

## Review Article

# Growth Hormone: Not Just a Pituitary Endocrine

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Growth Hormone (GH) is traditionally viewed as a pituitary endocrine, with widespread actions mediated through GH Receptors (GHRs) that are virtually ubiquitous in its target tissues. This viewpoint has, however, now been revised by the recent realization that GH gene expression is not confined to pituitary somatotrophs and actually occurs widely in numerous extra pituitary tissues, including many of its endocrine target sites, in which GH has local autocrine or paracrine actions of physiological or pathophysiological significance. The realization that GH is not just a pituitary endocrine but also a local growth factor is the focus of this mini review, which is largely based on studies from our laboratories during the last 20 years.

**Keywords:** Growth hormone; Pituitary; Extrapituitary; Autocrine; Paracrine

## Introduction

The discovery of GH immunoreactivity and GH mRNA in central [1-4] and peripheral [5,6] tissues of chickens, particularly in early chick embryos, led to our conceptualization of extrapituitary GH expression. The colocalization of GH receptors in many of these tissues [7-10] suggested GH was an autocrine or paracrine factor [11-15] and not just a pituitary endocrine.

### GH and GHR distribution

In addition to the brain, GH and GHRs have been detected in the neural retina, particularly in Retinal Ganglion Cells (RGCs) [16-20], but also in the Retinal Pigmented Epithelium (RPE) [19], the photoreceptor layer, the choroid, sclera, cornea and lens [21]. In the chick embryo, GH and GHRs have been tracked from fascicles in the Optic Filter Layer (OFL) to the Optic Nerve Head (ONH) into the Optic Nerve (ON), through the Optic Chiasm (OC) and into the Optic Tectum (OT), where the ON synapses with visual centers in the brain [17]. Within the eye, GH has also been found in the vitreous humor [22-23], in which it is specifically bound to the proteoglycan, opticon, secreted from adjacent RGCs [24].

In peripheral tissues, GH and GHRs have been found to be abundantly present in lymphoid tissues, including the thymus and spleen [5,8] and in birds, the bursa of Fabricius [9,25-29]. They have also been found throughout the male and female reproductive tracts [30-36]. GH and GHRs have similarly been found in the perinatal and postnatal lung [37-40].

### Autocrine/paracrine actions

The possibility that GH has local autocrine or paracrine actions was supported by the finding that a GH-Response Gene (GH-responsive gene-1, GHRG-1) was expressed in the brain, in tissues with GH- and GHR immunoreactivity [41]. GHRG-1 is a specific marker of GH action in birds and it is not expressed in GH-resistant dwarfs with dysfunctional GHRs and in normal chickens it is upregulated by exogenous GH. Extrapituitary GH has similarly been correlated with the expression of Insulin-Like-Growth factor (IGF)-1 activity in retinal ganglion cells [16-43] and in ovarian granulosa cells [44]. As IGF-1 is an established marker of GH action, this further supports

the possibility that extrapituitary GH has autocrine or paracrine roles.

### Local GH actions

Local actions of GH in the neural retina have been indicated by morphological differences between normal and GHR disrupted mice [45]. In the absence of local GH signaling there is a reduction in axial length and width of neural retina, including its neuroblastic, inner plexiform and OFN layers. In the absence of GH signaling, four proteins in the retinal proteome of the GHR<sup>-/-</sup> mice differed in abundance with those in the wild type littermates [45]. For instance, Brain Abundant Membrane Attached Signal Protein-1 (BASP-1) was down regulated, whereas protein kinase C inhibitor 1, cyclophilin A, KH domain-containing, mRNA-binding, signal transduction associated protein 3 were up-regulated in GHR<sup>-/-</sup> mice. These proteins are involved in retinal vascularization, neural proliferation and neurite outgrowth, retinal GH may thus have hitherto unsuspected roles in these processes during retinal development.

This conclusion was further supported by the finding that overexpression of bovine GH in transgenic mice resulted in an increase in the GH content of the neural retina and an increase in the axial length of the eye [46]. This increase was accompanied by a selective inner retinal dysfunction causing changes in the retinal Electroretinogram (ERG). Interestingly, these ERG changes are similar to those seen in patients with diabetic retinopathy. Thus, while ocular dysfunctions can result from pituitary GH excess or deficiency [47,48], they may also result from autocrine or paracrine etiologies of retinal GH [49].

Within RGCs, retinal GH has also been shown to promote cell survival by acting as an antiapoptotic factor [50]. Indeed, the immunoneutralization of endogenous GH quadrupled the incidence of apoptosis in RGC cultures. The molecular mechanisms responsible included increased Akt phosphorylation and an increase in caspase-3 expression [51] and activation and PARP-1 cleavage [52,53]. GH mediated survival of RGCs also involved reduced cleavage of caspase-9 and activation of Trk and Erk pathways that activate a cAMP Response Element Binding Protein (CREB) that initiates the transcription of pro- or anti-apoptotic genes [53,54]. These findings indicate that retinal GH is a neuroprotective factor during

developmental waves of apoptosis and that it utilizes intracellular pathways common to other neurotrophins (e.g. brain-derived growth factor, transforming growth factor beta-I and IGF-I) [54,55]. Moreover, as the simultaneous immunoneutralization of GH and IGF-I does not increase the level of apoptosis in RGC cultures above that achieved by immunoneutralization of GH alone, we concluded that the neuroprotective actions of GH in the developing retina are likely mediated in large part through the actions of IGF-I [53]. Autocrine or paracrine neuroprotective actions of GH in RGCs were also demonstrated by using a GH siRNA to silence the local synthesis of GH in a Quail-derived neural retina cell line (QNR/D). Knockdown of GH in these cells resulted in an increase in the appearance of apoptotic cells [56]. Similarly, the microinjection of a GH siRNA into the eye cup of developing chick embryos lowers IGF-I mRNA in the developing retina and increased the numbers of apoptotic cells on the developing eye [57]. Likewise, it was demonstrated that both GH and GHR are expressed in the green iguana retina, and are able to exert, either directly or mediated by IGF-1, a protective mechanism in neuroretina against damage caused by the administration of kainic acid [58].

In addition to being neuroprotective during developmental waves of apoptosis in the chick, retinal GH was also found to be neuroprotective against excitotoxic-induced cell death in RGCs. This was shown by the ability of GH overexpression in transfected RGCs to reduce the number of TUNEL-labeled cells as to reduce their release of lactate dehydrogenase [43]. This neuroprotective autocrine/paracrine action was mediated by increased STAT5 phosphorylation and increase bcl2 production and increased IGF-I expression. This neuroprotective action of retinal GH is likely to be of physiological significance as blocking the release of GH from QNR/D RGCs by GH immunoneutralization or by blocking the action of GH Releasing Hormone (GHRH) by GHRH immunoneutralization increased cell death [59]. This action is also likely to be of pathophysiological significance [60] as it was found that the presence of GH in RGCs correlated with RGC cell survival whereas an absence of GH in RGCs correlated with cell death [61]. Indeed, in a study that looked at the neural retinas of human cadavers that had eye disease, 39% of the RGCs were GH positive and 100% of these were TUNEL negative, whereas 465 of the RGCs that were TUNEL positive, 100% of these were GH negative.

This antiapoptotic action of local GH in the nervous system has also been demonstrated in the chicken cerebellum, in which GH immunoneutralization increased cell death [62]. In this study, it was also shown that this neuroprotective action was likely to be due to the 15-kDa variant of GH, that is the most abundant GH moiety expressed in extrapituitary tissues of chicks [48], including the cerebellum [63].

In addition to cell survival, another local role for GH within neural tissues was the promotion of axon growth and neurite sprouting [64,65]. The blockade of this action after the siRNA knockdown of retinal GH expression [65] suggests this is of physiological significance. Endogenous GH was found inside the cytoplasm of RGC neurite outgrowths and likely involved in the GH-induced increase in STAT5 phosphorylation and increased activity of Growth Associated Protein 43 (GAP43) and SNAP-25 immunoreactivity that accompanies synaptogenesis [66].

In the periphery, the expression of GH in the lung [37,38] has been shown to correlate with the expression of specific proteins during development [67]. Indeed, the functional significance of this role in alveolarization was shown by changes in the rat lung proteome after the knockout of lung GH mRNA by an aerosolized antisense Oligodeoxynucleotide (ODN) directed against the GH gene [40] and after the overexpression of lung GH after it adenoviral overexpression [39].

In the periphery, the expression of GH in male and female reproductive tracts has also been thought to reflect numerous autocrine or paracrine roles [68], such as the modulation of steroidogenesis [44] by stimulating the expression of cytochrome P450c mRNA, a rate-limiting enzyme during progesterone (P4) synthesis, and also inducing ovarian cell proliferation through the increase of IGF-1 and the phosphorylation of Erk 1/2 [31], which may be of functional significance in health or disease [60]. Autocrine GH, for instance, is thought to be causally involved in a number of disease states including prostate and mammary cancer [69], especially as autocrine GH is thought to be more oncogenic than pituitary GH [70].

As the extrapituitary production of GH in chick embryos occur in early embryogenesis, most embryonic growth (reflecting the completion of 40 of the 46 Hamburger and Hamilton stages of development, [71] therefore occurs in the absence of pituitary somatotrophs and circulating GH [13-49]. Early embryonic growth therefore reflects extrapituitary GH actions on growth and differentiation [72,73], as indicated by the specific expression of GHRG-1 in early chick embryos [74]. Early fetal growth similarly reflects the early ontogeny of extrapituitary GH production, which occurs prior to the ontogeny of pituitary GH [75,76].

## Summary

GH gene expression occurs widely in extrapituitary tissue pre- and post-natally and its expression has been shown to be of physiological or pathophysiological significance. GH is therefore not just a pituitary endocrine but also a local autocrine or paracrine growth factor.

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