ELSEVIER

Physiology & Behavior 89 (2006) 71 – 84

PHYSIOLOGY & BEHAVIOR

Ghrelin and the short- and long-term regulation of appetite and body weight

David E. Cummings *

Department of Medicine, Division of Metabolism, Endocrinology and Nutrition, University of Washington, VA Puget Sound Health Care System, 1660 South Columbian Way, S-111-Endo, Seattle, WA 98108, USA

Received 23 May 2006; accepted 24 May 2006

Abstract

Ghrelin, an acylated upper gastrointestinal peptide, is the only known orexigenic hormone. Considerable evidence implicates ghrelin in mealtime hunger and meal initiation. Circulating levels decrease with feeding and increase before meals, achieving concentrations sufficient to stimulate hunger and food intake. Preprandial ghrelin surges occur before every meal on various fixed feeding schedules and also among individuals initiating meals voluntarily without time- or food-related cues. Ghrelin injections stimulate food intake rapidly and transiently, primarily by increasing appetitive feeding behaviors and the number of meals. Preprandial ghrelin surges are probably triggered by sympathetic nervous output. Postprandial suppression is not mediated by nutrients in the stomach or duodenum, where most ghrelin is produced. Rather, it results from post-ingestive increases in lower intestinal osmolarity (information probably relayed to the foregut via enteric nervous signaling), as well as from insulin surges. Consequently, ingested lipids suppress ghrelin poorly compared with other macronutrients. Beyond a probable role in meal initiation, ghrelin also fulfills established criteria for an adiposity-related hormone involved in long-term body-weight regulation. Ghrelin levels circulate in relation to energy stores and manifest compensatory changes in response to body-weight alterations. Ghrelin crosses the blood–brain barrier and stimulates food intake by acting on several classical body-weight regulatory centers, including the hypothalamus, hindbrain, and mesolimbic reward system. Chronic ghrelin administration increases body weight via diverse, concerted actions on food intake, energy expenditure, and fuel utilization. Congenital ablation of the ghrelin or ghrelin-receptor gene causes resistance to diet-induced obesity, and pharmacologic ghrelin blockade reduces food intake and body weight. Ghrelin levels are high in Prader–Willi syndrome and low after gastric bypass surgery, possibly contributing to body-weight alterations in these settings. Extant evidence favors roles for ghrelin in both short-term meal initiation and long-term energy homeostasis, making it an attractive target for drugs to treat obesity and/or wasting disorders.

Keywords: Ghrelin; Obesity; Body-weight regulation; Energy homeostasis; Weight loss; Cachexia; Reward; Meals; Meal initiation

1. Energy homeostasis and the obesity pandemic

Obesity has become so prevalent and is so strongly associated with medical co-morbidities and mortality that it is overtaking infectious diseases as the most significant contributor to ill health worldwide [1,2]. Despite obvious health benefits of weight loss, medical and behavioral approaches remain limited in their efficacy, generally facilitating no more than a 5–10% reduction of body weight, and recidivism after even this modest decrease is nearly universal [3,4]. A principal reason for this is that body weight is regulated by a powerful homeostatic system that, in response to weight loss, triggers compensatory changes in appetite and energy expenditure to promote weight regain [5]. Implicit in this regulatory system is the existence of peripheral factors that communicate the status of body energy stores to the brain. A key research objective is to identify and characterize all of these molecules, as they represent obvious targets for novel anti-obesity therapeutics.

Peripheral signals involved in energy homeostasis are often catalogued into long-acting adiposity signals, such as leptin and insulin, which regulate overall body weight, and short-acting gastrointestinal factors that are acutely affected by ingested nutrients and influence the details of individual meals [6]. Members of the latter category, in which gastric distension and cholecystokinin (CCK) are the prototypes, traditionally mediate postprandial satiation, communicating the sense of fullness that accompanies food ingestion and thereby helping to terminate

* Tel.: +1 206 764 2335; fax: +1 206 764 2689.
E-mail address: davidec@u.washington.edu.

0031-9384/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.physbeh.2006.05.022

meals and limit meal size. Physiologic signals that mediate the common sensation of pre-meal hunger and favor meal initiation, thus regulating meal number, have long remained elusive.

With one exception, all of the peripheral factors that participate in both the short- and long-term control of appetite and adiposity are anorexigenic, promoting reductions in food intake and body weight. The gastrointestinal peptide ghrelin is the only known circulating orexigen.

The current review presents evidence that favors roles for ghrelin in the short-term regulation of mealtime hunger and meal initiation, acting as a unique orexigenic counterpart to gut-derived satiation factors, such as CCK. Also discussed are data demonstrating that ghrelin satisfies established criteria to be viewed additionally as a participant in long-term body-weight regulation—a potential orexigenic counterpart to leptin and insulin in this regard.

2. Ghrelin: the only known appetite-stimulating hormone

Although ghrelin was initially discovered as an endogenous ligand for the growth hormone secretagogue receptor (GHS-R) [7], subsequent reports showing that it powerfully increases food intake and body weight [8–10] shifted much of the focus of research on this new peptide to its roles in energy homeostasis. Ghrelin stimulates short-term food intake more effectively than does any known molecule except neuropeptide Y, with which it is approximately equipotent [11,12], and ghrelin is unique in its ability to exert this effect whether injected peripherally or centrally. It is also the only mammalian substance that has been shown to increase appetite and food intake when delivered to humans [12–17]. Chronic administration durably increases body weight in multiple species, including humans, as a result of anabolic effects on food intake, energy expenditure, and fuel utilization [8,10,11,18–21]. Ghrelin has been reported to stimulate appetite and food intake even more in obese than lean humans, increasing the possibility that blockade of ghrelin action might promote weight loss in obese individuals [16]. Consequently, vigorous efforts are underway in the pharmaceutical industry to develop ghrelin-receptor antagonists to treat obesity, as well as agonists to treat wasting conditions.

The GHS-R is expressed widely in the brain and peripheral tissues (especially the pituitary, stomach, intestine, pancreas, thymus, gonads, thyroid, and heart) [22–26]. Accordingly, ghrelin can exert diverse biological actions, including effects on hormone secretion, glucose homeostasis, pancreatic function, gastrointestinal motility, cardiovascular function, immunity, inflammation, cell proliferation and survival, bone metabolism, reproduction, memory, sleep, and more [27]. The physiologic relevance of most of these actions has yet to be demonstrated, and ghrelin's roles in energy homeostasis are generally viewed as its most important functions. Although ghrelin's potent pharmacologic impact on GH secretion remains of great interest, considerable evidence challenges whether this action is physiologically important. Available data suggest that ghrelin may act as a gain-setter to enhance the magnitude of GHRH-stimulated GH pulses [28].

3. Chemistry and tissue distribution of ghrelin and its receptor

Ghrelin is a 28-amino acid peptide cleaved from a larger precursor, *preproghrelin*, which bears a signal sequence dictating secretion into the circulation [7]. The peptide undergoes a post-translational modification in which the serine-3 residue is covalently linked to a medium-chain fatty acid, typically octanoic acid, through an ester bond. The stomach can only acylate ghrelin with medium-chain, and not with short- or long-chain fatty acids [29]. Because animals do not synthesize medium-chain fatty acids, octanoic acid from dietary sources is probably utilized for ghrelin adduction [29]. This type of post-translational modification is entirely unique to ghrelin within the animal kingdom and is required for the peptide to bind to and activate its classical receptor, the GHS-R1a [7]. Consequently, most biological actions of ghrelin, especially those involving endocrine and anabolic effects, require acylated ghrelin [27]. Whether des-acyl ghrelin has physiologic roles is a controversial question. If it does, an alternate ghrelin receptor must exist for the des-acylated ligand, and the existence of functional ghrelin receptors beyond GHS-R1a is also a hotly debated issue, which is reviewed elsewhere [27,30]. The observation that octanoylation is unique to ghrelin and required for most of its effects has potential therapeutic implications, should blockade of ghrelin signaling prove clinically useful. Antagonists of the putative, undiscovered transacylation enzyme that octanoylates ghrelin would inactivate the hormone in a highly selective manner.

Experiments in mice lacking the *GHS-R* gene proved definitively that the orexigenic and GH-stimulatory effects of acylated ghrelin are mediated by this receptor [22,25,31]. Thus, the "GHS-R" can now be properly re-named the "ghrelin receptor" [32]. It is a rhodopsin-like, Family A seven-membrane-spanning receptor. Canonical signaling is through Gq/phospholipase C [22,33], and the importance of this transduction pathway is demonstrated by the observation that mice lacking Gq alpha subunits in neurons and glia have impaired hypothalamic responses to ghrelin [34]. The ghrelin receptor can also couple to Gs/protein kinase A pathways in some tissues [33,35–37], and the importance of this type of signaling is under investigation. Interestingly, the ghrelin receptor exhibits an unusual feature of significant ligand-independent constitutive activity [37,38]. These properties have important implications for pharmaceutical companies developing ghrelin-receptor blockers as potential anti-obesity agents. The most effective compounds may be inverse agonists, rather than neutral competitive antagonists, and they may need to inhibit more than one type of intracellular signaling pathway. Besides ghrelin and synthetic GHSs, adenosine and the somatostatin-like neuropeptide, cortistatin, can also act as agonists of the ghrelin receptor, although the physiologic significance of these interactions is unknown [27].

The receptor-binding pharmacophore of ghrelin appears to consist of the first seven (or fewer) amino acids at the N-terminus, plus the fatty-acid moiety, because full receptor binding and activation are achieved with only these residues