Peptides 100 (2018) 236–242

Contents lists available at ScienceDirect

Peptides

journal homepage: www.elsevier.com/locate/peptides

Ghrelin regulation of glucose metabolism

Anne-Laure Poher[a], Matthias H. Tschöp[a,b], Timo D. Müller[a,*]

[a] Institute for Diabetes and Obesity, Helmholtz Diabetes Center (HDC), Helmholtz Zentrum München and German National Diabetes Center (DZD), 85764, Neuherberg, Germany

[b] Division of Metabolic Diseases, Department of Medicine, Technische Universität München, 80333, Munich, Germany

ARTICLE INFO

Keywords:
Ghrelin
Glucose metabolism
Insulin sensitivity
Diabetes
Diet-induced obesity

ABSTRACT

The a 28-amino acid peptide ghrelin was discovered in 1999 as a growth hormone (GH) releasing peptide. Soon after its discovery, ghrelin was found to increase body weight and adiposity by acting on the hypothalamic melanocortinergic system. Subsequently, ghrelin was found to exert a series of metabolic effects, overall testifying ghrelin a pleiotropic nature of broad pharmacological interest. Ghrelin acts through the growth hormone secretagogue-receptor (GHS-R), a seven transmembrane G protein-coupled receptor with high expression in the anterior pituitary, pancreatic islets, thyroid gland, heart and various regions of the brain. Among ghrelins numerous metabolic effects are the most prominent the stimulation of appetite *via* activation of orexigenic hypothalamic neurocircuits and the food-intake independent stimulation of lipogenesis, which both together lead to an increase in body weight and adiposity. Ghrelin effects beyond the regulation of appetite and GH secretion include the regulation of gut motility, sleep-wake rhythm, taste sensation, reward seeking behaviour, and the regulation of glucose metabolism. The latter received recently increasing recognition because pharmacological inhibition of ghrelin signaling might be of therapeutic value to improve insuin resistance and type 2 diabetes. In this review we highlight the multifaceted nature of ghrelin and summarize its glucoregulatory action and discuss the pharmacological value of ghrelin pathway inhibition for the treatment of glucose intolerance and type 2 diabetes.

1. Introduction

Obesity and diabetes are major health threats of our society, leading annually to more than 1.5 million casualties [1]. The obesity pandemic affects nowadays almost every culture and ethnic civilization, placing an enormous burden on modern health care systems. From the numerous co-morbidities associated with excess body fat are the most prominent type 2 diabetes, cardiovasclar diseases and certain types of, predominantly gastrointestinal, cancer [2,3]. Underscoring the relevance of adequate glucose buffering, type 2 diabetes represents as of today the most frequent cause of overweight-related death [4]. In line with obesity being the major risk factor for the development of type 2 diabetes, weight loss achieved by either dieting [5] or through pharmacology [6] or bariatric surgery [7,8] improves glucose handling and numerous clinical studies have demonstrated that placebo-subtracted weight loss in the magnitute of even 5% is sufficient to show meaningful improvements in systemic glucose metabolism and of other obesity linked co-morbidities [9–12]. Further underlining the direct relation between body weight and glucose control, weight loss induced by bariatric surgery most often results in complete resolution of type 2 diabetes, an observation that prompted the American Diabetes Association (ADA) to even recommend such surgical intervention under certain circumstances for the treatment of type 2 diabetes [13–15]. Since the correlation between body weight and glucose control is solidly confirmed by numerous preclinical and clinical studies [16,17], drugs to control body weight appear intuitively promising to also improve glucose metabolism. In line with this notion, prominent examples of such strategy is *e.g.* the administration of GLP-1 mimetics, which not only improve glycemic control *via* their insulinotropic action but that also indirectly improve glucose metabolism *via* their ability to decrease body weight through central regulation of food intake [18–21]. While a plethora of weight lowering drugs have been shown to offer beneficial effects on glycemia, including GLP-1 mimetics [22], thyroid hormone [23,24], amphetamines [25], serotonergics [26] or lipase inhibitors [27], hormones with the ability to increase body weight are commonly known to rather impair glucose metabolism. A prominent example of the latter is the gut-derived peptide hormone ghrelin, which increases body weight and body fat mass *via* activation of orexigenic hypothalamic neurocircuits and *via* food-intake independent stimulation of lipogenesis [28–31]. In this manuscript we will summarize the

* Corresponding author at: Institute for Diabetes and Obesity, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany./ Business Campus Garching – Hochbrück, Parkring 13; 85748, Garching, Germany, Phone No.: +49-89-3187-2106; fax: +49-89-3187-2182.
E-mail address: timo.mueller@helmholtz-muenchen.de (T.D. Müller).

https://doi.org/10.1016/j.peptides.2017.12.015
Received 30 October 2017; Received in revised form 15 December 2017; Accepted 16 December 2017

multifaceted nature of ghrelin with a special focus on its role to regulate glucose metabolism. A key central aspect is thereby be the question of whether blocking of ghrelin signaling might be of therapeutic value to improve glucose metabolism?

2. Ghrelin production, activation and degradation

Ghrelin is derived from preproghrelin, a 117 amino-acid precursor that is produced by X/A-like cells within gastric oxyntic glands of the stomach [32]. Preproghrelin is cleaved into a small signal peptide, ghrelin and obestatin. Obestatin has previously been thought to play a role in food intake *via* acting on the G protein-coupled receptor 39 (GPR39) but this was not supported by all studies [33,34]. Cleaved from preproghrelin, the 28 amino acid peptide ghrelin is highly conserved among species with only two amino acids differing between the rat and human peptide [35].

Ghrelin promotes its biological action *via* binding to the growth hormone secretagogue receptor 1a (GHSR1a), a seven transmembrane G protein-coupled receptor with highest expression in the pituitary, pancreatic islets, adrenals, thyroid gland, the myocardium, the hypothalamic arcuate nucleus (ARC), hippocampus, the substantia nigra pars compacta (SNpc), the ventral tegmental area (VTA), and raphe nuclei [36,37]. In the feeding center of the hypothalamus, *GHSR1a* is localized in neurons that express neuropeptide Y (*Npy*) and Agouti related peptide (*Agrp*), well known neuropeptides stimulating food intake [38]. GHSR1 is present in two forms, the long form (GHSR1a), which is mediating most, if not all, of acyl-ghrelins metabolic effects and a truncated form, GHSR1b [36].

To activate its only known receptor, ghrelin needs to be post-translationally modified (acylated) to carry a fatty acid, preferably C:8 or C:10, on its third N-terminal amino acid position, which is a serine [35]. This rare post-translational modification is achieved by the ghrelin O-acyl-transferase (GOAT), a member of the membrane bound O acyltransferase (MBOAT) family [39,40]. GOAT is essential to acylate ghrelin *in vivo*, as demonstrated by the absence of acyl-ghrelin in plasma of mice deficient for GOAT [39,41–44].

The reported half-life of acyl-ghrelin varies between 30 min in rats to 240 min in humans [45]. Reflecting the species-related differences in ghrelin degradation, butyrylcholinesterase is the main enzyme inactivating ghrelin in humans whereas in rodents carboxylesterases allow for an 8-times faster des-octanoylation of ghrelin [45].

3. Physiological effects of unacylated ghrelin

While substantial evidence indicates that most metabolic effects of ghrelin require acylation of the peptide, there is accumulating evidence suggesting that also des-acyl ghrelin has physiologically relevant effects on systems metabolism, potentially *via* a receptor that yet still needs to be identified. In line with this notion, desacyl ghrelin affects differentiation of C2C12 skeletal muscle cells [46], prevents muscle atrophy [47], has protective effects on the heart [48,49] and affects glucose metabolism *via* pathways that are independent of GHSR1 [50–52]. When injected directly into the third ventricle of the hypothalamus, des-acyl ghrelin seems to acutely stimulate food intake through mechanisms that are independent of GHSR1a and Npy signaling [51]. When injected into the periphery, des-acyl ghrelin is either reported to not affect food intake [51] or to even decrease food intake [53]. Nevertheless, mice overexpressing des-acyl ghrelin under control of the FABP4 promoter seem to be protected from diet-induced obesity and show reduced body fat mass when fed with a standard chow diet [52]. These data align with a growing body of evidence testifying des-acyl ghrelin a certain potential to prevent diet-induced obesity and to improve HFD-induced derangements in glucose and lipid metabolism [54,55]. Interestingly, the glycemic effects of ghrelin to increase blood glucose through inhibition of insulin secretion seems to be antagonized by co-administration of des-acyl ghrelin [56]. Despite not supported by all studies [57], also several human studies report positive effects of des-acyl ghrelin on insulin sensitivity [58,59]. In line with this notion, there is recent evidence suggesting that des-acyl ghrelin promotes survival of pancreatic β-cells and protects from streptozotocin-induced β-cell damage [60–63].

4. Ghrelins effects beyond the stimulation of food intake

The most prominent effect of ghrelin is its ability to stimulate food intake *via* activation of hypothalamic neurocircuits [28]. In line with this notion, in the hypothalamic arcuate nucleus (ARC), ghrelin increases the activity of neurons expressing neuropeptide y (*Npy)* and the agouti-related protein (*Agrp)* while at the same time inhibiting neurons that express proopiomelanocortin (*Pomc*) [29,38]. Ghrelin signaling *via* these neurons is essential for ghrelins orexigenic effect since ghrelin fails to increase food intake in mice lacking *Npy* and *Agrp* [64]. Intracerebroventricular (icv) injection of ghrelin further increases food intake in rats, but fails to do so when NPY and AgRP neurons were blocked [65], further underlining the importance of the hypothalamic melanocortinergic system. In line with its effect on the melanocortinergic system, a ying yang balance between ghrelin and leptin has been suggested and ghrelin accordingly seems to counteract food intake inhibition by leptin [66]. Beside its ability to stimulate food intake, ghrelin activates gastric emptying and motility, as well as gastric acid secretion (Fig. 1) [67,68]. Ghrelin further modulates food reward and taste sensation, increases locomotor activity, motivation towards food reward, and enhances olfactory sensitivity [69–74]. As a pulsatile hormone, ghrelin is also involved in sleep regulation as suggested by different studies [75–77].

Acutely, ghrelin seems to induce anxiolytic and anti-depressant like effects in mice, most likely *via* stimulating the activity of the HPA axis [78,79]. Under stress, also the preference for HFD seems to be affected by ghrelin signaling [80]. Collectively, these data suggest a role for ghrelin in sleep regulation, stress and depression. Ghrelin also enhances differentiation and fusion of skeletal muscles cells *in vitro* and impairs skeletal muscle atrophy in mice [46,47]. Ghrelin further increases myocardial contractility, has a protective effect on the heart, and plays a role in atherogenesis [81]. Acute or chronic administration of ghrelin improves left ventricular (LV) dysfunction, and limits LV abnormal development in patients with chronic heart failure. Ghrelin also increases exercise capacity in both rats and humans [82,83]. In healthy humans, forearm blood flow is further increased by ghrelin, suggesting also a role in vasodilatation [84].

Effects on energy expenditure are frequently reported upon administration of ghrelin. Single peripheral or central (icv) injection of ghrelin suppresses BAT sympathetic nerve activity, thereby decreasing BAT temperature *via* CNS-dependent mechanisms [85,86]. Chronic ghrelin treatment further decreases *Ucp1* mRNA expression in the BAT [87]. Corroborating a role of ghrelin in regulating BAT function, mice lacking ghrelin or administration of *GHSR* antisense mRNA increases BAT activity [88,89].

5. Preclinical studies on ghrelins role in glucose metabolism

Numerous studies have evaluated ghrelins effects on glucose metabolism (as reviewed in [30]). Ghrelin inhibition of insulin secretion has been shown in a variety of species including mice [90], rats [91], pigs [92] monkeys [93,94] and humans [95]. In line with ghrelins ability to decrease insulin release *in vivo*, levels of blood glucose are typically decreased in mice lacking either ghrelin or GHSR relative to wildtype controls [96]. When exposed to a HFD, mice deficient for ghrelin or its receptor show a better glucose tolerance and insulin sensitivity when compared to wildtype controls [97,98]. Underling ghrelins role in glucose metabolism, ghrelin deletion in ob/ob mice decreases hyperglycemia and enhances glucose-induced insulin secretion, thereby improving insulin sensitivity in peripheral tissues relative