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Extrapituitary growth hormone and growth?

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ABSTRACT

While growth hormone (GH) is obligatory for postnatal growth, it is not required for a number of growth-without-GH syndromes, such as early embryonic or fetal growth. Instead, these syndromes are thought to be dependent upon local growth factors, rather than pituitary GH. The GH gene is, however, also expressed in many extrapituitary tissues, particularly during early development and extrapituitary GH may be one of the local growth factors responsible for embryonic or fetal growth. Moreover, as the expression of the GH receptor (GHR) gene mirrors that of GH in extrapituitary tissues the actions of GH in early development are likely to be mediated by local autocrine or paracrine mechanisms, especially as extrapituitary GH expression occurs prior to the ontogeny of pituitary somatotrophs or the appearance of GH in the circulation. The extrapituitary expression of pituitary somatotrophs or the appearance of GH in the circulation. The extrapituitary expression of GH in embryos has also been shown to be of functional relevance in a number of species, since the immunoneutralization of endogenous GH or the blockade of GH production is accompanied by growth impairment or cellular apoptosis. The extrapituitary expression of the GH gene also persists in some central and peripheral tissues postnatally, which may reflect its continued functional importance and physiological or pathophysiological significance. The expression and functional relevance of extrapituitary GH, particularly during embryonic growth, is the focus of this brief review.

1. Introduction

Pituitary growth hormone (GH), as its name suggests, is synonymous with postnatal growth. Indeed, it is well established that a pituitary GH deficiency or a defect in tissue GH receptor (GHR) signaling results in dwarfism, whereas an excess of pituitary GH secretion results in gigantism in juveniles or acromegaly in adults. Despite this recognized role, it is generally believed that embryonic or early fetal growth is independent of pituitary GH (Waters and Kaye, 2002). This possibility is supported by the finding that decapitation of the pig fetus at 45 d of gestation does not alter body weight when compared to controls at 110 d of gestation (Kraeling et al., 1978; McCusker and Campion, 1990). Similarly, the hypophysectomy of fetal lambs does not reduce their body weight or body length at term (Parkes and Hill, 1985; Enemar, 2003). Hypophysectomy also does not reduce the weights of the brain, liver or kidney in fetal lambs, suggesting that the growth of these organs is not dependent upon pituitary GH or other pituitary hormones (Deayton et al., 1993). Embryonic or early fetal growth are thus thought to reflect growth-without-GH syndromes that are dependent upon other local growth factors instead of pituitary GH (Geffner, 1996; Phillip et al., 2002). The extrapituitary expression of the GH gene is, however, likely to be one of these local growth factors in early development, before the onset of pituitary GH secretion. The extrapituitary expression of the GH gene also persists in some peripheral tissues postnatally, which may reflect its continued functional importance and physiological or pathophysiological significance. The expression and functional relevance of extrapituitary GH, particularly during embryonic growth, is the focus of their brief review.

2. Pituitary GH gene expression

The GH gene was thought to be specifically expressed in pituitary somatotrophs in response to the pituitary specific expression of its Pit-1 transcription factor. Indeed, "no other site of GH synthesis" was thought to exist (Karin et al., 1990). It is, however, now known that GH gene expression is not confined to pituitary somatotrophs and indeed it occurs widely in many extrapituitary tissues (Harvey, 2010). This widespread expression party reflects the distribution of Pit-1 which is not confined to the pituitary gland, as once thought (Harvey et al., 2000a). Moreover, while

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Pit-1 was thought to be obligatory for GH expression, it is now known that GH expression is Pit-1 independent in many sites (Harvey et al., 2000a) and GH expression even occurs outside the pituitary gland, in Ames mice that are genetically Pit-1 deficient (Sun et al., 2005a,b).

Somatotrophs are, nevertheless the principle site of GH gene expression and the main source of the GH found in systemic circulation, since circulating GH concentrations are barely detectable following hypophysectomy or pituitary ablation. Pituitary GH is thus largely responsible for the endocrine actions of GH during perinatal and postnatal growth. The GH concentration in the pituitary gland is thus far higher than that in any extrapituitary location, but as the pituitary gland is much smaller than many extrapituitary tissues, the total amount of GH produced outside the pituitary gland is likely to be greater than that produced within it (Hull et al., 2005). In most cases the extrapituitary GH produced is thought to act in local autocrine or paracrine regulation, rather than to contribute to the pool of GH in peripheral circulation, although mammary GH increases circulating GH concentrations in dogs to levels that can induce acromegaly (Eigenmann, 1984; Mol et al., 1999).

3. Pituitary GH expression: ontogeny

Somatotrophs are present in all vertebrates prenatally, but species differ in the embryonic or fetal age at which they appear. For instance, somatotrophs are present in the human pituitary by the end of the first trimester of gestation (Baker and Jaffe, 1975; Bugnon et al., 1976) (by 0.33 gestation), whereas they are not present in the pituitary glands of rats (Setalo and Nakane, 1976; Khorram et al., 1983; 0.78 gestation), and mice (Gross and Longer, 1979; Wilson and Wyatt, 1993; 0.84 gestation) until the last trimester. Their ontogenic appearance in cows is at 0.29 of gestation (Dubois, 1971), in sheep at 0.34 gestation (Stokes and Boda, 1968), in pigs at 0.41 gestation (Danchin and Dubois, 1982; Dacheux, 1984) and in chickens at 0.57 of incubation (Porter et al., 1995). Fetal or embryonic growth prior to the appearance of pituitary somatotrophs therefore occurs in the absence of pituitary GH and its secretion into systemic circulation (Harvey et al., 1998, 2000b). Organogenesis therefore occurs long before the ontogenic differentiation of Rathke's pouch into the pituitary gland (Murphy and Harvey, 2001). Indeed, in chick embryos, 38 of the 46 identified Hamilton and Hamburger stages of morphogenesis (Hamburger and Hamilton, 1951; Davis and Garrison, 1968) occur before embryonic day 12 (ED12), the day on which somatotrophs are thought to be functionally present in the pituitary gland (Porter et al., 1995, 2001). Circulating GH is, however, not present in the plasma of chick embryos until ED17 (Harvey et al., 1979), or not until Hamburger and Hamilton stage 43, when embryogenesis is almost complete.

4. Extrapituitary GH expression

Whereas pituitary GH expression does not occur in early embryonic or fetal development, extrapituitary GH is expressed much earlier and prior to organogenesis. GH mRNA is, for instance, found in rainbow trout zygotes within days of fertilization (Yang et al., 1999), with the commencement of embryonic genome transcription activity (EGTA) (Li et al., 2006, 2007). Similarly, the expression of GH mRNA can be detected in the larvae of the orange-spotted grouper within 1 day of hatching (Li et al., 2005). GH mRNA and GH-immunoreactive proteins also found in zebrafish embryos within 12 h of fertilization and in sea bass embryos within 76 h (Besseau et al., 2013). GH mRNA and GH-immunoreactivity are similarly found in chick embryos within 2 days of the onset of incubation, before the appearance of discernible organ structures (Harvey, 2013).

In the chick embryo, the expression of the GH gene appears to be almost ubiquitous and in every cell at ED4 (Harvey, 2013). GH-immunoreactivity is similarly widespread in early ED4 chick embryos, although by ED8 it is less abundant and more specific, being absent from some tissues and not present in every cell in those tissues that are GH-immunoreactive (Harvey et al., 2000b, 2001a). The presence of GH immunoreactivity in the ED5 chick is shown in (Fig. 1). GH appears to be abundantly and predominantly present in various nerve tracks of the spinal cord (Fig. 1A and C), including projecting axons innervating the limbs (Fig. 1A and D) and vertebral inclusions (Fig. 1A and E) in the spinal cord (Fig. 1A and C). GH was also detected in dorsal root ganglion (DRG) (Fig. 1A and B) and in bone in vertebral inclusions (Fig. 1A and E) and in the bone collar (Fig. 1C). The presence and presumptive role of GH in bone might be transient as GH immunoreactivity is no longer present there by ED7 (Murphy and Harvey, 2001) while it is detected in intercostal rib muscles at this later stage. Interestingly, GHR distribution mirrored that of GH, as it was detected in identical spinal tracts (Fig. 2), but also in DRG and bone. This suggests that GH and GHR might have an autocrine/paracrine role in these structures. Of interest, GH and GHR have been detected in projection neurons of the CNS, in particular in the visual system (Baudet et al., 2003, 2007; Harvey et al., 2007) where GH has been demonstrated to promote axon outgrowth and cell survival (Baudet et al., 2007; Harvey et al., 2006). It is thus possible that GH has broad autocrine/paracrine roles in projection neurons of the CNS.

5. Extrapituitary GH and embryonic growth

Studies on the presence of extrapituitary GH have demonstrated its colocalization with GHR mRNA and/or GHR immunoreactivity in early embryos, within days of fertilization (e.g. in rainbow trout embryos, Li et al., 2007; in chick embryos, Harvey et al., 2000b; in mouse preimplantation embryos, Pantaleon et al., 1997). Similarly, GHR immunoreactivity in the ED chick embryo (Fig. 2) is clearly found in the same tissues that express GH immunoreactivity (Fig. 1). These findings suggest autocrine or paracrine actions of extrapituitary GH during early embryonic development. Indeed, the functional relevance of the GHRs in preimplantation mouse embryos was first shown by Pantaleon et al. (1997), by the demonstration that exogenous GH induced bell-shaped dose response curves for 3-0-methyl glucose transport and for protein synthesis in these embryos. Exogenous GH was similarly found to regulate carbohydrate, lipid and energy metabolism in preimplantation bovine embryos, and to improve their ultrastructural features (Kolle et al., 2004).

The possibility that these actions are receptor-mediated is supported by the fact that exogenous GH is able to increase the formation of both blastocysts and hatched blastocysts when incubated with two-cell-stage mouse embryos, especially as this action is blocked in the presence of 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). These authors further showed that the proliferation of these cells in the mouse blastocyst is also suppressed by GHR antibodies. Interestingly, the immunoneutralization of endogenous GH did not affect the inner cell mass of these blastocysts, whereas the antibodies raised against insulin-like growth factor (IGF-)-1 did not affect the number of trophectoderm cells but did reduce the number of cells in the inner cell mass. The actions of GH are therefore not

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