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Hormonal Programming / Imprinting Phenomena as Related to the Liver and Pancreas

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Abstract

A short overview is presented on hormonal programming / imprinting phenomena in liver and pancreas. The main focus is made on some data related to the concept of DOHaD. It is proposed to enhance research efforts in this important area in the near future.

Keywords: Programming; Imprinting; Glucocorticoids

Abbreviations: CBG: Corticosteroid-Binding Globulin; DOHaD: Developmental Origins of Health and Disease; GC: Glucocorticoids; GH: Growth Hormone; IGFBP: Insulin-like Growth Factor-Binding Proteins; SA: Serum Albumin; TRH: Thyrotropin-Releasing Hormone

Introduction

At present there are some suggestions explaining programming / imprinting phenomena for kidneys, heart and blood vessels (see discussion in) [1]. However, for liver and pancreas the data are scarce, although the liver may be considered as principal metabolic "bioreactor" in human and animal body, whereas the pancreas has enormous significance in diabetology. Therefore, we decided to fill this lacune, also taking account of our previous experience with liver cell cultures. Preliminary evaluations of this topic for the liver have already been performed by us earlier [2,3].

Hormonal Regulation of Liver Functions in Ontogeny

In order to serve as candidates for mediators in mechanisms of programming / imprinting phenomena, the hormonal bioregulators must be able to affect target tissues in early development, preferably in perinatal period. We have studied hormonal effects in primary cultures of liver cells enriched by hepatocytes, obtained from fetal and prepubertal rats.

It was shown that glucocorticoids (GC) and thyroid hormone, insulin and growth hormone (GH) stimulated total RNA and protein biosynthesis already in cultured liver cells of fetal rats. Moreover, GC, insulin and GH stimulated the production of immunoreactive serum albumin (SA) by these cells. With some exceptions, hormonal reactions of cultured liver cells obtained from prepubertal animals were similar to those in fetal rats [4-6].

All these data were obtained in parallel to seminal epidemiologic studies of David Barker and his colleagues. However, at that time we were not aware of these epidemiologic studies, since our goals were biochemical and pharmacologic ones, and not related to public health. Equally, we did not know about DOHaD concept, performing later similar age-related studies in primary cultures of anterior pituitary cells, nor during investigations of age-associated peculiarities of GC action on somatic and organ growth of rats in vivo. Only after being involved in epidemiologic studies in the first decade of current century were we able finally to re-evaluate our previous cell culture data on the basis of DOHaD paradigm.

Nevertheless, in at least one article about liver cells we have already mentioned the possibility of imprinting phenomenon, in order to interprete the absence of GC action on total RNA and protein biosynthesis after culturing in selective medium containing GC and barbiturate [7]. However, later we tried to explain this phenomenon simply by possible elimination of Kupffer

cells and therefore, the action of cytokines produced by them on macromolecular synthesis in hepatocytes [8]. It is important that in the same work the effects of insulin and GH were preserved. Moreover, later we were able to discover stimulatory action of thyrotropin-releasing hormone (TRH) on total protein synthesis in rat fetal liver cells grown in the same selective medium [9].

Of course, there exist another explanations for the above mentioned absence of GC action, for example, down-regulation (or desensitization) of GC receptors or stimulation of GC metabolism by barbiturate included in selective medium. In any case, till the present time cell culture techniques are not routinely used by researchers in DOHaD area (with some rare exceptions, as in [10]). But our previous studies have already clearly shown the maintenance in culture of somewhat like a "memory" about in vivo situation by cells isolated from animals of different age groups (see, e.g.) [11].

What about the interpretation of in vivo data related to DOHaD paradigm?

Possible Role of Hepatic Alterations in Programming / Imprinting Phenomena

First of all, there is a great difference in the effects of GC on liver and anterior pituitary. In fact, GC inhibit DNA and total protein biosynthesis in adenohypophyseal cells, but stimulate total RNA and protein synthesis in liver cells in vitro. This corresponds well to important role of the liver in production of serum proteins including SA, as well as acute phase proteins. Moreover, GC decrease protein synthesis and augment proteolysis in skeletal muscles but stimulate transaminases and gluconeogenesis in the liver.

However, the disadvantage of primary cultures is the destruction of native tissues during cell isolation. For example, the intact liver in adult animals and humans appears to have the gradients of hepatocyte properties, according to tissue streaming from putative stem or progenitor cells in periportal regions to perivenous spaces. Probably, during perinatal programming / imprinting such gradients are altered [12], causing predominance of gluconeogenesis over glycogenesis [13], but this suggests that hormonal mediators like GC may affect hepatic stem or progenitor cells or the properties of tissue streaming.

Usually it is proposed that GC inhibit somatic and organ growth, favoring cell differentiation and inhibiting cell proliferation. However, in the liver a process of polyploidization should be also considered with DNA replication without cytokinesis, one of the principal reasons for us not to evaluate DNA synthesis in our experiments on liver cell cultures as indicator of cell proliferation.

In addition, higher blood perfusion through the liver in fetal period as a consequence of malnutrition may also affect the gradients of hepatocyte properties in subsequent ontogeny [14]. Another possibility of liver involvement is alteration of the production by hepatocytes of various hormone-binding proteins, such as transcortin or corticosteroid-binding globulin (CBG), several binding proteins for insulin-like growth factors (IGFBP) etc. [15]. All these suggestions await for adequate confirmation or refusal in subsequent experimental studies.

One more disadvantage of primary cultures of rat liver cells in our hands was the necessity of seeding cells on thin layer of collagen isolated from rat tail tendons above the plastic bottom, since native extracellular matrix probably would be able to improve the functional activity of hepatocytes. It is interesting that in experiments with selective medium we could obtain liver cell cultures without collagen layer on the bottom, directly on plastic treated only with bovine serum.

As referred to replicative senescence of other cell types, it was already outlined that culture conditions, especially oxygen content in atmosphere, and even some routine procedures like subculturing or medium change may represent cell-stressing factors that should be considered in evaluation and interpretation of results obtained. However, in order to study hormonal regulation of human progenitor or stem cells, bioethical barriers should be overcome, probably, by means of using induced pluripotent stem cells in culture (see discussions in) [16,17], therefore we have to modify the culture conditions, in order to approximate them as close as possible to embryonic intrauterine environment in vivo.

Programming / Imprinting as Related to the Pancreas

It appears that in prenatal period GC can inhibit beta-cell development in pancreatic islets [18]. On the other hand, lower number of pancreatic beta-cells can result in relative glucose overload in postnatal period, with higher risk of insulin resistance and diabetes mellitus type 2 [19]. Finally, GC may alter exocrine development in the pancreas.

Final Comments

In conclusion, the liver may be different from other organs where GC have generally catabolic action, however programming / imprinting phenomena in this organ are quite possible. Perhaps, in order to reveal them, challenging tests like partial hepatectomy should be performed. What for the pancreas, the attention should be attracted to studying the possible programming / imprinting phenomena of its exocrine part. In any case, researchers in DOHaD area must pay much more attention to studies on hepatocytes and pancreatic cells both in vivo and in vitro, considering enormous amounts of data collected already for biochemistry, cell biology, pharmacology etc. of the liver, as well as the importance of pancreatic islet research in diabetology.

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