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News and reviews

Role of neuropeptides in appetite regulation and obesity – A review

Sarika Arora *, Anubhuti

Department of Biochemistry, Lady Hardinge Medical College, Shaheed Bhagat Singh Marg, Connaught Place, New Delhi, Delhi 110 001, India

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Abstract

Obesity represents the most prevalent nutritional problem worldwide which in the long run predisposes to development of diabetes mellitus, hypertension, endometrial carcinoma, osteoarthritis, gall stones and cardiovascular diseases. Despite significant reductions in dietary fat consumption, the prevalence of obesity is on a rise and is taking on pandemic proportions. Obesity develops when energy intake exceeds energy expenditure over time. Recently, a close evolutionary relationship between the peripheral and hypothalamic neuropeptides has become apparent. The hypothalamus being the central feeding organ mediates regulation of short-term and long-term dietary intake via synthesis of various orexigenic and anorectic neuropeptides. The structure and function of many hypothalamic peptides (neuropeptide Y (NPY), melanocortins, agouti-related peptide (AGRP), cocaine and amphetamine regulated transcript (CART), melanin concentrating hormone (MCH), orexins have been characterized in rodent models The peripheral neuropeptides such as cholecystokinin (CCK), ghrelin, peptide YY (PYY3-36), amylin, bombesin regulate important gastrointestinal functions such as motility, secretion, absorption, provide feedback to the central nervous system on availability of nutrients and may play a part in regulating food intake. The pharmacological potential of several endogenous peripheral peptides released prior to, during and/or after feeding are being explored. Long-term regulation is provided by the main circulating hormones leptin and insulin. These systems implicated in hypothalamic appetite regulation provide potential targets for treatment of obesity which could potentially pass into clinical development in the next 5 years. This review summarizes various effects and interrelationship of these central and peripheral neuropeptides in metabolism, obesity and their potential role as targets for treatment of obesity.

Keywords: Appetite regulation; Role of hypothalamus in appetite regulation; Neuropeptide Y (NPY); Leptin; Insulin; Gut peptides; Pro-opiomelanocortins (POMC); Agouti-related peptide (AGRP); Cocaine- and amphetamine-related transcript (CART); Amylin

1. Introduction

Obesity is a serious medical condition whose prevalence is increasing in developing countries also. This growing incidence represents a pandemic that needs urgent attention if the potential morbidity, mortality, and economic tolls that will be left in its wake are to be avoided. Obesity predisposes to increased risk of a number of medical conditions including type II diabetes mellitus, hypertension, coronary heart disease, osteoarthritis, respiratory problems and cancers of breast, endometrium, prostate, bowel cancers (Neary et al., 2004).

Obesity represents a state of excess storage of body fat. Although very similar, the term overweight is defined as an excess body weight for height. The body mass index (BMI), also known as the Quetelet index is a WHO accepted index for classifying the degree of obesity. Standards defining overweight and obesity on the basis of BMI were developed by the International Obesity Task Force of the World Health Organization (WHO Report, 1998) and adopted by an expert committee of the NHLBI (NHLBI guidelines, 1998). BMI = (weight [kg])/(height $[m]^2$). Under this convention for adults, grade 1 overweight (commonly and simply called overweight) is a

* Corresponding author. Tel.: +91 11 25506229.
E-mail address: sarikaarora08@rediffmail.com (S. Arora).

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BMI of 25–29.9 kg/m^2. Grade 2 overweight (commonly called obesity) is a BMI of 30–39.9 kg/m^2. Grade 3 overweight (commonly called severe or morbid obesity) is a BMI greater than or equal to 40 kg/m^2.

The laws of thermodynamics are applicable here also because if energy expenditure by the body is less than the consumption, it will be stored in the body in the form of adipose tissue. Appetite regulation is important because it modulates the energy consumption side of the equation. Appetite includes various aspects of eating patterns such as frequency and size of eating episodes (gorging versus nibbling), choices of high fat or low fat foods, energy density of foods consumed, variety of foods accepted, palatability of diet and variability in day-to-day intake. Feeding behavior is controlled by a series of short-term hormonal, psychological and neural signals that derive from the gastrointestinal tract, such as cholecystokinin whereas other signals may initiate meals, such as the recently discovered hormone, ghrelin. Other hormones such as insulin and leptin, together with circulating nutrients, indicate long-term energy stores. All these signals act at several central nervous system (CNS) sites but the pathways converge on the hypothalamus, which contains a large number of peptides and other neurotransmitters that influence food intake (Table 1). As energy deficit is most likely to compromise survival, it is not surprising that the most powerful of these pathways are those that increase food intake and decrease energy expenditure when stores are depleted.

When energy stores are low, production of leptin from adipose tissue, and thus circulating leptin concentrations fall, leading to increased production of hypothalamic neurotransmitters that strongly increase food intake, such as neuropeptide Y (NPY), galanin and agouti-related protein (AGRP) and decreased levels of α-melanocyte-stimulating hormone (α-MSH), cocaine and amphetamine-regulated transcript (CART). The hypothalamus has been recognized as a central region of feeding regulation (Wilding, 2002). The appetite control system of the brain normally establishes a weight 'set-point' and tries to maintain it even when food supplies vary a great deal.

2. Role of hypothalamus

The role of hypothalamus in feeding control has been revealed by classical (but crude) experiments and some of the nuclei have been discretely referred to as 'feeding' and 'satiety' centres. The main regions of hypothalamus involved in feeding and satiety are:

Arcuate (ARC), acts as a feeding control center and integrates hormonal signals for energy homeostasis (Funahashi et al., 2000). The Arcuate Nucleus encloses the third ventricle and lies immediately above the median eminence. The ARC-median eminence area is one of the 'circumventricular' organs where the blood–brain barrier is specially modified to allow entry of peripheral peptides and proteins including insulin and leptin, both of which are considered to be signals of fat mass. (Friedman and Halaas, 1998; Schwartz et al., 1992a,b). The ARC contains populations of neurons that express neuropeptide Y (NPY), agouti-related peptide (AGRP) and the melanocortin precursor pro-opiomelanocortin (POMC). Thus arcuate nucleus is a privileged site which can sample the peripheral circulation through semi-permeable capillaries in the underlying median – eminence and is the ideal position to integrate hormonal signals for energy homeostasis.

The paraventricular nucleus (PVN) is adjacent to the superior part of the third ventricle in the anterior hypothalamus. The PVN is the main site of corticotropin releasing hormone (CRH) and thyrotropin releasing hormone (TRH) secretion. Numerous neuronal pathways implicated in energy balance converge in PVN, including major projections from NPY neurons of the ARC, Orexins, POMC derivative α-melanocyte stimulating hormone (α-MSH) and the appetite stimulating peptide galanin. Thus PVN plays a role in the integration of nutritional signals with the thyroid and hypothalamic-pituitary axis (Neary et al., 2004).

Ventromedial nucleus of hypothalamus (VMH) is mainly acting as satiety centre. It has been identified as a key target for leptin, which acts on the hypothalamus to inhibit feeding, stimulate energy expenditure and cause weight loss. Lesions of either ventromedial hypothalamic nuclei or PVN produce syndromes of hyperphagia and obesity (Satoh et al., 1997).

The dorsomedial hypothalamic nucleus (DMH), has extensive connections with other medial hypothalamic nuclei and the lateral hypothalamus and serves the function of integration and processing of information from these nuclei (Elmquist et al., 1998).

The lateral hypothalamic area (LHA) is the classical 'feeding centre', also contains glucose-sensitive neurons that are stimulated by hypoglycemia (by ascending pathways from brainstem) and it is crucial in mediating the marked hyperphagia which is normally induced by hypoglycaemia (Bernardis and Bellinger, 1996). The approximate locations of different hypothalamic nuclei are shown in Fig. 1.

The brainstem. There are extensive reciprocal connections between the hypothalamus and brainstem, particularly the Nucleus of Tractus Solitarius (NTS) (Ter Horst et al., 1989; Ricardo and Koh, 1978; van der Kooy et al., 1984). The NTS has a high density of NPY-binding sites (Harfstrand et al., 1986), including Y_1 receptors (Glass et al., 2002) and Y_5 receptors (Dumont et al., 1998). Extracellular NPY levels within the NTS fluctuate with feeding (Yoshihara et al., 1996), and NPY neurons from this region project forward to the PVN (Sawchenko