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Domestic Animal Endocrinology 29 (2005) 111–144
DOMESTIC ANIMAL ENDOCRINOLOGY
www.journals.elsevierhealth.com/periodicals/dae

Physiology of ghrelin and related peptides

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Abstract

Growth hormone (GH) released from pituitary under direct control of hypothalamic releasing (i.e., GHRH) and inhibiting (i.e., sst or SRIF) hormones is an anabolic hormone that regulates metabolism of proteins, fats, sugars and minerals in mammals. Cyril Bowers' discovery of GH-releasing peptide (GHRP-6) was followed by a search for synthetic peptide and nonpeptide GH-secretagogues (GHSs) that stimulate GH release, as well as a receptor(s) unique from GHRH receptor. GHRH and GHSs operate through distinct G protein-coupled receptors to release GH. Signal transduction pathways activated by GHS increase intracellular Ca^{2+} concentration in somatotrophs, whereas GHRH increases cAMP. Isolation and characterization of ghrelin, the natural ligand for GHS receptor, has opened a new era of understanding to physiology of anabolism, feeding behavior, and nutritional homeostasis for GH secretion and gastrointestinal motility through gut–brain interactions. Other peptide hormones (i.e., motilin, TRH, PACAP, GnRH, leptin, FMRF amide, galanin, NPY, NPW) from gut, brain and other tissues also play a role in modulating GH secretion in livestock and lower vertebrate species. Physiological processes, such as neurotransmission, and secretion of hormones or enzymes, require fusion of secretory vesicles at the cell plasma membrane and expulsion of vesicular contents. This process for GH release from porcine somatotrophs was revealed by atomic force microscopy (AFM), transmission electron microscopy (TEM) and immunohistochemical distribution of the cells in pituitary during stages of development.

Keywords: Ghrelin; Growth hormone secretagogues; Growth hormone regulation

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doi:10.1016/j.domaniend.2005.02.033

1. Introduction

Growth hormone (GH) produced by somatotrophs of the adenohypophysis is the anabolic hormone crucial for long bone growth, muscle accretion, energy homeostasis and the metabolism of proteins, sugars, fats, and minerals in mammals. A series of stimulatory and inhibitory releasing hormones of hypothalamic and peripheral origins controls the pulsatile release of GH from somatotrophs. Until recently, the consensus was that two antagonistic hypothalamic peptides: a stimulatory GH-releasing hormone (GHRH) and an inhibitory somatostatin-14 (sst or SRIF) controlled the pulsatile pattern of GH secretion [1,2]. GH participates in its own rhythmic secretion through feedback action on GHRH and SRIF neurons [3]. GHRH and SRIF receptors belong to the family of seven transmembrane receptors coupled to a heterotrimeric GTP-binding protein. SRIF receptor and subtypes are coupled to a G_i protein and its activation inhibits adenylate cyclase. The GHRH receptor is coupled to a G_s protein and its activation stimulates adenylate cylase activity that results in increased intracellular cyclic AMP and protein kinase A levels. GHRH, a 1–44 amino-acid peptide, and its analogs (i.e., human pancreatic GRF [hp GRF(1, 40)OH; Nle^{27} rGRF(1, 29)NH_2; rhGRF(1–32)OH] are potent releasers of GH in vivo in cattle [4,5] and pigs [6].

1.1. Peptidyl and non-peptidyl GH-secretagogues

In 1976, C.Y. Bowers et al., working with Met enkephalin, discovered a series of small peptides called GH-releasing peptides (GHRP) with potent GH-releasing activity in cultured pituitary cells [7–11]. Thus, the first GHRP was synthesized before the isolation of GHRH in1982 by Guillemin et al. [12] and Rivier et al. [13]. GHRPs were initially based on an opioid structure, but they lack opioid activity. A great number of peptidyl and non-peptidyl GH-secretagogues (GHS) have been developed that effectively release GH when administered intravenously, subcutaneously, intranasally and orally [11,14]. Non-peptidyl classes of benzolactam and spiroindolamine GHS (i.e., L-692,429, L-692,585, L-163,255, MK-677) with some improved oral bioavailability and pharmacokinetic properties were developed [1,15–17].

1.2. GHS receptor and ghrelin

Earlier biological studies revealed a complementary and synergistic action by co-administration of GHS and GHRH on GH release in rat, pig, cattle and monkey [6,17]. Although GHS and GHRH were considered to act on different receptors, Howard et al. in 1996 isolated a receptor in pituitary and hypothalamus that was unique for GHS action on GH release [18]. The seven transmembrane GHS receptor (GHSR) showed a high degree of homology in human, pig, dog, rat and mouse ranging from 93 to 99% identity [14,18–21]. Thus, GHSR was a classic orphan receptor until 1999 when Kojima et al. reported the natural ligand isolated from stomach and they designated the GH-releasing peptide ‘ghrelin’ [22]. With this chronology, discussion of the physiology of GHS-related peptides will be followed by the physiology of ghrelin focused primarily on livestock species.