General and Comparative Endocrinology 220 (2015) 103–111

Contents lists available at ScienceDirect

General and Comparative Endocrinology

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

Autocrine/paracrine roles of extrapituitary growth hormone and prolactin in health and disease: An overview

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ARTICLE INFO

Article history:
Available online 15 November 2014

Keywords:
Growth hormone
Prolactin
Pituitary
Autocrine
Paracrine

ABSTRACT

Growth hormone (GH) and prolactin (PRL) are both endocrines that are synthesized and released from the pituitary gland into systemic circulation. Both are therefore hormones and both have numerous physiological roles mediated through a myriad of target sites and both have pathophysiological consequences when present in excess or deficiency. GH or PRL gene expression is not, however, confined to the anterior pituitary gland and it occurs widely in many of their central and peripheral sites of action. This may reflect "leaky gene" phenomena and the fact that all cells have the potential to express every gene that is present in their genome. However, the presence of GH or PRL receptors in these extrapituitary sites of GH and PRL production suggests that they are autocrine or paracrine sites of GH and PRL action. These local actions often occur prior to the ontogeny of pituitary somatotrophs and lactotrophs and they may complement or differ from the roles of their pituitary counterparts. Many of these local actions are also of physiological significance, since they are impaired by a blockade of local GH or PRL production or by an antagonism of local GH or PRL action. These local actions may also be of pathophysiological significance, since autocrine or paracrine actions of GH and PRL are thought to be causally involved in a number of disease states, particularly in cancer. Autocrine GH for instance, is thought to be more oncogenic than pituitary GH and selective targeting of the autocrine moiety may provide a therapeutic approach to prevent tumor progression. In summary, GH and PRL are not just endocrine hormones, as they have autocrine and/or paracrine roles in health and disease.

1. Introduction

Growth hormone (GH) and prolactin are both endocrines produced by the anterior pituitary gland and both have numerous physiological roles, in target sites that are almost ubiquitous. GH and prolactin are also produced within many of these target sites, in which they have autocrine or paracrine actions locally (Ben-Jonathan et al., 1996; Harvey, 2010; Harvey et al., 2012). These local roles are of both physiological and pathophysiological significance, as demonstrated by blocking their extrapituitary production or local action. The functional roles of extrapituitary GH and prolactin in health and disease is an emerging concept and the focus of this brief review.

2. Extrapituitary pituitary hormones

While most hormones are expressed in specific endocrine glands, all cells have the potential to express every gene present in their genome. This may thus account for the ectopic expression of some hormones in "aberrant" locations, including the extrapituitary production of anterior pituitary hormones.

The anterior pituitary gland is the main source of GH, prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyrotropin (TSH) and adrenocorticotropin (ACTH) found in peripheral circulation, since the concentrations of these hormones decline or are abolished following hypophysectomy (Harvey et al., 2012). The anterior pituitary is not, however, the only site in which the genes for these hormones are expressed. Indeed, the extrapituitary production of all of these hormones has been demonstrated in neural, immune, reproductive and alimentary tissues (Harvey et al., 2012). In most cases the contribution of the extrapituitary sources to the hormone concentrations in plasma is low, although their hypersecretion can mimic pituitary pathologies, such as acromegaly, hyperprolactinemia, hyperthyroidism, hypergonadism and Cushing's syndrome (Harvey et al., 2012).

Some of the actions of these extrapituitary pituitary hormones therefore complement the endocrine actions of their pituitary counterparts, although other local autocrine or paracrine roles, are likely to be related to tissue growth or differentiation

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http://dx.doi.org/10.1016/j.ygcen.2014.11.004
0016-6480/

(Sanders et al., 2008). These local roles may be of particular importance in early embryonic or fetal development, before the acquisition of their classical endocrine roles, since extrapituitary hormones are produced in early development prior to the ontogeny of the pituitary gland (Sanders and Harvey, 2004; Harvey et al., 2012). Extrapituitary production of pituitary hormones may also be a cause or consequence of abnormal (tumorous) development and has often been associated with tumor progression. The widespread extrapituitary production of pituitary hormones may thus have physiological or pathophysiological relevance.

3. Extrapituitary growth hormone: distribution

The widespread distribution of GH in extrapituitrary tissues was comprehensively reviewed four years ago (Harvey, 2010). Its presence was determined in neural tissues (in the brain and neural retina), in immune tissues (primary and secondary), in reproductive tissues (ovarian, uterine, mammary, placental, testicular and prostate), in gastrointestinal tissues (hepatic, pancreatic, salivary, alimentary tract), in skeletal and dental tissues, in integumentary tissue (skin), in muscular tissue, in cardiovascular tissue, and in respiratory tissue (lungs and gills). It is also abundant and widespread in embryonic tissues, in which it is expressed before its ontogenic appearance in pituitary somatotrophs (Harvey and Baudet, 2014). "Aberrant" GH expression is also a characteristic of many tissues undergoing neoplastic transformation, particularly the induction of breast and prostate cancer.

4. Extrapituitary growth hormone: functional relevance

The functional relevance of extrapituitary GH in autocrine or paracrine regulation has been demonstrated in studies in which endogenous GH production is blocked by siRNA's (e.g. Baudet et al., 2009, reducing neurite outgrowths and Sanders et al., 2010, increasing cell death). GH antisense oligonucleotides may similarly block endogenous GH production, which has been correlated with reduced neovascularization (Wilkinson-Berka et al., 2007), reduced cell proliferation (Weigent et al., 1991) and alterations in the tissue proteome (Beyea et al., 2005; 2009). Blocking endogenous GH action by immunoneutralization has also been correlated with increased cell death (Sanders et al., 2005, 2006), with reduced cell proliferation (Sabharwal and Varma, 1996; Markham and Kaye, 2003) and with abnormal cellular differentiation (Nguyen et al., 1996; Turnley et al., 2002). It has also been shown to reduce the expression of IGF-1 (insulin-like growth factor-1), a marker of GH action (Baxter et al., 1991). Blocking endogenous GH action using a GH receptor (GHR) antagonist has similarly been associated with increased cell death (Jeay et al., 2000) and with a reduced ability to stimulate cytokine production in immune cells (Malarkey et al., 2002). Blocking the endogenous secretion of GH, using somatostatin (SRIF), a GH release-inhibitory hormone, also results in an impairment of cellular (neural) differentiation (Turnley et al., 2002).

Functional autocrine/paracrine actions of endogenous GH have also been demonstrated by the induced expression of the GH gene in extrapituitary tissues. For instance, the expression of bovine GH in the CNS of mice has been shown to induce hyperphagia-induced obesity and appropriately, to increase the hypothalamic expression of neuropeptide Y and agouti-related proteins (Bohlooly et al., 2005). Similarly, the expression of human (h) GH in the cerebral cortex of mice is correlated with the induction of dwarfism, as a result of increased hypothalamic SRIF transcription and reduced GH-releasing hormone (GHRH) expression (Hollingshead et al., 1989). hGH expression in the GHRH neurons of the rat hypothalamus similarly increases SRIF transcription and reduces GHRH (Pellegrini et al., 1997) and similarly induces dwarfism (Flavell et al., 1996). Dwarfism is also induced in rats after hGH is expressed in the vasopressin neurons of their hypothalami (Wells et al., 2003).

Functional autocrine/paracrine actions of endogenous extrapituitary GH have also been demonstrated during early development (Harvey and Baudet, 2014). Before the ontogeny of the pituitary gland, endogenous GH increased the formation of balstocysts in two-cell-stage mouse embryos, since this action was blocked by specific GHR antibodies (Fukaya et al., 1998). The addition of exogenous GH to two-cell mouse preimplantation embryos was similarly shown to increase the number of cells in the trophectoderm (Markham and Kaye, 2003). The functional importance of extrapituitary GH for embryonic growth was also demonstrated by the loss of sprouting neurites and the reduction in neurite size when endogenous GH in chick embryonic retinal ganglion cells (RGC's) was reduced by siRNA knockdown (Baudet et al., 2009), which also reduced RGC cell survival during development (Baudet et al., 2009; Sanders et al., 2010, 2011). The immunoneutralization of endogenous GH in chick embryo RGC's similarly resulted in cell death (Sanders et al., 2005, 2006, 2008, 2009a,b), as also induced by GH antibodies in cerebellar neurons of chicken embryos (Alba-Betancourt et al., 2013). The importance of extrapituitary GH signaling in the chicken embryo is also demonstrated by the abundance and widespread expression of a specific GH-response gene (GHRG), GHRG-1, in central and peripheral tissues of 8-day old embryos (Harvey et al., 2001). GHRG-1 is a marker of GH action in chickens and its presence prior to somatotroph ontogeny (at approximately embryonic day 15; Harvey and Baudet, 2014) is a functional reflection of extrapituitary GH expression in the early chick embryo. Extrapituitary GH is also functional in the development of the mammalian fetus, as shown by the finding that the immunoneutralization of endogenous GH impaired the differentiation of the Wolffian duct in fetal rats, by a mechanism that was overcome by exogenous GH (Nguyen et al., 1996).

5. Extrapituitary growth hormone: pathophysiological roles

GH has numerous roles as a cytokine and is produced by many immune tissues and immune cells (Chappel, 1999; Waters et al., 1999; Jeay et al., 2002). Not surprisingly, it has therefore been implicated in the etiology of autoimmune pathologies (Jeay et al., 2002), including arthritis. Local GH production is thought to contribute to both osteoarthritis and rheumatoid arthritis, since synovial fluid GH levels are higher than blood GH levels in both disease states (Denko and Malemud, 2005) and GH immunoreactivity is present in articular cartilage (Costa et al., 1993). This possibility is supported by the finding that the overexpression of bovine GH in transgenic mice results in lesions of the articular cartilage that are consistent with that described in osteoarthritis (Fernandez-Criado et al., 2004). Moreover, the efficacy of exogenous SRIF in reducing joint pain and synovial thickness (Silveri et al., 1994, 1997; Coatri et al., 1995) might reflect its inhibition of local GH production.

Extrapituitary GH expression has also been correlated in tumor development, in which autocrine GH has been implicated in neoplastic transformation (Perry et al., 2006). Autocrine GH is thought to enhance cell proliferation, protect against apoptosis and to promote aberrant morphogenesis. In breast cancer, this is in marked contrast to exogenous GH, which does not induce tumor formation, nor protect cancerous cells against the apoptosis that results from serum withdrawal (Kaulsay et al., 2000, 2001). This selective effect of endogenous GH may reflect the greater augmentation of STAT5-mediated gene transcription induced by autocrine GH compared with exogenous GH (Kaulsay et al., 1999). Autocrine