Benso A, Casanueva FF, Ghigo E, Granata A (eds): The Ghrelin System.
Endocr Dev. Basel, Karger, 2013, vol 25, pp 91–100 (DOI: 10.1159/000346590)

Ghrelin – A Key Pleiotropic Hormone-Regulating Systemic Energy Metabolism

Timo D. Müller · Matthias H. Tschöp

Institute for Diabetes and Obesity, Helmholtz Zentrum München and Department of Medicine, Technische Universität München, Munich, Germany

Abstract

The gastrointestinal peptide hormone ghrelin was discovered in 1999 as the endogenous ligand for the growth hormone secretagogue receptor (GHSR-1a). Since its discovery tremendous research efforts have been directed at unraveling ghrelin's mechanisms of action, revealing that ghrelin is a pleiotropic hormone implicated in myriad of molecular signaling mechanisms. Accordingly, ghrelin is the only known circulating peripheral hormone with the ability to promote a positive energy balance by stimulating food intake while decreasing energy expenditure and body fat utilization. Moreover, beyond its ability to promote the release of growth hormone from the anterior pituitary, ghrelin stimulates gut motility and gastric acid secretion, modulates sleep, taste sensation and behavior, and regulates glucose metabolism. Due to ghrelin's ability to promote body weight gain and adiposity via centrally mediated signaling mechanisms, modulation of the endogenous ghrelin system is considered a promising strategy to treat individuals with pathologically reduced body weight, such as patients with anorexia nervosa or cachexia. The aim of this chapter is to summarize the current knowledge of how ghrelin affects systemic energy metabolism.

Discovery of Ghrelin as the Endogenous Ligand of the Growth Hormone Secretagogue Receptor 1a (GHSR-1a)

In the late 1970s, the pioneering work of Bowers and colleagues led to the generation of a group of synthetic opioid peptide derivates that promoted the release of growth hormone (GH) from the anterior pituitary [1, 2]. The molecules, which Bowers referred to as GH secretagogues (GHSs), were generated by chemical modification of met-enkephalin and gave rise to the generation of a series of potent GH-releasing peptides (GHRPs), such as GHRP-6, GHRP-2, and hexarelin [3]. The mechanism of how these molecules promote the release of GH was distinct from the later discovered GH-releasing hormone (GHRH)/somatostatin pathway and remained elusive until

cloning of the GH secretagogue receptor 1 (GHSR-1) from swine pituitary and hypothalamus in 1996 [4]. GHSR-1 was identified as a G protein-coupled receptor predominantly expressed in the pituitary, hippocampus, and hypothalamus [5]. In the arcuate nucleus (ARC), GHSR-1 was co-expressed with neuropeptide Y (NPY) [6] and its activation by GHRP-6 increased c-fos expression in NPY neurons [7]. Together, these data suggested the presence of a yet unknown endogenous ligand for GHSR-1 and indicated that this ligand, beyond its ability to promote the release of GH, might be implicated in the regulation of systemic energy metabolism. Thus, after the discovery of GHSR-1 in 1996, research efforts focused on identifying the endogenous ligand for this receptor. However, it remained unknown until 1999 when Kojima et al. [8] identified the cognate ligand for GHSR-1, which they purified from rat stomach extracts, as the 28 amino acid peptide 'ghrelin'. The name ghrelin originates from 'ghre', the Proto-Indo-European root of the word 'grow' [8]. More than a decade after its discovery, ghrelin is one of the most important peripheral key players in the regulation of systemic energy metabolism. Accordingly, ghrelin is yet the only known circulating peripheral hormone with the ability to promote body weight gain and adiposity through stimulation of food intake while decreasing energy expenditure and body fat utilization [9]. Moreover, beyond its ability to promote the release of GH from the anterior pituitary, ghrelin stimulates gastric acid secretion and gastric motility, influences taste sensation, sleep and behavior, and modulates glucose metabolism via regulation of pancreatic exocrine and endocrine function [10, 11].

Synthesis and Activation of Ghrelin

Ghrelin is predominantly synthesized and secreted by X/A-like cells in the oxyntic glands of the gastric fundus [12, 13]. As the stomach is the major source of ghrelin secretion, plasma levels of ghrelin are substantially decreased in both rats [14–19] and humans [20–29] after bariatric gastrectomy. However, lower amounts of ghrelin-producing cells were also found in the intestine [12], pituitary [30, 31], pancreas [32–34], kidney [33, 35], lung [33, 36] ovaries [33] and brain [33, 37, 38]. Notably, not all human studies report changes in plasma ghrelin concentrations after bariatric gastrectomy [39–41], indicating that other sources of ghrelin secretion can, at least to some extent, compensate for the removal of a portion of the stomach.

Ghrelin is synthesized as a 117 amino acid pre-prohormone and is posttranslationally cleaved into a 28 amino acid peptide. The amino acid sequence is highly conserved between mammals, and rat and mouse ghrelin differ by only two amino acids from the human peptide. To activate its only known receptor, ghrelin requires acylation of its serine 3 residue with an n-octanoic or n-decanoic acid, a post-translational modification that is achieved by the ghrelin *O*-acyltranferase (GOAT) [42, 43] and that is unique in peptide chemistry (fig. 1). The highest level of GOAT expression is found in ghrelin-expressing tissues, such as the pancreas and stomach in humans and

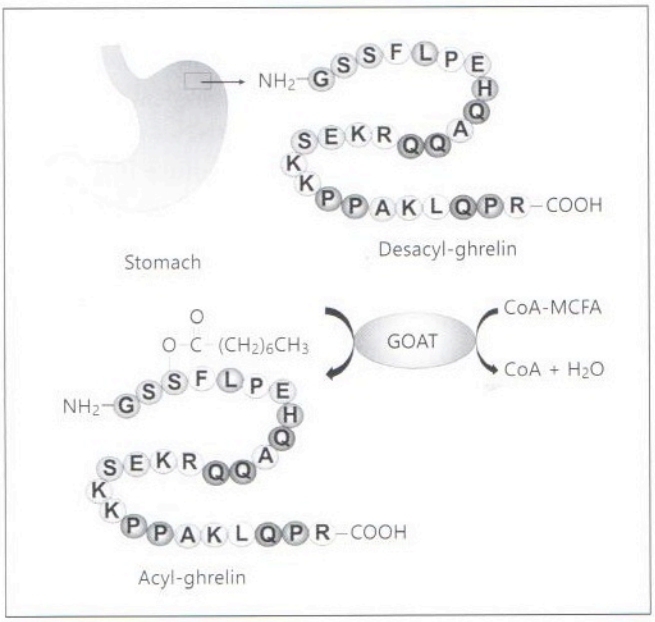

Fig. 1. Posttranslational activation (acylation) of ghrelin by GOAT. MCFA = Medium chain fatty acid; CoA = coenzyme A.

the stomach and intestine in mice [42, 44]. Notably, acyl-ghrelin is absent in mice lacking *Goat,* thus indicating that Goat is the only enzyme activating ghrelin in vivo [43]. The vast majority of ghrelin's metabolic effects, including the modulation of GH release from the anterior pituitary and the regulation of energy metabolism via hypothalamic neurocircuitries, are mediated by GHSR-1, and thus depend on the n-octanoylation of serine 3. However, only 10–20% of circulating ghrelin is acylated and, even though no receptor for des-acyl ghrelin has been identified, several studies suggest that des-acyl ghrelin promotes differentiation and fusion in C2C12 skeletal muscle cells [45], has a cardioprotective effect on endothelial cells and cardiomyocytes [46, 47], and might have some GHSR-1 independent effects on energy and glucose metabolism [48–50].

Ghrelin-Mediated Regulation of Food Intake and Energy Metabolism

Several forms of ghrelin (octanoyl-, desacyl, (nonoctanoyl) acyl-ghrelin) can be found in the circulation and most available immunoassays do not sufficiently disclose to which of those ghrelin analogues they are binding and to what extent they are cross-reacting with other ghrelin-related peptides, e.g. motilin. It is likely that most assays measure total ghrelin-like immunoreactivity including desacyl ghrelin, which accounts for up to 90% of total ghrelin in the circulation. Nevertheless, plasma levels of ghrelin are generally negatively correlated with body weight and increase in response

to fasting with a subsequent decrease upon refeeding [9, 51, 52]. Plasma concentrations of ghrelin are typically lower in obese compared lean individuals [53–55] and are elevated in individuals with pathologically reduced body weight, such as patients with anorexia nervosa [56–58], as well as in patients with cachexia associated with chronic heart failure [59, 60], renal failure [61, 62], chronic obstructive pulmonary disease [63, 64] and various forms of cancer [65–67].

Secreted into the circulation in response to fasting, ghrelin was long considered to be a 'hunger' hormone that signals the gastrointestinal fuel status from the periphery to the CNS in order to adjust energy balance through centrally regulated signaling mechanisms. The role of ghrelin as a 'hunger' hormone was supported by the observation that plasma levels of ghrelin follow a circadian rhythm with a preprandial rise, which peaks directly at meal initiation, followed by a postprandial decrease to baseline levels within the first hour after a meal [51, 52, 68]. Current opinion questions whether ghrelin is a 'hunger' hormone, as more recent studies suggest that ghrelin acts more as a nutrient sensor, preparing the CNS for incoming nutrients. This nutrient sensor role of ghrelin is based on the observation that the acyl side chain necessary for ghrelin activation can originate directly from dietary lipids [69]. In line with this observation, mice that overexpress GOAT/ghrelin show increased energy expenditure compared to wild-type control mice when fed with a diet enriched with non-naturally occurring medium-chain triglycerides (MCT diet) [69]. Moreover, in line with its role as a nutrient sensor, ghrelin, independent of its effect on food intake, promotes lipogenesis in white adipose tissue via direct control of the hypothalamic melanocortinergic system [70].

Both peripheral and central administration of ghrelin potently promotes body weight gain and adiposity through a stimulation of food intake while decreasing energy expenditure and body fat utilization [9]. The orexigenic effect of ghrelin is thereby achieved through centrally regulated signaling mechanisms. In the ARC, GHSR1a is co-expressed with Npy and agouti-related peptide (AgRP). Both are anabolic neuropeptides that potently stimulate food intake while decreasing energy expenditure [71]. Accordingly, ghrelin-mediated activation of GHSR1a entails an increased expression and release of Npy and AgRP in the ARC, which, in turn, leads to the activation of anabolic downstream pathways that ultimately results in the stimulation of food intake and a decrease of energy expenditure [72, 73]. Inhibition of AgRP/Npy neurons diminishes ghrelin's effect on food intake, thus indicating that the orexigenic effect of ghrelin is mainly mediated through the hypothalamic melanocortinergic system [74].

Independent from its effect on food intake and energy expenditure, ghrelin stimulates the expression of genes related to lipogenesis in white adipose tissue, such as lipoprotein lipase, acetyl-CoA carboxylase-α, fatty acid synthase, and stearoyl-CoA desaturase-1 [75]. Moreover, in brown adipose tissue, ghrelin decreases the expression of thermogenesis-related genes, such as the uncoupling proteins 1 and 3, an effect that is most likely mediated by ghrelin's ability to decrease the activity of the sympathetic

nervous system [75]. In summary, the endogenous GOAT/ghrelin system plays a key role in the neuroendocrine regulation of systemic energy metabolism, and modulation of the endogenous ghrelin system is considered as a promising strategy for the treatment of individuals with pathologically reduced body weight such as patients with anorexia or cachexia.

Ghrelin in the Treatment of Eating/Wasting Disorders and Cachexia

Cachexia (Greek: kakós – bad; hexis – condition) is a multifactorial syndrome characterized by an involuntarily loss of skeletal muscle and adipose tissue mass as a result of a chronic excess of catabolic over anabolic processes [76–78]. Cachexia often occurs in the advanced stages of life-threatening diseases, such as chronic heart failure, chronic obstructive pulmonary disease, end-stage renal disease, sepsis, AIDS and cancer [77, 79]. Patients with cachexia typically have a poor quality of life, poor prognosis, lower response to drug treatment and an increased mortality rate compared to patients without cachexia [76, 80]. Cachexia is often, but not necessarily, accompanied by a loss of the desire to eat (anorexia) and is believed to be the immediate cause of 10–20% of all deaths in cancer patients [80].

Anorexia Nervosa

Anorexia nervosa (AN) is an eating disorder that is characterized by an abnormal eating behavior with disturbances of attitudes towards body weight and shape [81]. Plasma concentrations of ghrelin are typically elevated in patients with AN [56–58], especially in the acute phase of the disease, and rapidly decline when body weight increases during therapeutic intervention [82–84]. Plasma levels of acyl-ghrelin are likewise elevated in patients with AN [56, 58], even when compared to BMI-matched lean women [57, 85]. This indicates that impaired ghrelin sensitivity due to persistent hyperghrelinemia might play a role in the pathogenesis of AN, similar to the frequently reported leptin resistance in obese individuals [78]. Several human studies have assessed the orexigenic effect of ghrelin and its analogs and confirm that ghrelin promotes food intake and adiposity in both healthy individuals [86–88] and patients with AN [89]. Notably, these studies report no adverse side effects of ghrelin treatment.

Cachexia

Plasma levels of ghrelin are typically elevated in patients with cachexia associated with chronic heart failure [59, 60], renal failure [61, 62], chronic obstructive pulmonary disease [63, 90] and cancer [66, 67]. The hyperghrelinemia in these patients might be a compensatory mechanism to counteract the excessive loss of skeletal muscle and adipose tissue mass. Animal studies generally support the potential of ghrelin and its analogs to promote food intake and adiposity in cachexia associated with heart failure [91–94], chronic kidney disease [95] and cancer [96–98]. In line with these reports,

several human studies report a positive effect of ghrelin on appetite and body mass in patients with cachexia associated with renal failure [99, 100], chronic heart failure [101], chronic obstructive pulmonary disease [102], and cancer [103]. Notably, these studies support the safety and tolerability of ghrelin treatment and no adverse side effects have so far been reported [103, 104].

In summary, the endogenous ghrelin system plays a key role in the neuroendocrine regulation of systemic energy metabolism, and modulation of the GOAT/ghrelin system is a promising strategy for the treatment of pathologically reduced body weight and tissue wasting, the key clinical feature of cachexia. However, further studies in larger populations are necessary to clarify the long-term effects of ghrelin treatment and to assess the possible impact of ghrelin and ghrelin-induced growth factor release on tumor growth and carcinogenesis.

References

1 Bowers CY, Momany F, Reynolds GA, Chang D, Hong A, et al: Structure-activity relationships of a synthetic pentapeptide that specifically releases growth hormone in vitro. Endocrinology 1980;106:663–667.

2 Momany FA, Bowers CY, Reynolds GA, Chang D, Hong A, et al: Design, synthesis, and biological activity of peptides which release growth hormone in vitro. Endocrinology 1981;108:31–39.

3 Smith RG, Van der Ploeg LH, Howard AD, Feighner SD, Cheng K, et al: Peptidomimetic regulation of growth hormone secretion. Endocr Rev 1997;18:621–645.

4 Howard AD, Feighner SD, Cully DF, Arena JP, Liberator PA, et al: A receptor in pituitary and hypothalamus that functions in growth hormone release. Science 1996;273:974–977.

5 Guan XM, Yu H, Palyha OC, McKee KK, Feighner SD, et al: Distribution of mRNA encoding the growth hormone secretagogue receptor in brain and peripheral tissues. Brain Res Mol Brain Res 1997;48:23–29.

6 Willesen MG, Kristensen P, Romer J: Co-localization of growth hormone secretagogue receptor and NPY mRNA in the arcuate nucleus of the rat. Neuroendocrinology 1999;70:306–316.

7 Dickson SL, Luckman SM: Induction of c-fos messenger ribonucleic acid in neuropeptide Y and growth hormone (GH)-releasing factor neurons in the rat arcuate nucleus following systemic injection of the GH secretagogue, GH-releasing peptide-6. Endocrinology 1997;138:771–777.

8 Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, et al: Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 1999;402:656–660.

9 Tschop M, Smiley DL, Heiman ML: Ghrelin induces adiposity in rodents. Nature 2000;407:908–913.

10 Kojima M, Kangawa K: Structure and function of ghrelin. Results Probl Cell Differ 2008;46:89–115.

11 van der Lely AJ, Tschop M, Heiman ML, Ghigo E: Biological, physiological, pathophysiological, and pharmacological aspects of ghrelin. Endocr Rev 2004;25:426–457.

12 Sakata I, Nakamura K, Yamazaki M, Matsubara M, Hayashi Y, et al: Ghrelin-producing cells exist as two types of cells, closed- and opened-type cells, in the rat gastrointestinal tract. Peptides 2002;23:531–536.

13 Date Y, Kojima M, Hosoda H, Sawaguchi A, Mondal MS, et al: Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. Endocrinology 2002;141:4255–4261.

14 Masuda T, Ohta M, Hirashita T, Kawano Y, Eguchi H, et al: A comparative study of gastric banding and sleeve gastrectomy in an obese diabetic rat model. Obes Surg 2011;21:1774–1780.

15 Cummings BP, Bettaieb A, Graham JL, Stanhope KL, Kowala M, et al: Vertical sleeve gastrectomy improves glucose and lipid metabolism and delays diabetes onset in UCD-T2DM rats. Endocrinology 2012;153:3620–3632.

16 Yan L, Zhu Z, Wu D, Zhou Q, Wu Y: Effects of sleeve gastrectomy surgery with modified jejunoileal bypass on body weight, food intake and metabolic hormone levels of rats. J Huazhong Univ Sci Technolog Med Sci 2011;31:784–788.

17 Wang Y, Yan L, Jin Z, Xin X: Effects of sleeve gastrectomy in neonatally streptozotocin-induced diabetic rats. PLoS One 2011;6:e16383.

18 Li F, Zhang G, Liang J, Ding X, Cheng Z, et al: Sleeve gastrectomy provides a better control of diabetes by decreasing ghrelin in the diabetic Goto-Kakizaki rats. J Gastrointest Surg 2009;13:2302–2308.
19 Wang Y, Liu J: Plasma ghrelin modulation in gastric band operation and sleeve gastrectomy. Obes Surg 2009;19:357–362.
20 Leonetti F, Silecchia G, Iacobellis G, Ribaudo MC, Zappaterreno A, et al: Different plasma ghrelin levels after laparoscopic gastric bypass and adjustable gastric banding in morbid obese subjects. J Clin Endocrinol Metab 2003;88:4227–4231.
21 Ariyasu H, Takaya K, Tagami T, Ogawa Y, Hosoda K, et al: Stomach is a major source of circulating ghrelin, and feeding state determines plasma ghrelin-like immunoreactivity levels in humans. J Clin Endocrinol Metab 2001;86:4753–4758.
22 Bohdjalian A, Langer FB, Shakeri-Leidenmuhler S, Gfrerer L, Ludvik B, et al: Sleeve gastrectomy as sole and definitive bariatric procedure: 5-year results for weight loss and ghrelin. Obes Surg 2010;20:535–540.
23 Goitein D, Lederfein D, Tzioni R, Berkenstadt H, Venturero M, et al: Mapping of ghrelin gene expression and cell distribution in the stomach of morbidly obese patients – a possible guide for efficient sleeve gastrectomy construction. Obes Surg 2012;22:617–622.
24 Karamanakos SN, Vagenas K, Kalfarentzos F, Alexandrides TK: Weight loss, appetite suppression, and changes in fasting and postprandial ghrelin and peptide-YY levels after Roux-en-Y gastric bypass and sleeve gastrectomy: a prospective, double blind study. Ann Surg 2008;247:401–407.
25 Langer FB, Reza Hoda MA, Bohdjalian A, Felberbauer FX, Zacherl J, et al: Sleeve gastrectomy and gastric banding: effects on plasma ghrelin levels. Obes Surg 2005;15:1024–1029.
26 Peterli R, Steinert RE, Woelnerhanssen B, Peters T, Christoffel-Courtin C, et al: Metabolic and hormonal changes after laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy: a randomized, prospective trial. Obes Surg 2012;22:740–748.
27 Ramon JM, Salvans S, Crous X, Puig S, Goday A, et al: Effect of Roux-en-Y gastric bypass vs. sleeve gastrectomy on glucose and gut hormones: a prospective randomised trial. J Gastrointest Surg 2012;16:1116–1122.
28 Lee WJ, Chen CY, Chong K, Lee YC, Chen SC, et al: Changes in postprandial gut hormones after metabolic surgery: a comparison of gastric bypass and sleeve gastrectomy. Surg Obes Relat Dis 2011;7:683–690.
29 Basso N, Capoccia D, Rizzello M, Abbatini F, Mariani P, et al: First-phase insulin secretion, insulin sensitivity, ghrelin, GLP-1, and PYY changes 72 h after sleeve gastrectomy in obese diabetic patients: the gastric hypothesis. Surg Endosc 2011;25:3540–3550.
30 Korbonits M, Kojima M, Kangawa K, Grossman AB: Presence of ghrelin in normal and adenomatous human pituitary. Endocrine 2001;14:101–104.
31 Korbonits M, Bustin SA, Kojima M, Jordan S, Adams EF, et al: The expression of the growth hormone secretagogue receptor ligand ghrelin in normal and abnormal human pituitary and other neuroendocrine tumors. J Clin Endocrinol Metab 2001;86:881–887.
32 Prado CL, Pugh-Bernard AE, Elghazi L, Sosa-Pineda B, Sussel L: Ghrelin cells replace insulin-producing beta cells in two mouse models of pancreas development. Proc Natl Acad Sci USA 2004;101:2924–2929.
33 Ueberberg B, Unger N, Saeger W, Mann K, Petersenn S: Expression of ghrelin and its receptor in human tissues. Horm Metab Res 2009;41:814–821.
34 Volante M, Allia E, Gugliotta P, Funaro A, Broglio F, et al: Expression of ghrelin and of the GH secretagogue receptor by pancreatic islet cells and related endocrine tumors. J Clin Endocrinol Metab 2002;87:1300–1308.
35 Volante M, Allia E, Fulcheri E, Cassoni P, Ghigo E, et al: Ghrelin in fetal thyroid and follicular tumors and cell lines: expression and effects on tumor growth. Am J Pathol 2003;162:645–654.
36 Volante M, Fulcheri E, Allia E, Cerrato M, Pucci A, et al: Ghrelin expression in fetal, infant, and adult human lung. J Histochem Cytochem 2002;50:1013–1021.
37 Cowley MA, Smith RG, Diano S, Tschop M, Pronchuk N, et al: The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. Neuron 2003;37:649–661.
38 Hou Z, Miao Y, Gao L, Pan H, Zhu S: Ghrelin-containing neuron in cerebral cortex and hypothalamus linked with the DVC of brainstem in rat. Regul Pept 2006;134:126–131.
39 Brinckerhoff TZ, Bondada S, Lewis CE, French SW, Deugarte DA: Metabolic effects of sleeve gastrectomy in female rat model of diet-induced obesity. Surg Obes Relat Dis 2011.
40 Patrikakos P, Toutouzas KG, Gazouli M, Perrea D, Menenakos E, et al: Long-term plasma ghrelin and leptin modulation after sleeve gastrectomy in Wistar rats in comparison with gastric tissue ghrelin expression. Obes Surg 2011;21:1432–1437.
41 Lopez PP, Nicholson SE, Burkhardt GE, Johnson RA, Johnson FK: Development of a sleeve gastrectomy weight loss model in obese Zucker rats. J Surg Res 2009;157:243–250.
42 Gutierrez JA, Solenberg PJ, Perkins DR, Willency JA, Knierman MD, et al: Ghrelin octanoylation mediated by an orphan lipid transferase. Proc Natl Acad Sci USA 2008;105:6320–6325.

43 Yang J, Zhao TJ, Goldstein JL, Brown MS: Inhibition of ghrelin *O*-acyltransferase (GOAT) by octanoylated pentapeptides. Proc Natl Acad Sci USA 2008;105:10750–10755.
44 Sakata I, Yang J, Lee CE, Osborne-Lawrence S, Rovinsky SA, et al: Colocalization of ghrelin *O*-acyltransferase and ghrelin in gastric mucosal cells. Am J Physiol Endocrinol Metab 2009;297:E134–E141.
45 Filigheddu N, Gnocchi VF, Coscia M, Cappelli M, Porporato PE, et al: Ghrelin and des-acyl ghrelin promote differentiation and fusion of C2C12 skeletal muscle cells. Mol Biol Cell 2007;18:986–994.
46 Li L, Zhang LK, Pang YZ, Pan CS, Qi YF, et al: Cardioprotective effects of ghrelin and des-octanoyl ghrelin on myocardial injury induced by isoproterenol in rats. Acta Pharmacol Sin 2006;27:527–535.
47 Baldanzi G, Filigheddu N, Cutrupi S, Catapano F, Bonissoni S, et al: Ghrelin and des-acyl ghrelin inhibit cell death in cardiomyocytes and endothelial cells through ERK1/2 and PI 3-kinase/AKT. J Cell Biol 2002;159:1029–1037.
48 Thompson NM, Gill DA, Davies R, Loveridge N, Houston PA, et al: Ghrelin and des-octanoyl ghrelin promote adipogenesis directly in vivo by a mechanism independent of the type 1a growth hormone secretagogue receptor. Endocrinology 2004;145:234–242.
49 Toshinai K, Yamaguchi H, Sun Y, Smith RG, Yamanaka A, et al: Des-acyl ghrelin induces food intake by a mechanism independent of the growth hormone secretagogue receptor. Endocrinology 2006;147:2306–2314.
50 Zhang W, Chai B, Li JY, Wang H, Mulholland MW: Effect of des-acyl ghrelin on adiposity and glucose metabolism. Endocrinology 2008;149:4710–4716.
51 Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, et al: A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes 2001;50:1714–1719.
52 Tschop M, Wawarta R, Riepl RL, Friedrich S, Bidlingmaier M, et al: Post-prandial decrease of circulating human ghrelin levels. J Endocrinol Invest 2001;24:RC19–RC21.
53 Hansen TK, Dall R, Hosoda H, Kojima M, Kangawa K, et al: Weight loss increases circulating levels of ghrelin in human obesity. Clin Endocrinol (Oxf) 2002;56:203–206.
54 Shiiya T, Nakazato M, Mizuta M, Date Y, Mondal MS, et al: Plasma ghrelin levels in lean and obese humans and the effect of glucose on ghrelin secretion. J Clin Endocrinol Metab 2002;87:240–244.
55 Tschop M, Weyer C, Tataranni PA, Devanarayan V, Ravussin E, et al: Circulating ghrelin levels are decreased in human obesity. Diabetes 2001;50:707–709.
56 Nakai Y, Hosoda H, Nin K, Ooya C, Hayashi H, et al: Short-term secretory regulation of the active form of ghrelin and total ghrelin during an oral glucose tolerance test in patients with anorexia nervosa. Eur J Endocrinol 2004;150:913–914.
57 Tolle V, Kadem M, Bluet-Pajot MT, Frere D, Foulon C, et al: Balance in ghrelin and leptin plasma levels in anorexia nervosa patients and constitutionally thin women. J Clin Endocrinol Metab 2003;88:109–116.
58 Harada T, Nakahara T, Yasuhara D, Kojima S, Sagiyama K, et al: Obestatin, acyl ghrelin, and des-acyl ghrelin responses to an oral glucose tolerance test in the restricting type of anorexia nervosa. Biol Psychiatry 2008;63:245–247.
59 Nagaya N, Uematsu M, Kojima M, Date Y, Nakazato M, et al: Elevated circulating level of ghrelin in cachexia associated with chronic heart failure: relationships between ghrelin and anabolic/catabolic factors. Circulation 2001;104:2034–2038.
60 Xin X, Ren AJ, Zheng X, Qin YW, Zhao XX, et al: Disturbance of circulating ghrelin and obestatin in chronic heart failure patients especially in those with cachexia. Peptides 2009;30:2281–2285.
61 Yoshimoto A, Mori K, Sugawara A, Mukoyama M, Yahata K, et al: Plasma ghrelin and desacyl ghrelin concentrations in renal failure. J Am Soc Nephrol 2002;13:2748–2752.
62 Aygen B, Dogukan A, Dursun FE, Aydin S, Kilic N, et al: Ghrelin and obestatin levels in end-stage renal disease. J Int Med Res 2009;37:757–765.
63 Lainscak M, Andreas S, Scanlon PD, Somers VK, Anker SD: Ghrelin and neurohumoral antagonists in the treatment of cachexia associated with cardiopulmonary disease. Intern Med 2006;45:837.
64 Itoh T, Nagaya N, Yoshikawa M, Fukuoka A, Takenaka H, et al: Elevated plasma ghrelin level in underweight patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004;170:879–882.
65 Shimizu Y, Nagaya N, Isobe T, Imazu M, Okumura H, et al: Increased plasma ghrelin level in lung cancer cachexia. Clin Cancer Res 2003;9:774–778.
66 Garcia JM, Garcia-Touza M, Hijazi RA, Taffet G, Epner D, et al: Active ghrelin levels and active to total ghrelin ratio in cancer-induced cachexia. J Clin Endocrinol Metab 2005;90:2920–2926.
67 Wolf I, Sadetzki S, Kanety H, Kundel Y, Pariente C, et al: Adiponectin, ghrelin, and leptin in cancer cachexia in breast and colon cancer patients. Cancer 2006;106:966–973.
68 Williams DL, Cummings DE: Regulation of ghrelin in physiologic and pathophysiologic states. J Nutr 2005;135:1320–1325.
69 Kirchner H, Gutierrez JA, Solenberg PJ, Pfluger PT, Czyzyk TA, et al: GOAT links dietary lipids with the endocrine control of energy balance. Nat Med 2009;15:741–745.

70 Perez-Tilve D, Heppner K, Kirchner H, Lockie SH, Woods SC, et al: Ghrelin-induced adiposity is independent of orexigenic effects. FASEB J 2011;25: 2814–2822.
71 Barsh GS, Schwartz MW: Genetic approaches to studying energy balance: perception and integration. Nat Rev Genet 2002;3:589–600.
72 Kamegai J, Tamura H, Shimizu T, Ishii S, Sugihara H, et al: Central effect of ghrelin, an endogenous growth hormone secretagogue, on hypothalamic peptide gene expression. Endocrinology 2000;141: 4797–4800.
73 Kamegai J, Tamura H, Shimizu T, Ishii S, Sugihara H, et al: Chronic central infusion of ghrelin increases hypothalamic neuropeptide Y and Agouti-related protein mRNA levels and body weight in rats. Diabetes 2001;50:2438–2443.
74 Nakazato M, Murakami N, Date Y, Kojima M, Matsuo H, et al: A role for ghrelin in the central regulation of feeding. Nature 2001;409:194–198.
75 Theander-Carrillo C, Wiedmer P, Cettour-Rose P, Nogueiras R, Perez-Tilve D, et al: Ghrelin action in the brain controls adipocyte metabolism. J Clin Invest 2006;116:1983–1993.
76 von Haehling S, Lainscak M, Springer J, Anker SD: Cardiac cachexia: a systematic overview. Pharmacol Ther 2009;121:227–252.
77 Ashby D, Choi P, Bloom S: Gut hormones and the treatment of disease cachexia. Proc Nutr Soc 2008; 67:263–269.
78 Muller TD, Perez-Tilve D, Tong J, Pfluger PT, Tschop MH: Ghrelin and its potential in the treatment of eating/wasting disorders and cachexia. J Cachexia Sarcopenia Muscle 2010;1:159–167.
79 Ashitani J, Matsumoto N, Nakazato M: Ghrelin and its therapeutic potential for cachectic patients. Peptides 2009;30:1951–1956.
80 Langhans W: Peripheral mechanisms involved with catabolism. Curr Opin Clin Nutr Metab Care 2002; 5:419–426.
81 Hebebrand J, Muller TD, Holtkamp K, Herpertz-Dahlmann B: The role of leptin in anorexia nervosa: clinical implications. Mol Psychiatry 2007;12:23–35.
82 Otto B, Cuntz U, Fruehauf E, Wawarta R, Folwaczny C, et al: Weight gain decreases elevated plasma ghrelin concentrations of patients with anorexia nervosa. Eur J Endocrinol 2001;145:669–673.
83 Otto B, Tschop M, Fruhauf E, Heldwein W, Fichter M, et al: Postprandial ghrelin release in anorectic patients before and after weight gain. Psychoneuroendocrinology 2005;30:577–581.
84 Haas V, Onur S, Paul T, Nutzinger DO, Bosy-Westphal A, et al: Leptin and body weight regulation in patients with anorexia nervosa before and during weight recovery. Am J Clin Nutr 2005;81:889–896.
85 Germain N, Galusca B, Grouselle D, Frere D, Tolle V, et al: Ghrelin/obestatin ratio in two populations with low bodyweight: constitutional thinness and anorexia nervosa. Psychoneuroendocrinology 2009; 34:413–419.
86 Druce MR, Wren AM, Park AJ, Milton JE, Patterson M, et al: Ghrelin increases food intake in obese as well as lean subjects. Int J Obes (Lond) 2009;29: 1130–1136.
87 Wren AM, Seal LJ, Cohen MA, Brynes AE, Frost GS, et al: Ghrelin enhances appetite and increases food intake in humans. J Clin Endocrinol Metab 2001;86: 5992.
88 Garcia JM, Polvino WJ: Effect on body weight and safety of RC-1291, a novel, orally available ghrelin mimetic and growth hormone secretagogue: results of a phase I, randomized, placebo-controlled, multiple-dose study in healthy volunteers. Oncologist 2007;12:594–600.
89 Hotta M, Ohwada R, Akamizu T, Shibasaki T, Takano K, et al: Ghrelin increases hunger and food intake in patients with restricting-type anorexia nervosa: a pilot study. Endocr J 2009;56:1119–1128.
90 Burdet L, de Muralt B, Schutz Y, Pichard C, Fitting JW: Administration of growth hormone to underweight patients with chronic obstructive pulmonary disease. A prospective, randomized, controlled study. Am J Respir Crit Care Med 1997;156:1800–1806.
91 Nagaya N, Kangawa K: Ghrelin, a novel growth hormone-releasing peptide, in the treatment of chronic heart failure. Regul Pept 2003;114:71–77.
92 Nagaya N, Kangawa K: Ghrelin improves left ventricular dysfunction and cardiac cachexia in heart failure. Curr Opin Pharmacol 2003;3:146–151.
93 Nagaya N, Uematsu M, Kojima M, Ikeda Y, Yoshihara F, et al: Chronic administration of ghrelin improves left ventricular dysfunction and attenuates development of cardiac cachexia in rats with heart failure. Circulation 2001;104:1430–1435.
94 Xu XB, Pang JJ, Cao JM, Ni C, Xu RK, et al: GH-releasing peptides improve cardiac dysfunction and cachexia and suppress stress-related hormones and cardiomyocyte apoptosis in rats with heart failure. Am J Physiol Heart Circ Physiol 2005;289:H1643–H1651.
95 Deboer MD, Zhu X, Levasseur PR, Inui A, Hu Z, et al: Ghrelin treatment of chronic kidney disease: improvements in lean body mass and cytokine profile. Endocrinology 2008;149:827–835.
96 Hanada T, Toshinai K, Kajimura N, Nara-Ashizawa N, Tsukada T, et al: Anti-cachectic effect of ghrelin in nude mice bearing human melanoma cells. Biochem Biophys Res Commun 2003;301:275–279.

97 Hanada T, Toshinai K, Date Y, Kajimura N, Tsukada T, et al: Upregulation of ghrelin expression in cachectic nude mice bearing human melanoma cells. Metabolism 2004;53:84–88.
98 DeBoer MD, Zhu XX, Levasseur P, Meguid MM, Suzuki S, et al: Ghrelin treatment causes increased food intake and retention of lean body mass in a rat model of cancer cachexia. Endocrinology 2007;148:3004–3012.
99 Wynne K, Giannitsopoulou K, Small CJ, Patterson M, Frost G, et al: Subcutaneous ghrelin enhances acute food intake in malnourished patients who receive maintenance peritoneal dialysis: a randomized, placebo-controlled trial. J Am Soc Nephrol 2005;16:2111–2118.
100 Ashby DR, Ford HE, Wynne KJ, Wren AM, Murphy KG, et al: Sustained appetite improvement in malnourished dialysis patients by daily ghrelin treatment. Kidney Int 2009;76:199–206.
101 Nagaya N, Moriya J, Yasumura Y, Uematsu M, Ono F, et al: Effects of ghrelin administration on left ventricular function, exercise capacity, and muscle wasting in patients with chronic heart failure. Circulation 2004;110:3674–3679.
102 Nagaya N, Itoh T, Murakami S, Oya H, Uematsu M, et al: Treatment of cachexia with ghrelin in patients with COPD. Chest 2005;128:1187–1193.
103 Neary NM, Small CJ, Wren AM, Lee JL, Druce MR, et al: Ghrelin increases energy intake in cancer patients with impaired appetite: acute, randomized, placebo-controlled trial. J Clin Endocrinol Metab 2004;89:2832–2836.
104 Strasser F, Lutz TA, Maeder MT, Thuerlimann B, Bueche D, et al: Safety, tolerability and pharmacokinetics of intravenous ghrelin for cancer-related anorexia/cachexia: a randomised, placebo-controlled, double-blind, double-crossover study. Br J Cancer 2008;98:300–308.

Prof. Matthias H. Tschöp
Institute for Diabetes and Obesity, Helmholtz Zentrum München and Department of Medicine
Technische Universität München
DE–85764 Munich (Germany)
E-Mail tschoep@helmholtz-muenchen.de