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Review

Expression and function of growth hormone in the nervous system: A brief review

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ABSTRACT

There is increasing evidence that growth hormone (GH) expression is not confined exclusively to the pituitary somatotrophs as it is synthesized in many extrapituitary locations. The nervous system is one of those extrapituitary sites. In this brief review we summarize data that substantiate the expression, distribution and characterization of neural GH and detail its roles in neural function, including cellular growth, proliferation, differentiation, neuroprotection and survival, as well as its functional roles in behavior, cognition and neurotransmission. Although systemic GH may exert some of these effects, it is increasingly evident that locally expressed neural GH, acting through intracrine, autocrine or paracrine mechanisms, may also be causally involved as a neurotrophic factor.

1. Introduction

Many functions of the central nervous system (CNS), including sleep, cognitive function, mood, and neuroprotection are regulated by the somatotrophic axis (by growth hormone releasing hormone (GHRH), growth hormone (GH), and insulin-like growth factor 1, IGF-1) (Schneider et al., 2003). Indeed, the central and peripheral nervous systems are endocrine target sites for circulating GH, secreted from pituitary somatotrophs (Harvey and Hull, 2003). The GH receptor (GHR) and GH binding protein (GHBP) are therefore present in the CNS and both are regulated differently than their liver counterparts (Lobie et al., 2000). Neural tissues are not, however, just sites of GH action, but also extrapituitary sites of GH gene expression, suggesting that the neural GHR's may additionally respond in autocrine or paracrine regulation ways to GH produced locally. It is now well known that GH is widely synthesized in the CNS and its regulation also differs from that in the pituitary. Within the CNS, IGF-1 is also induced, as in the periphery by GH (Lobie et al., 2000). GH and IGF-1 are both critical for neural development and both regulate the size, morphology and function of CNS cells (Lobie et al., 2000). It thus is of interest to discern if there is a specific involvement of locally produced (intracrine/autocrine/paracrine) GH in comparison to pituitary-derived (endocrine) GH in the physiological and/or pathological functions of the nervous system. The expression and functional roles of GH in neural tissues of vertebrates, particularly in the chicken during development, is the focus of this brief review.

2. Neural GH expression

The presence of GH and GH mRNA in neural tissues is now well established (Harvey and Hull, 2003; Harvey, 2010) in vertebrates.

In fish, GH mRNA expression was detected in the head of the rainbow trout (*Oncorhynchus mykiss*) during embryonic development, and in high levels in the adult brain (Yang et al., 1999). In giant groupers the expression of both GH and IGF-I mRNAs was most abundant in the pituitary and liver, but low levels were also detected in the brain, spleen and ovary (Dong et al., 2010). Likewise, in the hermaphroditic fish *Kryptolebias marmoratus*, GH mRNA expression constantly increased in the brain until stage 5 of development (5 h post-hatch) (Rhee et al., 2012). In birds, strong GH-immunoreactivity was found by SDS/Western blot in the hypothalamus and several extrahypothalamic regions in the chicken brain (Render et al., 1995). In the embryonic chick brain GH expression has also been observed in several regions, such as the hippocampus, the hypothalamus and the pallium, as shown in Fig. 1. In adult avian brains, GH immunoreactivity has similarly been reported to be present in several hypothalamic nuclei and the median eminence of chickens, turkeys and ducks (Ramesh et al., 2000). This likely reflects the expression of the GH gene, since GH mRNA has been isolated and sequenced from the chicken

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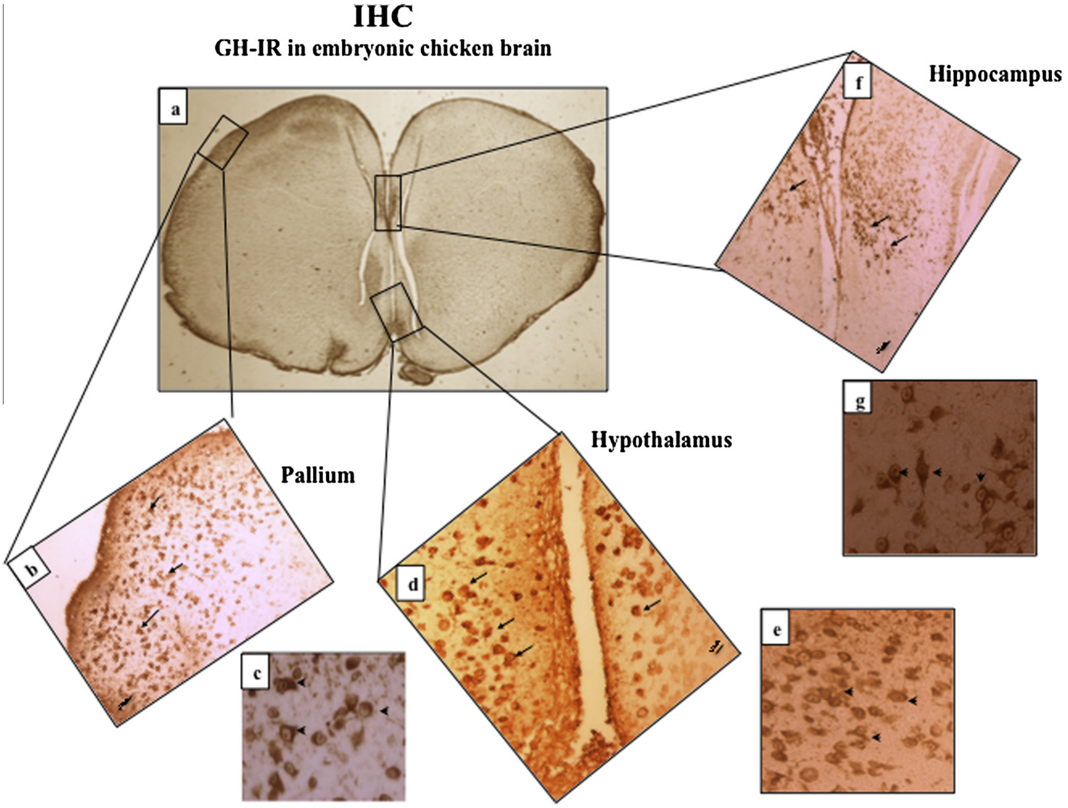

Fig. 1. Distribution of GH-immunoreactivity (GH-IR) in the embryonic chicken brain. (a) Panoramic view of a coronal section of chicken embryonic (embryonic day (ED) 18) brain showing GH-IR in the pallium, hypothalamus, and hippocampus (magnification 4×). (b) GH-IR in the pallium was mainly observed in the neuron cells (arrows, magnification 10×), particularly in (c) the soma of the cells (arrowheads, magnification 40×). (d) GH-IR in the hypothalamus was near to the third ventricle and the median eminence (arrows, magnification 20×), and expressed mainly in (e) the soma of the cells (arrowheads, magnification 40×). (f) GH-IR was also present in some hippocampal cells (arrows, magnification 10×), and was found in (g) cell bodies as well as in some dendritic processes (arrowheads, magnification 40×). (Modified from Alba-Betancourt et al. (2011).)

hypothalamus (Render et al., 1995). In early chick embryos, GH immunoreactivity has been seen in the gray matter of the cerebellum, coincident with the appearance of GH in the caudal lobe of the pituitary gland (Harvey et al., 2001). More recently, it was found that the GH gene expressed in the cerebellum is identical to pituitary GH and that the GH-immunoreactivity is mainly present in Purkinje cells and in the cells of the granular layer (Alba-Betancourt et al., 2011) (Fig. 2). The GH moieties in the cerebellum include several size variants (15, 23, 26, 29, 35, 45, 50, 55 and 80 kDa), of which the 15-kDa isoform predominates (>30% among all developmental stages). The cerebellar GH concentration is also age-related and higher in adults than in embryos (Alba-Betancourt et al., 2011). In mammals, GH mRNA expression in the rat brain was significantly increased after oral administration of ginseng extracts (Yoshizato et al., 1999). In recent studies, cell bodies exhibiting GH immunoreactivity were found to be widely distributed in many brain regions of mice, particularly in the hypothalamus, in which retrograde labeling suggested that some project to the median eminence (Addison and Rissman, 2012). The expression of GH in the mouse brain is, however, sexually dimorphic, since ovary-intact mice have elevated GH mRNA in the arcuate nucleus and medial preoptic area (MPoA) compared with gonad-intact males. In males, castration increased GH mRNA in the MPoA, whereas ovariectomy in females decreased GH mRNA in both regions. Estradiol treatment increased GH expression in gonadectomized females, but had no effect in castrated males. This action of estrogen was receptor-mediated, and not observed in the presence of tamoxifen (Addison and Rissman, 2012). In the rat hypothalamus, GH gene expression is augmented by GH-releasing hormone (GHRH) and suppressed by stress, under conditions that have minimal effects on pituitary GH mRNA (Yoshizato et al., 1998). In addition to the hypothalamus, GH expression has been demonstrated in hippocampal tissues (Tang et al., 2011), in which GH expression is Pit-I independent, as it occurs in Ames (Prop-1 deficient) mice that do not express the pituitary GH gene. Although Pit-1 independent (Sun et al., 2005), hippocampal GH expression is, however, dependent upon CREB-I induced c-Jun translation (Zearfoss et al., 2008). As in the hypothalamus, GH expression in the hippocampus is also sexually dimorphic and higher in females than males and increased by estrogen in ovariectomized mice and in primary neural cultures (Donahue et al., 2006b). Hippocampal GH expression in rats is increased by neurological insults, like hypoxia, that cause cognitive deficits (Li et al., 2011b). In addition to the hippocampus, GH gene expression also occurs in the amygdala and the temporal lobe, in which it is greatly increased (88-fold) during epileptogenesis, in the absence of any change in pituitary GH expression (Kato et al., 2009).

3. Neural GH actions

3.1. Neuroprotection

Several studies have shown that growth hormone may be related to important actions in the central nervous system (CNS) (Nyberg, 2000). It has been reported that GH treatment affects neurogenesis, myelin synthesis and dendritic branching, and is also able to activate a subpopulation of neural stem cells, which induce