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PAPP-A2 a new key regulator of growth

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Abstract

Short stature is the main problem that paediatric endocrinologists have to grapple with. Endocrine disorders account for only 5% of patients with short stature, but this is still one of the most common causes of reports to the endocrine clinic and hospitalisation in the endocrine department. A properly functioning growth hormone/insulin-like growth factor 1 (GH/IGF1) axis is one of the most important factors in proper growth. A lot of genetic defects in this axis lead to syndromes marked by impaired growth, like Laron syndrome, mutations in the *STAT5B*, insulin-like growth factor 1 (*IGF1*), and insulin-like growth factor 1 receptor (*IGF1R*) and mutations in the acid labile subunit (*ALS*). Two proteases important for the proper functioning of the GH/IGF1 axis: pregnancy-associated plasma protein-A (PAPP-A) and pregnancy-associated plasma protein-A2 (PAPP-A2), have been described. The first description of the new syndrome of growth failure associated with mutation in the *PAPP-A2* gene was given by Andrew Dauber et al. This review evaluates the current data concerning PAPP-A2 function, and particularly the effect of *PAPP-A2* mutation on growth. **(Endokrynol Pol 2017; 68 (6): 682–687)**

Key words: *growth, short stature, GH, IGF1, PAPP-A2*

Introduction

Depending on the stage of a child's development, we can highlight a number of factors that have an impact on growth. In addition to nutrition, thyroid hormones, and sex hormones, one of the most important is a properly functioning GH/IGF1 axis. Growth hormone produced by the somatotropin cells of the pituitary acts directly on the growth plate and through the somatomedins, IGF1 and IGF2, respectively.

The liver is the main source of insulin-like growth factors (IGFs), their production is mainly under the control of growth hormone (GH), and there is evidence for negative feedback regulation by IGF1 at the level of the pituitary to decrease GH secretion [1]. IGFs do not circulate freely in the serum. They are bound to the six insulin-like growth factor-binding proteins (IGFBPs). IGF1, insulin-like growth factor-binding proteins 3 (IGFBP3), and insulin-like growth factor-binding-protein 5 (IGFBP5) also bind with ALS and together form a ternary complex, which increases the half-life of IGFs [2]. IGFBPs have a high affinity to IGFs, and over 95% of IGFs in serum and other biological fluids remain bound with IGFBPs.

Regulation of IGF1 bioavailability for IGF1R activation is associated with specific proteolytic cleavage of IGFBPs, resulting in cleavage of fragments with reduced affinity to IGF1 [3]. Two proteases, PAPP-A and PAPP-A2 (Fig. 1), belong to the metzincin superfamily of pappalysins and to the class of Zn^{2+}-dependent metalloproteases described [4–8].

The role of IGFs

IGFs influence the proliferation, differentiation, and apoptosis of osteoblasts and are required for bone development, mineral deposition and skeletal growth [9–11]. The most abundant IGFBP in bone is IGFBP5 [12, 13]. IGFs are also potent mitogenic polypeptides with important regulatory roles in cellular processes such as mitosis, cell migration, and apoptosis, which are critical for embryonic development [14, 15].

Pregnancy-associated plasma protein-A (PAPP-A)

Pregnancy-associated plasma protein-A (PAPP-A) specifically cleaves insulin-like growth factor-binding protein 4 (IGFBP4) [16]. This cleavage causes the release of IGF1 from a ternary complex and allows IGF1 to interact with the cellular receptor [17]. The cleavage of IGFBP4 by PAPP-A depends on the presence of IGF1 [16]. IGF1 binds to IGFBP4 and causes structural reorganisation of the C-terminal domain in IGFBP4, releasing or disrupting access of PAPP-A to the cleavage site [18]. This protease is secreted from fibroblasts [17], osteoblasts

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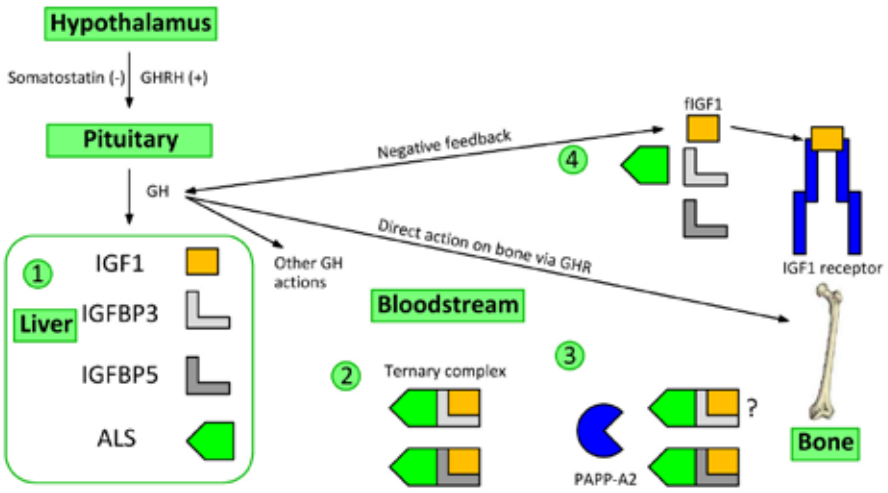

Figure 1. *The impact of PAPP-A2 on the GH/IGF1 axis. Growth hormone secreted by the pituitary stimulates production of IGF1, IGFBP3, IGFBP5, and ALS in the liver. IGF1, IGFBP3, IGFBP5, and ALS bind together and form a ternary complex, which decreases the bioactivity of IGF1. PAPP-A2 cleaves IGFBP5 and possibly IGFBP3. This cleavage causes release of IGF1 from the ternary complex and allows it to interact/bind free IGF1 (fIGF1) with IGF1 receptor*

[17, 19], marrow stromal cells [17], and vascular smooth muscle cells [20]. It is also present in pregnancy serum [21] and ovarian follicular fluid [22].

Pregnancy-associated plasma protein-A2 (PAPP-A2)

PAPP-A2 is a homologue of PAPP-A. Mature PAPP-A2 shares 45% of its residues with PAPP-A [23]. This protease cleaves IGFBP5 at one site between Ser-143 and Lys-144 and possibly also IGFBP3. This action does not require the addition of IGF1 [23]. This cleavage causes the release of IGF1 from a ternary complex and allows IGF1 to interact with the cellular receptor. Proteolytic activity of PAPP-A2 has been reported in pregnancy serum [24, 25], seminal plasma [26], culture media from smooth muscle cells [27], granulosa cells [28], osteosarcoma cells [29], osteoblasts [30], and fibroblasts [31].

Consequences of PAPP-A2 deletion on animal models

Based on a previous study that suggested zebrafish embryos are suitable for an in vivo model to study PAPP-A2 function, Kjaer-Sorensen et al. found that PAPP-A2 is required for normal development of cranial cartilages and angiogenesis [32].

Tests were also conducted on *PAPP-A2*-knockout mice, which showed no significant difference in body mass pre- and perinatally, but exhibited postnatal growth deficiency beginning at the age of three weeks. The knockout mice also displayed disproportionally reduced dimensions of specific bones, including skull, mandible, humerus, femur, tibia, pelvic girdle, and tailbone, with size reductions being more severe than would be expected from the decrease in total body mass and length [32–35]. The mice with PAPP-A2 gene deletion had shallower mandible and pelvic girdles with a more feminine shape [35]. Osteoblast-specific Pappa2 deletion did not affect the circulating IGFBP5 level, but increased the local IGFBP5 level, leading to reduced IGF1 availability as a plausible mechanism [35]. Locally produced IGF1 affects bone development and physiology [36], and deletion of IGF1 in chondrocytes, osteocytes, or cells of the osteoblastic lineage reduce bone growth [37–39].

PAPP-A2: influence on glucose metabolism

Seeing that IGFs and IGFBPs play roles in diverse processes like glucose metabolism and the regulation of adiposity [40–42], the influence of Pappa2 gene deletion on glucose metabolism and adiposity was examined, and the researchers did not find any effect, either on a standard chow diet or a high-fat diet. There was no effect of PAPP-A2 gene deletion on weight gain on a high-fat diet, or the total weight of fat deposits, when correcting for body size [43].

Novel syndrome of growth failure

Andrew Dauber et al. first described two different unrelated families with confirmed mutations in *PAPP-A2*, associated with progressive growth failure with a height below the mid-parental target height, moderate

microcephaly, long thin bones, mildly decreased bone density, elevated circulating total IGF1, IGFBP3, IGFBP5, ALS, and IGF2 concentration, and decreased fIGF1 concentration [44]. The bone age was consistent with chronological age [44]. The concentration of GH was elevated (in the first family the spontaneous secretion of GH was evaluated and in the second family GH after stimulation tests), similar to the total concentration of IGF1, IGF2, IGFBP3, IGFBP5, and ALS. The concentration of fIGF1 was decreased. The concentration of PAPP-A2 was also measured and in the first family it was undetectable, whereas in the second family it was detectable but within the low normal range [44]. A mutation in the IGF1R gene was excluded. Auxological analysis, particularly in the second family, showed that growth retardation became more prominent with age [44]. Researchers observed normal fasting glucose concentrations in both families, and mild hyperinsulinemia in some [44].

The dysmorphic features observed in affected members of both families were similar to those observed in *PAPP-A2* knockout mice [33, 34].

The obtained results draw attention to the elevated levels of GH and the disproportion between the total IGF1 concentration and the free IGF1 concentration, thus indicating that PAPP-A2 is a relevant regulator of human growth and IGF1 bioactivity by regulation of the proportion between free IGF1 and that bound to IGFBPs.

The elevated level of GH might be an indirect cause of the mild fasting insulinaemia observed in some family members.

This novel syndrome of growth failure indicates that PAPP-A2 is a key regulator of IGF1 bioactivity and that the deregulation of IGFBP proteolysis can have significant consequences in human physiology [44].

A trial with recombinant human IGF1 (rhIGF1) treatment seems promising. It is possible that increasing total IGF1 could change the equilibrium of the GH/IGF1 system and increase the bioactive IGF1 concentration, and finally improve growth velocity [44]. Munoz-Calvo et al. treated two prepubertal siblings, a 10.5-year-old female and a six-year-old boy, born to nonconsanguineous Spanish parents with confirmed mutation in the PAPP-A2 gene, short stature, increased level of GH and IGF1, and decreased level of free IGF1 and PAPP-A2 [45]. The children were treated for one year. Initially 40–80 μg/kg of rhIGF1 were administered subcutaneously twice daily for six months. After nine months of treatment, the dose was progressively increased to 120 μg/kg twice daily [45]. Treatment with rhIGF1 accelerated growth velocity, improving the height SDS according to age and sex in both patients [45]. No significant changes in weight, BMI, head circumference, or skeletal maturation were observed. The researchers did not observe side effects of rhIGF1 treatment, such as the enlargement of kidney and spleen [45]. Treatment of PAPP-A2-deficient patients with rhIGF1 induced modifications in the GH/IGF1 axis, which could affect the long-term response.

To sum up, rhIGF1 treatment of children with PAPP-A2 deficiency improves short-term growth with no apparent adverse effects, although further long-term studies are necessary.

Concluding remarks

A properly functioning GH/IGF1 axis is an essential element of optimal human growth. A lot of genetic defects in this axis lead to syndromes marked by impaired growth, and have helped to further our understanding of growth physiology [46]; for example, Laron syndrome with significant growth failure caused by mutation in the GH receptor gene [47]. Mutations in the *STAT5B* [48], *IGF1* [49], and IGF1 receptor (*IGF1R*) [50, 51]) genes cause varying degrees of pre- and postnatal growth retardation, and mutations in *ALS* cause mild short stature [52]. For the first time, Dauber et al. described a mutation in the *PAPP-A2* gene — encoding a regulatory protein PAPP-A2, a protease specific for IGFBP3 and IGFBP5 — leading to dysregulation of the GH/IGF1 axis and short stature [7]. This is a novel syndrome most characteristically associated with progressive growth failure with a height below the mid-parental target height, dysmorphic features such as moderate microcephaly, thin long bones, elevated GH level with a disproportion between total IGF1, and free IGF1 concentrations. The obtained results indicate that PAPP-A2 is a key regulator of IGF1 bioactivity and that the deregulation of IGFBPs proteolysis can have significant consequences in human physiology [44]. This novel syndrome should be considered as the cause of short stature in children who have not yet had an identifiable reason for growth failure, with proper secretion of GH and IGF1 concentrations, after exclusion of any mutation in the IGF1 receptor gene. We are looking to conduct further long-term studies so as to place more hope in treatment with rhIGF1.

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