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Review article

Somatolactogens and diabetic retinopathy

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ABSTRACT

Importance: Diabetic retinopathy (DR) is one of the most common of all diabetic complications. The number of people with DR in the United States is expected to increase to 16 million by 2050. DR is the leading cause of blindness among working-age adults in many different countries, including the United States. In later DR stages, neovascularization is associated with extensive retinal capillary non-perfusion and vitreo-proliferation leading to retinal detachment. This neovascularization is orchestrated by an imbalance of growth factors in the retina from which somatolactogens (pituitary growth hormone, GH-N; placental growth hormone, GH-V; prolactin, PRL; and placental lactogen, PL, also referred as chorionic somatomammotropin, CSH), may play an important role.

Observations: Somatolactogens are a group of hormones that share many structural and functional features. They are important for physiological changes in pregnancy, for adequate development of the fetus, and in the case of GH-N, for promoting growth after birth. GH-N is synthesized by the anterior pituitary, GH-V and PL are secreted by the placenta, whereas, PRL is synthesized by the anterior pituitary and uterine decidua.

However, in recent years the expression of GH-N and PRL and their receptors have been detected in other tissues including the retina, acting as neuroprotective and pro-angiogenic agents. The relationship of GH-N and diabetic retinopathy (DR) was established many years ago when it was observed that its deficiency was related to regression of DR while an increase in serum levels of GH-N, GH-V, and PL promoted DR. While more studies are needed to define the potential implications of GH-V and PL in DR pathogenesis, it has been demonstrated that GH-N and PRL participate in DR by enhancing neovascularization. Some PRL isoforms, however, have shown an anti-angiogenic activity rather than pro-angiogenesis and appears to be PRL's main role in the regulation of retinal vasculature.

Conclusions: Somatolactogens are a group of hormones with a significant role in neuroprotection and angiogenesis regulation in the eye. Understanding the mechanisms of angiogenesis regulation by somatolactogens will potentially lead to the development of new drugs for DR.

1. Somatolactogens overview

This review compiles the information about the implications of somatolactogens in DR pathogenesis. Similar reviews have been published in the context of GH-N [1] and some isoforms of prolactin with antiangiogenic properties [2]. Also, Marano et al. and Ben-Jonathan et al. have written reviews about extrapituitary prolactin secretion and function [3,4]. Pituitary growth hormone (GH-N, also referred to as somatotropin), prolactin (PRL), placental growth hormone (GH-V) and placental lactogen (PL, also called chorionic somatomammotropin

Abbreviations: GH-N, Pituitary growth hormone; GH-V, placental growth hormone; PRL, prolactin; PL, placental lactogen; CSH, chorionic somatomammotropin hormone; IGF-I, insulin-like growth factor I; GHR, growth hormone receptor; PRLR, prolactin receptor; DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; JAK2, Janus kinase 2; STAT5, signal transducer and activator of transcription 5

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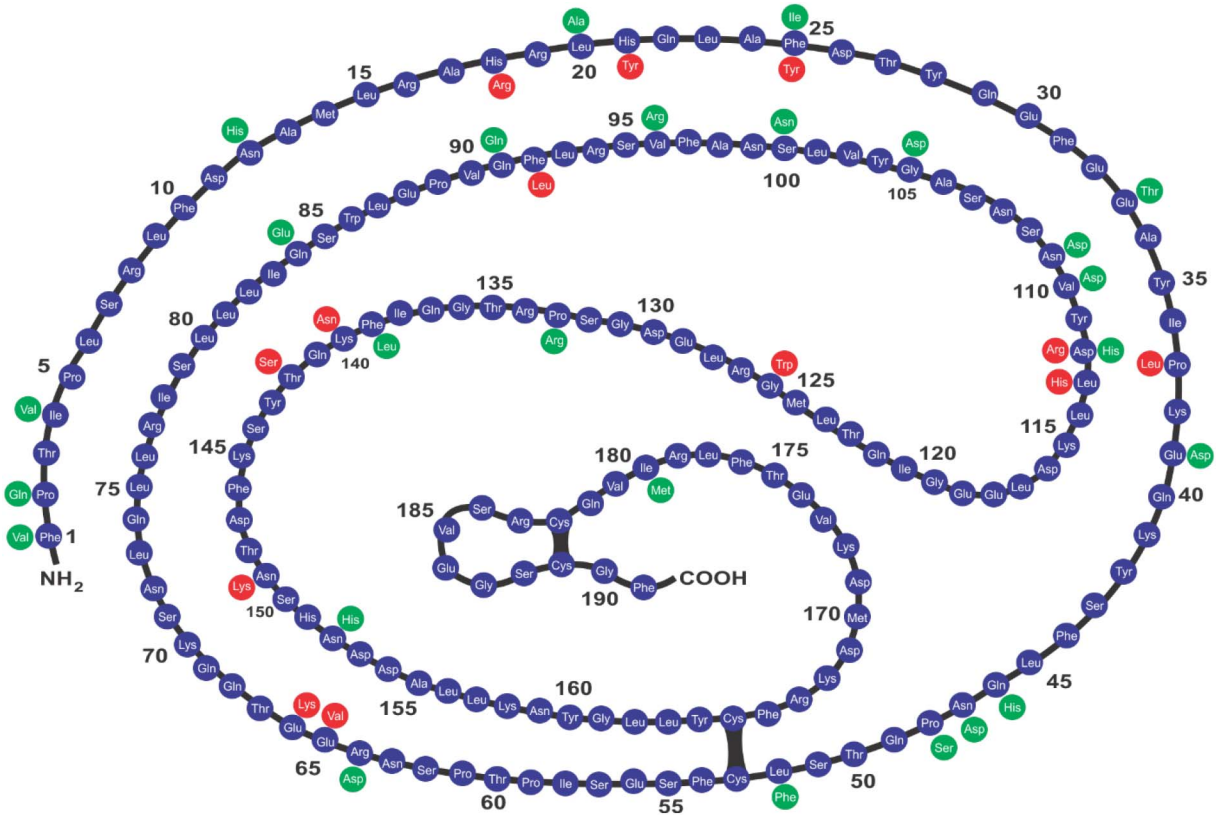

Fig. 1. Growth hormone structure. Placental lactogen (green) and placental growth hormone (red) amino-acid substitutions are highlighted in the primary structure of pituitary GH.

hormone or CSH) constitute a family of related proteins called the somatolactogens protein family. These four hormones share some structural and biological features. For instance, GH-N, GH-V, and PL are 22 kDa single chain polypeptides with their genes found clustered in the same locus [5]. All three mature proteins have 85% amino acid sequence (Fig. 1) identity. Despite the high structural identity between GH-N and PL, PL has a 2300 fold less affinity for the GH receptor (GHR) [6]. Whereas animal studies show that despite its decreased affinity, PL is still able to stimulate GHR [7], but there is no evidence showing that the human GHR is activated by PL. Even though these three hormones share only 25% of their amino acid sequence with PRL [8], they can activate PRL receptor (PRLR) [9,10]. Due to these similarities in their structure and overlap of their functions, it was postulated that the genes encoding the somatolactogens evolved from the same ancestral gene [11].

In general, this family of hormones is required for pregnancy, the normal development of the fetus, and for body growth. While GH-N and PRL are mainly secreted by the pituitary gland, PL and GH-V are secreted by the placenta [12,13]. Recent findings indicate that GH-N might have functions other than overall growth promotion and metabolic regulation.

1.1. Growth hormone

GH-N's most remarkable function is to promote growth after birth. It has two secretion peaks, in the first year of life and during puberty; afterward, its levels gradually decline throughout life. Peripheral secretion of GH-N has been found in several tissues such as the brain [14], mammary gland [15], the immune system [16], skin [17], testis [18], ovary [19], and uterus [20], and more recently, also in the retina [21] (Table 1). Among new properties, it has been proposed that the local action of the hormone helps to not only promote an adequate development but also maintain tissue homeostasis after a stressful event [22,23].

Table 1
Extrapituitary expression of somatolactogens.

Hormone	Organ of presence
GH-N	Brain [14]
	Mammary gland [15]
	Immune system cells [16]
	Skin [17]
	Testis [18]
	Ovary [19]
	Uterus [20]
	Retina [21]
PRL	Brain [37]
	Endometrium [38]
	Myometrium [39]
	Endothelial cells [40]
	Retina [41]
	Immune system cells [42]
GH-V	Placenta [13]
PL	Placenta [12]

GHR is a transmembrane protein member of the type I cytokine receptor family which is activated by dimerization. GH-N has two binding sites called site 1 and site 2. The hormone initially binds one GHR at site 1 and subsequently recruits another GHR molecule at site 2. This GHR dimerization triggers cell survival pathways and stimulates insulin-like growth factor 1 (IGF-1) secretion *via* JAK2-STAT5 activation [24]. In addition, GH-N is able to activate JAK1-STAT3 in many tissues to a lesser extent, but its implications still are not well known [25–30]. GH-N is transported in the bloodstream by a soluble form of GHR, GH binding protein (GHbp), which is an isoform derived by alternative splicing from the same transcript for the GHR gene [31].

The importance of GH-N for the embryological development of several neuronal tissues has been described. The expression of its gene, *HGH-N*, has been found in the CNS of the human fetus [32] suggesting that GH-N is important for its early development. Distinct brain-derived