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Glucocorticoid-Induced Growth Inhibition: An Update

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Review Article

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Abstract

The mini-review is presented, including both early and recent investigations, on growth inhibition induced by glucocorticoids. These data are discussed, together with current concepts of growth regulation, involving tissue streaming and some evidence, as referred to stem and progenitor cells. It is outlined that future studies on cultures of induced pluripotent stem cells may open translational perspective for such area, important for endocrine aspects of pediatrics and perinatology.

Keywords: Glucocorticoids; Growth; Stem Cells; Tissue Streaming

Abbreviations: GC: Glucocorticoids; GH: Growth Hormone; HPA: Hypothalamo-Pituitary-Adrenal; IGF: Insulin-like Growth Factors; IGFBP: Insulin-like Growth Factors Binding Proteins; SC: Stem Cells; PC-Progenitor Cells; <DC: Less Differentiated Cells; >DC: More Differentiated Cells; A/R: Apoptosis and Removal; IPSC: Induced Pluripotent Stem Cells.

Introduction

Earlier we have evaluated the age-associated differences in effects of glucocorticoids (GC) on body and organ growth in vivo and on macromolecular biosynthesis and secretion *in vitro* [1]. These studies have established that during neonatal period in rats somatic and cellular growth (at least in pituitary gland) appear to be more sensitive to GC, as compared to prepubertal and adult animals. On the other hand, we and others have shown inhibitory GC action on proliferation of various cell lines [2,3].

Our later research on linearization of somatic growth plots in rats and humans has revealed at least two transitions, juvenile and pubertal, that separate postnatal ontogeny to three phases. These phases coincide in rats with the stages of sequential growth limitation by means of changes in growth mechanisms from predominant hyperplasia to combined hyperplasia and hypertrophy, and from that combination to predominant hypertrophy [4]. In our hands, GC have not altered the ages of juvenile and pubertal transitions, although diminished total body growth.

It is important that synthetic GC is widely used in obstetrics, neonatology and pediatrics. Moreover, these pharmacotherapeutic agents provoke body growth inhibition as one of principal adverse effects in children and adolescents [5] and are suspected to cause programming / imprinting phenomena, together with growth retardation and long-term consequences, when used in perinatal period [6].

However, mechanisms of GC-induced growth inhibition continue to be poorly understood, in spite of the decades of intensive research. Therefore, we decided to perform an update on this important topic, evaluating both early and recent investigations that were not discussed yet in our previous works, focusing at last on possible regulatory actions of GC on progenitor and stem cells.

Historical Perspective and Phenomenology of Glucocorticoid-Induced Growth Retardation

Shortly after their discovery at the end of forties in last century, the publications appeared about growth inhibition provoked by GC [7,8]. Moreover, in one of them Hans Selye, the founder of stress concept, was the first to show that such impact can be counteracted by growth hormone (GH) [9]. In the decades of seventies to eighties of 20th century many other studies have confirmed this notable adverse action of GC, together with their neurotoxic effects [10-15]. In recent years these data were expanded even more [16,17] in various species of vertebrates, including birds [18-21].

In our studies at the beginning of the current century we have observed an important inhibitory action of GC on tissue hydration, suggesting later their participation in age-related decrease in water content during early postnatal ontogeny and in aging [22]. Moreover, we have suggested that growth inhibitory GC action may be mediated by leptin, a hormone with anorectic properties [23], considering that pro-inflammatory cytokines, another bioregulators with anorectic action [24], stimulate hypothalamo-pituitary-adrenal (HPA) axis, but GC in turn inhibit cytokine secretion [25].

However, although GC stimulate leptin release, nevertheless, leptin in turn inhibits GC production [26]. Moreover, circadian rhythms of leptin and GC are inversely regulated, as well as the levels of GC and leptin during stress response [27]. On the contrary, the levels of GC and pro-inflammatory cytokines can increase in parallel, due to capacity of the latter to cause GC resistance [28]. Therefore, at present we consider that GC-induced growth inhibition may be also mediated by pro-inflammatory cytokines possessing anorectic properties, as leptin. In this regard, it is interesting that leptin and its receptor are similar to interleukin-6 and its receptor. In addition, pro-inflammatory cytokines can stimulate leptin secretion [29].

Surely, these are only some mechanisms of GC-induced growth retardation. What are the other possible mechanisms? In order to answer this question, we should update at first the topic of growth bioregulation.

Present State of Growth Regulation by Hormones and Other Factors

At present hormones are considered to be the principal regulators of body growth. Among them, GH is probably the most important anabolic factor, and GC are essential bioregulators with catabolic action. Nevertheless, growth regulation is highly complex. For example, GH action is dependent on insulin-like growth factors (IGF) and their binding proteins (IGFBP). On the other hand, proliferation of lymphocytes and other cells of immune system is regulated in endocrine-like mode by many cytokines, including interleukins and growth factors [30]. By the way, the role of immune system in growth regulation may be suggested, what allows to understand better the stimulatory action of GH and inhibitory influence of GC on immunity. It is important also that immune system is more sensitive to GC suppressive action in neonatal period [31].

The main problem to study actually is a complex structure of tissues and organs, composed of heterogenous mixture of various cell types. 30 years ago we have employed an idea of tissue streaming elaborated in the works of Gershom Zajicek and his colleagues in Israel, in order to propose a theoretical model of anterior pituitary cytoarchitectonics [32]. Recently we have updated it, suggesting also a similar model for adrenal cortex [33]. In both cases the structure of endocrine tissues is basically the same, allowing for cellular flows from the layer of stem or progenitor cells to layers of more differentiated cell types and terminating in the layer of aged cells that should be eliminated by apoptosis and phagocytosis (Figure 1). During tissue streaming, the sequential commitment of different cell types occurs, with subsequent maturation, for example, by means of accumulation of secretory products in adenohypophyseal cells.

Therefore, the previous idea of hyperplasia and hypertrophy is only approximate one, since it was based on biochemical evaluation of DNA and total protein contents in tissues and organs, when their fine structure is averaged or lost. What about growth regulation for stem or progenitor cells?

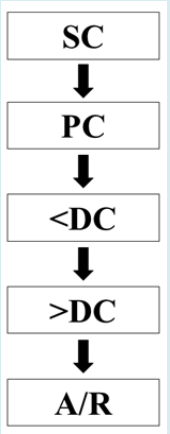

Figure 1: General scheme of cell flows in tissues (streaming).
Designations: SC-stem cells, PC-progenitor cells, <DC-less differentiated cells, >DC-more differentiated cells, A/R-apoptosis and removal (for example, by phagocytosis).

Some Historical Aspects and Recent Advances in Stem Cell Research, As Related to Growth Regulation

At first, we should remember in brief the history of stem cell investigations. It was a Russian histologist Maximow AA (that later worked in Chicago, USA) who used the term "stem cells" for the first time, as referred to bone marrow hematopoiesis, at the beginning of 20th century [34]. Another Russian researcher, Friedenstein AY has discovered mesenchymal stem cells, also in bone marrow [35]. But only in the first decades of current century the area of stem cell research has greatly expanded, mainly after seminal studies that elaborated the first cultures of embryonic stem cells. The next important step was the discovery of transcription factors necessary for stemness, what resulted in elaboration of induced pluripotent stem cells (IPSC). The application of these biotechniques to adult human cells was essential for partial disruption of bioethical barriers in research with human embryonic stem cells, although the last ones may be different from IPSC.

What are the main advances in studies of hormonal bioregulation, as applied to stem and progenitor cells? Earlier the important roles of various cytokines in the control of stem cell functions were shown. Unfortunately, for GC the progress was much slower. At present, the role of GC is suggested for regulation of precursor cells in bone and adipose tissues. In this regard, it appears that GC are diverting the differentiation of mesenchymal stem cells from the bone to adipose lineage [36]. It is interesting that it explains, in principle, the parallel tendencies to osteoporosis and obesity in aging humans.

Conclusion

In conclusion, it seems to us that a lot of research efforts should be made in near future, in order to understand better the mechanisms of GC-induced growth inhibition and the role of stem and progenitor cells for this important adverse GC action in pediatric clinics. But it is already quite clear that cell cultures of embryonic and adult stem cells and especially, human IPSC [37] can be very helpful in this endeavour.

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