during the perinatal period [21]. IUGR is strictly coupled with the phenomenon called catch up, a greater growth rate than that expected for the age, after the release from growth-inhibiting conditions. Catch up in children with retarded growth occurs between 6-24 months [7, 10]. The reduction in size of the kidneys and the number of glomerule, and changes in cardiac structure were also observed [22, 23]. Moreover, IUGR is linked with reduction of the mass of the gastrointestinal tract, the number of cells, and altered pattern of enzyme maturation, as well as decreased secretion of insulin later in life, lowered proliferation of cells β of the pancreatic islet, and expansive apoptosis of these cells [21, 24]. Studies on animals have shown that intrauterine growth retardation led to hyperglycemia and hyperinsulinemia later in life. Experimental animals showed diabetes within 6 months after birth. The reason for diabetes type 2 may be the result of insufficient secretion of insulin,

lowered proliferation of cells β of the pancreatic islet, and expansive apoptosis of these cells [4, 21]. A study on lambs treated with exogenous cortisol for 7 days after the 108th day of pregnancy showed that the proliferation of cells of the crypts doubled, and also enhanced the migration of enterocytes along the intestinal villi [25, 26]. Other studies indicate histomorphometrical changes in the liver, duodenum and jejunum of piglets treated with dexamethasone at multiple minimal therapeutic doses during prenatal time. Maternal treatment with DEX decreased and limited the expression of claudin and cadherin in the epithelium. DEX led to thinning of the myenteron of the duodenum and the middle part of the jejunum in weaned piglets, and influenced the duodenal glands which became more elongated, compared with control glands [27, 28]. The changes described of prenatal development of the gastrointestinal tract prove the possibility of prenatal programming of metabolic diseases related to lipid dysfunction and carbohydrate metabolism [25, 29].

GCs and skeleton development. Newborns survival and ability to adapt to the environment depends on locomotor function connected with mineralization of the skeletal system. The structural quality of bones is determined mainly by genes, and fluctuates with age and health as it is under the influence of hormonal and nutritional modification during prenatal and postnatal time in both animals and humans [5, 13, 30]. Peak bone mass – the maximum amount of bone reached at skeletal maturity – is also influenced by changes in metabolic processes of bone development during both periods. Documentary evidence provided of the number of prenatally-induced bone diseases of children and adults has risen in recent years [4, 5]. Osteoporosis is the most common form of metabolic bone disease, leading to the combinatory loss of bone density and structural integrity [30]. Studies on pregnant sheep have shown lowered foetus weight by about 25%, and length of the femur [31]. Other data prove that DEX given to pregnant sows during the last 24 days of gestation inhibits growth and mineralization of bones, according to reduced bone mineral density, diameters of the cross-sectional area of femur and humerus of their offspring [32]. The foetuses had a geometrically immature skeleton, caused by reduced marrow cavity, and in consequence, reduced biomechanical parameters. Moreover, DEX reduced the concentration of bone markers such as osteocalcin [32]. Another study proved that catch-up in the whole skeleton of male offspring born to sows treated with DEX at total dose of 36 mg during the last 24 days of gestation, is not reached during the first 30 days of postnatal life. A strong reduction of mechanical parameters and mineralization of bones was observed [30]. The offspring born by DEX-treated sows had reduced body weight and bone mineral density, which was still observed at the age of 9 months. DEX administration to sows during the last 45 days of pregnancy influence the morphology of articular cartilage in both female and male newborns, and may lead to the alteration within cartilage during normal function, and with time, arthritic changes could follow. These changes were connected with an enhanced concentration of IL-1, IL-6 and TNF-alpha [33]; however, all the consequences of prenatal GCs exposure are not yet known.

OPG/RANKL/RANK. In previous years, one mechanism has been studied which nowadays is defined as complex OPG/RANKL/RANK [34]. RANKL is strongly expressed in osteoblast and mRNA RANKL is observed in the chondrocytes of 15-day-old embryos of mice. Osteoprotegrin (OPG) is a protector of bone, it is an effective inhibitor of osteoclasts maturation and activation. Expression of OPG is down-regulated by glucocorticoids. The OPG/RANKL/RANK pathway may play an important role in both the pathologic and physiologic calcification processes. Inhibition of RANKL via OPG prevents bone loss and has a beneficial effect. RANKL expression can be up-regulated by bone-resorbing factors such as: glucocorticoids, interleukins (IL-1, IL-6, IL-11, IL-17), tumour necrosis factor-alpha (TNF-alpha). IL-1 and tumour necrosis factor-alpha are 2 of the most powerful stimulators of bone resorption by the activation of mature osteoclasts and induction of the secretion of additional cytokines (IL-6 and IL-11). IL-4 and IL-13 and interferon gamma may inhibit bone resorption by decreasing prostaglandin production and the development of preosteoclasts. Glucocorticoids, IL-4 and IL-13 stimulate prostaglandin synthesis and bone resorption [34].

What may limit the impact of natural GCs? The foetus is protected against the negative action of an over-excess of maternal cortisol by 11-β-hydroxysteroid dehydrogenase type 2 (11-β-HSD-2), an enzyme present in the placenta and vital organs of the foetus. High activity of 11-β-HSD-2 is detected in many foetal tissues since half pregnancy in rats, and probably is also in humans. After 26 weeks of prenatal time, mRNA 11-β-HSD-2 is detected only in the kidneys of the foetus in human. Decrease of 11-β-HSD-2 activity at the end of pregnancy correlates with increase in the diffusion of maternal GCs through the placenta to the foetus at perinatal period [2, 3, 35, 36]. Moreover, the concentration of corticosteroid binding globulin (CBG) influence the amount of GC reaching the target tissue in the foetus, and the affinity of receptors binding GCs [37].

CONCLUSION

The human and animal foetus may change their metabolic processes, even through different conditions from normal physiological processes. The mother, placenta and foetus interact in this programming. Synthetic GCs given to pregnant females (experimentally or therapeutically/inhaled or orally), and the increase of endogenous GCs, caused by different stressors lead to identical changes in the process of foetus development and enhance survival. Synthetic GCs administered therapeutically or an enhanced level of endogenous GCs in stress appearing during the early foetal life, also causes a long-term effect in the central nervous system. Postnatal abnormalities observed after suboptimal intrauterine environment are multifactorial and involve many organs and neurohormonal systems. The mechanisms responsible for the alteration in the maturational pattern of the foetus during the prenatal period in animals and humans with retarded growth, are not fully known. Moreover, it is also not known whether these alterations are transient or permanent after birth and whether they persist, and the extent to which they may be reversed therapeutically [21].

Knowledge about the mechanisms of permanent intrauterine programming of the phenotype, psychomotor and behavioural abnormalities in the offspring of animals and humans is still very limited. But an increasing number

of studies show a relationship between alterations induced by the impact of the mother during pregnancy on the embryo or foetal development, and the many consequences observed in their offspring.

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