Growth Hormone & IGF Research 29 (2016) 28–32

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Growth hormone and ocular dysfunction: Endocrine, paracrine or autocrine etiologies?

Steve Harvey *, Carlos G. Martinez-Moreno

Department of Physiology, University of Alberta, Edmonton T6H 2H7, Canada

ARTICLE INFO

Article history:
Received 22 October 2015
Received in revised form 17 March 2016
Accepted 21 March 2016
Available online 28 March 2016

Keywords:
Growth hormone
Retinopathy
Glaucoma
Insulin-like growth factor-1
Endocrine
Autocrine
Paracrine

ABSTRACT

The eye is a target site for GH action and growth hormone has been implicated in diabetic retinopathy and other ocular dysfunctions. However, while this could reflect the hypersecretion of pituitary GH, the expression of the GH gene is now known to occur in ocular tissues and it could thus also reflect excess GH production within the eye itself. The possibility that ocular dysfunctions might arise from endocrine, autocrine or paracrine etiologies of GH overexpression is therefore the focus of this brief review.

1. Introduction

It is now more than 10 years since Frystyk considered growth hormone (GH) and insulin-like growth factor (IGF)-1, its classical mediator, as causal factors in the development of diabetic retinopathy (The Growth Hormone Hypothesis — 2005 Revision, [37]). At that time it was thought that this might reflect endocrine actions of pituitary GH within the eye or actions of GH and IGF-1 within the periphery that secondarily induced ocular dysfunction. However, it is now known that GH expression is not restricted to the pituitary gland and that it occurs in ocular tissues, in which autocrine or paracrine actions of GH might contribute to the etiology of ocular dysfunction. These possibilities are the focus of this brief review.

2. Endocrine etiologies: direct effects of growth hormone

As GH receptors (GHRs) are present in the eye they are target sites of GH produced locally and/or for GH derived from the pituitary gland [56,57]. The retinopathy associated with GH could thus reflect direct actions of GH on the proliferation of microvascular endothelial cells, which occurs in vitro at physiological concentrations [111] and results in angiogenesis [126]. A causal relationship between pituitary hormones and vision-threatening proliferative diabetic retinopathy (PDR) was first realized when retinal neovascularization in a diabetic patent was found to regress after pituitary infarction [105]. Pituitary ablation was then adopted as a therapeutic approach for retinopathy over the following two decades [36,62,66,71,80,125]. The efficacy of this approach was due to the postsurgical reduction in circulating GH, as shown by Wright et al. [138]. The association between GH secretion and PDR was confirmed in numerous clinical studies (e.g. [44,78,79,98]) and the efficacy of treatment was correlated with the degree of GH suppression achieved [138]. A role for pituitary GH in retinopathy is supported by the finding that exogenous GH treatment induced retinal neovascularization in two non-diabetic patients independent of their degree of glucose tolerance [72]. Exogenous GH was also seen to induce retinopathy in non-diabetic growth-restricted children [99]. Although rare [8,140], retinopathy has also been seen in acromegalic patients with GH hypersecretion [7] and circulating GH concentrations are higher in type 1 diabetic patients who have retinopathy than those without retinopathy [69,120]. Full remission of GH-induced retinopathy is also seen after GH treatment cessation [49].

In early studies it was also realized that diabetic patients who were GH deficient have little if any diabetic retinopathy [5,90–92] and reduced retinal vascularization was seen similarly in children who were GH deficient [59]. An essential role of GH in retinal neovascularization was also reported by Smith et al. [124], by their finding that transgenic mice expressing a GH antagonist gene reduced retinal neovascularization. They also found that mice given an inhibitor of GH secretion (MK678) also had reduced neovascularization. GHR antagonists and GHR antisense oligonucleotides and IGF-1 immunoneutralizing

* Corresponding author at: 7-41 Medical Sciences Building, 87th Avenue, 114th Street, Edmonton T6H 2H7, Canada.
E-mail address: steve.harvey@ualberta.ca (S. Harvey).

http://dx.doi.org/10.1016/j.ghir.2016.03.004
1096-6374/

antibodies similarly reduced hypoxia-induced retinal neovascularization in mice [134]. GHR antagonists were also proposed for clinical use as a treatment for diabetic retinopathy [21,39,73,93–95].

Inhibiting pituitary GH secretion was, however, suggested as a therapeutic treatment to reduce retinopathy. Medroxyprogesterone acetate (MAP) was amongst the first treatments proposed [18], as was the administration of antibodies raised against human GH [40] and the use of cholinergic antagonists [35,65]. These treatments were not recommended for clinical use, however, as the effects were short-lived and/or accompanied by unpleasant adverse effects. The possibility that SRIF, an antagonist of pituitary GH secretion, might be an effective treatment for PDR was then investigated. However, while inhibiting GH secretion, its short half-life and lack of specificity (having multiple effects in the gastrointestinal tract) suggested that it was unsuitable for clinical use [29]. Somatostatin analogs with greater stability and specificity were then developed [96,102,103]. Of these, octreotide (SMS 201-995) was found to be somewhat effective, but largely because of its suppression of serum IGF-1 levels [64]. Other early studies with octreotide concluded that it only had modest effects on GH, IGF-1 or glucose metabolism and minimal effects on retinopathy [109,122] even after 1 year of continuous s.c. infusion [70]. However, somatostatin analogs have been found to improve vision in some patients [41,134] to reduce vascular leakage [23,85] and vitreous hemorrhage and improve visual acuity [16] and to retard the progression of advanced retinopathy [42,81]. Although long-term treatment with octreotide was used to treat PDR in diabetics, signs of resistance to the drug were noted after six months [81]. Resistance to SRIF was similarly seen in Type 1 diabetic patients and this was thought to contribute to their elevated GH secretion rates [24].

The role of pituitary GH in retinopathy is, however, controversial as retinopathy is rare in acromegaly [7,19] and GH replacement therapy is not always associated with retinal changes [13] and GHR blockade [73] does not reduce retinopathy in all patients [12]. Moreover, diabetic retinopathy has also been seen in patients in the absence of GH [107] and in patients with a GH gene deletion [75] and retinopathy is not always associated with GH secretion [44,58].

3. Endocrine etiologies: indirect effects of growth hormone

The progression of diabetic retinopathy is exacerbated by factors that lead to poor metabolic control. Indeed, the Early Treatment Diabetic Retinopathy Study (ETDRS) identified a number of important factors that decreased visual acuity, including high levels of hemoglobin AIC (HbAIc), decreased hematocrit and increased serum lipids [110]. Hyperglycemia results in an increase in HbAIc and hyperglycemia induces a sequela of biochemical events that result in endothelial proliferation, capillary closure, the loss of retinal pericytes and neovascularization [87,88] Hyperglycemia itself may be a causal factor in the induction and progression of PDR [129,130,132,134], especially as it also may cause neuronal dysfunction, oxidative stress and inflammation, which collectively promote the pathogenesis of retinopathy [4,121].

As pituitary GH is a hyperglycemic hormone, its involvement in retinopathy might reflect this role, especially as patients with poorly controlled insulin dependent diabetes mellitus (IDDM) have high basal and integrated serum GH concentrations and enhanced GH responses to GH secretagogues [86]. Hyperglycemia itself rather than accompanying increase GH secretion was also thought to account for the diabetic retinopathy seen in some patients with acromegaly [7]. Merimee [88] also considered that GH might contribute to the development of diabetic retinopathy in a number of other ways. It could, for instance, augment thrombus formation [88,137], leading to the closure of capillaries. GH might also increase the plasma levels of von Willebrand factor (vWF) [67], which is a marker for endothelial dysfunction and its increased levels in diabetes might promote stasis in retinal circulation and cause hypoxia [25,33,77]. GH can also influence the composition of arteriolar walls and increases the likelihood of vascular occlusions as GH antibodies prevent its occurrence [76]. GH may also contribute to retinopathy thought its induction of IGF-1, since IGF-1 concentrations are elevated in diabetic patients with retinopathy [89]. Finally, GH is a lipolytic hormone [141] and GH-induced lipid levels in plasma may lead to the progression of PDR and to the formation of hard retinal exudates [110,132].

4. Autocrine/paracrine etiologies

In recent years, it has been realized that GH, like other pituitary hormones [51,52] is widely expressed in many extrapituitary tissues [53]. For instance, it is produced within the CNS, where it has autocrine or paracrine roles in health and disease [50]. Within the CNS, retinal ganglion cells (RGCs) are an established extrapituitary site of GH production [11] and retinal GH has autocrine or paracrine roles in ocular development and vision [56,57]. Within the retina the control of retinal GH secretion is thought to be similar to that of pituitary GH [52,83], especially as SRIF is expressed within the eye [52]. SRIF receptors are also expressed in the retina and actions of octreotide on endothelial cell growth [28] or retinal neovascularization [60] might account for the efficacy of octreotide on retinopathy. The actions of octreotide might also reflect its blockade of local and systemic GH and IGF-1 production [41,74,136] and its inhibition of retinal neovascularization [60].

The neuroretinal damage that occurs in diabetic retinopathy is accompanied by functional abnormalities in vision, as reflected by abnormal electroretinograms. These abnormalities occur before the onset of vascular retinal pathology [68]. It is thus of interest that transgenic mice that lack GH receptor (GHR) signaling have inner retinal abnormalities similar to those of diabetic patients [82]. This could reflect an autocrine or paracrine lack of GH signaling, especially as the retinal anatomy and retinal proteome is also abnormal in these transgenic mice [10].

The possibility that retinopathy might reflect an autocrine or paracrine effect of GH produced in the eye is supported by the fact that GH is present in the vitreous of diabetic patients with PDR [56,57,118]. This is however, unlikely, as the vitreal GH concentrations of diabetics are not higher than those in non-diabetic controls [118,139]. Vitreal GH concentrations may, however, be dependent upon the amount of opticin, a proteoglycan abundantly produced in the eye that acts as a specific GH binding protein within the vitreous [117]. Opticin may thus have a role to ensure a sufficient supply of GH for ocular vascularogenesis [34], but concentrations of opticin in diabetics and non-diabetics are currently unknown.

As IGF-1 is also produced in the eye [38,123] it might be causally involved in the etiology of diabetic retinopathy. Indeed, Hyer and Kohner [63] and Frystyk [37] suggested that local changes in IGF-1 levels within the eye rather than systemic changes in its circulating concentrations were likely to be the primary cause for the development of PDR. This view was supported by the fact that both type 1 and type 2 diabetic patients develop PDR, despite major differences in circulating GH and IGF-1 levels [17]. This view was supported by Wilkinson-Berka et al. [134] who reported that IGF-1 and IGF-1 binding proteins (IGFBPs) are expressed throughout the retina in vascular, neuronal and glial cells and that the concentration of IGF-1 in the vitreous was increased in diabetic patients with PDR [47,97,123,134].

It has been proposed that the overexpression of IGF-1 in transgenic mice results in paracrine effects of IGF-1 that induce VEGF expression and PDR [142]. The possibility that IGF-1 may have an autocrine/paracrine role in diabetic retinopathy was also suggested by the finding that IGF-1 overexpression is detrimental to pericyte survival. Pericytes are contractile cells located on the outer wall of micro-vessels and are particularly important in the retina, where the ratio of these cells to vascular endothelial cells is the highest of any tissue [48,61]. Pericyte loss or "dropout" is an early event in diabetic retinopathy and a causal factor in the stimulation of new blood vessel growth. Pericytes have IGF-1 receptors and IGF-1 overexpression results in pericyte loss [134]. The local production of IGF-1 in Muller cells of the eye is also thought to generate