REVIEW OF NEUROPEPTIDE G PROTEIN-COUPLED RECEPTORS IN NEUROENDOCRINOLOGY

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Introduction. A neuropeptide is a protein substance produced and released by neurons that acts on neuronal targets. Humans possess a wide variety of neuropeptides that influence a broad range of physiological and behavioral activities. The primary functions of neuropeptides include the regulation of appetite, growth, water balance, and lipid and glucose metabolism. Most neuropeptides exert their effects through G protein-coupled receptors (GPCRs), which constitute the largest family of cell membrane receptors. Neuropeptides and their GPCRs are associated with a number of pathological conditions, including obesity, infertility, growth retardation, pain, narcolepsy, diabetes insipidus, gastrointestinal diseases, and mood disorders. Elucidating the role of neuropeptide GPCRs in the rapidly evolving field of neuroendocrinology is an urgent task in modern medicine.

Aim. Elucidating the role of neuropeptide G protein-coupled receptors in neuroendocrinology.

Materials and methods. PubMed, Scopus, and the Cochrane Library databases were searched to identify all reports related to neuropeptide GPCRs in neuroendocrinology. The following search terms were included: "neuropeptide", "GPCR", "ghrelin", "vasoactive intestinal peptide", "pituitary adenylate cyclase-activating polypeptide", "gonadotropin-inhibitory hormone", "apelin", "prokineticin", "bombesin", "hypothalamo-pituitary-thyroid axis". Key outcomes reported in individual studies included the pathogenetic role of neuropeptides in the development of neuroendocrine disease.

Results. Kojima M. et al. (1999) first reported ghrelin, a 28-amino-acid acylated peptide initially isolated from the rat stomach, which stimulates growth hormone release from pituitary cells through activation of a GPCR, the growth hormone secretagogue receptor (GHSR). Le May et al. (2021) reported that selective silencing of GHSR-positive cells in the lateral parabrachial nucleus inhibited food intake and reduced fat mass, indicating that these GHSR-expressing cells are involved in hyperphagia and weight gain. The review by Lu et al. (2021) discusses the mechanisms of action of liver-expressed antimicrobial peptide 2 as both an inverse agonist and an antagonist of GHSR1a, as well as the potential applications of this novel peptide in various pathologies, including obesity.

Harmar A. J. et al. (2012) reported that vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide are two related peptides that act via three GPCRs. Georg et al. (2021) investigated the possible impact of vasoactive intestinal peptide/vasoactive intestinal polypeptide receptors 2 signaling on the expression of thyroid clock genes. Their data indicate that the thyroid clock is largely independent of the master suprachiasmatic nucleus clock. The neurotrophic and neuroprotective effects of vasoactive intestinal peptide and pituitary adenylate cyclase-activating

polypeptide are partly mediated by a glial protein termed activity-dependent neuroprotective protein. Gozes I. and Shazman S. (2022) discuss the possible involvement of activity-dependent neuroprotective protein gene mutations at protease cleavage sites in autism and Alzheimer's disease.

The study by Tsutsui K. et al. (2000) reports gonadotropin-inhibitory hormone, a C-terminally amidated dodecapeptide initially isolated from the quail brain based on its ability to inhibit gonadotropin release. In a hypothesis and theory article, Dores R. and Chapa E. (2021) explore the phylogenetic development of the melanocortin 2 receptor and its crucial accessory protein – melanocortin receptor accessory protein 1. Building on this, Wang et al. (2021) examined the internal symmetry of the melanocortin receptor accessory protein 2 homodimers, revealing that the orientation of its domains plays a key role in modulating melanocortin 4 receptor activity.

The study by De Mota N. et al. (2004) reports apelin – a 36-amino-acid peptide that antagonizes the antidiuretic effects of vasopressin. In the review, Girault-Sotias et al. (2021) examine the opposing roles of apelin and vasopressin in the regulation of diuresis and highlight the therapeutic promise of apelin agonists in managing the syndrome of inappropriate antidiuresis.

Prokineticins comprise two secreted polypeptides that regulate a range of neuroendocrine processes, including reproduction, feeding behavior, and circadian rhythms, by activating two GPCRs: Prokineticin receptor 1 and Prokineticin receptor 2 (PKR2). Verdinez J. and Sebag J. (2021) identified two N-linked glycosylation sites in the N-terminal domain of PKR2 that are critical for receptor trafficking to the plasma membrane and for effective Gαs-mediated signaling.

Bombesin, as described by Gonzalez N. et al. (2008), is a member of a family of bioactive peptides that also includes neuromedin B and gastrin-releasing peptide. These peptides exert their effects via three distinct GPCRs: the neuromedin B receptor, the gastrin-releasing peptide receptor, and bombesin receptor subtype 3, which are currently designated by the Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology as bombesin receptors-1, -2, -3, respectively. Moody T. et al. (2021) summarize evidence indicating that bombesin-related peptides and their receptors are often overexpressed in various tumor cell types, highlighting their potential utility in tumor imaging and targeted therapeutic approaches, particularly in neural malignancies.

The hypothalamo-pituitary-thyroid (HPT) axis is a key regulator of energy homeostasis. Ortiga-Carvalho T. M. et al. (2016) investigated the regulation of HPT axis activity, demonstrating that it is predominantly controlled by the neuropeptide thyrotropin-releasing hormone acting through its cognate GPCR expressed on pituitary thyrotrope cells. Parra-Mones de Oca et al. (2021) examine sexual dimorphism in the regulation of HPT axis activity, emphasizing that it arises not only from the actions of sex steroids but also from variations in diet, levels of physical activity, and differential stress responses.

Conclusions. Neuropeptides constitute an essential class of signaling molecules operating in the brain as well as in peripheral organs. More than one hundred neuropeptides have been characterized to date, and most of them mediate their effects

through G protein-coupled receptors. These receptors are integral to neuroendocrine control mechanisms governing appetite, reproductive function, somatic growth, fluid and electrolyte homeostasis, and adaptive responses to stress. Given their central role in physiology, G protein-coupled receptors are also among the most important molecular targets for the design and development of new pharmacological therapies.

Keywords: neuroendocrinology, neuropeptides, biologically active peptides, G protein-coupled receptors, neuroendocrine disease.