Developmental Anatomy

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Review

Serotonin/growth hormone/insulin-like growth factors axis on pre- and post-natal development: a contemporary review

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Abstract

Introduction

L-tryptophan is the precursor of serotonin. Serotonin regulates the secretion of pituitary growth hormone-which in turn stimulates production of insulin-like growth factors (IGFs). IGFs are necessary for development and growth.

We reviewed the most recent literature regarding the role of serotonin/growth hormone/IGF-I axis on development and growth. The link between serotonin, growth hormone and IGF production is widely reported in the literature. Many studies demonstrate impaired growth and development in off spring of pregnant rats with low levels of plasmatic serotonin. The most recent literature shows the possible negative influence of serotonin in excess on differentiation of serotonergic neurons with consequent reduction in pituitary growth hormone production, which has a direct effect on hepatic production of IGF-I, particularly in the post-natal period. Recent literature also shows that hyperserotonemia in pregnant rats causes disorders in offspring, such as lower body mass and a lower survival rate. In addition, data show that high serotonin levels could inhibit development of serotonin neurons and lead to anatomic and functional alterations of the brain. Also, a recent study by us supports the negative effects of hyperserotonemiaon pre- and post natal development. In this paper, we considered the influence of different growth factors and hormones on pre- and post-natal development.

Conclusion

Pre- and post-natal development depends on genetic, environmental factors and several growth factors. The ability of the placenta to provide the foetus for all molecular components is fundamental to allow a normal development and growth. This paper expresses brief considerations on some aspects of pre- and post-natal development. It gives a synthetic overview on the role of serotonin/growth hormone/IGF-I axis on development and growth.

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Introduction

Serotonin (5HT) is one of the most important molecules derived from L-Tryptophan (L-Trp). It is a tryptamine, monoamine neurotransmitter synthesized in serotonergic neurons in the central nervous system (CNS) and in the enterochromaffin cells of the gastrointestinal tract. Peripheral 5HT mediates cardiovascular and gastrointestinal functions and platelet activation.[1] In the brain, 5HT regulates serotonergic outgrowth and maturation of some cerebral regions in the developing brain[2], while in the adult brain it has the role of a neurotransmitter regulating function and plasticity[3]. A fundamental activity of 5HT is its influence in the secretion of pituitary growth hormone (GH). In humans, it is assumed that 5HT leads to an increased pituitary GH secretion by inhibiting the production of hypothalamic somatostatin (SS) which has an inhibitory effect on the secretion of pituitary GH. 5HT mainly causes release of pituitary GH through serotonergic projections that, from the medial and dorsal raphe nuclei of the brainstem, reach the hypothalamus. Importance of pituitary GH on pre- and post-natal development is well known. The GH/IGFs axis plays a key role in these processes[4]. IGFs are a group of peptide hormones with anabolic functions, mainly produced by the liver stimulated by pituitary GH. IGFs especially promote differentiation of myoblasts and osteoblastic tissue[5], fundamental for development and growth. IGFs are detectable in many foetal tissues since the first trimester of pregnancy and the concentrations of IGFs in the foetal circulation increase during the whole pregnancy[6]. The nutritional status of the mother is crucial in determining the future pattern of growth and metabolism in the child, thus the foetus is affected by nutritional alteration in the diet of the mother and its rate of growth could be permanently affected[6]. In addition, also in the first period of life, proteins of the diet will influence GH secretion so both depletion and excess intake of some nutrients such as L-Trp, that is the precursor of 5HT, in maternal diet may have effects on pre- and post-natal development. Particularly, in our paper we have considered the influence of pituitary GH on the production of insulin-like growth factors (IGFs), essential for development and growth.

L-Trp/5HT

Peripheral 5HT is synthesized from L-Trp by the action of tryptophan

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hydroxylase (Tph) and aromatic L-amino acid decarboxylase. 5HT is released into portal circulation and accumulated into platelets, and it mediates cardiovascular and gastrointestinal functions and platelet activation[1]. In the brain, neurons that synthesize 5HT are in the raphe nuclei, regions of the brainstem, that throw their axons into various regions of the brain[7]. 5HT regulates serotonergic outgrowth and maturation of some cerebral regions in the developing brain[2], while in the adult brain it has the role of a neurotransmitter regulating function and plasticity[3]. Optimal levels of 5HT in the body are fundamental for both maintaining functionality of the nervous system and regulation of the biological clock localized in the suprachiasmatic nucleus[8]. The rate of 5HT production in the brain depends on uptake of plasmatic L-Trp. Uptake of L-Trp or other amino acids can be influenced by diet that can positively or negatively influence the serum concentrations of L-Trp. Recent data show that the consumption of meals with a variable protein composition causes changes on the concentration of both L-Trp and 5HT in the brain[9]. After experimental administration of L-Trp, 5HT levels are higher in the plasma and brain[10]. When the serum concentration of L-Trp increases as a result of a higher intake with the diet, this leads to an increase in 5HT production (hyperserotonemia) not only in serotonergic neurons, but also in pinealocytes and in the enterochromaffin cells of the gastrointestinal tract[11]. Other experimental animal data confirm that the L-Trp depletion reduces the availability of 5HT in the brain[12].

5HT/GH

GH is a polypeptide of 191 amino acids with a molecular weight of 21,500 daltons. GH, also called somatotropin, is a hormone produced in the adenohypophysis. It exerts its action in all cells of the body, promoting synthesis of proteins, accumulation of carbohydrates as glycogen and use of energy resources as lipids. It is essential during development since it acts mainly in the growth plates of the bones resulting in the stature of the adult. In humans, in the first hours of post-natal life there is an increase in the production of GH. In pre-puberty, GH production remains stable and then increases in puberty, also due to the influence of sex steroids. From late puberty, in the transition to adulthood, there is a gradual decline that continues until middle age. This decline is despite the presence of sex steroids and is accompanied by a gradual decrease in plasma levels of insulin-like growth factor-I (IGF-I). The reduction of GH in old age is also linked to decreased physical activity, menopause in women and decreased testosterone in men. GH is not essential only for post natal development, but also for tissue homeostasis in adult[13]. It stimulates the longitudinal growth of bones, muscle growth and the reduction of adipose tissue.

Secretion of GH, by the somatotrope cells of the hypophysis, is pulsatile. Mainly two hypothalamic hormones regulate the secretion of pituitary GH: the GH-releasing hormone (GHRH) stimulates, while SS inhibits it. Other factors regulate production of GH, by acting directly on the adeno hypophysis or modulating the release of GHRH and SS from hypothalamus, among them we mention thyrotropin-releasing hormone, ghrelin, dopamine, norepinephrine, acetylcholine and 5HT. 5HT stimulates GH secretion through the release of hypothalamic GHRH in the rat. In humans, administration of 5-hydroxytryptophan, precursor of 5HT, determines an increase in the plasma level of GH. According to some data, it could be assumed that human 5HT results in an increase in GH secretion by inhibiting the secretion of hypothalamic SS, which in turn has an inhibitory effect on the secretion of GH, and then in the absence of SS, GHRH works better in stimulating the release of pituitary GH[14]. 5HT mainly causes the release of pituitary GH through serotonergic projections that, from the medial and dorsal raphe nuclei of the brainstem, reach the hypothalamus. Data on the exact role of 5HT on the release of GH are actually controversial[15] this is probably due to the complexity of the serotonergic system and the many receptor sub types involved. Furthermore, there are many evidences that 5HT acts not only through the action of the hypothalamus, but also directly on the pituitary gland[16]. Therefore, it seems that 5HT affects the *basal* secretion of pituitary GH through some of its receptors, as well as through the hypothalamic mechanism of GHRH/SS. According to many studies, 5HT can be found in the hypophysis, in fact its presence has been demonstrated in nerve fibres of the neurohypophysis and in intermediate and anterior lobes[17]. Thanks to the presence of 5HT in the hypophysis, this monoamine could affect hormone secretion through a local paracrine or neurocrine mechanism. Differences in GH secretion between men and women are highlighted, women generally respond to pharmacological stimuli with an increased production of GH than men. Also in rats, differences in GH secretion between males and females exist. In rats, it seems that also gonadal steroids are important determinants of the patterns of GH secretion, different between the sexes. Several data indicate that oestrogen may play a role in modulating the pattern of GH secretion. The physiological significance of these differences in patterns of GH secretion between males and females is not known, but it is possible to think this is connected to gender differences related to size and height of the adult[18]. Given the importance of GH in body growth and metabolism, it is not surprising that hormones secreted by several endocrine glands

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may also play a role in the regulation of GH secretion, including glucocorticoids, gonadal sex hormones, thyroid hormones and also various growth factors such as IGF-I, in fact high plasma levels of IGF-I inhibit GH production[19].

GH/IGFs

Pre- and post-natal developments are co-ordinated by environmental, genetic factors and several growth factors. Among the latter, IGFs are essential for development and growth. The GH/IGFs axis plays an essential role in these processes[4]. IGFs are a group of peptide hormones with anabolic properties produced by the liver stimulated by GH secreted by the hypophysis. There are different isoforms of IGFs expressed in different tissues and classified into two large categories: IGF-I, maximum in puberty, decreases in old age and it is strictly dependent on GH; IGF-II, mainly present in foetal life, is only partially dependent on GH and intervenes especially during the differentiation of skeletal muscle tissue in the pre-natal period[20]. IGFs are the mediators of GH on bone, cartilage and skeletal muscle. In general they stimulate protein, DNA and RNA synthesis, and then increase in number and size of the cells; they mainly promote differentiation of myoblasts and osteoblastic tissue. They are important for growth and development in all vertebrates studied to date[21,22]. Though the anabolic properties are often attributed to GH, IGF-I is actually the anabolic hormone that performs this task. This is because IGF-I is closely dependent on the production of GH. Even if one of the effects of GH is the increase in IGF-I of hepatic origin, GH induces synthesis of IGF-I also in most of non-hepatic tissues, such as pancreas, muscle, kidney, brain, intestine and adipose tissue[23]. It is increasingly evident that IGF-I may also have GH-independent functions[4]. Genetic studies show that IGFs play a major role respect to GH in pre-natal development. Other factors can regulate expression of IGF-I in peripheral tissues, thus IGF-I is induced by oestrogen in the uterus, by follicle-stimulating hormone in the ovary, and by parathyroid hormone and oestrogen in bone. D'Ercoleet al.[24] were among the first to discover that many tissues express IGF-I, this led to re-evaluation of the original-hypothesis of somatomedins[25]. It was initially proposed that GH secreted by the pituitary gland, had influence on growth by inducing the IGF-I production[26]. So IGF-I was acting on target tissues such as epiphyseal growth plate, leading to the longitudinal growth of the bone. The discovery of a local production of IGF-I induced to include an autocrine–paracrine function of IGF-I, in addition to the classical endocrine role. It was still believed that the non-hepatic production of IGF-I was entirely dependent on GH and that all the effects of GH were mediated by both IGF-I produced by the liver and non-hepatic tissues[24,27]. Therefore, the original hypothesis of somatomedins was reviewed including the autocrine–paracrine role of IGF-I[4]. Indeed the effects of IGF-I from liver or other tissues are hardly separable, thus in mice, the reduction of both plasmatic IGF-I and expression of IGF-I in tissues are partially dependent on GH[28,29].

Discussion

The authors have referenced some of their own studies in this paper. The protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. Animal care was in accordance with the institution guidelines.

5HT/GH/IGF-I axis and pre- and post-natal development

Enterochromaffin and neural cells use two different Tph enzymes to synthesize 5HT, Tph1 and Tph2, respectively[30], and the blood–brain barrier prevents 5HT entering from one compartment into the other. So central and peripheral 5HT compartments are separated from one another (Figure 1). Furthermore, during foetal and early post natal development of the brain, the blood–brain barrier is not yet formed and compartments are connected[31]. In the CNS, 5HT induces pituitary GH production with a hormonal mechanism, thanks to serotonergic projections that from the raphe reach the hypothalamus activating the hypothalamic GHRH/SS system, or with a complex local paracrine mechanism[17]. Among these physiological processes, the first is by far prevalent, so an alteration in some elements of this process could result in dysfunction of pituitary GH production, with consequences on development and growth. Literature widely reports the link between 5HT, influence of 5HT on GH production and hence GH-dependence on IGF-I production[2,32]. In previous studies we investigated the lack of L-Trp, precursor of 5HT, in the diet of pregnant rats to analyse the effects on offspring. We showed impaired growth and development in pups of experimental rats and also alterations in sexual development in growing rats[33]. The most recent literature[31,34] shows the possible negative influence of the excess of 5HT on differentiation of serotonergic neurons of the raphe nuclei in the brainstem; consequently the reduction of pituitary GH production has a direct effect on hepatic production of IGF-I. It is particularly relevant in the post-natal period in which influence of IGF-I, among several isoforms, prevails on tissue differentiation and global growth of the organism[35]. Recent literature shows that the hyper serotonemia, induced in experimental conditions in pregnant rats, causes disorders in offspring, such as a lower body mass and a lower survival rate[31,34]. In addition, data show that high 5HT levels could inhibit development of 5HT neurons and lead to anatomic and functional alterations of the brain[36].

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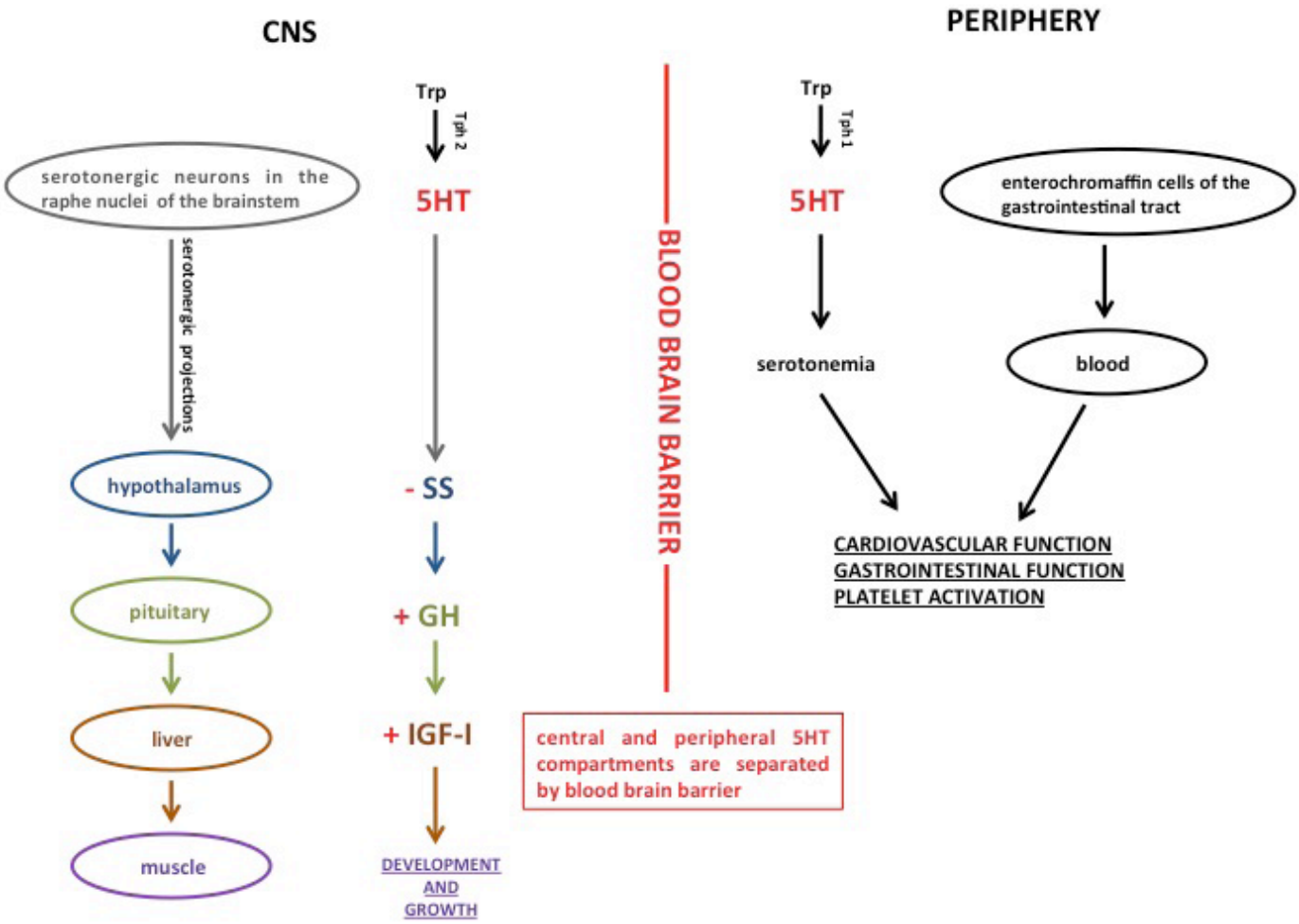

Figure 1: 5HT secretion and function in humans. Blood–brain barrier separates central and peripheral 5HT compartments. 5HT synthesized in the CNS influences development and growth. 5HT synthesized in enterochromaffin cells of the gastrointestinal tract influences serotonemia and consequently several physiological functions. CNS, central nervous system; Trp, tryptophan; Tph1 and 2, tryptophan hydroxylase 1 and 2; 5HT, serotonin; SS, somatostatin; GH, growth hormone; IGF-I, insulin-like growth factor-I.

Our recent study[37] also supports the negative effects of hyperserotonemia on pre- and post- natal development. An excess intake of L-Trp in maternal diet may result in dysregulation of the peripheral 5HT homeostasis, leading to high concentrations of 5HT in blood. The mechanism of hyperserotonemia and its relation to central 5HT dysfunction are not yet fully understood. Possible alterations in the expression of one of 5HT elements could lead to the dysregulation of 5HT transmission in the brain[36,38]. Since during foetal and early post-natal development, the blood–brain barrier is not yet formed, these high 5HT levels could inhibit development of 5HT neurons and lead to the anatomic and functional alterations of the brain[31,36]. In this hypothesis, the inhibited development of 5HT neurons and the anatomic and functional alterations of the brain could lead to a lower production of pituitary GH, that will mean lower hepatic IGF-I production with related consequences on development and growth (Figure 2). In the CNS, the excess of 5HT prevents the normal differentiation of serotonergic neurons of the raphe nuclei with consequences on 5HT production by these neurons and the impossibility that their serotonergic processes, not developed as they should, could reach the hypothalamus. Therefore, regulating function of 5HT in the hypothalamic GHRH/SS system is blocked and under this condition the absence of GHRH, in rats, (or excess of SS in human) determines a lower production of GH by hypophysis. Lower production of pituitary GH results in lower hepatic IGF-I production because of its close dependence on the pituitary GH. Finally, low levels of IGF-I involve negative

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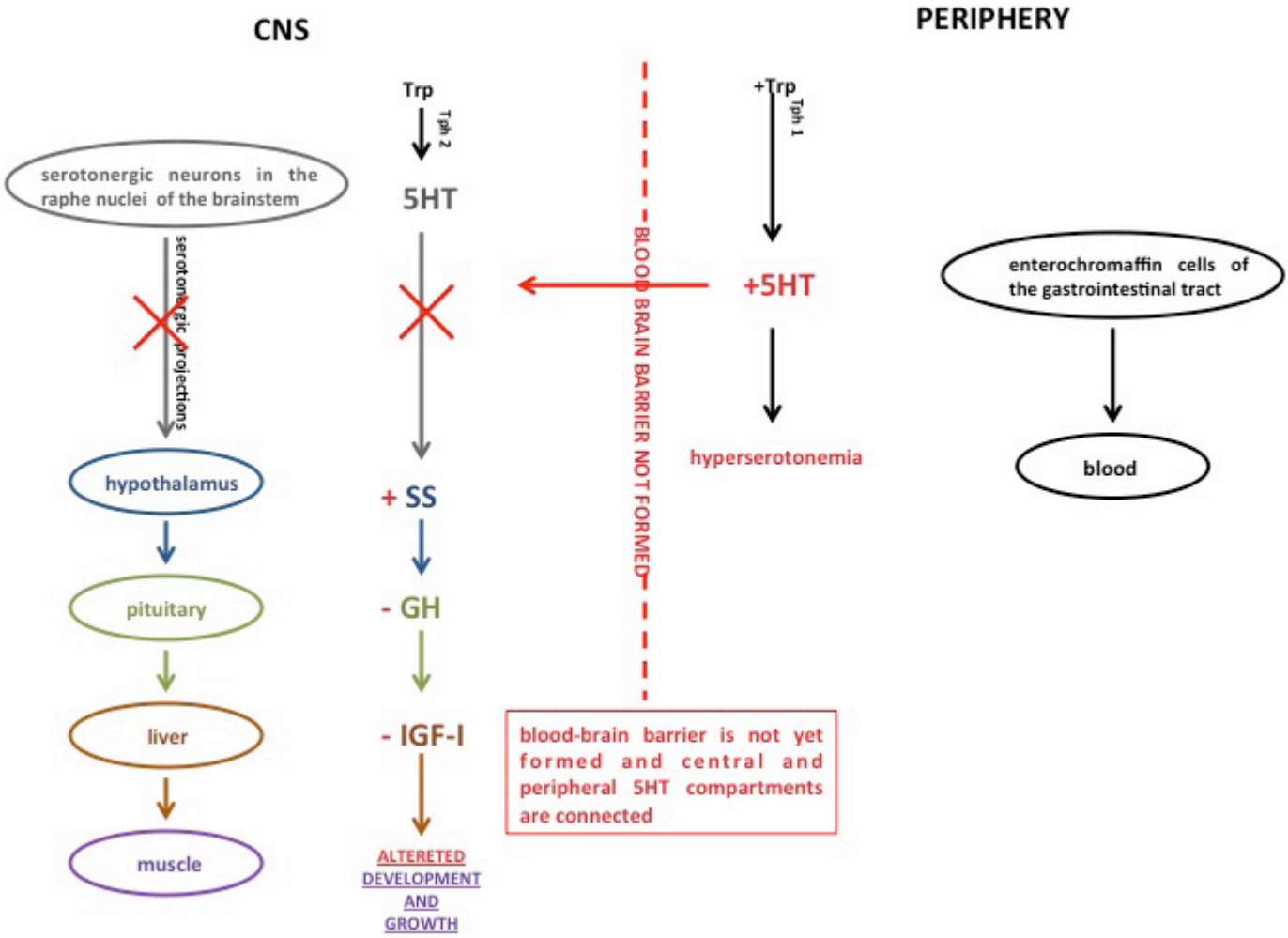

Figure 2: 5HT secretion and function during development and growth in induced hyperserotonemia status. Blood–brain barrier is not yet formed and central and peripheral 5HT compartments are connected. In an induced hyperserotonemia status, 5HT can move to the central compartment where 5HT in excess determines a lower production of pituitary GH. Lower production of pituitary GH results in lower hepatic IGF-I production. Lower levels of IGF-I determine negative consequences on body growth. CNS, central nervous system; Trp, tryptophan; Tph1 and 2, tryptophan hydroxylase 1 and 2; 5HT, serotonin; SS, somatostatin; GH, growth hormone; IGF-I, insulin-like growth factor-I.

consequences on muscular and osteoblastic tissue differentiation that is on body growth[37].

Conclusion

Pre- and post-natal development depends on genetic, environmental factors and several growth factors. The primary factor of foetal growth is not only foetal genotype but also the ability of the placenta to provide the foetus for all molecular components that allow a normal development and growth. For many years it was thought that GH did not have a role in foetal growth, as the expression of receptor for GH is relatively low in foetal tissues, however, congenital deficiency of GH is associated with a reduction of length at birth. Actually, IGFs are the most important endocrine components of foetal growth. IGFs are detectable in many foetal tissues since the first trimester of pregnancy and their concentrations in foetal circulation increases during all pregnancy. Though IGFs are not necessary for survival, their lack has an influence on development of many tissues, as shown by many studies in which IGFs-knockout mice are much smaller than controls (up to 70%).

This paper expresses brief considerations on some aspects of pre- and post-natal development. Conscious that this topic involves very complex processes and aspects of molecular biology and that much more should be still discovered, this study gives a synthetic overview on the role of 5HT/GH/IGF-I axis on development and growth of an organism.

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Abbreviations list

CNS, central nervous system; GH, growth hormone; GHRH, growth hormone-releasing hormone; IGFs, insulin-like growth factors; L-Trp, L-tryptophan; 5HT, serotonin; SS, somatostatin.

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