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Short Commination

Possible Explanation of Metabolic Inhibitor in Anterior Pituitary

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Abstract

It is suggested that putative metabolic inhibitor in anterior pituitary may correspond to chromogranin-like protein, and onset of its accumulation in prepubertal phase may be related to metamorphosis-like process, juvenile transition of somatic growth and to principal transformation from development to aging.

Key words: chromogranin; ontogeny; pituitary.

Introduction:

Famous proverb affirms that "new" facts are really old ones that were already forgotten… Indeed, fifty years ago, in 1974 Denckla has shown the existence in rat anterior pituitary of an agent capable to decrease stimulatory action of thyroid hormones on the oxygen consumption in tissues, i.e. representing some sort of metabolic inhibitor [1]. Unfortunately, during the next decades nobody tried to identify this agent, in spite of enormous progress of biochemistry and molecular biology at that time.

However, another evidence has established pituitary as important organ for mammalian aging, according to results on some alterations after hypophysectomy (see discussion in [2]). On the other hand, data on caloric restriction and dwarf mice appeared to suggest the essential role of an axis GHRH – GH – IGF-I in aging retardation. Perhaps, because of these data reforced by the role of insulin-like hormones in aging of other species, the works on pituitary gland besides GH were largely delayed or simply vanished.

We have entered the vast area of research in experimental endocrinology since 1977, and two years later our first article was published demonstrating higher secretion of GH and PRL in pituitary cell cultures of rats with alloxan-induced experimental diabetes [3], thus favoring the data of Houssay, the Nobel prize laureate [4]. These our preliminary results, not confirmed till the present time, were obtained by means of non-denaturating PAGE in alkaline conditions (pH ~ 9) after prelabelling of pituitary proteins with ^{14}C-L-leucine.

Although this method allows to identify and evaluate PRL and GH as the main proteins of anterior pituitary, one of its disadvantages is accumulation of proteinaceous products on the boundary between concentrating and separating gels. Therefore, later, in 1988 we have used PAGE in mildly acidic conditions (pH ~ 3-4), in attempt to resolve these remnant pituitary proteins. In fact, we have developed not only analytical, but also preparative PAGE in acidic conditions that have shown, besides GH and PRL, one more pituitary protein that unfortunately, was not identified yet [5] (see also discussion in [6]). However, in our later works we repeatedly mentioned it as a candidate for metabolic inhibitor proposed by Denckla [7, 8].

In short commentary presented here we shall try to put forward an hypothesis about chromogranin-like protein of anterior pituitary as unidentified protein that together with GH and PRL constitutes the main bulk of hypophyseal proteinaceous products. Although the main function of chromogranins and secretogranins appears to be the package of hormonal proteins in secretory granules, they may have another important role to serve as precursors of several biologically active peptides [9].

In this respect, earlier we have observed by means of PAGE in alkaline and acidic conditions not only accumulation of prelabelled proteins in cultured pituitary cells, but also their release to incubation medium [3, 10] (and unpublished observations).

It is important that although GH synthesis and secretion are already relatively high in cultures of pituitary cells obtained from neonatal rats [11, 12], the production of PRL gradually increases in postnatal development with the age of donors of pituitary cells for cultivation [13]. It can be suggested therefore that the content of chromogranin-like proteins in pituitary should also increase with the age of animals, at least for providing the package function in secretory granules.

Another line of our investigations in the past was related to construction of the curves of somatic growth, as well as to their linearization in mono- and bilogarithmic coordinates. These procedures have allowed us to observe the transitions of postnatal ontogeny, according to the breaks of straight lines in linearized plots of somatic growth [14, 15]. Both in rats and humans at least two transitions were evident: juvenile and pubertal, but in humans we were able to register one more, infantile transition.

Since we were interested in transformation from development to aging, earlier we suggested that especially juvenile transition could be a good candidate for metamorphosis-like process both in humans and rats [16], coinciding with inversion of the trend of mortality, at least in humans. Later we have proposed that infantile, juvenile and pubertal transitions correspond to the stages of commitment of progenitor cells in the cytodifferones of pituitary gland and adrenal cortex, as well as to drastic changes in environment of early vertebrates [17, 18].

Here it is pertinent to mention that according to Denckla [1], the accumulation of putative metabolic inhibitor in anterior pituitary begins in prepubertal rats, i.e. probably, close to juvenile transition. This corresponds well to the role of such transition as principal transformation from development to aging, serving basically to diminish the rate of oxygen consumption, thus prolonging the period of ontogeny with acceptable levels of lesions caused be reactive oxygen species, but at the same time enhancing the risk of metabolic syndrome.

Probably, increases in levels of glucocorticoids during infantile transition may potentiate the changes in oxygen consumption during subsequent juvenile transition, whereas increases in the levels of sex steroids in pubertal phase may attenuate these effects, especially in females. Of course, interactions between glucocorticoids, thyroid hormones and sex steroids should be studied in much more details during the whole postnatal ontogeny in future investigations.

In conclusion, short commentary presented here serves to put forward an hypothesis about chromogranin-like pituitary protein as metabolic inhibitor, but further progress will depend largely on characterization of peptide products generated during physiological proteolysis of chromogranins.

Abbreviations

GH – growth hormone

GHRH – growth hormone-releasing hormone

IGF-I – insulin-like growth factor type I

PAGE – polyacrylamide gel electrophoresis

PRL – prolactin

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