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Review

The Role of Ghrelin in Anorexia Nervosa

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Abstract: Ghrelin, a 28-amino acid peptide hormone expressed in X/A-like endocrine cells of the stomach, is the only known peripherally produced and centrally acting peptide that stimulates food intake and therefore attracted a lot of attention with one major focus on the treatment of conditions where an increased energy intake or body weight gain is desired. Anorexia nervosa is an eating disorder characterized by a pronounced reduction of body weight, a disturbed body image and hormonal alterations. Ghrelin signaling has been thoroughly investigated under conditions of anorexia nervosa. The present review will highlight these alterations of ghrelin in anorexia and discuss possible treatment strategies targeting ghrelin signaling. Lastly, gaps in knowledge will be mentioned to foster future research.

Keywords: animal model; body weight; brain-gut axis; drug; eating disorder; food intake; gut-brain axis; hormone; hunger; metabolism; psychosomatic; satiety

1. Introduction

Ghrelin was discovered in 1999 by Kojima and colleagues as an endogenous ligand of the growth hormone secretagogues receptor 1a (GHSR1a) stimulating the release of growth hormone (GH) from the pituitary [1] leading to the release of insulin-like growth factor 1 (IGF-1) [2]. Interestingly, GHSR1a is expressed, among others, in the arcuate nucleus, colocalized in neurons expressing Agouti-related peptide (AgRP) and neuropeptide Y (NPY) that regulate food intake [3]. Ghrelin was found to be secreted from oxyntic glands in the gastric fundus [1] and the subsequent description of ghrelin's effects on food intake, glucose metabolism and body weight followed soon thereafter [4].

Ghrelin is derived from preproghrelin and activated by acylation, namely by the attachment of a fatty acid side chain to its serine 3 residue catalyzed by the ghrelin-*O*-acyl transferase (GOAT) [5]. Interestingly, another peptide hormone is derived from this precursor, namely obestatin [6]. However, since the initially proposed effects were not reproducibly by several other groups as well as by the original authors, its role is controversially discussed [7] Therefore, we will not focus on obestatin in the present review.

Acylated ghrelin is able to bind to and activate the GHSR1a leading to, among other effects, a stimulation of food intake [8], reduction of insulin secretion resulting in hyperglycemia [9] and stimulation of gastric motility [10], whereas desacyl ghrelin—long thought to represent a non-active form of ghrelin—is assumed to counterbalance the orexigenic effect of acyl ghrelin [11,12]. It is to note that desacyl ghrelin does not bind to the GHSR1a at physiological but acts as agonist at supraphysiological levels [13,14]. Further supporting a counterbalancing effect, mice overexpressing desacyl ghrelin were shown to consume less food associated with a loss of body weight and fat mass as well as reduced linear growth [15].

Ghrelin is not only produced in X/A-like cells of the stomach [16], but also in pancreatic cells [17], the intestine as well as to lesser extent in kidney, liver, spleen, heart, lung, gonads, skin and adipose tissue [18]. Similarly, also GOAT is expressed in the stomach, pancreas, intestine, hypothalamus, ovary, placenta, muscle, heart and adrenal glands and has been detected in the circulation as well [19–23]. Since the lumen of the stomach provides the medium-chain fatty acids necessary for ghrelin's acylation, the main source of acylated ghrelin is assumed to be in the stomach [24]. The X/A-like cells are stimulated through β_1 adrenergic [25], GIP (gastric inhibitory polypeptide/glucose-dependent insulinotropic peptide) [26], alpha transducin and gustducin and Tas1R3 receptor pathways [27], and inhibited via somatostatin receptors [28,29].

Besides its stimulatory effect on food intake, in the last two decades ghrelin was shown to be implicated in various functions giving rise to a pleiotropic mode of action [30] with stimulatory effects on gastrointestinal motility, lipogenesis, blood glucose levels and inhibitory effects on blood pressure and luteinizing hormone as well as follicle stimulating hormone [31]. It is also to note that ghrelin exerts protective and/or therapeutic effects in rodents via the GHSR1a in different tissues including the spinal cord [32], heart [33], kidney [34], pancreas [35–38], ulcerated oral mucosa [39,40], stomach and duodenum [41–43] as well as colon [43–45].

Early on, it was described that ghrelin is regulated in a meal-dependent fashion with a fasting/pre-prandial increase of gastric *ghrelin* and *GOAT* mRNA expression [23] resulting in increased circulating ghrelin levels [46] and a decrease after the meal with lipids being especially potent to reduce circulating ghrelin [47,48]. Interestingly, low gastric pH increases the release of desacyl ghrelin from the stomach [49], probably to initiate the termination of food intake. Moreover, also chronic alterations of body weight were shown to affect circulating ghrelin levels with a decrease observed under conditions of overweight/obesity [50] and an increase in patients with cachexia [51] as well as anorexia nervosa [52] as detailed below.

Peripheral ghrelin's orexigenic effect is thought to be mediated centrally, namely after crossing the blood-brain barrier via binding to its receptor located on NPY- and AgRP-expressing neurons in the arcuate nucleus initiating the mTORC1/S6K1 (mechanistic target of rapamycin complex 1/p70 ribosomal protein kinase 1) pathway [53,54]. Moreover, ghrelin can also bind to vagal afferents that signal to the brainstem to induce an orexigenic effect [55]. Consequently, ghrelin is a hallmark hormone of the gut-brain axis and early on attracted attention as possible target in the treatment of conditions where stimulation of food intake or weight gain is desired.

Patients suffering anorexia nervosa (AN) intentionally loss body weight by reducing food intake, hyperactivity, self-induced vomiting and abuse of laxatives [56]. The body mass index (BMI) defined as $\leq$17.5 kg/m^2 and can reach life-threatening values under 12; consequently, the disease has a high mortality between 5% and 20% [57]. The rising prevalence of eating disorders worldwide [58] underlines the necessity to expand the knowledge about their pathophysiology. Recent studies give rise to an important role for ghrelin in the pathophysiology and clinical course of AN.

Therefore, the present review will describe the alterations of ghrelin under conditions of AN and ghrelin's putative role as a drug candidate in the treatment of AN. Moreover, gaps in knowledge will be addressed to stimulate future research.

2. Alteration of Ghrelin in Anorexia Nervosa

2.1. Basal Circulating Total Ghrelin Levels

In 2001 a significant difference between fasting plasma ghrelin levels in anorexic patients compared to age-matched healthy controls was observed for the first time [52]. Ghrelin levels were elevated in AN patients and reduced after therapeutically induced increase of BMI resulting in a negative correlation between BMI and ghrelin [52]. Subsequent studies corroborated these findings [59,60], alterations also observed in an animal model for anorexia nervosa, activity-based anorexia (ABA) [61,62]. Since ghrelin

correlates positively with the extent of physical activity [63], hyperactivity is likely to play a role in the elevation of ghrelin.

Additionally, a negative correlation between fasting ghrelin and insulin levels was observed [64]. Another study extended these findings by the observation of negative correlations between percent body fat and serum cholesterase in AN as well as a positive correlation with serum amylase [65]. Interestingly, this study, using a self-developed radioimmunoassay, differentiated between anorexic patients of the binge eating/purging type (AN-BP) and the restricted type (AN-R), showing significantly higher fasting mean plasma levels of ghrelin in those with binge eating/purging behavior, pointing towards an effect of bingeing and purging on ghrelin release/concentration [65], additionally illustrating a positive correlation between frequencies of binge/purge cycles with plasma ghrelin concentration [66]. In contrast, a negative correlation was observed between frequency and severity of binge eating and purging behavior as measured by BULIT-R (bulimia test) total scores and ghrelin concentrations, and lower plasma ghrelin concentrations in patients with AN-BP compared to those suffering from AN-R [67]. These opposing results may result from different BMI values of included subjects (13.7 $\pm$ 1.9 and 13.6 $\pm$ 1.5 in [65], 13.9 and 14.4 in [66] vs. 16.0 $\pm$ 2.4 in [67]). It has to be noted that the results were obtained using different radioimmunoassays, self-developed [65] or commercially purchased [67] possibly also contributing to the different levels observed. An additional study included emergently hospitalized AN patients, showing higher ghrelin levels in those patients compared to patients with AN-BP, AN-R and age-matched healthy female controls [68]. Further supporting a link between purging and ghrelin, examinations using the Three-Factor Eating Questionnaire demonstrated a positive correlation between ghrelin secretion during the cephalic phase and the tendency to lose control over eating in AN [69].

Following up on these findings in studies comparing AN to normal weight controls, in 2003 a study compared AN patients with BMI-matched healthy subjects showing that AN patients had doubled fasting and 24-h plasma ghrelin levels compared to constitutionally lean subjects [70], giving rise to a role of ghrelin in the development or maintenance of AN. Another study even showed reduced ghrelin levels in constitutionally lean subjects compared to normal weight controls, while ghrelin levels in AN were increased [71]. Moreover, AN subjects also displayed higher ghrelin levels compared to cancer patients developing cachexia [72]. The underlying mechanism responsible for this specific up-regulation remains to be unraveled.

In 2005, a study examined ghrelin's secretion in adolescents in detail, demonstrating that its concentration is not only higher in AN but also its nadir as well as total area under the curve over 12 h of nocturnal sampling were elevated [73]; this period of time was chosen since ghrelin rises physiologically under conditions of fasting such as during sleep, likely to stimulate subsequent food intake [53]. In addition, secretory burst amplitude and burst mass were increased in AN resulting in higher pulsatile and total ghrelin secretion [73]. Hereby, fasting ghrelin was related toGH burst frequency with predictive value [73]. Nutritional markers such as BMI and body fat correlated with nadir and post-glucose but not fasting ghrelin levels, whereas those were negatively related to fasting insulin, insulin resistance, leptin, insulin-like growth factor (IGF-1) and HOMA-IR (homeostasis model assessment of insulin resistance) [73,74]. Low levels of IGF-1 and insulin are likely related to low energy and nutritional status in AN, since IGF-1 stimulates cell growth whereby an adequate energy state is necessary [75], and insulin is responsible for anabolic processes suppressed due to the lack of energy [76]. Furthermore, ghrelin was associated with total T_3 (triiodothyronine) and luteinizing hormone levels, but only nadir ghrelin independently predicted cortisol burst frequency [73]. A different study observed this positive correlation between ghrelin and cortisol only in female AN patients but not in female healthy controls [67], likely reflecting/contributing to the stress component of the disease.

2.2. Expression of Ghrelin

In immunohistological expression analyses of pituitary from healthy humans and anorexic subjects, ghrelin was localized mainly in somatotrophs [77]. Controls showed only limited immunoreactivity, whereas in the tissue of anorexic subjects immunoreactive cells were observed in nerve fibers and Herring bodies of the posterior pituitary and pituitary stalk [77]. Moreover, in contrast to controls ghrelin was additionally apparent in the anterior pituitary [77]. Higher central ghrelin signaling is likely a compensatory mechanism to stimulate food intake and body weight gain in AN. It is important to note that human data are lacking so far that describe the alterations of peripheral ghrelin expression under conditions of AN.

ABA mice displayed an increase of *preproghrelin* mRNA-expressing cells of the stomach in proportion to body weight loss [78]. Interestingly, hypothalamic *preproghrelin* mRNA expression was suppressed in ABA mice [78], possibly pointing toward differential effects of central and peripheral ghrelin.

It has been reported that under conditions of food restriction in rats oxidative soleus type muscles are more susceptible to circulating ghrelin compared to those of the glycolytic gastrocnemius type [79], giving rise to a differential regulation of the ghrelin receptor due to anorexia, as was reported for e.g., hypothyroidism [80], a hypothesis to be further investigated.

2.3. Acyl and Desacyl Ghrelin

Subsequent studies investigated different forms of ghrelin showing that acyl ghrelin was significantly increased in AN [81,82], likely to stimulate food intake in a compensatory fashion. It is to note that another group described opposing results: an increase of desacyl ghrelin in AN and a negative correlation with BMI, while acyl ghrelin was not/only slightly different without reaching significance compared to healthy controls [83,84]. Adding more confusion, a study reported both, acyl and desacyl ghrelin to be increased in patients with AN-R [85], whereas in constitutionally lean individuals acyl ghrelin was observed to be decreased compared to normal weight controls [86]. These differences might be due to different BMI values of the anorexic subjects studied (13.9 ± 1.0 [81] vs. 15.5 ± 2.6 [84] vs. 13.4 ± 0.3 [85]) or population size ($n = 5$ [81] vs. $n = 30$ [84] vs. $n = 10$ [85]). Observing a circadian profile, patients with AN-R showed higher total and acyl ghrelin levels compared to controls, whereas subjects with AN-BP displayed decreased total and acyl ghrelin levels; moreover, the ratio of acyl/total ghrelin was decreased in AN-BP [87,88]. The incongruence to findings mentioned before presenting highest levels in AN-BP, followed by high levels in AN-R and the lowest levels of ghrelin in healthy controls [65] could be explained by the different time points/period of time of blood sampling as well as by the different BMI values (15.4 ± 1.4 and 15.2 ± 1.6 in [87] vs. 13.7 ± 1.9 and 13.6 ± 1.5 in [65]).

ELISA (enzyme-linked immunosorbent assay) examinations showed decreased auto-antibodies, namely immune globulin G (IgG), IgM and IgA against acyl ghrelin and elevated levels of IgG auto-antibodies against desacyl ghrelin in AN but not healthy subjects [89]. These auto-antibodies against desacyl ghrelin were found mostly in immune complexes with desacyl ghrelin and were negatively associated with plasma acyl and desacyl ghrelin, whereas acyl ghrelin IgM auto-antibodies correlated with BMI [89]. It might be hypothesized that IgG against acyl ghrelin are reduced to allow free acyl ghrelin to stimulate food intake, whereas desacyl ghrelin's effect to lower food intake might be inhibited by IgG bound to desacyl ghrelin leading to immune complexes in AN. In infants with Prader-Willi syndrome elevated levels of desacyl ghrelin were observed, which have been implicated in the anorexia observed at the beginning of the disease [90], giving rise to desacyl ghrelin's inhibition as a possible target in the treatment of anorexia (nervosa).

2.4. Nutrient-Related Alterations of Ghrelin

Physiologically, ghrelin is elevated before a meal and decreases after food consumption. However, unlike in control subjects, acyl ghrelin levels in plasma from anorexic women did not decrease after meal consumption [91]. Other studies observed a moderate (−25%) reduction of acyl ghrelin with

a delayed onset (60–90 min after the meal) in subjects with AN following a mixed meal [64] or a high-carbohydrate breakfast [92] which may represent a compensatory action to promote further food intake. It is to note that especially fat intake predicted ghrelin values in plasma of patients with AN [93], likely related to the need of fatty acids for ghrelin's acylation in the stomach [24]. This is further supported by the finding that consumption of medium-chain triglycerides elevates ghrelin levels by activation of GOAT [94].

In contrast to food intake, modified sham feeding, where food is smelled and chewed but not swallowed, resulted in an elevation of circulating ghrelin concentrations which was higher in AN compared to age-matched healthy women [69], pointing towards an increased vagal tone in AN, whose hyperactivity was described in adolescents suffering from AN before when investigating cardiac functions [95].

Interestingly, in AN subjects the consumption of both favorite and unfavorite foods resulted in the reduction of ghrelin levels while in healthy as well as former anorexic subjects eating of favorite food further increased ghrelin levels [96]. To investigate underlying mechanisms, functional magnetic resonance imaging can be used that indicated a positive relation between fasting acyl ghrelin and activity in the right amygdala, hippocampus, insula, orbitofrontal cortex in response to high caloric foods in normal weight subjects [97]. The association between acyl ghrelin and hippocampus activity following a visual stimulus showing high caloric food was absent in AN but restored in AN patients following weight recovery [97] indicating altered reward responsivity in AN.

During the oral glucose tolerance test (oGTT) subjects receive 75 mL of glucose solution which induced a reduction of circulating ghrelin levels in healthy subjects [98]. An early study reported that after an oGTT total ghrelin concentrations in plasma decreased both in AN (−49%) and healthy age-matched controls (−57%); likewise, mean levels of plasma acyl ghrelin decreased in both groups [81]. Interestingly, the type of AN had an impact on the kinetics of ghrelin changes with a 58-% reduction of total ghrelin after 120 min in AN-BP, while in AN-R the 80-% decline was observed 180 min after the oGTT [99]. The mechanisms underlying this different time course warrant further investigation. Another study did not observe a decrease of total ghrelin following glucose neither in AN patients nor in healthy controls, while acyl ghrelin was significantly reduced [82] resulting in a significantly reduced acyl/total ghrelin ratio [82,83,100]. Interestingly, early after the test (at 30 and 60 min) total [101], acyl and desacyl ghrelin [85] were increased.

In contrast to the ghrelin responses observed, less than one third of adolescent patients showed an adequate reduction of GH levels following an oGTT [101]. Since ghrelin levels did not predict the oGTT-induced response of GH [101] altered GHSR1a sensitivity might play a role, a hypothesis to be further investigated.

2.5. Treatment-Related Alterations of Ghrelin

Weight regain of 14% in patients undergoing psychotherapy was associated with a 25-% reduction of fasting plasma ghrelin levels [52], other studies even reported a normalization [102] or a decline of plasma ghrelin below levels of control subjects [103]. Subsequent studies investigated these alterations in more detail. Treatment encompassing cognitive behavioral therapy and nutritional therapy led to a decrease of ghrelin levels in patients with AN emergently hospitalized as well as in AN-BP patients, while in AN-R ghrelin levels even exceeded levels before beginning of treatment and control levels [68]. It is to note that AN-BP patients still had elevated ghrelin levels at the end of the treatment [68], likely due to the fact that they did not reach the desired weight gain. Another study reported that relative ghrelin changes did not differ before and after treatment, while absolute values of postprandial ghrelin decreased from admission, partial weight gain and discharge, respectively (871.9, 597.0, 570.4 pg/mL) [104]. These changes were also observed over a long period of time (24 weeks) [105] and could be reinstated after a short nutritional rehabilitation program [106].

Investigating the different forms of ghrelin, a study applying cognitive behavior therapy and nutritional rehabilitation described a decrease of desacyl ghrelin resulting in an increased acyl/total

ghrelin ratio [88]. This decrease of desacyl ghrelin was also observed in another study [107] and might be accompanied by a reduction in anorexigenic signaling.

A study investigating acute meal-related changes observed that the postprandial decrease of ghrelin was similar in anorexic patients and healthy controls reaching the nadir at 120 min [108]. However, in AN, ghrelin levels remained higher in comparison to healthy controls even after therapy comprised of inpatient behavioral treatment involving operant techniques, nutritional rehabilitation, psychotherapy, family therapy, and behavioral counseling, application of serotonin reuptake inhibitors and sulpiride as well as nutritional therapy [108]. It is important to note that other multimodal treatment approaches—here including cognitive behavioral psychotherapy and programmed nutritional rehabilitation, combined with olanzapine or placebo—did not induce alterations of ghrelin in AN patients [109], likely associated with the severity of the disease at the beginning of the treatment (BMI 12.4 $\pm$ 1.7 vs. 16.3 $\pm$ 0.7).

3. Genetics Contributing to Altered Ghrelin Signaling in Anorexia Nervosa

Two studies in 2006 examined the association between several polymorphisms of the *ghrelin* gene including Gln90Leu, Leu72Met, Arg51Gln described in obese and healthy humans before [110,111] and the development of AN, observing no significant difference in the frequency of those gene variants among anorexic and healthy subjects in Caucasian women or a mixed European population from Italy, Spain, Germany, Slovenia, France, Austria and United Kingdom [112,113].

Subsequently, a significant correlation between the polymorphism Leu72Met, a region potentially responsible for posttranslational processing, and the prevalence of AN-BP was documented [114]. This polymorphism was predominantly detected in subjects with low BMI, fat mass and fasting respiratory quotient [114]. In addition, regarding the Gln90Leu72 haplotype a significant transmission misbalance in AN patients was detected, analyzing AN patients and both parents in a French population [114].

Regarding the recovery potential of anorexic patients, the TT genotype at 3056 T→C in the *ghrelin* gene showed higher probability to achieve normal body weight [115]. An above-average prevalence of the G/G genotype at the SNP (single nucleotide polymorphism) vs100096097 was discovered in German anorexic subjects, resulting in a genetic variation in the GOAT enzyme [116]. Since GOAT is reduced in patients with AN [21] and may thereby contribute to the reduced orexigenic drive in these patients, this genetic alteration may well play a role in the pathophysiology of the disease. These changes and a possible impact on treatment outcomes should be further evaluated in future studies.

4. Effects of Exogenous Ghrelin in Anorexia Nervosa

4.1. Effects of Ghrelin Administration

Due to the robust orexigenic effect of ghrelin, several studies investigated a potential therapeutic use of the peptide. In ABA mice a GHSR1a antagonist, injected either acutely intracerebroventricularly or chronically peripherally, inhibited food-anticipatory behavior but had no effect on total food intake [62]. Intraperitoneal injection of ghrelin led to a blunted reduction of food intake under conditions of ABA, preventing the development of ABA, nonetheless, animals still lost body weight [117]. When combined with plasmatic anti-ghrelin IgG from obese, which is able to protect ghrelin from degradation, thereby enhancing ghrelin's orexigenic effects [118], ghrelin inhibited physical activity during feeding and stimulated the activity after meal consumption resulting in an elevated relation of consumed food to running distance during feeding time in ghrelin plus IgG-receiving animals [117].

Modulations of ghrelin signaling were also tested in humans. Intravenous injection of ghrelin only moderately increased GH, giving rise to a desensitization of the GHSR1a under conditions of AN [119]. However, ghrelin induced a regular increase of ACTH (adrenocorticotropic hormone) and cortisol in AN [119], possibly pointing towards the mediation by different receptor subtypes. Another study observed that ghrelin subjectively did not induce appetite but sleepiness in AN patients compared to

constitutionally lean subjects [120], probably due to the ability of ghrelin to promote slow wave sleep in humans [121]. Moreover, acyl ghrelin infused intravenously over 5 h increased glucose levels in AN and even more in constitutionally lean subjects [122], possibly due to larger glycogen stores under constitutionally lean conditions.

Chronic intravenous application (twice a day over 14 days) of ghrelin at a dose of 3 ug/kg body weight resulted in improved epigastric discomfort and constipation in four of five patients, likely associated with increased gastric motility [123]. Also hunger scores were increased leading to an increased energy intake of 12% to 36% [123]. Similarly, in another study following the same administration protocol, ghrelin suppressed upper abdominal fullness inducing stomach rumble and hunger sensation but not constipation in five AN-R patients associated with an increase of daily energy intake by 20% [100]. Despite these encouraging results, these findings must be followed up in a larger sample under controlled conditions.

4.2. Effects of Ghrelin-Related Products and Ghrelin Receptor Agonists

Not only ghrelin itself displayed beneficial effects in the course of AN, but also the ghrelin enhancer rikkunshito, a traditional Japanese medicine, was shown in vitro to antagonize serotonin's action in POMC (pro-opiomelanocortin) neurons of the arcuate nucleus, whose release has been described to be increased in AN [124]. Additionally, in cisplatin-treated rats rikkunshito was able to prevent the reduction of plasma ghrelin levels by inhibiting ghrelin's desacylation, resulting in an augmented acyl/desacyl ghrelin ratio associated with a blunted decrease of food intake [125].

In humans, the effect of rikkunshito has been tested in chemotherapy-induced anorexia only, leading to a reduction of nausea and emesis and a stimulation of appetite [126]. These findings should be followed up in patients with AN as well. Very recently, a study investigated the effects of relamorelin (subcutaneously daily over a period of four weeks), a ghrelin agonist, in an outpatient cohort (n = 10–12/group) of AN showing a significant acceleration of gastric emptying as well as a trend towards an increase of body weight (+0.9 kg vs. 0.3 kg in the control group, $p < 0.07$) [127]. Again, larger follow up studies are needed. These findings are surprising as ghrelin levels are already elevated, and ghrelin resistance is suspected as described above. Nonetheless, the further increase of ghrelin to supraphysiological levels might still be a promising approach to stimulate food intake in a supportive manner.

5. Conclusions

In conclusion, ghrelin is the only known peripherally produced and centrally acting peptide hormone that stimulates food intake and gastric motility. Additionally, ghrelin increases blood glucose levels by reducing glucose-stimulated insulin secretion, insulin sensitivity and inducing glucagon secretion [31]. In states of severe undernutrition and underweight such as AN, ghrelin is increased compared to healthy controls, even if those are BMI-matched [70], which can be normalized through weight gain and renutrition [102]. Genome-wide association studies demonstrated a relationship between polymorphisms in the ghrelin gene [114] as well as in the gene of the enzyme acylating ghrelin, GOAT [116] and the prevalence of AN [114], pointing towards a ghrelin-related genetic component of AN. In AN not only central [77] and peripheral [78] ghrelin expression is increased, but also ghrelin signaling and modulation are impaired as indicated by a delayed or absent postprandial decrease of ghrelin [64,91], the inability to suppress GH secretion adequately after glucose digestion [101] or the insufficiency of glucose elevation after exogenous ghrelin application [119], suggesting ghrelin resistance in AN (Figure 1). Noteworthy, exogenous ghrelin (by raising ghrelin to supraphysiological levels) or ghrelin receptor agonists still might be able to improve the course of AN by stimulating appetite and reducing gastric discomfort leading to an increase of energy intake and body weight [100,123,127]. Since these data are derived from small pilot studies, these effects should be corroborated—or refuted—in larger clinical trials.

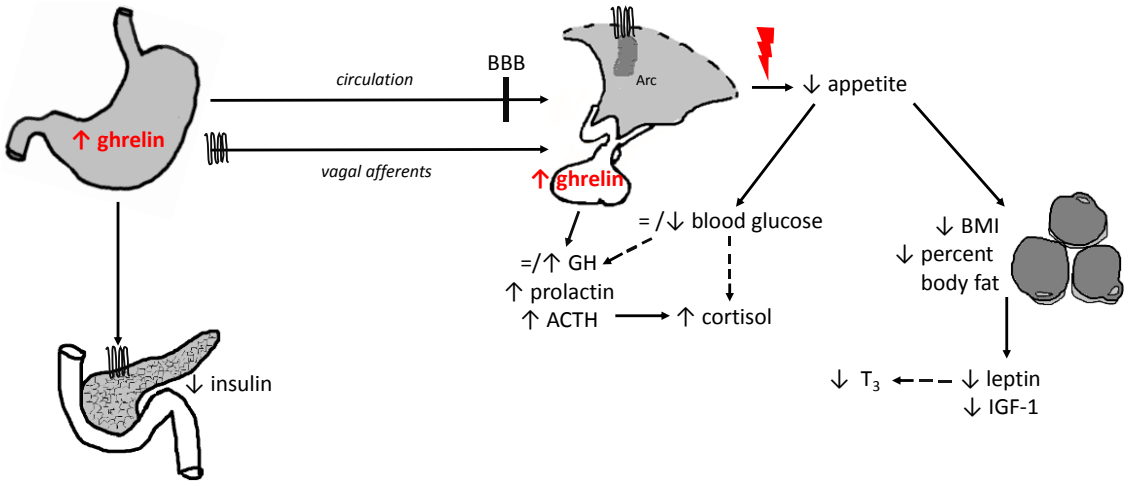

Figure 1. Hypothesized alterations of ghrelin's signaling in anorexia nervosa. growth hormone secretagogue receptor 1a; mechanisms contributing to insufficient stimulation of food intake irrespective of high ghrelin levels; = no alteration; ↑ increase/stimulation; ↓ decrease/inhibition, - - > indirect effect; ACTH, adrenocorticotropic hormone; BBB, brain-blood barrier; BMI, body mass index; GH, growth hormone; IGF-1, insulin-like growth factor-1; T_3, triiodothyronine.

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Abbreviations

GHSR	growth hormone secretagogue receptor
AgRP	agouti-related peptide
NPY	neuropeptide Y
GOAT	ghrelin-*O*-acyl transferase
GIP	gastric inhibitory polypeptide/glucose-dependent insulinotropic peptide
mRNA	messenger ribonucleic acid
mTORC1/S6K1	mechanistic target of rapamycin complex 1/p70 ribosomal protein kinase 1
AN	anorexia nervosa
BMI	body mass index
ABA	activity-based anorexia
AN-BP	anorexia nervosa of bingeing/purging subtype
AN-R	anorexia nervosa of restrictive subtype
BULIT-R	bulimia test—DSM-III-R
GH	growth hormone
IGF	insulin-like growth factor
HOMA-IR	homeostatic model assessment—insulin resistance
T_3	triiodothyronine
ELISA	enzyme-linked immunosorbent assay
Ig	immune globulin
IGF-1	insulin-like growth factor 1
oGTT	oral glucose tolerance test

SNP	single nucleotide polymorphism
ACTH	adrenocorticotropic hormone
POMC	pro-opiomelanocortin

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