Ghrelin in The Hunger, The Brain and The Pain

5.årsoppgave Profesjonsstudiet Medisin
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Keywords: *Ghrelin, The Gut-Brain Axis, obesity, functional disorders, eating disorders*

SAMMENDRAG

Bakgrunn

Oppgaven er en litteraturstudie som sammenfatter det siste tiårets forskning på nevrohormonet ghrelin, innenfor en holistisk forståelse av The Gut Brain Axis som et felles fysiologisk spektrum for flere ulike følelser, som sult, metthet og smerte.

Mål med studien

Å presentere en litterær oversikt over ghrelin med vekt på hvordan hormonet er integrert i The Gut Brain Axis, og hvordan det er involvert i vektregulering, sult, spiseatferd, funksjonelle tilstander og inflammasjon.

Material og metode

Søk i PubMed og Cohrane databasen

Resultat

Ghrelin stimulerer sult og appetitt. Det er også en ligand til veksthormonfrisettende reseptor GHS-R1a, og en promoter av motilitet i magesekken. Det er en negativ assosiasjon mellom ghrelin og BMI, så vel som insulin og insulinfølsomhet. Forstyrrelser i vekt, spiseatferd og inflammatoriske tilstander kjennetegnes av endringer i ghrelinsekresjonen, og en forstyrret relasjon mellom de molekylære formene av hormonet.

Konklusjon

Virkningene av ghrelin bør sees innen en holistisk forståelse av The Gut Brain Axis. Videre forskning på ghrelin bør vurdere begge molekylære former av hormonet.

ABSTRACT

Background

This paper is a literary review of the past ten years of research on the neuropeptide hormone ghrelin, with a holistic understanding of The Gut Brain Axis as a common physiological spectrum for several sensations, such as hunger, satiety and pain.

Aim of study

To present a literary review of ghrelin with emphasize on how it is integrated in the gut-brain axis, and how it is involved in weight regulation, hunger, eating behavior, functional conditions and inflammation.

Materials and Methods

Searches in PubMed and The Cochrane Library.

Results

Ghrelin stimulates hunger and appetite. It is also a ligand for the growth hormone-releasing receptor GHS-R1a, and a promoter of gastric motility. There is a negative correlation between ghrelin and BMI, as well as insulin and insulin sensitivity. Distortions of weight, eating behavior and inflammatory conditions are characterized by changes in ghrelin secretion, and a disturbed relation of the molecular forms.

Conclusion

The effects of ghrelin should be seen within a holistic understanding of The Gut Brain Axis. Clinical trials in the years to come should consider both molecular forms of ghrelin.

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BACKGROUND

Introduction

"The Hunger, The Brain and The Pain" summarizes the most important results from a literary study of the peptide hormone ghrelin and its functions within The Gut Brain Axis.

This paper shows the various functions of this hormone within a holistic understanding of The Gut Brain Axis as a common physiological spectrum. Ghrelin is shown as an example of how various functions of metabolism, digestion, weight control, eating behavior and functional disorders are integrated.

The title mirrors the major physiological aspects of The Gut-Brain Axis. The Gut Brain Axis refers to all afferent and efferent neural, endocrine and nutrient signalling across the CNS and GI-tract. It connects higher cortical areas, hypothalamic nuclei and the limbic system to the essential processes of the digestive tract. Ghrelin has also been referred to as the most important endocrine organ of the body. 1.

The major reason for choosing ghrelin as an example is that still this is the only hormone known to have orexigenic actions. It is also among the very few hormones that is expressed both in central as well as in peripheral tissues. Ghrelin is involved in gut motility and metabolism, and it is associated with body weight and inflammatory

disorders. Ghrelin has gained increasing interest because of its various characteristics.

A common physiological spectrum mediating different sensations?

Greenough et al. was the first group referring to The Gut Brain Axis as a common physiological spectrum.[2] Sanger et al. refers back to this group in their major review article on The Gut Brain Axis. What is interesting about the gut brain axis is that different sensations appear to be controlled by the very same physiological processes both through efferent and afferent connections.[1] Alterations of the gut-brain interactions are associated with induction of symptoms of functional disorders, modulation of the immune system in inflammation as well as the pathogenesis in disturbed eating behavior. [1]

This paper understands "the common physiological spectrum" as how the different sensations of hunger, satiety and pain are controlled within the mechanisms of the gut-brain axis, and how different conditions of pathology, obesity, functional disorders and inflammation can be understood as dysregulation within this axis - or it might as well be associated with changes of components within it.

This paper wants to clarify that the hormone ghrelin alone cannot explain any of the pathological conditions referred to alone, but it intends to investigate how this hormone is associated with such conditions, presenting it with a holistic understanding of The Gut Brain Axis.

The different sensations within The Gut Brain Axis appear to be integrated with each other. Appetite is indifferently interlinked with the process of digestion and with metabolic state.[1] Sanger et al. refer to an article by Greenough et al., in which this is further discussed. [2]

The authors detected that infusion of CCK, a satiety hormone, was also able to induce nausea, but with no effects on food intake or hunger. [2] Interestingly, the subjects experiencing gastrointestinal disturbance actually had a smaller suppression of hunger. They conclude that there must be more than only CCK regulating this, and that a large dose of satiety hormone induces nausea.

The authors refer back to previous publications, claiming that CCK induced this effect by releasing neurohypophyseal hormones such as oxytocin and vasopressin, surprisingly not by a natural satiety. [2]

The past years of research have revealed a more complicated association of the different components making up this common physiological spectrum. One stimulus can induce more than one sensation. The experience of hunger is opposed by nausea, whereas pain in general opposes hunger.[3] Sensation of hunger, satiety, nausea and - to a certain extent - abdominal pain, actually work within the same spectrum of physiological mechanisms. [2]

Neurological and endocrine components of the Gut-Brain Axis

All hormone-producing organs communicate through secretion of hormones and mediating factors, as well as by two-way interaction between the CNS and peripheral tissues transmitted by autonomous nervous connections.[4] Mayer et al. point out, that in order to co-ordinate functions of the GI-tract with the homeostatic state of the organism, a communication between the CNS and the GI-tract is required.[5] In other words, there must be a way of transmitting signals between the gut and the brain. From the gut, afferent neurological connections project to the CNS. [5]

However, the enteric nervous system of the gut is not alone in generating responses to different stimulies; the spinal cord as well as central tissues are involved in homeostatic reflexes.[5] Furthermore,

descending signals from the cortico-limbic structures of the CNS can also be affected by cognitive and emotional stimulies.[5] As well afferent as efferent signalling transmitted by the vagus is involved in the regulation of hunger, satiety and appetite.[6] Signals are transmitted from the gut via the solitary tract of the brainstem and the hypothalamus. [6]

Several different peptide hormones are released from the GI-tract on ingestion of nutrients, affecting motility, secretion and exocrine processes. [6] The most important are summarized in the table below.

Peptide	
CCK	Reduction of food intake and induction of satiety by binding to the CCK-I receptor, partly mediated by vagal afferents.
Bombesin	Anorexigenic mediated by way of the solitary tract.
Motilin	Induces a premature phase III of the MMC
Obestatin	From the pro-ghrelin transcript. Reduction of food intake, antagonizing ghrelin, but effects are controversial.
PP	Released on digestion of lipids. Reduces food intake, unknown mechanism.
GIP	Incretin effect, prolongs the glucose-dependent secretion of insulin. Promotes energy storage.
GLP-1	Incretin effect, prolongs the glucose-dependent secretion of insulin. Suppresses gastric acid. Promotes lipogenesis, but controversial.
Oxyntomodulin	Inhibits gastric acid, reduces food intake
Peptide YY	Delayed gastric emptying, reduces food intake, activate the anorectic POMC-neurons. Physiological levels reduce food intake but do not induce nausea.

Table 1: Summary of gut hormones and their effects [7, 6, 1]

In summary, there are more than 20 different gut hormones operating within the gut-brain axis, and many of them are strong appetite-regulating signals.[8]

The interaction between the gut peptide signals and the hypothalamus are deeply involved in the short-term regulation of energy state.[9] A lot of this integration of neuroendocrine signals happens in the arcuate nucleus of the hypothalamus. [10]

The arcuate nucleus is the most important component of the central nervous system concerning nutrition, food intake and interaction with

the digestive tract, and the most important neuronal populations involved in the regulation of appetite and food intake are the Agouti Related Peptides and the Neuropeptide Y expressing peptides.[1] These neurons express receptors sensitive for insulin, leptin, corticosteroids and ghrelin.[11] These functions provide them with a unique potential for integration of signals controlling hunger and satiety.

In addition to the orexigenic stimulies, which are integrated in the AgRP- and NPY-neurones, the arcuate nucleus is also involved in integrated anorexigenic signals. [6] The population of neurones called Pro-Opio Melanocortin Neurons are also integrated in the hypothalamus, [6, 10] some of them projecting into the paraventricular nucleus. [10]

The hypothalamus integrates effector pathways, comprising metabolic, neural and hormonal signals in an appetite-regulating network.[12] Distortions of these afferent signals would promote excess energy intake. [12]

Hunger, satiety and nausea all appear to activate both sensory and emotional processes, localized in the GI-tract and brain. By way of indirect, complex pathways, cognitive processes could influence the neuro-enteric system.[13] Common to both non-painful sensations, like satiety, and painful sensations, is the propagation along autonomic nerve fibres. [13] Impulses lead by autonomic nerve fibres activate low-threshold or high-threshold mechanoceptors.[14] However, the connections composing all the relaying stations are still, at least in part, unknown.

Rhee et al. state that the signal molecules of the gut, such as catecholamines, serotonin, dynorphin and cytokines signalling stress

situations, are most likely released by neurons, immune cells and the enterochromaffine cells of the gut, modulated by the CNS.[14] Thus, the CNS can transmit stressful experiences to the gut, affecting the permeability, activation of cells and changes in epithelial morphology. [14] Rhee et al. conclude that such distortions might be an important component in the IBS pathogenesis. [14]

Ghrelin - A Connecting Breakthrough

In the era of an outrageous prevalence of obesity, any orexigenic agent and promoter of weight increase and positive energy balance would be of interest, especially if it could be proven functional both within the digestive tract and the CNS, possibly influencing weight regulation and being involved in motility, immunology and cognitive aspects. The answer to this description is ghrelin.

Ghrelin is a 28-amino acid neuropeptide

Ghrelin was first discovered as the endogenous ligand of the growth hormone releasing receptor GSH-R. [15] Functionally, it works as a Growth Hormone Secretagogue, stimulating release of GH by way of somatotrope cells of the pituitary. [16, 15] Ghrelin was also discovered to be a strong orexigenic agent, stimulating appetite through its direct action on the arcuate nucleus. [17] However, ghrelin is also known to induce numerous biological effects, among them gastrointestinal motility, affecting the adrenocorticotrophic axis, influencing cognitive processes and glucose- and insulin function. [18, 19, 20, 21] The hormone connects numerous processes of the organism involved in a complex regulation of energy balance, eating behaviour and weight regulation.

The major location of ghrelin synthesis and modulation is the X/A-like cells of the oxyntic glands of the stomach fundus. [22, 18] These cells have a most peculiar location, in that they lie close to the capillary network of the gut mucosa. [18] The cells synthesize about 65 % of total ghrelin in humans. [21]

The gene carrying the code for ghrelin is located on the third chromosome; the 3p25-26 locus. Its mRNA is composed from the transcripts of 4 exons.[23] It is further transcribed and syntesized as pre-pro-ghrelin, a well-conserved precursor in most mammals, consisting of 117 amino acid residues. [23] 3 peptides are generated from pre-proghrelin; acyl-ghrelin, des-acyl ghrelin and obestatin, [24, 1, 21] the latter an endogenous ligand of an orphan G-coupled receptor GPR39.[1]

Ghrelin is expressed in several different tissues; the stomach, the pancreas, adrenals, testis and ovaries. [25, 26, 27] It circulates in plasma both free and protein-bound. [28, 29] Des-acyl ghrelin binds primarily to HDL, whereas acyl-ghrelin binds all lipoproteins. [30] This might also influence biological effects. [30]

The Growth hormone releasing receptor GHS-R

The ghrelin receptor is a G-protein coupled protein with two known transcripts; type 1a and type 1b (the latter is a truncated protein)[31] The receptor is expressed in both central and peripheral tissues, but the highest frequency of receptor is in the hypothalamus and the pituitary.[31]

The release of GH happens by way of ghrelin binding to the receptor GHSR1a, which amplifies ?of the GHRH, stimulating normal GH-release from the pituitary.[16] It has been suggested that more than one ghrelin receptor is involved, because the known GHS-R1b receptor is not responsive to ghrelin, but that cell lines positive for the GHS-R1b are responsive to ghrelin.[32]

The Modulation of Ghrelin

The orexigenic, growth hormone releasing functions of ghrelin are entirely dependent on its n-terminal octanoylation of a serine residue, the third positioned amino acid, with an n-octanoic acid, or another

medium length chain fatty acid. [23, 33] This modification is dependent on the enzyme ghrelin O-acyltransferase (GOAT). [34, 35] Apparently, the enzyme has distinctive substrate specificity for acyl acids. [35]

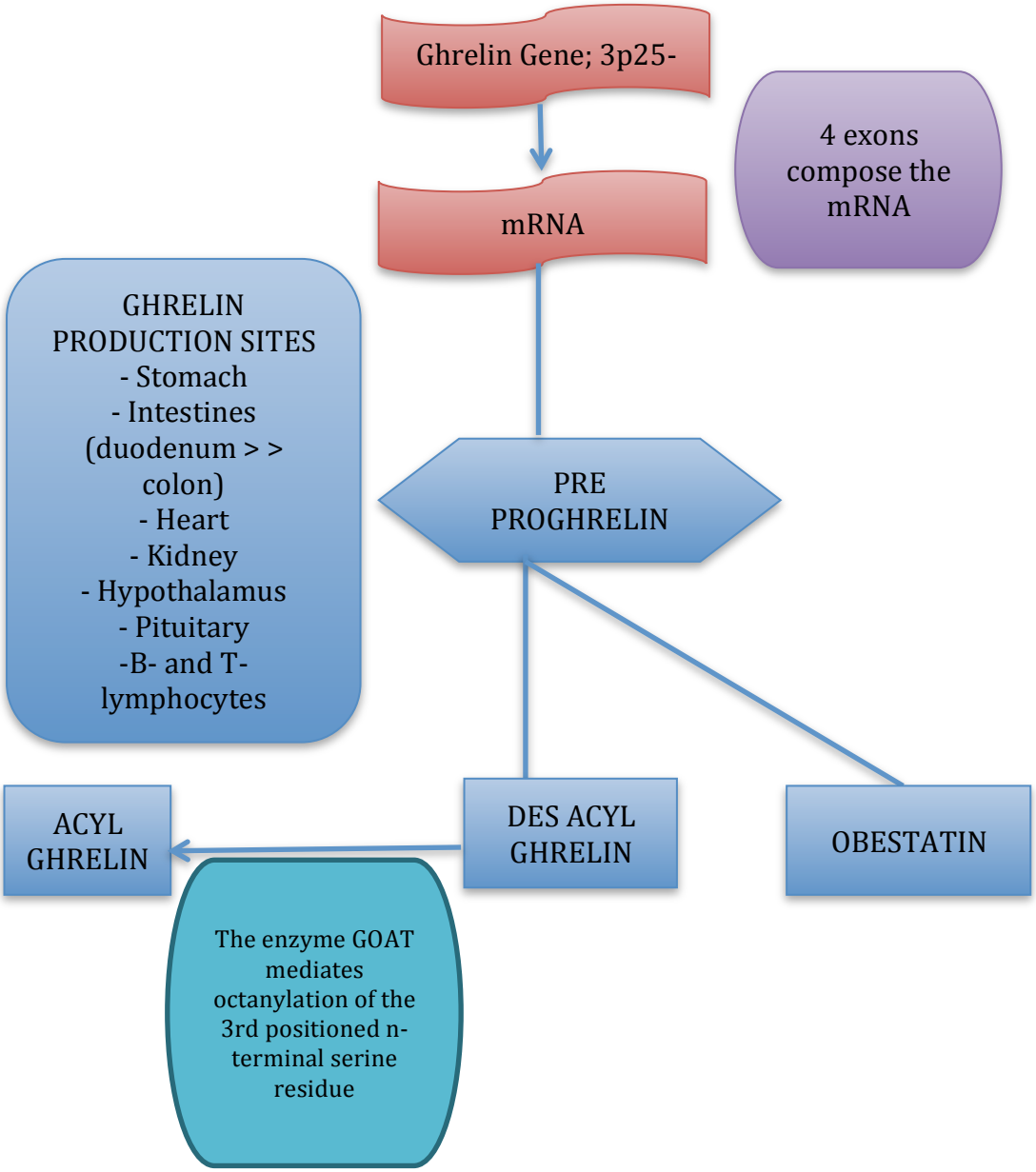

Figure 1: Overview of synthesis and modulation of ghrelin. [23, 34, 35, 18]

Per time, one has not completely outlined the entire function of the GOAT-enzyme. Modification of an N-terminal amino-acid as well as the third serine residue has been suggested. [36] The modification of ghrelin by adding a fatty acid on the serine residue creates the active form of ghrelin, referred to as acyl-ghrelin.[37] GOAT has also been discussed as an important signal of energy state, and a modulator of appetite. [38, 39]

Acyl and Des-Acyl Ghrelin

About 85 % of circulating ghrelin exists in des-acyl form, whereas about 15 % is in acyl form.[16] Acyl and des-acyl ghrelin are shown to be active on the same cells. [32]

Acyl-ghrelin has been referred to as the hormone determining food intake at every meal - the short-term regulator of appetite.[40] Acyl-ghrelin is also increased in states of fasting, [41] and reduced after eating. [22, 42] This is consistent with the fact that acyl-ghrelin is the molecular form responsible for the orexigenic effects. In general, one observes the same pattern for total-ghrelin, although acyl-ghrelin is only approximately 15 % of total-ghrelin concentration in healthy normal weight subjects. Acyl ghrelin is regarded also a signal of energy intake. [43]

Interestingly, during long-term fasting, acyl ghrelin is in fact reduced, while total ghrelin remains stable. [44] Thus, total ghrelin might remain unchanged. With feeding, both forms of ghrelin are suppressed. [39] This means, that during long-term fasting, des-acyl ghrelin is increased.

No mammals known are able to synthesize endogenous octanoic acid, but needs to be obtained through diet.[45] In a situation of energy depletion, there is not enough substrate to convert des-acyl to acyl

ghrelin.[39]

Several research groups claim that des-acyl ghrelin opposes the orexigenic effects of the bioactive acyl-ghrelin in humans. [46, 47, 48]

Important associations between ghrelin and other hormones

GH

There is a significant correlation between ghrelin and GH-pulses.[49] Ghrelin mediates secretion of GH on the hypothalamic level, [50] and effectuates release from the pituitary.[16] It has been a discussion whether ghrelin operates by way of more mechanisms than GnRH in releasing GH. [51]

Cortisol

GHS-R, as well as ghrelin mRNA is expressed in human adrenal glands. [52, 53] There are reports of a significant inverse relation between ghrelin and cortisol. [53, 54, 55] However, there are also publications reporting no such association, [56] and one group has failed showing alteration of ghrelin levels on administration of CRH. [57] There is an increased response to ghrelin, measured by ACTH-secretion in patients with Cushing's disease, after administration of the drug Ketoconazole. [58] Another group has reported a possible coexisting regulation of ACTH by ghrelin, CRH and somatostatin. [59]

Obestatin

The pre-proghrelin gene encodes, in addition to ghrelin, several ghrelin-associated peptides. One of them is the 23-amino acid peptide obestatin; binding to the GPR39-receptor.[60] Obestatin has been reported to show the same characteristic effects as ghrelin. [61] However, more recent findings indicate that the balance between ghrelin and obestatin appears to be important, [62] as some groups find that the ghrelin:obestatin ratio is lowered, and that obestatin is increased in obesity [63, 64], whereas one group reports it to be

increased. [65]

The orexigenic ghrelin - the central regulation of appetite

From experiments of infusing exogenous ghrelin, it has been detected that the hormone enhances appetite in humans by 40 %. [66] The ghrelin receptor GHS-R1a is mainly expressed in the arcuate nucleus of the hypothalamus, on AgRP and NPY-neurons. [31, 15, 67] GHS-R1a also exists in the more proximal nuclei, such as the lateral hypothalamus, the ventromedial, suprachiasmatic, paraventricular, anterior, pre optic and the tuberomamillary nuclei, and it is also expressed in the substantia nigra of the basal ganglia, the dorsal and median raphe nuclei, the ventral tegmental area and the hippocampus. [31, 67] By activating the NPY- and AgRP-neurons, ghrelin performs its metabolic- and appetite modulating effects. [68, 42, 69, 17, 70, 71] The activation has also been demonstrated by electrophysiological activation on administrating exogenous ghrelin. [67, 17] In humans, ghrelin sensitive fibres have been discovered in the infundibular (homologue to the arcuate nucleus), supraoptic nucleus, the suprachiasmatic nucleus, the periventricular nucleus, paraventricular nucleus, in the ventral prefornical region, the dorsomedial- and ventromedial nuclei and the mammillary nucleus. [72] Two types of ghrelin sensitive fibres, thick and thin, have been demonstrated. [72] However, the different functions of these types are yet not known. [72] The arcuate nucleus is also the seat of interaction between ghrelin and leptin. [73] Special attention has been granted the ventral tegmental area, the insula and amygdala. [74]

The adipogenic effects of ghrelin

Ghrelin has been described as an adipogenic substance, promoting storage of fat. [75] The hormone apparently reduces the utilization of fat, and increases fat storage. [76, 77] An association between visceral fat and ghrelin has also been reported. [78, 79, 80]

Ghrelin is involved in gastric motility and pain

Ghrelin works as a prokinetic agent increasing gut motility by affecting receptors on myenteric neurons. [18, 19, 20] These neurons further transmit signals by way of the enteric nervous system [18] and vagal connections. [18, 15, 81, 82, 18, 83] Both motilin and ghrelin are associated with a provocation of a premature phase III of the Migrating Motor Complex. [84, 85]

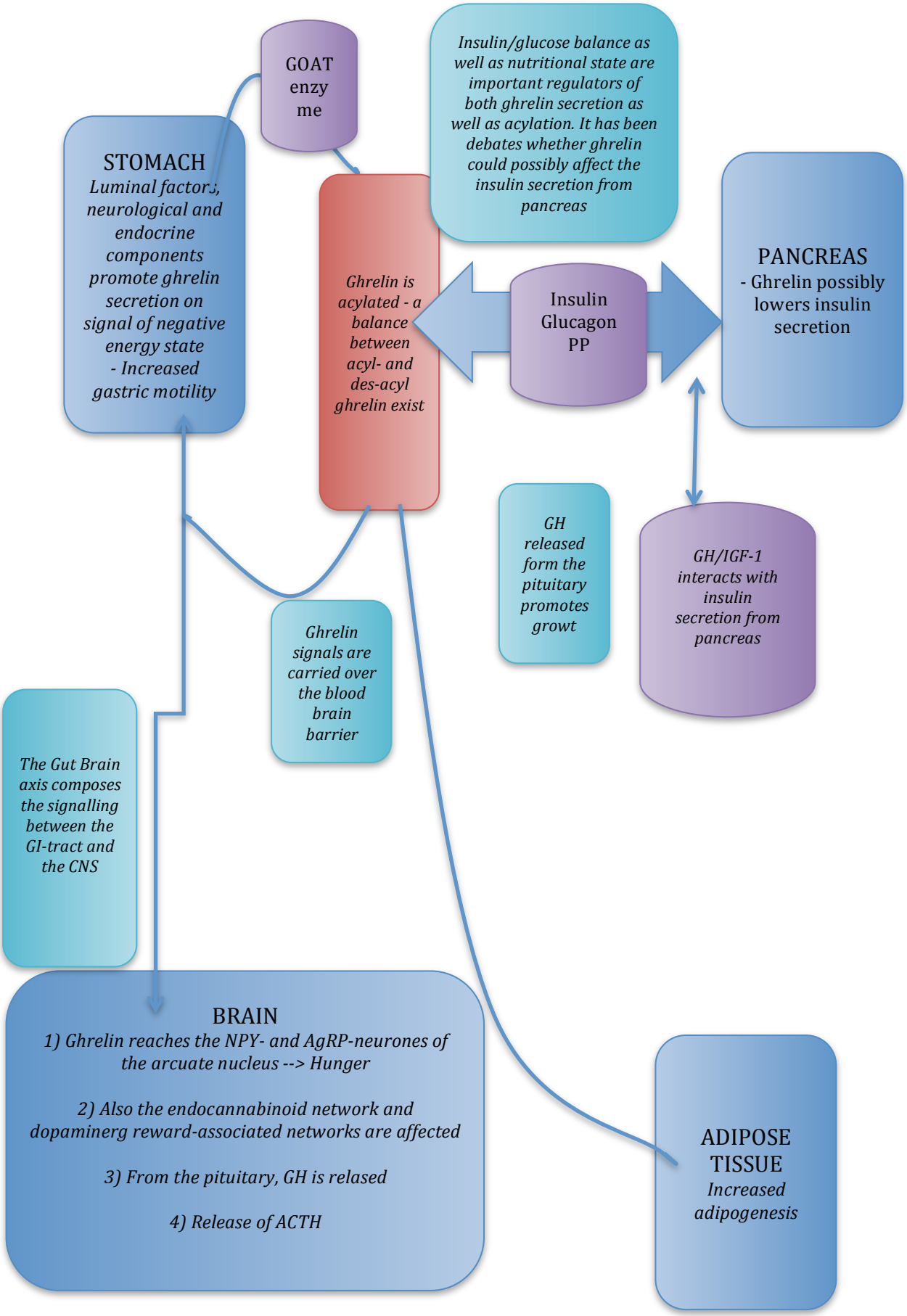
GOAT
enzy
me
Insulin/glucose balance as well as nutritional state are important regulators of both ghrelin secretion as well as acylation. It has been debates whether ghrelin could possibly affect the insulin secretion from pancreas
STOMACH
Luminal factors, neurological and endocrine components promote ghrelin secretion on signal of negative energy state
- Increased gastric motility
Ghrelin is acylated - a balance between acyl- and des-acyl ghrelin exist
Insulin
Glucagon
PP
PANCREAS
- Ghrelin possibly lowers insulin secretion
GH released form the pituitary promotes growt
GH/IGF-1 interacts with insulin secretion from pancreas
Ghrelin signals are carried over the blood brain barrier
The Gut Brain axis composes the signalling between the GI-tract and the CNS
BRAIN
1) Ghrelin reaches the NPY- and AgRP-neurones of the arcuate nucleus --> Hunger
2) Also the endocannabinoid network and dopaminerg reward-associated networks are affected
3) From the pituitary, GH is relased
4) Release of ACTH
ADIPOSE TISSUE
Increased adipogenesis

Figure 2: The different effects from ghrelin in various tissues and how they are connected. [17,15, 22, 41, 42, 68, 18, 19, 20]

AIM OF STUDY

The intentions of this paper are to answer the following questions presented in the project application:

1) How is ghrelin integrated in the Gut Brain Axis, and what are its distinguishing characteristics and effects as a neuro-hormone and as a ligand of a growth hormone receptor?

2) How does ghrelin mediate appetite, hunger and satiety? How is it involved in energy balance and weight regulation?

3) To what extent is ghrelin involved in neuropsychological aspects concerning eating behaviour? How is ghrelin implicated in conditions of disturbed eating behaviour?

4) How is ghrelin involved in conditions of functional pain and inflammation?

MATERIALS AND METHODS

An initial search in the Cochrane Library Database was done in order to start the process of gaining further background knowledge, apart from what has been achieved from the study of basal medical physiology and pathology.

- A search of the term *ghrelin* was restricted to findings in title, abstract or keyword fields in The Cochrane Database search motor. The search retrieved 322 clinical trials performed.

- 206 out of these searches were later retrieved through a similar search in PubMed/ EndNote, while the latter had to be retrieved by way of specific searching in Pub/Med.

- In total, 211 clinical trials from the search in the Cochrane

Database were collected, published from 2000 until 2010.

- The abstracts were read, and then compared to the inclusion criteria defined:

A definitive end-point for selection to the section of discussion was a clear relevance to clinical, physiological or pathological conditions within the gut-brain axis. A closer definition was «observation of ghrelin in the setting of»;

- Obesity
- Insulin/glucose balance/ the metabolic syndrome
- Hunger, satiety or appetite
- Neuropsychological aspects:
- Neurological or endocrinological implications of ghrelin on the gut brain axis.
- Functional disorders
- Eating disorders
- Inflammatory conditions

Only findings in humans were included. Animal studies were excluded from the discussion. However, certain publications that referred to animals in their keyword list have provided important background information. In particular, this is the situation of a lot of research on central nervous tissues. Publications that provided a source of background information on ghrelin were included.

In order to restrict the paper, several important issues needed to be omitted. First, publications investigating effects from different macronutrients and different fibres have been omitted. This is defended by an important ascpect pointed out in a Cochrane-

acknowledged article by Parnell et al. Ghrelin is secreted by the stomach, which does not have a mechanism sensing nutrients, as referred to by several other studies. [86]

Three orienting searches were then performed in PubMed via the reference manager program *End Note X2 (later updated to version X3 and X4)*. The search was not limited to the EndNote library, but was linked up to PubMed. Four limited searches were also performed in PubMed.

Not all studies have been included in the tables. The exclusion criteria were:

- The publication has not been retrievable through the accesses of the University of Tromsø
- The actual experiments were performed in animals
- Language other than English
- The numbers were not available from the article
- The number of individuals were not specifically defined.

Exclusion of primary articles, both from Cochrane as well as those retrieved through the PubMed/EndNote searching, has been performed by one person only. This is a definitive weakness of the selection process.

All articles have been provided through access from the University Library of the University of Tromsø.

RESULTS

Phrase	Field	Result
Gut brain axis + ghrelin	any field	42

Gut brain axis + review	any + any	193
Gut brain axis + pathophysiology	any field	159
Gut brain axis + methods		67
Ghrelin + hunger	abstract, title, keywords	259
Ghrelin + pain	abstract, title, keywords	39
Ghrelin + nausea	abstract, title, keywords	20
		779 - 182 duplicates
Ghrelin	any field	2759
Total number of referances		**3356 - 210 duplicates**
Ghrelin	Cochrane library abstract, title, keyword	**322 references, 206 retrieved in PubMed for EndNoteX2**

Table 2: Summary of searches

A search in PubMed not connected to EndNote was performed, receiving 2759 results. A sorting function of EndNote allowed selection of all publications published 1999 or later, receiving a number of 2382 references. A search for ghrelin + hunger in abstract, title or keyword retrieved 259 result, ghrelin + pain retrieved 39 results and ghrelin + nausea retrieved 20 results. Furthermore it was performed 4 open searches in any field of The Gut Brain Axis + either ghrelin, review, pathophysiology or method. Together, this retrieved 3356 results, minus 210 duplicates. These were removed. 206 results from the Cochrane-search were retrievable. Then, all these results were examined by the criteria of exclusion and inclusion.

As this paper aimed to give a summary on the history of ghrelin as a neuroendocrine mediator and component of the gut brain axis, publications concerning the bare molecular basics and clinical

implications outside the field of hunger, satiety, pain and nausea were excluded. A natural inclusion concerning the molecular basics is therefore the 1999 publication by Kojima et al. on the discovery of ghrelin, as well as the 2008 review by Kojima.

Further information from tables and graphs of the paper is presented in the tables of Appendix 1 for more extensive information.

Secretion of ghrelin

Mechanisms for ghrelin release

Food intake, blood glucose and how the meal is composed of macronutrients are regarded the most important promoters of ghrelin release in humans. [23]

Several groups have discussed the difference between so-called "open" type and "closed" type X/A-like cell. The cells of the stomach are "closed" type cells, whereas the cells of the lower GI-tract are so-called "open" type cells. [21, 87, 88] This difference is shown in that "open" type only releases des-acyl ghrelin, whereas "closed" type also releases acyl-ghrelin. [89] Fetissov et al. suggest that this difference is due to a different potential for being affected by certain stimulies; that the cells of the stomach primarily respond by hormonal factors, whereas cells of the lower GI-tract respond to luminal factors. [21.] Hosoda et al. point out that open-type cells communicate with the gastrointestinal lumen, whereas closed-type cells have no such connection. [88] Referring to a publication by Fijuimiya et al., the authors point out that the reason why "open"-type cells only release des-acyl ghrelin could be that they are affected by pH of the stomach. [89] However, it is not confirmed that pH regulates secretion of ghrelin per se. It is demonstrated that starvation increases immunoreactivity of ghrelin producing cells. [97]

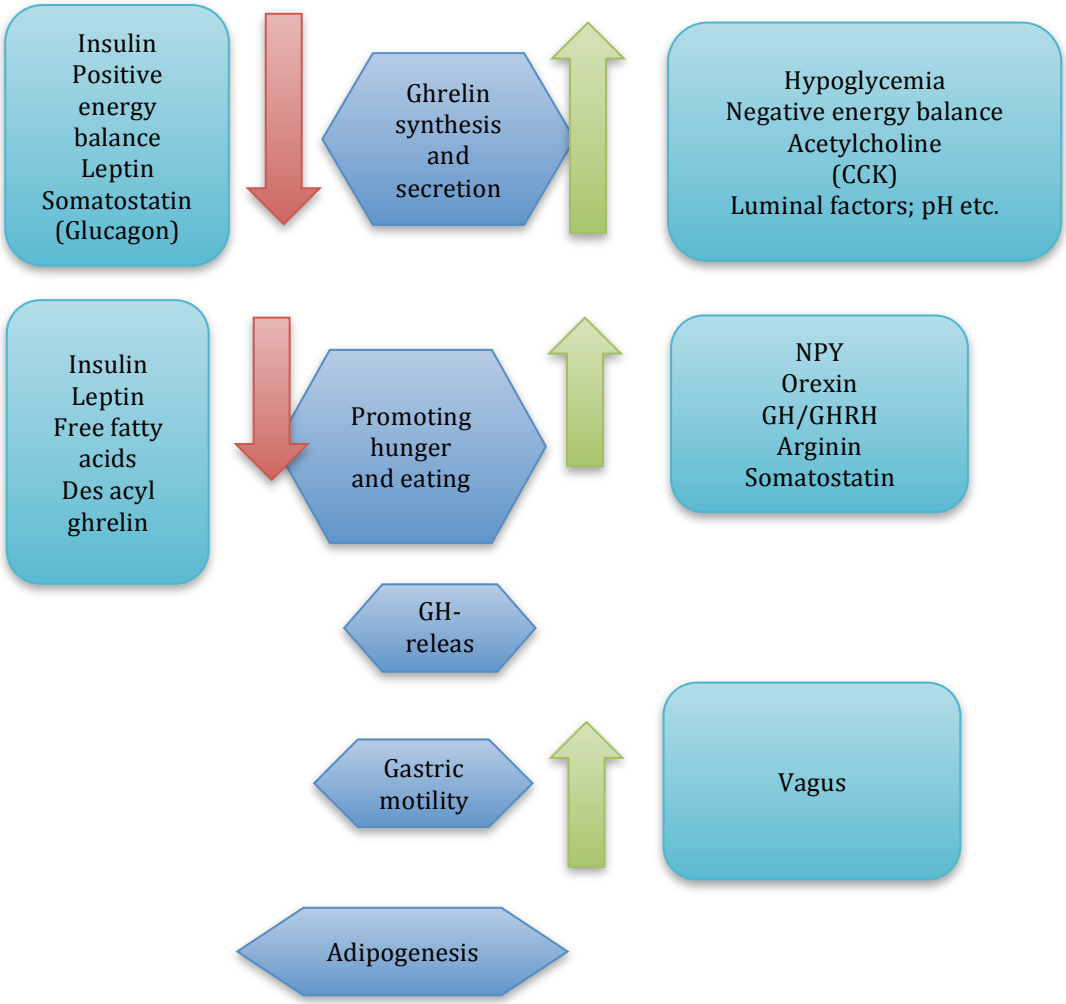

Figure 3) Regulation of ghrelin secretion [23, 90, 41, 91, 7, 92, 93, 94, 95, 96, 16]

Diurnal rhythms

Plasma ghrelin shows 24-hour variations, again mediating eating behaviour and appetite, referred to as diurnal rhythms. [98, 41, 99] Ghrelin peaks before food intake, and is suppressed post-prandial. [41] It is also reported a 24hour variation, with a nadir at 08 am., a peak in the afternoon, and then a gradual decline through late evening and night. [53]

Nutritional state

Conditions of negative energy balance increases ghrelin, [100] whereas positive energy balance suppresses it. [98, 101] The release of ghrelin is mostly controlled by feeding and energy state. [90, 41, 91] Thus, ghrelin acts as a trigger for meal initiation.

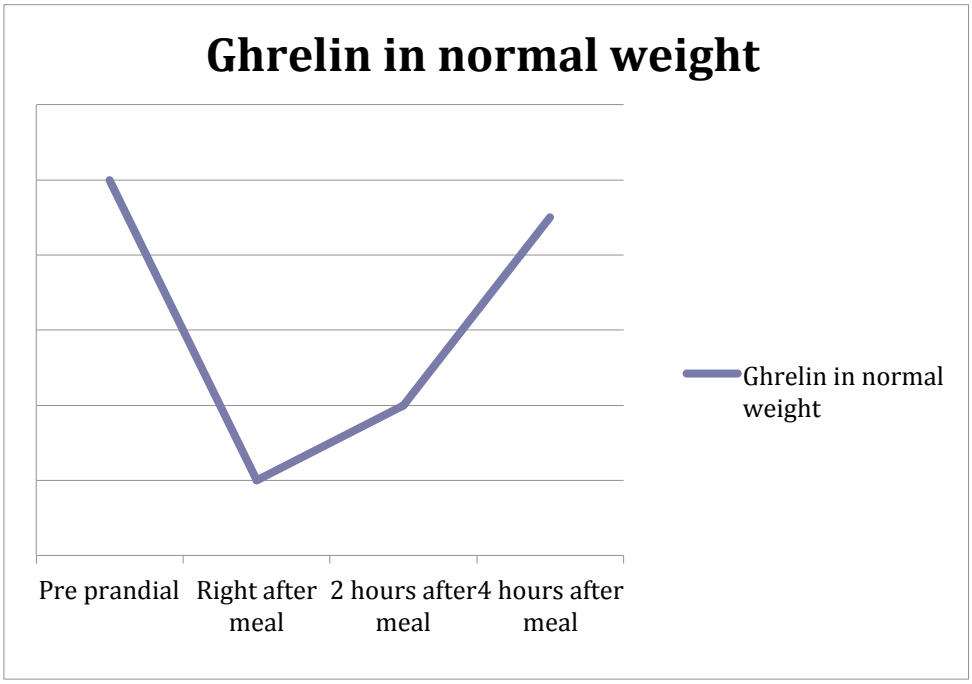

Figure 4) Ghrelin secretion pre- and post-prandial in normal weight subjects. The figure shows how a high level of ghrelin right before a meal is suppressed by eating, and then increases later on. This is an illustration only, and is not based upon real numbers. The increase starts apparently 90 minutes after meal. [102]

Fasting appears to induce another diurnal rhythm of ghrelin not observed in the fed state, [103] which has been interpreted as the ability of stomach X/A-cells to override the anterior pituitary producing ghrelin. [103] The relationship of acyl to des-acyl ghrelin has been observed to approach a higher component of des-acyl ghrelin during fasting. [104]

Several studies have reported that ghrelin is suppressed by different macronutrients or fibres, but to a different extent. [105] , [106], [107] ,[108]

Meal size has also been reported to be an important determinant of the suppression of ghrelin post-prandial. One research group reports a proportional relation between ghrelin suppression and calories ingested. [109]

CCK

It has been reported that CCK suppresses ghrelin release, [111], [112]. and a functional antagonism between the two peptides has been suggested.[7]

Leptin

Leptin has also been discussed as a possible satiety signal in man, [113] and it has been referred to as the natural antagonist to ghrelin. [92] The inverse relationship between ghrelin and leptin is discussed as the possible mechanism of initiating hunger.[43] The balance between leptin and ghrelin has been referred to as a final common pathway of appetite expression in the hypothalamus, as well as a reciprocal, rhythmic pattern.[12] Leptinemia is reported to happen simultanously with increased peripheral and central ghrelin secretion.[114]

Insulin and the endocrine pancreas

Ghrelin secretion shows a strong association with food intake, a significant negative correlation to insulin, and is inhibited by somatostatin, both secreted from the pancreas. [94] When the body is

depleted of insulin, as during fasting or food depletion, ghrelin is increased, which probably results from lack of the normal inhibition insulin has on ghrelin. [93]

It has been reported that the post-prandial suppression is stronger in meals high in calories or carbohydrates. [115] Increased blood glucose is correlated with a reduction in endogenous plasma ghrelin. [98] Several publications conclude that blood glucose is affected by ghrelin by way of modulation of insulin, and these two hormones express an apparently inverse relationship. [116, 117, 118, 119]

This is consistent with the diurnal profile one observes for ghrelin and insulin in that insulin is decreased and ghrelin is increased ahead of meals. [41] However, the exact mechanism is not known, and one group has suggested insulin to be a permissive factor in the post-prandial ghrelin suppression, but that this is not dependent on the mere increase in insulin. [120] Only one group claims that ghrelin directly inhibits insulin. [121]

There is also a significant correlation between insulin resistance, ghrelin and obesity. [122]

Other factors regulating ghrelin

Acetylcholine and muscarinergic agonists have been demonstrated to affect ghrelin concentration,[95] although not to a very important extent.[96] Ghrelin effects are refractory to cholinergic agonists and antagonists.[96]

The control of ghrelin secretion is a complicated process

Regulation of ghrelin secretion should be understood as a complex interaction within the gut-brain axis, controlled both by other hormones, nutritional state, neurological networks and possibly also luminal factors of the gut, such as pH.

The Hunger

Exogenous ghrelin infusion increases appetite and food intake. Administration of exogenous ghrelin is followed by an increased VAS-score for appetite and hunger. [66, 123, 124] This effect appears to be stronger in obesity. [123, 124, 125, 66, 126] One publication that do not describe optimal plasma sampling procedures, reports a trend towards a dose-dependent increase.[126]

	Effect from ghrelin infusion in obese subjects	Effect from ghrelin infusion in lean subjects
Schmid et al. 2005	Increased VAS-score for hunger	
Huda et al. 2009	Increased VAS-score for hunger, but flatter profile than lean subjects	Increased VAS-score
Druce et al. 2005	Increased food intake, + 70 %	Increased food intake, + 20 %
Wren et al. 2001	Increased VAS-score for hunger and food intake	
Akamizu et al. 2004	No significant increase in VAS-score for hunger	No significant increase in VAS-score for hunger

Table 3: Effects from exogenous ghrelin infusion in lean and obese subjects. Dose of ghrelin administrated varies between studies. All results are significant apart from Akamizu et al. [123, 124, 125, 69, 126]

There is a negative correlation between ghrelin and BMI, in children as well as adult subjects. [127, 128, 129, 130, 125, 131, 90, 98, 64, 78, 132, 133.]

	Fasting p-ghrelin in obese subjects/ SD (pg/ml	Fasting p-ghrelin in lean subjects/ SD (pg/ml)
Misra et al. 2009	* 134.2/ 58.9	* 187.6/ 61.2
Soriano-Guillen et al. 2004	420/ 29	796/ 61
Bacha et al. 2005	1507.1/ 185.2 (boys) 1057.3/ 123.4 (girls)	2044.9/ 448.2 (boys) 2024.3/ 187.9 (girls)

Table 4: Fasting p-ghrelin in obese and lean children. All results are significant. * = p- acyl ghrelin. [127, 129, 130]

In order to make them easier to compare, some numbers are converted to pg/ml. Numbers in original units are found in tables in Appendix 1. The conversion method used is multiply pmol/L with 3.38 as published by Moran et al. 2007. Moran LJ, Noakes M, Clifton PM et al. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. Am J Clin Nutr. 2007 Dec;86(6):1603-10.

	n (obese) n (lean)	Fasting p-ghrelin obese/ SD (pg/ml)	Fasting p-ghrelin lean / SD (pg/ml)
Tschoep et al. 2001	8 7	358.3/ 84.5	523.9/ 77.7
Shiiya et al. 2002	11 28	0.68 *	1 *
Vicenatti et al. 2007	20 12	Lower than lean subjects	
Bellone et al. 2002	36 29	229.5	426
English et al. 2002	10 13	1098.5/ (689.52-1754.22)*	2896.7/ (2119.26-3957.98)*
Carlson 2009	13 10	1087/ 187	1418/ 232

Table 5: Ghrelin in obese subjects compared to lean controls. 90, 98, 64, 250, 133, 132

In order to make them easier to compare, some numbers are converted to pg/ml. Numbers in original units are found in tables in Appendix 1. The conversion method used is multiply pmol/L with 3.38 as published by Moran et al. 2007. Moran LJ, Noakes M, Clifton PM et al. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. Am J Clin Nutr. 2007 Dec;86(6):1603-10.

Acyl ghrelin is also increased in obese subjects, compared with lean controls.

	Acyl ghrelin in obese subjects/ SD (pg/ml)	Acyl ghrelin in normal weight subjects/ SD (pg/ml)
Katsuki 2004	68,8/ 6,3	48,9/ 4,1
Zwirska-Korczala 2007	194/27	199/ 23
Marzullo 2004	180,4/ 18,5	411,8/ 57,4
Rodriguez 2009	28,4/ 3,7	11,5/ 2

Table 6: Acyl ghrelin in obese versus lean subjects. 79, 179, 178, 77

In order to make them easier to compare, some numbers are converted to pg/ml. Numbers in original units are found in tables in Appendix 1.

The conversion method used is multiply pmol/L with 3.38 as published by Moran et al. 2007. Moran LJ, Noakes M, Clifton PM et al. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. Am J Clin Nutr. 2007 Dec;86(6):1603-10.

Obese subjects have a reduced suppression of ghrelin after meal. This is reported in children and grown-up subjects, and might contribute to a distorted control of hunger and satiety. [133, 122, 132, 134, 135, 136, 137, 138, 139] Dietary intervention and weight loss does not seem to alter this post-prandial suppression significantly, although one study reports increased suppression from a test meal of a specific dietary composition.

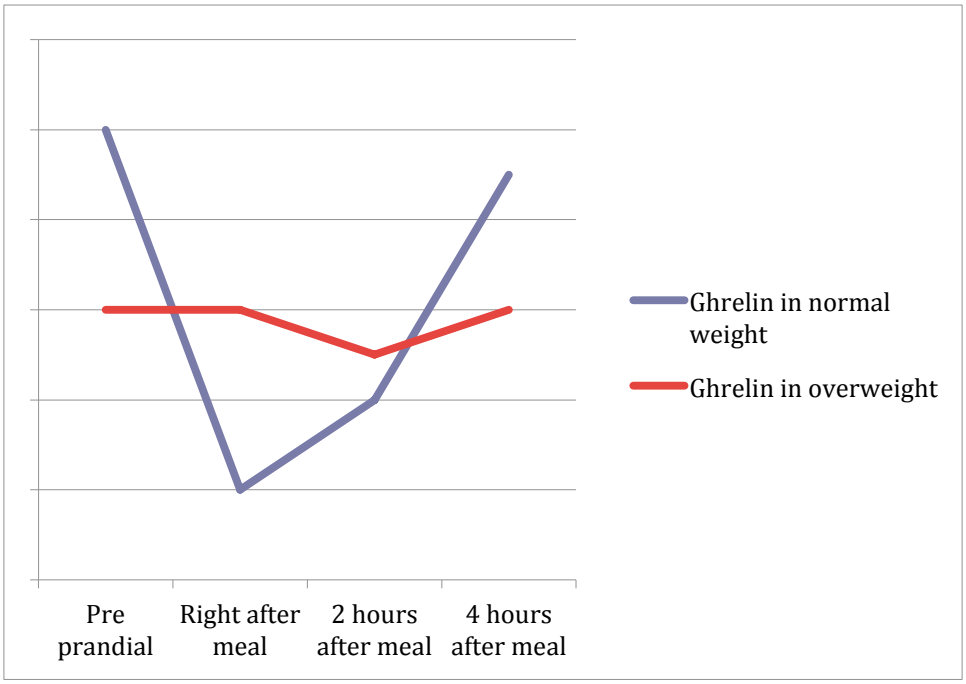

Figure 5) Ghrelin secretion after meal in normal weight versus overweight subjects. This is an illustration of how overweight subjects have a flatter curve of ghrelin, and do not experience the same post-prandial suppression after eating, and is not based upon real numbers!

Weight loss leads to an increased p-total ghrelin in both children and adults. [140, 141, 142, 143, 144, 145, 146, 147, 135, 148, 149, 150, 151] This effect is reported also in normal weight subjects.[140]

	n	p-ghrelin before weight loss/ SD (pg/ml)	p-ghrelin after weight loss/ SD (pg/ml)
Foster-Schubert et al. 2005	87	599/ 38	+ 32 % / 16 %
Garcia et al. 2006	25	589/ 52	704/ 64*
Cummings et al. 2002	13		+ 24 %
Hansen et al. 2002	8	424.8/ 63.2	476.2/ 59.5
Zahorska-Markiewicz et al. 2004	35	224.1/ 46.3	249.1/ 50.24
Olszanecka-Glinianowicz et al. 2008	22	63.5/13.0	72.8/15.1
Romon et al. 2006	17	1860/1050	2280/ 1480
Crujeiras et al. 2010	104	952/ 326	964/ 343

Kotidis et al. 2006	14	1970/770	3590/880

* Increase is only transient!

Table 7: Effects from weight loss on fasting ghrelin. 141, 142, 144, 143, 145, 147, 135, 148, 149

In order to make them easier to compare, some numbers are converted to pg/ml. Numbers in original units are found in tables in Appendix 1. The conversion method used is multiply pmol/L with 3.38 as published by Moran et al. 2007. Moran LJ, Noakes M, Clifton PM et al. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. Am J Clin Nutr. 2007 Dec;86(6):1603-10.

Several publications have presented des-acyl ghrelin as a counter-actor of the metabolic response towards the acylated ghrelin. 46, 152, 153 Des-acyl ghrelin has been discussed as a mediator of anabolic and proliferative effects of several tissues, as well as regulation of glucose and insulin metabolism and insulin secretion. 24

Des-acyl ghrelin is not regarded a ligand of the acyl-ghrelin receptor GHS-R1a. It has been discussed if des-acyl ghrelin does not lead to any increase in GH-secretion, and therefore must be operating independent of GHS-R1a, 154 and that the metabolic effects also are executed independent of this receptor. 155 A later publication verified by the Cochrane claimed that des-acyl ghrelin functions as a full agonist of the GHS-R1a, and that it is possible to block it with agonists. 153 There is no functional antagonism in this relationship, but that des-acyl ghrelin competes with acyl ghrelin for binding, with a Kd four times higher than acyl ghrelin. 153

The orexigenic effects of des-acyl ghrelin are debated. Some groups report it as appetite suppressive. 155 Some groups have suggested that there is an antagonism between des-acyl and acyl ghrelin regulating appetite, and that distortion of this balance could be a cause of the development of anorexia of disease. 156, 157 Studies in patients with anorexia nervosa have detected higher levels of des-

acyl ghrelin, indicating that this is a mechanism for limiting food intake, through suppression of appetite. 158, 159, 156

Exogenous ghrelin infusion increases GH-secretion. 160, 161, 162, 50, 163, 164, 165, 166 Food intake and VAS-score in elderly, malnourished subjects are lower, but total ghrelin is apparently higher compared with welnourished controls. 167, 168, 169, 71, 170, 171, 172, 173 Acyl ghrelin appears to be lower in most studies. 174

	P-ghrelin in subjects with cachexia/ anorexia of disease / SD (pg/ml)	P-ghrelin in controls/ SD (pg/ml)
Nagaya 2001*	799,2 / 67	495,7 / 37,2
Tacke 2003	777,4/ (range 317,7 - 2430,7)	709,8 (range 466,4 - 1078,2)
Marchesini 2004 **	1399/ 554,3	1345/479,7
Itoh 2004	799,2/ 502,2	530,7/ 37,2
Shimizu 2003	607/63,2	445,1/ 29,7
Xin 2009	1237,8/ 47,9	985,5/ 64,2

Table 8 : Ghrelin levels in subjects with anorexia nervosa and cachexia compared with healthy subjects. 173, 171, 452, 170, 71, 309

* The control group in the publication by Nagaya et al. is a group of patients with chronic heart failure, but no cachexia/anorexia.
** = Not significant

In order to make them easier to compare, some numbers are converted to pg/ml. Numbers in original units are found in tables in Appendix 1. The conversion method used is multiply pmol/L with 3.38 as published by Moran et al. 2007. Moran LJ, Noakes M, Clifton PM et al. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. Am J Clin Nutr. 2007 Dec;86(6):1603-10.

Exogenous ghrelin infusion suppresses insulin. 175, 160 Subjects with conditions characterized by increased basal insulin level (insulin resistance, metabolic syndrome or type 2 diabetes) have significantly higher levels of basal ghrelin. 176, 177, 77, 178, 179, 79, 180, 181 Euglycemic hyperinsulinemic clamp testing reveals that higher concentrations of insulin induces lower concentrations of ghrelin.

	n	P-ghrelin in obese with reduced insulin sensitivity/ SD (pg/ml)	p-ghrelin in obese with normal insulin sensitivity/ SD (pg/ml)
Mc. Laughlin et al. 2004	20 20	352/ 19	412/ 35
Anderwald et al. 2003	6 6	713.2/ 47.4	818/ 155.6
Rodriguez et al. 2009	19 20	28.4/3.7*	16.2/3.0*
St-Pierre et al. 2007	31 29	1063/399 114/57*	1246/369 98/47*

* P-acyl ghrelin

Table 9: Fasting ghrelin in obese subjects with reduced insulin sensitivity versus obese subjects with normal insulin sensitivity. 181, 180, 77, 176

In order to make them easier to compare, some numbers are converted to pg/ml. Numbers in original units are found in tables in Appendix 1. The conversion method used is multiply pmol/L with 3.38 as published by Moran et al. 2007. Moran LJ, Noakes M, Clifton PM et al. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. Am J Clin Nutr. 2007 Dec;86(6):1603-10.

The Roux-en-Y gastric bypass, the sleeve gastrectomy and the biliopancreatic diversion apparently induce a suppression of ghrelin, 144, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206 while the gastric banding procedure apparently induce an increase. This happens despite a strong reduction of body weight, usually inducing a strong increase in ghrelin. 207, 208, 185, 209, 200 However, there is a trend towards a possible increase in ghrelin after 12 months.

Study	P-ghrelin (pg/ml)/ SD	Time (months)
Fruhbeck 2004	355,7/ 11,4	0
	117/ 34	6
Foschi 2008	92,1/ 5,44	0
	73/ 6,36	4,5
Dadan 2009	81,2/ 21,9	0
	37,4/ 16,4	1 day

	66,6/ 31,8	1 week
	92,8/ 38,9	1
	80,2/ 27,6	3
Couce 2006	932,4/ 52,2	0
	622,7/ 59,4	6
Liou 2008	63,2/ 26,7	0
	61,18/ 19,3 *	6
	58,14/ 16,2 *	12
Mancini 2006	742/ 174	0
	765/ 258*	12
Morinigo 2008	863,1/ 56	0
	728/ 46,1	1,5
	862,5/ 83,5	12
Holdstock 2003	293,7/ 135,9	0
	422,5/ 240,7	6
	476,6/ 237,3	12
Stoeckli 2004	240,4/ 47,4	0
	408/ 147,8*	24
Borg 2006	784,16/ 243,4	0
	1118,78/ 321,1*	6
Stratis 2006	633/43	0
	675/39*	3
Karamanakos 2008	638/189	0
	714/ 230 *	12
Sundbom 2007	814 (range 735-904)	0
	436 (range 397-478)	1 day
	1114 (range 964-1288)	12
Lin et al. 2004	355/20	0
	246/ 13	Immediately post-op.
Garcia-Fuentes et al. 2008	734,3/286,1	0
	1137,6/ 316,1	7
Ybarra et al. 2009	324/ 12	0
	270/ 33	6
	266/52	12

Table 10: P-Ghrelin at different time points before and after Roux-en-Y gastric bypass. There is a trend towards an increase in ghrelin with time 183, 186, 185, 354, 453, 454, 455, 131, 348, 349, 347, 202, 188, 456, 465 * = Not significant

In order to make them easier to compare, some numbers are converted to pg/ml. Numbers in original units are found in tables in Appendix 1. The conversion method used is multiply pmol/L with 3.38 as published

by Moran et al. 2007. Moran LJ, Noakes M, Clifton PM et al. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. Am J Clin Nutr. 2007 Dec;86(6):1603-10.

Study	Time (months)	P-ghrelin/ SD (pg/ml)
Langer et al. 2005	0	369,6/ 121,3*
	6	120,7/ 45,8 *
Cohen et al. 2005	0	781/ 96
	6	589/ 61
Karamanakos et al. 2008	0	605/ 185
	1	364/ 83
	3	399/ 135
	6	398/ 100
	12	399/ 97
Bohdjalian et al. 2010	0	593 52
	12	593/ 52
	60	219/ 23
Wang et al. 2009	0	447,3/ 71,2
	24	319,7/ 91,9

Table 11: P-ghrelin at different time points before and after sleeve gastrectomy. All results are significant. 201, 355, 202, 359, 200

* = S-ghrelin

In order to make them easier to compare, some numbers are converted to pg/ml. Numbers in original units are found in tables in Appendix 1. The conversion method used is multiply pmol/L with 3.38 as published by Moran et al. 2007. Moran LJ, Noakes M, Clifton PM et al. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. Am J Clin Nutr. 2007 Dec;86(6):1603-10.

Study	Time (months)	P-ghrelin/ SD (pg/ml)
Schindler et al. 2004	0	338,5/ 47,9
	6	502,4/ 97
Fruhbeck et al. 2004	0	362,2/ 19,3
	7	480/ 78
Leonetti et al. 2003	0	407,3/ 21,6
	3	314,2/ 84,3
Langer et al. 2005	0	248,5/ 92,3
	6	353,7/ 190

Hanusch- Enserer et al. 2004	0	790,9/179,1
	6	784,16/ 179,1
	12	882,2/243,4
Cohen et al. 2005	0	1062,9/ 116,7
	18	1225,1/ 619
Foschi et al. 2005	0	92,1/5,44
	4	172/26
Dadan et al. 2009	0	94,2/52,9
	1 day	42,4/12,3
	1 week	87,2/24,4
	1	79,6/21,8
	3	140,6/ 49,2
Nijhuis et al. 2004	0	742/ 246
	24	904/ 127

Table 12: P-ghrelin at different time points before and after gastric banding. 362, 182, 192, 201, 458, 355, 186, 185, 208

In order to make them easier to compare, some numbers are converted to pg/ml. Numbers in original units are found in tables in Appendix 1. The conversion method used is multiply pmol/L with 3.38 as published by Moran et al. 2007. Moran LJ, Noakes M, Clifton PM et al. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. Am J Clin Nutr. 2007 Dec;86(6):1603-10.

Study	Time (months)	P-ghrelin/ SD (pg/ml)
Valera-Mora et al. 2007	0	573/ 77,9
	18	574,1/ 32,7 *
Garcia-Fuentes et al. 2008	0	740,2/ 220,2
	7	779/ 210,7
Frubeck et al. 2004	0	306,5/ 43,5
	4,5	406/ 86
Kotidis et al. 2006	0	1440/ 770
	18	990/ 350
Garcia-Unzueta et al. 2005	0	277/ 206
	1	313/ 195
	3	327/212
	12	375/190

Table 13: P-ghrelin at different time points before and after biliopancreatic diversion. 457, 456, 182, 149, 204

* = Not significant

In order to make them easier to compare, some numbers are converted to pg/ml. Numbers in original units are found in tables in Appendix 1. The conversion method used is multiply pmol/L with 3.38 as published by Moran et al. 2007. Moran LJ, Noakes M, Clifton PM et al. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. Am J Clin Nutr. 2007 Dec;86(6):1603-10.

The Restraint in the Brain

Ghrelin is increased in individuals with anorexia nervosa, characterized by increased cognitive restraint as well as low weight. 158, 127, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220 Ghrelin is apparently reduced through treatment and weight gain. 221, 222, 223

Study	P-ghrelin in subjects with anorexia nervosa/ SD (pg/ml)	P-ghrelin in controls/ SD (pg/ml)
Miljic et al. 2006	985,3/ 165,4	443,7/ 78,7
Germain et al. 2007	2369,4/ 186	1027,5/ 89,3
Germain et al. 2009	4181/533	2998/ 223
Tanaka et al. 2003	1760/94	449,2/ 74,4
Nakahara et al. 2007	1463,9/ 421,8	728,7/ 728,7

Table 14: P-ghrelin in subjects with anorexia nervosa compared to controls. 390, 459, 460, 223, 221

In order to make them easier to compare, some numbers are converted to pg/ml. Numbers in original units are found in tables in Appendix 1. The conversion method used is multiply pmol/L with 3.38 as published by Moran et al. 2007. Moran LJ, Noakes M, Clifton PM et al. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. Am J Clin Nutr. 2007 Dec;86(6):1603-10.

Ghrelin levels are increased in subjects with bulimia nervosa, characterised by binge/purge behaviour. 224, 225, 226, 217, 216, 237, 223 Results concerning binge eating disorder are inconclusive, and might be confounded by obesity/ high BMI.

Study	P-ghrelin in subjects with bulimia nervosa / SD (pg/ml)

Fassino 2005	560,2/ 97,2
Tanaka 2002	969,2/ 494,8
Monteleone 2008a	217,4/ 111,8
Tanaka 2006	1019,7/ 63,9
Kojima 2005	895,7/ 86,2
Tanaka 2003a	1008,6/ 459

Table 15: P-ghrelin in subjects with bulimia nervosa. 224, 226, 225, 217, 227, 219

In order to make them easier to compare, some numbers are converted to pg/ml. Numbers in original units are found in tables in Appendix 1. The conversion method used is multiply pmol/L with 3.38 as published by Moran et al. 2007. Moran LJ, Noakes M, Clifton PM et al. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. Am J Clin Nutr. 2007 Dec;86(6):1603-10.

The Pain

Ghrelin appears to be increased in functional disorders of the GI-tract, whereas it appears to be suppressed in conditions of gastroparesis and dysmotility. 228, 229, 230 Ghrelin is increased in conditions of inflammation, such as inflammatory bowel syndrome. 231, 232, 233, 234

DISCUSSION

Methodological issues

The intentions of the paper was to be a summary, but also a systematic review of a decade of research on ghrelin. Therefore, the publications are not limited to a certain study design. Some of them are described as both double blinded as well as randomized and controlled by acknowledged methods, whereas others are pure descriptive prevalence studies. A significant amount would however, be classified as observational. This could perhaps be criticized.

Furthermore, two significant problems arose while investigating the papers. As the assays and sample procedures during the past decade had changed, not all studies are easily compared. Some publications measure ghrelin in serum whereas most refer to plasma

samples.

Most publications do describe their sampling procedures, but a major bias to be avoided was the fact that not all studies actually compare the same components of ghrelin. Some refer to active ghrelin whereas others refer to the total amount. In particular, this might be a significant error in conditions of obesity and insulin regulation, directly influencing the ratio of these molecular forms. The fact that the different articles have several important methodological differences challenges the comparison and contrasting different studies.

The most important assay kits used are the Phoenix Pharmaceuticals assay kit and The Linco Research assay. The Linco Research assay It has a lower detection limit of 10 ng/L and a higher limit of 2000 ng/L. The intra-assay CV is 7.4 % and the inter-assay CV 13.5 % [235] The antibody used is binding the receptor, and thereby determines the biological function of the hormone. Acidification of the sample is necessary due to the chemical instability of the side chain, and a frequent problem is that studies do not assess these criteria [236, 235] Therefore, not all analyses of the active ghrelin component are reliable. Optimum plasma sampling procedures has been described by Hosoda et al. Blood samples should be collected with EDTA-tubes, samples should be chilled and centrifuged within 30 minutes, and the sample should be acidified. [237] Especially, the storage under chilled conditions is of major importance for stability of ghrelin. [236, 237]

Mitsubishi Kagaku Iatron Inc. is a newer kit than what has traditionally been used (The Phoenix Pharmaceuticals and the Linco Research kits). Some articles have reported that the measured des-acyl ghrelin has been different from the calculated result (achieved from subtracting acylated ghrelin from total). [177, 238] This might be due to circulating fragments of ghrelin.[238] Furthermore, as pointed

out by Hassouna et al., it is not known if the assays used identify free fractions, bound fractions or both, and if this might influence the results. [30]

THE HUNGER

Is ghrelin the endogenous meal initiator?

The pattern of a pre-prandial increase and post-prandial nadirs,[17, 41, 22, 42, 109] and the correlation between increase in ghrelin and sensation of hunger [239] are what indicates that ghrelin is an endogenous meal initiator. Diurnal variation also seems to be related to a stable meal pattern, [240, 239] and this pattern exists also in absence of food and time cues, in subjects eating ad libitum. [239]

Some publications oppose this theory of ghrelin initiating meals. [40, 246] or even being in control of stimulating hunger. [241] One study reported that fasting plasma total ghrelin was in fact *negatively* correlated with ad libitum food intake.[242] However, there are several important methodological weaknesses of this study.

The post-prandial ghrelin suppression is reported to be dose-dependent with the ingestion of calories. The higher amount of energy provided, the greater the ghrelin suppression.[109] It has also been suggested that ghrelin suppression is also related to insulin increase after a meal. [243] Despite the fact that ghrelin increase and decrease follow diurnal rhytms, there is an important argument difficult to investigate. This is the possibility that a regular, learned meal pattern affects ghrelin secretion. [244] In other words, it is possible that ghrelin regulation is affected also by cognitive processes.

The negative correlation of ghrelin and BMI - a signal of energy state?

Energy balance influences ghrelin secretion.[245] A negative energy balance induces increased secretion of ghrelin, and this is reverted to

normal on restoring energy balance. [41, 246] Total - and acyl-ghrelin are both reduced after food intake. [247] Obese individuals have a lower average ghrelin than normal weight/lean controls. [248, 125, 127, 98, 90, 131, 64, 128, 249, 250, 78, 251] One group reported as much as 32 % lower ghrelin in obesity.[90] Only one publication opposes the association between a lower ghrelin and obesity/ increasing BMI. [145]

Apparently, ghrelin is reduced with weight gain. [98, 252, 144, 253, 254] It is also reported that short-term overfeeding does not induce significant suppression of ghrelin. [255] Therefore, it is argued that the depression of ghrelin seen in chronic obesity is due to an energy intake in excess of one's needs over time.

Ghrelin and the effects in adipose tissue

Basal ghrelin concentration is correlated with visceral fat mass/ waist circumference. [256, 78, 77, 80, 79, 177] This correlation is highly significant even when adjusting for other predictors, such as BMI and insulin sensitivity.[78] The question is whether ghrelin influences storage of adipose tissue, or if this tissue by itself is able to produce ghrelin. The majority of the literature claims that acyl-ghrelin has a lipogenic, anti-lipolytic effect on adipocytes. [257, 77] Furthermore, the majority of literature finds that the receptor GHS-R1a is expressed in adipose tissue. [258, 77]

Both acyl- and des-acyl ghrelin seem to promote accumulation of fat through lipogenesis, [257, 77] but Kos et al. point out that the des-acyl ghrelin expresses some anti-lipolytic functions, and works by way of the adipose tissue in preventing weight loss. [257] Another group claims that it is the mere elevation of acyl-ghrelin that mediates a lipogenic effect. [77]

Acyl vs. des-acyl ghrelin - distorted in overweight?

Acyl-ghrelin, responsible for most metabolic actions, is increased in

states of positive energy balance. In other words when the subject is well supported of substrate for acylation.

One of the reasons differentiating acyl from des-acyl ghrelin is important when analyzing the apparent suppression in obesity, is that it is not clear if both molecular forms are suppressed to the same extent. In a state of chronic over-supplementation of fatty acids, acyl-ghrelin is supposed to increase, opposite of total- and des-acyl ghrelin.

The apparent suppression of total ghrelin might also resemble a distorted relationship between bioactive- and inactive forms of the hormone.[143] Obese individuals could in fact have an *increased acyl ghrelin*, masked by a lower level of des-acyl, or there could be a lack of des-acyl ghrelin. Therefore, the apparent reduction in total ghrelin could actually represent a "false" observation; even if the total ghrelin is reduced, the effects from ghrelin could actually be increased.

In vivo, the relationship between des-acyl and acyl ghrelin is normally 9:1.[259] Obese subjects with insulin resistance have been reported to have a higher ratio of acyl to des-acyl ghrelin. [177, 176, 77, 179] One publication reports as much as about 20 % of total ghrelin.[53]

However, in real numbers several of these publications actually report a higher acyl-ghrelin in lean subjects, or no significant difference. [178, 179] One group suggests that obesity leads to a total inhibition of the ghrelin system, explaining the depression both in acyl- as well as total ghrelin observed in obese subjects compared to lean controls. [178]

One group has suggested that there is state of des-acyl ghrelin deficiency in obesity. [260] Considering what is known about the effects

of these isoforms, this would contribute to an increased orexigenic effect, an increased adipogenesis and possibly a reduction of insulin sensitivity [77] - in other words: a vicious circle of obesity and insulin resistance.

Alterations in diurnal rhytm, ghrelin secretion and dynamics in overweight

There are several interesting reports on how the diurnal rhythm and pattern of secretion of ghrelin is changed in obesity.

Unfortunately, few studies present a good overview of daily variation of ghrelin in overweight, compared to normal weight. It has been reported that being overweight leads to a smaller increase of ghrelin during night, and a generally smaller variation in daytime concentration.[32]

There are two main conclusions in literature about ghrelin secretion- and dynamics in obesity. First, apparently there is no correlation between ghrelin and hunger and satiety, measured by VAS-score in obese subjects, opposite of normal weight. [261, 262] Furthermore, one group claims that obese subjects apparently have a lower treshold for increase in appetite and hunger from exogenous infusion of ghrelin, and that this suggests a generally lower treshold for initiating hunger and eating, compared to lean controls.[125]

Second, the post-prandial suppression of ghrelin is also influenced, as the reduction in ghrelin after a meal that probably reduces ghrelin, does not operate in the same way. After a test meal, obese subjects have either a total lack of or a blunted response to ghrelin suppression. [133, 263, 264, 207, 90, 98, 41, 265, 266, 267, 268, 269] Only one group observes the same suppression as in normal weight controls. [135] The same profile is demonstrated for children with overweight/ obesity as for adults and a negative correlation between post-

prandial ghrelin suppression and adiposity is reported.; [136, 139, 137]

It is reported that baseline ghrelin concentration is a significant predictor of the post-prandial decrease in ghrelin.[133] In other words, one should expect a change in ghrelin suppression after meal when the basal ghrelin concentration is reduced in obesity.

English et al. launched the theory of *"maximal suppression of drive to eat".* [136]The apparent loss of post-prandial decrease might be due to *an already activated maximal suppression* in obese subjects*.* It's simply nothing more to suppress! [133] This seems plausible, considering that obese subjects have a generally lowered total ghrelin compared to lean controls. English et al. therefore outlined that one needs to determine *the threshold* for ghrelin to initiate this drive in both lean and obese subjects.[133]

This is interesting, because it might explain both why obese subjects have less suppression, but also the reports that they have a stronger orexigenic effect from a certain ghrelin infusion with a different treshold for effect compared to lean controls. It could be interpreted as an unequal responsiveness towards ghrelin between lean and obese individuals, and that obese have a lower treshold for stimulation of appetite.[125] Apparently this is a situation where obese subjects have a generally different treshold for effect from ghrelin; a lower treshold for initiating meals, but a higher treshold for satiety.

A problem with these publications is that administrate different test meals, some publications even administrate oral glucose tolerance tests or liquid meals, [109] and they examine subjects of completely different degree of insulin sensitivity. A rising problem in comparing liquid meals and glucose tolerance tests with mixed solid meals, is that rapid exposure of ghrelin secreting cells to simple carbohydrates

might induce a more rapid suppression of ghrelin than the solid meals. [138]

It should also be remarked that none of the publications examining differences in post-prandial ghrelin suppression between lean and obese subjects have been listed in the Cochrane Database of clinical trials.

Several explanations have been discussed in literature, among them the observation of an apparent delay of ghrelin suppression, which could possibly explain a smaller satiety response in obese subjects. [132, 270] One of these groups point out that the function of ghrelin as a stimulant of motility could lead to a faster passage through the GI-tract, and thereby a lack of satiety. [270]

Apparently, the post-prandial ghrelin suppression is not controlled or regulated by the same factors in obese subjects as in lean. A randomized controlled study reports that post-prandial suppression in ghrelin is associated with the intermeal interval in normal weight subjects, but not in obese.[271] Another randomized controlled trial discuss whether or not obese people have a distorted regulation of satiety, and if this regulation is more or less independent of endocrine and neurological regulation. [262] Is the mere distortion of these neurological and endocrinological mechanisms, normally operating in lean subjects, a primary cause of developing obesity in an environment of mostly ad libitum access to high caloric foods and fairly limited physical exercise? [262] Or are these distortions in ghrelin suppression a result of overweight? [262]

In summary, from several studies, the overall conclusion is that obese subjects simply don't experience the same suppression of the hunger hormone after eating. This might be due to a different

treshold for ghrelin effects. Therefore, a central question is whether this apparent hunger/ satiety limbo could explain the dysfunctional eating behaviour in overweight and obesity?

A conserved physiological mechanism for maintaining weight?

Most studies examining overweight and obese children and adolescents have discovered the same basal depression of ghrelin as in obese adults, compared to their healthy, normal weight peers. [249, 150, 151, 63, 127, 128, 272] Interestingly, some groups report that ghrelin levels are correlated with body mass even in neonates, [76, 273] and possibly even in utero, based on their intrauterine nutritional state. [76] Some groups even find an association between increased ghrelin and weight in babies born small for gestational age. [274, 275, 276, 277, 278, 279] These observations raises the question whether ghrelin regulation is a conserved physiological mechanism for inducing rapid growth and weight gain.

Cummings et al. in their review article refer to several publications demonstrating an association between weight in neonates and ghrelin levels as well; [280, 249, 281, 282, 283, 284] It should be pointed out that none of these publications satisfy the Cochrane RCT-criteria.

In other words, a lower birth weight than expected apparently leads to an increase in ghrelin, which is then followed by a significant weight regain during a shorter period of time. Park et al., from their intervention, suggest that ghrelin is a possible reason of accelerated growth in children with low birth weight.[273] Could a brief post-natal state of hypersomatotropism, with increased ghrelin and GH, be a physiological compensation initiated by ghrelin? The fact that ghrelin levels seem to control growth and weight development from birth, supports the theory of ghrelin as a sensitive, physiological mean of controlling the body weight homeostat. It seems plausible from a physiological point of view, that ghrelin is part of a mechanism for

catching up weight after birth, but it could also mean a lower threshold for developing obesity, due to an increased appetite.

The Paradox of Dieting

Comparing weight loss interventions is a major challenge due to different means of weight loss, different time perspectives, differences in energy state and different extents of loss of body mass. However, from examining the studies below, certain trends are observed.

First, with energy restriction, total ghrelin apparently increases. [144], [143], [91], [145], [285], [286] The mRNA-expression for ghrelin is also reported to be increased with caloric restriction. [41]

An increase in orexigenic hormones, in order to re-establish energy balance seems plausible in a state energy depletion. However, one apparently observes the same defence when the individual is trying to loose weight within a normal, physiological range. In other words, there is no "graded response" towards loss of body mass when it comes to ghrelin regulation. Could this be the reason why keeping a stable weight after weight loss appears to be difficult?

There are inconclusive reports in literature about how long the apparent increase in ghrelin lasts. One randomized controlled trial reported that ghrelin levels remained elevated even by the end of the intervention program for weight loss, despite the fact that the subjects had a fairly small reduction in weight. [141] However, this publication has been critizised for not reporting the subjects to have become weight stable at any point of their intervention, which could have influenced results. [142]

Another randomized controlled trial reported that ghrelin increased the first 6 months after weight loss, but was later reversed almost

back to baseline before weight loss within the next 12 months. [142] However, if the latter results resemble the normal situation after weight loss, why do former obese subjects still experience problems with maintaining weight loss several years later?

Several clinical trials merely confirm what is reported by the RCTs, a significant increase in ghrelin on weight loss. [145, 148, 143, 287] One publication however, suggests that a lack of increase in ghrelin could actually explain success in weight loss.[288]

The increase in ghrelin might be a reason why obese subjects trying to loose weight by dieting would have an even harder time trying to maintain their new weight. They would experience a stronger stimulation of appetite and hunger. An interesting finding reported in one study is a significant correlation between a lower basal ghrelin and regain of more than 10 % of their weight loss later on.[148]

Several publications report the same finding of increased ghrelin with weight loss in children as reported for adults. [249, 289, 150, 290]

It has been suggested that the increase in ghrelin on weight reduction is an adaptation towards a negative energy balance, [249] and it has also been reported that ghrelin is progressively increased during reduction of obesity.[289] Could these findings have revealed ghrelin as a protective hormone against unwanted weight loss? And even more interesting: could the act of *dieting per se* be one of the keys in explaining the obesity epidemic? Is the change in ghrelin among the reasons why weight loss over a longer time, or to a more moderate extent is more successful than rapid, huge weight losses? It is very unfortunate that none of these studies report changes in acyl vs. des-acyl ghrelin, which could have contributed with important information.

Ghrelin and hyposomatotropism– an issue in obesity?

Ghrelin, as a ligand of the GH-releasing receptor, is also a source of GH-secretion. Several publications have reported an increase in GH from exogenous infusion of ghrelin. [160, 161, 162, 51, 50, 164, 163, 165, 291]

Study	Ghrelin dose ug/kg	GH-peak ug/L
Arosio 2004	3,30	53
Popovic 2003	1	75,1
Takeno 2004	0,2	29,9
Alvarez-Castro 2006	1	68,5
Hataya 2001 - dose 1	0,08	5,5
- dose 2	0,2	39,8
- dose 3	1	79
- dose 4	5	109,8

Table 16: GH peak in ug/L from different doses of ghrelin in ug/kg. [162, 50, 164, 163, 165]

Further numbers and original units are found in tables in Appendix 1.

The most important mechanism discussed in literature is the apparent inhibition ghrelin executes on somatostatin, which again abolishes the inhibition of somatostatin on GnRH.[16] One group has suggested that ghrelin is a partial antagonist to somatostatin. [292] Furthermore, it seems like somatostatin could influence ghrelin, in that exogenous somatostatin suppresses ghrelin levels. [293]

One group has concluded that ghrelin increases GH, but that ghrelin again is inhibited by IGF-1.[93] GH inhibits insulin, and reduces glucose to skeletal muscle. [93] In other words, during fasting, ghrelin is increased whereas IGF-1 is reduced, which again results in increased GH. [93] In a state of low ghrelin, one should expect a lower GH and a higher IGF-1. The association between obesity and lower values of GH fits well with the co-existing lower values of ghrelin.[101]

In a state of suppression of acyl-ghrelin, a suppression of GH would also be plausible. A lack of secretion of GH might induce a situation

with a smaller component of lean body mass. [125] IGF-1 has been reported to have a negative correlation with ghrelin, but it is also influenced by BMI, insulin resistance and glycemic state. [294] In obese subjects loosing weight, IGF-1 is observed to increase, and ghrelin has been suggested to be the cause of this. [147, 194] This has been referred to as a feedback-suppression of ghrelin through the GH/IGF-axis. [295, 296] This theory is denied by another group. [297]

Apparently, obese subjects have a weaker effect on GH-release from exogenous ghrelin infusion, compared with normal subjects. [298, 125] Several reports indicate a correlation between GH-secretion, increased weight and fat storage from ghrelin infusion. [104, 90, 69, 17] Two research groups deny that the acute increase in GH from ghrelin infusion is due to changes in insulin or glucose. [163, 296]

Yet another mechanism has been suggested in the way ghrelin regulates GH-secretion. This mechanism is suggested to be cortistatin, [399] a peptide neuro-hormone with affinity to the ghrelin receptor GHSR-1a, and described by Kojima et al. as a possible link between ghrelin and the somatostatin systems. [300]

Ghrelin - A leptin antagonist - or vice versa?

A significant association between fasting ghrelin and leptin has been reported by several publications, [301, 302, 55, 303, 90] and a trend has been reported by groups not reaching stastical significance. [304]

However, a major debate has been whether ghrelin and leptin are involved in a reciprocal relationship or not. One publication suggested that the suppression of ghrelin might be due to the mere elevation of leptin in morbid obesity. [301] This launched the hypothesis that leptin counter-regulate ghrelin, as a homeostatic response to promote reduction of the hunger stimulus and thus reduce food intake in obesity. [131]

Both leptin and ghrelin seem to lack diurnal variation in obesity. [267] It has been suggested that leptin is an inhibitor of both ghrelin secretion as well as the orexigenic effect from it. [114] They illustrate this effect with a feedback-loop, consisting of leptin, ghrelin and NPY, which when abnormally regulated, leads to obesity. [114] However, three research groups conclude that leptin is not an important determinant of ghrelin. [249, 142, 123]

Ghrelin and appetite is reduced in older subjects, but ghrelin is apparently increased in malnourished, underweight subjects and with anorexia and cachexia of disease

Some studies have investigated the levels of ghrelin in older subjects, and the possible causal relationship with reduction of appetite. Several research groups have investigated both the differences in ghrelin profiles between young and old subjects, as well as the effects of ghrelin changes with age.

Two groups reported that older subjects have lower basal ghrelin levels, compared with younger controls, [168, 305] but this is rejected by two other groups. [306, 167]

However, it should be pointed out that older subjects also have a higher basal level of insulin, negatively correlated with ghrelin. [305] Insulin is a known inhibitor of ghrelin secretion. [307, 117, 118, 119] One of the negative groups comment that if insulin is not measured and level of insulin sensitivity not assessed, this might be a confounding factor. [174]

One group reports that older individuals have a flatter curve for acyl ghrelin compared with younger controls.[168] This is opposed by a randomized controlled trial, reporting that *well-nourished elderly* subjects still expressed the normal, diurnal variation of ghrelin, with

no significant difference to younger controls.[167] However, it is commented by a third group that this randomized controlled trial measures post-prandial ghrelin at a time point later than the others, when ghrelin is actually starting to increase.[169]

Elderly subjects do not express the same pattern of release as younger, and a lower ratio of acyl ghrelin for des-acyl is reported. [168] This is also supported by one of the groups being negative towards basal differences in total ghrelin.[174]

Totally different findings are reported for older, frail and malnourished individuals. One group reports that basal ghrelin was about 4 times higher in underweight subjects, compared with healthy controls, but this group examines severely malnourished subjects with an average BMI of 16.9.[167] This is opposite of what another group reports, they claim that basal ghrelin is in fact reduced in older, frail individuals. [169] It appears to be a loss of postprandial ghrelin response in older, frail subjects, which is not observed in older, non-frail subjects. [169.]

Furthermore, elderly subjects do not have a gradual increase in ghrelin within 4 hours post-prandial, like the younger subjects. [169] The same group does not observe any significant correlation between ghrelin and hunger within observation time of 4 hours post-prandial. However, in their discussion, they point out that the delay of gastric emptying also might influence decreased levels of ghrelin and contribute to the prolonged satiety and anorexia. [169.]

One publication does not report any significant correlation between ghrelin and changes in weight in elderly subjects. [308] This publication is omitted from the tables due to methodological issues.

Effects of ghrelin therapy in states of cachexia and the anorexia of disease

In states of calorie deficiency, cachexia and anorexia nervosa, basal ghrelin is also increased; [252], [171], [172] One of these groups describes non-optimal plasma sample handling procedures. [172]. One group describes no significant difference in ghrelin between subjects with cachexia and healthy individuals. [309]

Cachexia is a condition of wasting of body mass, involving loss of both fat and protein stores, leading to reduced appetite and weight loss. [310] The state of cachexia, also of disease apart from cancer, is associated with elevated levels of ghrelin. [71], [252], [172] Increase in ghrelin has been discussed as a result of wasting of the organism. [311] However, it has also been discussed as a feature of ghrelin resistance. [311], [252] In other words, both obesity and severe underweight are conditions in which ghrelin dysregulation and resistance is observed, either no suppression of drive to eat or no initiation of it. Two publications claim that these subjects are in a state of chronic ghrelin resistance. [312, 313]

Several groups have reported increased appetite and/or food intake from exogenous administration of ghrelin in patients with chronic diseases and cachexia. [314], [252], [315], [316, 317]

Some of these publications have important weaknesses, such as a small study population. [314, 317]

Ghrelin vs. Insulin

Several groups have reported a negative correlation between ghrelin and insulin, but also a correlation between ghrelin and insulin sensitivity. [90], [77], [181], [180], [98], [128], [56, 318] Ghrelin has been referred to as a diabetogenic hormone. [319]

Effects on insulin from ghrelin infusion

Several interventions have investigated the effects on insulin from administrating exogenous ghrelin. The question is whether ghrelin influences insulin secretion - or function?.

Ghrelin receptors in the liver have been presented as possible means of regulating blood glucose.[320] Ghrelin immunoreactive cells have been demonstrated in the beta cell islets of the pancreas, [321] and the GHS-R1a is present in the endocrine pancreas as well. [83] Ghrelin has also been suggested to be the modulator of the glucose-sensing neurons of the central nervous tissue, modulate insulin secretion and the glucose production of the liver. [48] However, none of these theories have been proven as causal mechanisms.

The general conclusion in literature is that exogenous ghrelin infusion increases blood glucose. [160, 154, 298, 46, 162] Furthermore, the general opinion in literature is that exogenous ghrelin also reduces insulin secretion. [160, 154, 298, 46, 162] Two randomized controlled trials both acknowledged by the Cochrane Library concluded that hyperglycemia occurred ahead of any increase in insulin. [160, 154] Most of these publications report fairly high doses of ghrelin administrated. Could this be the reason why they observe this hyperglycemia?

However, two publications find that ghrelin infusion actually weakens insulin sensitivity and that it in fact *enhances* insulin. [322, 153] One randomized controlled trial reports that insulin is not affected, but blood glucose and lipids are increased by ghrelin infusion, referred to as a peripheral insulin resistance. [322]

One study administrates acyl ghrelin only, concluding that acyl weakens phase 1 of the biphasic insulin response in healthy

subjects.[323] This is more consistent with experiences from patients with elevated levels of acyl-ghrelin, severe obesity, which is often associated with hyperinsulinemia and insulin resistance.

Lucidi et al investigated the effects from *physiological doses* of ghrelin. They discovered that these concentrations were not sufficient to induce significant changes in blood glucose or insulin in healthy subjects.[324] In other words, what remains unknown is whether the other experiments infused subjects with supra-physiological concentrations of ghrelin, and thereby creating an effect of no major importance in vivo. This conclusion is also interesting, because it indicates that at some point, there is a threshold for the fact that ghrelin may induce changes in blood glucose and insulin. Could this threshold be altered in states of pathology, such as in type 2 Diabetes or insulin resistance? And could this be releated to the apparent differences in threshold for inducing hunger and satiety between obese and lean subjects? If the subjects have a chronic elevation of acyl ghrelin, could the dose administrated be too small and administration time insufficient to induce changes?

Effects on ghrelin by insulin

The observations of reciprocal ghrelin and insulin changes after meals were the ones that lead to the hypothesis that ghrelin changes might be a result of changes in insulin. [325] Several research groups support the fact that insulin might also be a mediator of ghrelin. [295, 326, 324, 307, 118, 98] Several articles have later reported the same negative correlation of insulin and ghrelin, [128, 56, 318] even in children. [327, 150, 250, 128, 137, 130]

Some groups deny that insulin is the regulating factor of ghrelin. [328, 329, 330, 331, 332]

There is a significant lower level of total ghrelin in the insulin resistant

subjects, despite no significant difference in BMI or body weight. [181] It is also reported that insulin resistance, as defined by an elevated SSPG (steady state plasma glucose) is a significant predictor of ghrelin, together with, fasting plasma insulin, which is found to be an independent predictor. [181] However, discussing ghrelin without distinguishing between acyl and des-acyl ghrelin in this issue is pointless.

The general conclusion in literature is a negative association between insulin sensitivity and des-acyl + total ghrelin. [177, 333, 178] Not all groups agree that such an association between ghrelin and insulin resistance exists. [142, 334, 325] Several groups claim that it is hyperglycemia that influences ghrelin, and not insulin. [335, 336, 337] One randomized controlled trial find that ghrelin levels in subjects with type 2 diabetes is correlated with levels of HbA1c. [338] Another study reports a stronger suppression of basal ghrelin with diabetic complications from hyperglycemia. [337]

Initially, the association between insulin resistance and ghrelin was described as a vicious circle triggered by insulin resistance, possibly increasing acyl ghrelin, again increasing the orexigenic urge to eat, increasing weight and insulin resistance. In other words: an obesigenic loop. [137]

In order to evaluate the interplay between insulin and ghrelin, several research groups have tried to reproduce the situation of hyperinsulinemia with normal glucose level in a euglycemic, hyperinsulinemic clamp test. These tests search to display the effects of insulin on ghrelin secretion, not influenced by changes in glucose. The table below shows insulin peaks and ghrelin nadirs from 5 interventions, and suppression from basal ghrelin levels. Unfortunately, the interventions contain both serum- and plasma

values of ghrelin, subjects with fairly different characteristics concerning weight and metabolic state and different procedures for clamp-testing. There are several research groups reporting the same results in their abstracts, e.g. Mohlig et al. and Weickert et al. [119, 339]

Study	Insulin (pmol/L)	Ghrelin nadir (pg/ml)	Baseline ghrelin (pg/ml)
Flanagan et al.	444,48	569,86	770,04
Leonetti et al.	1040,36	179,03	205,53
Schaller et al.	1602	122	246
Caixas et al. *	370	358,4	358,4
Saad et al.	564	61	85

Table 17: Ghrelin concentration and suppression from basal level during euglycemic hyperinsulinemic clamp-testing.* Caixas et al. and Saad et al. report no significant suppression. [117, 116, 331, 330, 118]

In order to make them easier to compare, some numbers are converted to pg/ml. Numbers in original units are found in tables in Appendix 1. The conversion method used is multiply pmol/L with 3.38 as published by Moran et al. 2007. Moran LJ, Noakes M, Clifton PM et al. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. Am J Clin Nutr. 2007 Dec;86(6):1603-10.

The general trend is that higher concentrations of insulin are followed by lower concentrations of ghrelin. The two studies did infuse their subjects with the smallest amount of insulin, but report no significant suppression.

One group reported that acyl ghrelin was not suppressed (this is the only publication differentiating between acyl- and des-acyl ghrelin). [339] Therefore, they also concluded that the observed suppression of acyl ghrelin after meal is mediated by other mechanisms.[339] Rodriguez et al., commenting upon these results, point out that these groups could have infused their subjects with concentrations of

insulin lower than their habitual level. Rodriguez et al. refer back to several publications performing the same intervention in type 2 diabetic subjects, [79], [176], [340] all reporting a suppression of acyl ghrelin. However, these studies infused their subjects with higher amounts of insulin. Another study point out that although they administrated high concentrations of insulin, these are within an expected level for individuals examined, all being obese. [116] Their question is whether the ghrelin suppression observed among obese subjects, discussed earlier as a state of "maximal suppression" could be due to suppression from the very high insulin concentrations with obesity. [116]

Is ghrelin suppression in metabolic syndrome a result from hyperinsulinemia?

A significant association between plasma acyl-ghrelin and abdominal adiposity [260], hyperinsulinemia and insulin resistance/ type 2 diabetes has been reported by several groups. [79], [177], [333], [179] Several groups report that the ratio of acyl: des-acyl ghrelin is higher in insulin resistant subjects. [176], [177], [337] In other words, the cardinal components of the metabolic syndrome are associated with increased plasma acyl ghrelin.

The correlation between acyl ghrelin and whole-body insulin sensitivity [341] is reproduced in children, totally [342], [333] or in part. [343] This is another reason why the regulating abilities of ghrelin on metabolism could be thought of as conserved physiological mechanisms of energy storage and protection against starvation.

However, one group claims that the apparent association between ghrelin and the metabolic syndrome might be explained by a higher BMI. [344] The big issue is therefore to distinguish what is explained by obesity, and what is explained by insulin resistance in subjects with the metabolic syndrome, suppressed total ghrelin and elevated

acyl:des-acyl ghrelin ratio.

Is it the distorted acyl: des-acyl ghrelin ratio that leads to a reduction of insulin sensitivity, thereby increasing basal insulin, again suppressing insulin secretion? Or is increased acyl-ghrelin a result from hyperinsulinemia? This is not answered by the interventions investigated in this paper.

However, several studies conclude that the postprandial ghrelin suppression apparently depends on insulin secretion. [117, 119, 118] Samra et al. in their Cochrane-acknowledged trial detected that hyperinsulinemic subjects had a lower ghrelin secretion than normoinsulinemic controls after ingestion of a glucose drink, which was also followed by a lower food intake. They discuss the possibility of this as a mechanism in these subjects for limiting food intake in hyperinsulinemic subjects - a mechanism in order to promote weight stabilization. [345]

The gut-brain axis and ghrelin in bariatric surgery

Bariatric surgery is currently regarded among the most efficient means of permanent weight loss, [40] changing both the anatomy as well as the endocrine regulation of metabolism within The Gut-Brain-Axis. [199] It other words, the procedures totally change the structures and components of the gut-brain axis from anatomy to paracrine, endocrine and neurocrine signalling. Apparently, it also affects ghrelin.

There are four important issues that make comparing and contrasting these publications a challenge. First, intervention time varies from a few weeks post-operatively to several years. Second, the surgical procedures, assay kits and sampling procedures differ. The third issue is that the ratio of acyl and des-acyl ghrelin is hardly considered at all. The fourth issue is that changes in insulin/ blood

glucose are not discussed along with changes in ghrelin by several publications.

Apparently, procedures involving restriction of the stomach are the most effective in suppressing ghrelin. During the Roux-en-Y, it is the partitioning of the stomach that induces the greatest suppression of ghrelin, according to one study investigating each step in the surgical procedure on ghrelin. [188] However, it has also been reported that it is the extent of dysfunctionality in the fundus that determines the level of ghrelin. [182]

The Roux-en-Y

A reduction in ghrelin from this procedure has been reported by most research groups. [144, 182, 183, 184, 185, 186, 187, 188, 189] Several cross-sectional studies have also reported an apparent ghrelin suppression with weight loss. [190, 191, 192, 183, 193, 194, 195] A recent review article, acknowledged by the Cochrane CDS-group, summarizes 25 publications on changes in ghrelin from the Roux en Y. [346] Overall, they conclude from their review that the studies of strong design (prospective/ retrospective and controlled studies), conclude with a reduction of ghrelin after RYGBP.[346] It should be pointed out that only one publication is a double-blinded randomized controlled trial, and only one publication evaluates ghrelin and BMI changes more than 12 months after surgery.[187]

Some publications deny that ghrelin is suppressed from RYGBP; [131, 347] either no change [348, 349, 350] or even an increase in plasma ghrelin levels following gastric bypass procedures. [307, 347, 350] One group detected that ghrelin was elevated only in patients actively loosing weight, and not in those who had been weight stable for 6 months. [302] However, this explanation was rejected by others. [347, 350]

Ghrelin is, as mentioned earlier, the one and only known

endogenous orexigenic, adipogenic endocrine component within the gut-brain axis. If this treatment is a way of weight loss without the burden of increased ghrelin, and at the same time reverses the insulin resistance often seen in severe obesity, it might be a way of breaking the vicious cycle of obesity.

Several factors might contribute to these different conclusions concerning results from Roux en Y gastric bypass. As pointed out by Ashrafian et al., most of the studies that observe a reduction in ghrelin do this after assessing plasma samples shortly after surgery, which could actually reflect a state of pathophysiological stress, [351] as interpreted by Sundbom et al. as vagal dysfunction. [352] If this is interpreted as the habitual state, the decrease in ghrelin later on would reflect a false suppression.

Among the most interesting explanations of why ghrelin seems to be initially reduced was published by Cummings et al. [144] This group observed a reduction in total ghrelin, while diurnal variation was still distorted. Their explanation was the phenomenon of "override inhibition". This was defined as a state in which the permanent absence of nutrition triggers a continuous ghrelin signal, in the end leading to a suppression of ghrelin secretion. [144] Two research groups discuss how a lack of this effect might explain reduced effect from surgery. If the partitioning of the stomach is done slightly to much to the left, the gastric fundus is in contact with nutrients, ghrelin secretion is operative and the override inhibition undermined. [185, 353]

One group argues that the acute reduction in ghrelin observed 2 hours after surgery was within the range of what is discovered in patients undergoing other procedures of GI-surgery. [354] They further suggest that the trend towards normal ghrelin values after 6 months might be due to normalization after weight loss. [354]

In their 2009 article, Dadan et al. reported that the X/A-cells of the gastric fundus were hypoactive in obese subjects compared with controls. They suggest that this might be due to an increased insulin secretion. [185] Moreover, the Roux-en-Y appears to induce changes in insulin secretion- or response. [191, 194] It has been suggested that these changes are due to the anatomic changes of the digestive tract. [191] The studies observe that the insulin secretion is more efficient, and that ghrelin suppression is reversed towards normal after the RYGBP. However, this might also reflect a more rapid emptying from the ventricle. Engstrom et al. ask whether a rapid emptying of nutrients after the RYGBP might induce a dumping syndrome and a post-prandial hypoglycaemia in the susceptible patients, and if an earlier peak in insulin might induce a glucose-mediated glucose disposal. [194]

Sleeve gastrectomy

In particular, this procedure has been associated with a strong suppression in ghrelin. [197, 198, 199] Prolonged reduction of ghrelin secretion has been suggested to be responsible for the reduced food intake in these patients.[355] Considering that sleeve gastrectomy involves resecting most of the fundus of the ventricle, the location for most production of ghrelin, a strong reduction would be expected. The resection of ghrelin-producing tissue is the explanation by several groups why this procedure apparently reduces ghrelin to such great extent.[200] The majority of literature concludes that the sleeve gastrectomy is followed by more weight loss than the other bariatric procedures. [355, 201, 202]

One group reports that ghrelin is produced to a significant extent in other tissues. [356] The same group observes that patients treated with subtotal gastrectomy have only small changes in ghrelin secretion

compared to healthy controls. [356] This could be a reason why some subjects undergoing partial gastrectomy do not experience changes in ghrelin, reduction in hunger and weight loss.

However, one group suggests that subtotal gastrectomy is followed by a relative overproduction of ghrelin from the remaining cells, due to the fact that ghrelin levels only decreased 20 % in their study. [357]

Literature mentions several factors that might affect the results and interpretations of these studies; among them the size of the gastric pouch remaining and paracrine effects of other gut-hormones. [358]

However, a review article investigating the late effects of sleeve gastrectomy concluded 23 % of subjects showing regain of weight or complications with reflux in need for a conversion to a gastric bypass/ duodenal switch procedure. [359] This study also presents the longest follow-up period, detecting a change in plasma ghrelin significantly lowered after 5 years. [359] The nadir was observed after 12 months, but the slight increase was non-significant. [359]

Gastric banding

Gastric banding includes two procedures; vertical banded gastroplasty and adjustable gastric banding. Both are restrictive procedures, aiming to limit the gastric reservoir, thus make it more difficult to empty the stomach as well as limiting the stomach capacity. [205] The gastric banding is a purely restrictive procedure, which does not alter the anatomical position of the stomach (the restrictive obstacle against caloric excess is an elastic band), and it, to a certain extent, requires patient cooperation in order to succeed. [185]

Most publications report a significant increase in ghrelin from this procedure. [207, 360, 185, 209, 200] This is different from the other bariatric

procedures investigated, but consistent with what is reported form conservative methods of weight loss.

The increase in ghrelin has been explained with the energy restriction after surgical restriction, [185] but also with increased expression in ghrelin secreting cells in the gastric fundus. Since the procedure does not abolish parts of the stomach from contact with nutrients (RYGBP) or resects ghrelin producing tissue, one cannot expect the same reduction in ghrelin. Furthermore, the concept of "restraint" has been discussed. This is thoroughly discussed in a later paragraph, but several groups suggest that increased cognitive restriction of what to eat and not to eat contribute to increase ghrelin. [361, 362] Furthermore, this is also a matter of compliance. In order to lose weight, food intake needs to be restricted which is challenged by an increased ghrelin secretion. However, two groups deny that the hyperghrelinemia observed after this procedure explains the lack of weight loss. [363, 182, 209]

One publication also reported a blunted post-prandial suppression of both molecular forms when gastric banding is compared to the gastric bypass.[183] They also detected that their subjects treated by gastric banding did not show the same decrease in fasting insulin as the RYGBP-group. In another publication, the same group reports that based on VAS-scoring, RYGBP induces a stronger post-prandial satiety than gastric banding.[364]

Biliopancreatic Diversion

This includes two different procedures of restriction of the stomach; the Scopinaro and the duodenal switch. [205] The restriction is both of the absorptive area of the duodenum, as well as restriction of the stomach capacity.[205] Biliopancreatic diversion leaves a stomach volume of more than 300 mL in most cases. [206]

Results are inconclusive, but the majority of publications report a significant increase in ghrelin from this procedure. One publication reports an initial decline in ghrelin seen together with weight loss, [204] and another one claims the ghrelin suppression not to be to the same extent as RYGBP and sleeve gastrectomy. [195] One group reports an initial decline in, which later increases. [203]

A relation between ghrelin reduction and gain of insulin sensitivity?

Among the most interesting observations are the apparent improvement of insulin sensitivity followed by bariatric surgery, as well as suppression of total ghrelin. Could this ghrelin suppression, if it also involves a suppression of acyl-ghrelin, actually explain the fast weight loss, or is increased insulin sensitivity a consequence from the sudden large reduction of adipose tissue? [365] Two research groups suggest that the suppression of ghrelin happens because of the correction of insulin sensitivity. [206, 128]

One group concludes, based on the findings from another major publication [203], that insulin is the causal modulator of ghrelin secretion also after the Roux-en-Y. [354] This means that a reduction in total ghrelin would be associated with an increased insulin, which is not the general observation from bariatric surgery characterised by lower fasting insulin as well as suppression of ghrelin.

However, this is another example why investigating effects from ghrelin is hopeless without examining differences in acyl- and des-acyl ghrelin. Acyl ghrelin is increased in severe obesity. Insulin sensitivity is positively correlated with acyl ghrelin, [341] which is why interventions examining effects on acyl ghrelin from bariatric surgery is needed in order to explain possible relations between ghrelin suppression, weight loss and regain of insulin sensitivity.

Main points

* Exogenous infusion of synthetic human ghrelin increases food intake

* There is a negative correlation between total ghrelin and BMI, and it appears to exist a distorted relation between acyl- and des-acyl molecular forms in obesity.

* Increased des-acyl ghrelin and decreased acyl-ghrelin could be a part of the reason why subjects with anorexia nervosa or cachexia experience lack of appetite and hunger

* Ghrelin is also increased during weight loss, which could be another reason why weight loss caused by dieting is often followed by weight gain.

* Diurnal variation is blunted in obesity. Obesity apparently retains post-prandial ghrelin suppression, possibly by inducing lack of sensation of satiety

* The threshold for orexigenic effect from ghrelin infusion also appears to be altered in obesity

* The same associations are detected in children. This could represent a conserved mechanism for weight maintenance. Increased ghrelin in children born small for gestational age could be a mechanism for accelerating growth and weight gain

* Ghrelin shows a negative correlation with insulin, and acyl-ghrelin is associated with viscerial adiposity and insulin resistance. Acyl-ghrelin appears to be involved in increased storage of fat. These associations have been described as a vicious circle triggered by

insulin resistance, possibly increasing acyl ghrelin, drive to eat, weight and insulin resistance - a vicious obesigenic loop

* Bariatric surgery seems to induce a strong suppression of ghrelin, along with significant weight loss. At the same time, insulin sensitivity is improved.

THE RESTRAINT IN THE BRAIN

´Ghrelin is transported across the Blood Brain Barrier and is in part dependent on cholinergic pathways

Several mechanisms for transport from stomach to central nervous tissues have been discussed for ghrelin. Schellekens et al. refer to the transport of ghrelin from the stomach to the brain as a three-way transport, such as non-saturable transmembrane diffusion, saturable active transport over the Blood-Brain Barrier and vagal connections. [32]

Areas of the hypothalamus, called Sensory Circumventricular Organs are not protected by the Blood Brain Barrier, and the peptide hormone is probably transported across these structures. [366]

Signals counteracting satiety are transmitted from the GI-tract to the CNS via vagal connections [40, 367, 368, 4] and endocrine transmission by way of the general circulation. [369, 370] These connections involve autonomous functions of the brain stem, hypothalamus and higher centrae with clear cognitive functions. [369] The general opinion in literature has been that ghrelin affected central tissues by cholinergic mechanisms, transmitted by the vagus. [371, 372, 373] These conclusions are based on publications reporting a significantly depleted level of ghrelin [22] and suppressed orexigenic effect in

subjects treated with vagotomy. [374, 40] It has also been reported that ghrelin is capable of inhibiting the sympathetic nervous system in healthy subjects, and that the vagus is responsible for this effect. [124] Both the orexigenic and the motility stimulating effects of ghrelin are dependent on intact vagal connections. [369]

No production of ghrelin has been confirmed in the CNS in humans, however, in an intervention investigating ghrelin-sensitive neurons in the human hypothalamus, such fibres are detected in the external zone of the pituitary stalk, which by the authors are interpreted as a possibility for ghrelin synthesis in hypophysiotropic neurons. [72]

How is ghrelin involved in Neuropsychological Mechanisms for Regulating Eating Behaviour?

The mesolimbic dopaminergic system, or the dopaminergic neurons of the ventral tegmental area, are believed to be the system anticipating rewards. [74, 375] The system is also sensitive to ghrelin. [375] In other words, ghrelin also activates neurons within the mesolimbic pathways of reward, not only the AgRP and NPY-neurons of the arcuate nucleus. [376]

Several research groups have reported that ghrelin apparently enhances the urge for preferred foods [239, 123, 66] Abizaid et al., ask whether ghrelin might affect cognitive processes increasing the incentive towards “rewarding”, often high caloric foods, by dopaminergic neurons projecting to the forebrain and releasing dopamine. [375] Furthermore, infusion of intravenous exogenous ghrelin to healthy people has been reported to induce a significant increase in VAS-score as well as imaginations about food, and visual imagination of a favourite meal could be interpreted as an activation of the hippocampus. [123]

Furthermore, the endocannabinoid system has also been discussed

as a possible pathway for ghrelin in executing its function in central tissues. This is a lipid signalling system, consisting of the cannabinoid receptors, their ligands and enzymes responsible for inactivation and synthesis of these endogenous cannabinoids.[377]

Ghrelin as well as the endocannabinoids apparently perform some of the same molecular effects in adipose tissues and the hypothalamus, [32, 378] and both the GHS-R1a and the CB1 (cannabinoid receptor 1) are known to in vitro make receptor dimers with dopamine receptors. [32] One publication that has thoroughly discussed the importance of the endocannabinoid ligands in humans, concludes that not all endocannabinoid ligands are active on the internal cannabinoid receptors. But by vagal connections, the endocannabinoid oletylethanolamide is active in the GI-tract, regulating food intake. [379] Could these mechanisms describe how ghrelin is linked with the dopaminergic pathways of reward?

Cognitive processes involved?

As summarized in the review by Olszewski et al., [380] animal models of recent date have demonstrated how ghrelin is involved in more complex cognitive processes, such as memory, and establishment of reward pathways. [380]

Several studies have shown an increased level of ghrelin in individuals currently reducing weight. [144, 22, 71] A very interesting study by Schur et al. raise the question of a possible association between *cognitive restraint,* defined as a strict regulation of what to eat, and distorted levels of ghrelin, independent of body weight. [381] In other wordsThe big question is if the cognitive restriction with a diet could contribute to increase levels of ghrelin? The fact that a restrictive pattern of eating could lead to higher levels of ghrelin might explain the challenges with weight loss through control of food intake.

Because of this, ghrelin has also been discussed as a causal agent for "cravings" and increased food intake associated with dieting. [382] Ghrelin is also proven to be increased in situations with emotional stress, and the question is whether this is another cause of ghrelin elevation resulting in overeating.[382] Only one publication denies this association between ghrelin and restraint. [383]

One intervention study with binge eating subjects reported a successful reduction of binge eating episodes, along with a reduction of ghrelin while treated with a cognitive therapy intervention program. [384] Is this the key for success in weight loss - to actually treat the restraint, the negative patterns of thought and cognitive processes contributing to a dysregulation of the gut-brain axis?

Does Stress increase Ghrelin?

It has also been discussed if ghrelin induces a stress response. One study has shown that ghrelin increases apparently when cortisol does. [395] This study, however, has significant weaknesses.

During an acute response to stress, the adrenal release of catecholamines increases, suppressing appetite while mobilizing glycogen. [386] Stress also leads to fast eating provoking the sensation of reward, resuscitation and reduction of stress. [386]

Raspopow et al. detected that subjects with frequent episodes of emotional eating did not experience the post-prandial decline in ghrelin following a meal after a social stress test (the TSST). [387] They also observed a difference in high and low emotional eaters, in that the low degree of emotional eating displayed a 25 % reduction in ghrelin after eating. [387]

Another study has reported that elevated ghrelin might contribute to

sustained eating in emotional eaters, and even provide the same signal as has been suggested in binge eating disorders. [387] They also suggest that emotional eaters have a decreased reliance on hunger signals. [387]

Ghrelin - Implications in eating disorders

Several publications have discussed the involvement of different neuropeptides in the pathogenesis of eating disorders. Stoving et al. discuss how it is relevant understanding the gut-brain axis and the endocannabinoid system interacting with opiodergic pathways in this group of diseases. [388] As shown in the results tables, significant distortion of ghrelin is detected in these disorders.

Ghrelin profiles in anorexia nervosa

Anorexia Nervosa is a syndrome characterized by an extreme fear of weight gain, a distorted image of one's own body, significant weight loss and amenorrhea. [389]

Patients with anorexia nervosa have a higher basal level of ghrelin, compared with normal age-matched controls. [211, 220, 223, 218, 215, 216, 214, 212, 211, 127, 158, 210]

Patients loosing weight also seem to have a higher ghrelin than patients in recovery phase. [211] Ghrelin levels have been reported to be normal in weight stable subjects, and patients currently gaining weight. In other words; ghrelin elevation seems to be related to morbidity.

An interesting observation is that BMI-matched controls with constitutionally low weight have a lower ghrelin level than patients with anorexia. [216, 390, 220] Despite a very low BMI, the constitutionally thin subjects without anorexia nervosa had a normal diurnal rhythm of ghrelin, both total and acyl ghrelin. [216] In other words, the elevation

of ghrelin is not exclusively dose-dependent on weight. Could the process of restriction, or the concept of restraint, in terms of restricting oneself from food, be the reason why subjects with eating disorders have a higher secretion of ghrelin than healthy controls with the same weight and BMI?

Despite certain differences in conclusions, several studies support the theory that a distorted eating pattern leads to changes in ghrelin. [223, 216, 213, 391, 392] If restraint has this effect on ghrelin, have patients with anorexia nervosa developed a situation of GHS-R desensitization, obviously not responding to the constant endocrine urge to eat?

Tanaka et al. in their 2003-article, reported that patients with a subtype of anorexia nervosa, called the binging/purging type had a significantly higher mean ghrelin, compared with subjects with restricted type of disease. [223] Their conclusion is that both BMI and the binging/purging behaviour might affect plasma ghrelin, and that this happens by way of alimentary vagal afferent fibres. [223] However, this is opposite of Germain et al., reporting a reduction in ghrelin in subjects with binge/purge type. [216] This is interpreted as an indication of a certain nutritional supplementation. [216]

In their 2004-article, Tanaka et al. also suggested ghrelin to be both an indicator of nutritional state as well as an indicator of eating behaviour. [213] This is opposed by another research group. [210] It is a problem about the two studies by Tanaka et al. as patient's own report is used for deciding whether the subject had restrictive or binging/purging type of anorexia. [223, 213] Approximately half of all patients with anorexia nervosa develop some bingeing and purging over the years. [391] Therefore, as disease form varies throughout time, one could not actually randomize these groups without a certain risk

of bias.

Also, the relationship between acyl and des-acyl ghrelin is reported to be disturbed by the majority of literature. In general, anorexia leads to an elevated component of des-acyl ghrelin. [391, 393, 158] Inui et al. suggest that different patterns of eating behaviour might be due to distorted ratio of acyl: des-acyl ghrelin. Even short-term re-feeding of patients with anorexia nervosa is shown to lead to decreased levels of des-acyl ghrelin, and the reduction in des-acyl component decreases more rapidly and earlier in the process. [393] One research group also concludes that the des-acyl ghrelin could be used for assessing nutritional state in anorexic subjects, since this is apparently changed ahead of acyl ghrelin. [393]

Germain et al. concluded that the significant increased levels of total as well as acyl ghrelin in patients with restrictive anorexia represents an adaptation towards chronic under-nutrition, whereas the decreased ghrelin profiles in patients with binge/purge type of anorexia and bulimia nervosa represents an indication of episodes of food supplementation. [216.] However, this study is also based on patient's reports diagnosing either restrictive or binge/purge type. [216]

Several studies support the theory of a possible development of ghrelin resistance in subjects with anorexia. [294, 220, 22,] It has been sugggested that signalling from ghrelin does not happen normally in these subjects. [222] One group reported that plasma ghrelin remained elevated even after partial weight recovery. [394] Patients with anorexia nervosa tend to have a weakened response to exogenous ghrelin, [395, 212] which again tends to be normalized if weight gain, [395] and they do not have the expected increase in glucose on ghrelin administration.[212, 395] Even in recovery phase, subjects with anorexia nervosa have significantly lower hunger-scores, as measured by the

VAS-scale ghrelin infusion. [395] One group suggests that infusion of active ghrelin does not induce a normal GH- or appetite response in subjects with anorexia nervosa, most likely due to prolonged endogenous hyperghrelinemia, [395] interpreted as a form of ghrelin resistance by another group. [394]

Several groups have observed a post-prandial suppression in subjects with anorexia nervosa, [211, 158, 214] whereas other groups report that this suppression is impaired or abolished. [396, 223, 218] However, the different publications administrated different test meals to their subjects, possibly influencing the results. [388]

Ghrelin profiles in Bulimia Nervosa

Bulimia nervosa is characterized by a purging behaviour. The most known variant is through vomiting, but purging by way of laxatives is quite frequently seen. Self-destructive behaviour such as excessive exercise etc. is also recognized as purging behaviour. Although BN is characterized by purging, and many subjects also have episodes of binging behaviour, binging is not a necessary component of this disease. [389]

Results in literature are inconclusive for whether this condition leads to changes in ghrelin. Two publications detect significant elevated ghrelin in patients with bulimia nervosa; [223, 37] Three other publications oppose this finding. [217, 216, 398] On one side it is argued that bingeing opposes the increase in ghrelin from food restriction. [216]

The loss of post-prandial ghrelin suppression has been detected by most research groups. [399, 218, 410, 227] It is suggested that this lack of post-prandial ghrelin suppression might contribute to the lack of satiety and thus binge episodes in bulimia nervosa. [227, 218, 223] This association between lack of ghrelin suppression and bingeing/purging behavior is opposed by three other groups. [401, 402,

[398] One group has not detected any association with pre- or post-prandial changes in ghrelin and bulimia. [403]

It is reported that ghrelin is increased to a larger extent in bulimic subjects with higher frequency of binging and purging, [226, 219], and that ghrelin peaks are correlated with the frequency of binging and purging behaviour. [404] One group, however, denies that ghrelin explains binging/purging behaviour. [224]

The Effect of Binging

The binge eating disorder, in which purging is not executed through vomiting, use of laxatives or exaggerated physical activity [405] appears to be more difficult to examine that bulimia nervosa and anorexia nervosa. First, as the disease does not involve purging behavior, including starvation, most of these subjects would be expected to be overweight. In other words, ghrelin is affected both by the presence of an eating disorder as well as obesity/overweight. Binge eating has been associated with a dysfunction in the ghrelin signalling system, and with a reduction in the postprandial satiety. [406]

The majority of literature concludes that ghrelin is reduced in these patients, possibly due to suppression of the hormone after bingeing episodes. [405, 402] One group suggests that this is due to a dysregulation that might be arising from an increase in gastric capacity. [406]

Furthermore, it is reported that subjects with BED have a significantly smaller post-prandial suppression of ghrelin, compared with their obese subjects without BED and their subclinical BED controls. [405] This indicates that ghrelin is associated more with bingeing than the mere condition of obesity. [405, 144]

The question remaining to be answered is whether ghrelin is involved

in inducing binge-eating, or if binge-eating is the factor influencing ghrelin. An interesting finding by Montelone et al. is that ghrelin is depressed even in normal weight subjects diagnosed with binge eating disorder [402] This suggests that it is the mere disordered eating pattern that is responsible for the dysregulation of ghrelin. Obese women with BED and without the disease showed no differences in ghrelin, and ghrelin was not correlated with frequency of bingeing or severity of the disease. [402] However, the study sample in this study apparently have a slightly increased fat mass and BMI just above normal range. [402]

In other words, whether ghrelin influences binge-episodes, or the other way around, is not agreed on in literature examined by this paper.

Main points

* Ghrelin activates Agouti-related peptide neurons and Neuropeptide Y-neurons of the Nucleus accumbens and increases appetite and hunger

* Ghrelin also activates dopaminergic neurons within the mesolimbic pathways of reward, and probably promotes a rewarding response from eating

* Ghrelin seems to be involved in the activation of the endocannabinoid system

* Despite the fact that most research groups reject that leptin is a central regulator of ghrelin, an association between them has been observed.

* A restrained eating pattern, defined as strict regulation of what to eat or not to eat, is associated with an increased ghrelin. This has

been suggested to induce a trigger to overeat, increased appetite, cravings and to be a challenger towards keeping a stable weight after weight loss.

* In general, patients with anorexia nervosa and severe underweight have an elevated level of basal ghrelin. It has been suggested that this is caused by cognitive restraint of eating.

* The behaviour of binging apparently reduces ghrelin, possibly due to nutritional supply and correction of energy state.

* Patients with eating disorders apparently have a different diurnal pattern of ghrelin secretion, compared with their healthy controls.

THE PAIN IN SATIETY

Ghrelin Effects on Gastric Motility

Together with the pre-proghrelin transcript motilin, ghrelin is released during fasting and promotes gut motility.[1] When administrated to fasting subjects, exogenous ghrelin induces MMC phase III-like contractions and increases the contraction tone of the gastric fundus.[407, 408, 409, 410, 411, 43, 271, 412, 413, 414, 415] The increased motility is apparently limited to the ventricle, as no effect on colonic transit time is reported.[410] Two publications deny that ghrelin is a promoter of gastric motility.[416, 417] arguing that this seems contradictive, considering that ghrelin is in fact suppressed after meal.[416]

In particular, the conditions of gastroparesis have been investigated in order to outline the mechanisms by which ghrelin increases motility. Gastroparesis is a condition of delayed gastric emptying, which might induce symptoms like early satiety, nausea, vomiting and regurgitation of food.[418, 419] In literature, gastroparesis also

appears to be associated with a reduced level of ghrelin.

It has been suggested that this motility promoting effect of ghrelin is dependent on cholinergic/vagal mechanisms, but according to Levin et al., this is not reproduced in literature. [412] From literature discovered by this paper, the results concerning vagal connections and ghrelin in gastric motility appear inconclusive, with some positive findings [420], some partly positive findings [421] and some negative findings, concerning whether ghrelin is dependent on N.Vagus in regulating motility. Therefore, it is not clear whether neuropathy could explain a lack of ghrelin secretion in these patients. Patients with diabetic gastroparesis have a significantly lower fasting plasma ghrelin, compared with healthy controls. [422, 420, 418] A loss of rhythmicity in secretion, a change in diurnal rhytms, has also been detected. [420] However, it is difficult to know whether this is also due to diabetic complications such as insulin resistance and hyperglycemia and suppression due to obesity, or if the ghrelin suppression seen occurs because of other factors. In general, one observes a positive effect from exogenous ghrelin infusion in individuals with gastroparesis. [418, 419, 82]

Ghrelin involved in pain

Current literature reports two possible ways of ghrelin in signalling pain. First, by way of increasing motility, as outlined above. Secondly, the endogenous opioid system has been suggested to be involved in functional pain syndromes of the gut, affecting pain threshold, inhibiting peristalsis, secretion or transmission of acetylcholine. [13]

The latter mechanism is more thoroughly outlined by Rhee et al. The vagus is an important mediator of pain by way of its afferents, communicating probably with enterochromaffine cells, thus providing a direct pathway for neuronal transmission. [14]

Hellstrom et al. ask whether changes in the MMC, possible mediated through neuroendocrine peptides, explain motility disturbances involved in pain, hunger and nausea, or even mediate these conditions. [369] In other words, this group opens for a possible function of ghrelin and other hormones in regulating these sensations by way of changes in motility.

The association between ghrelin and motility is interesting also in the discussion on functional disorders. Are there associations between functional syndromes and changes in motility, or MMC, because of disturbed regulation through endocrine mediators, such as ghrelin? Several research groups ask whether different stressors, by way of motility and immunological functions and emotional perceptions lead to visceral events characteristic of functional syndromes. [423, 424]

Functional disorders have been explained with alterations within the gut-brain axis [5,] as well as a state of viscerial hyperalgesia. [425] These alterations might induce a state of pain and nausea instead of satiety.

Functional disorders also illustrate how sensations such as nausea, pain, hunger and satiety are integrated within a common physiological spectrum. Along with orexin A and B, ghrelin is regarded an anti-nociceptive component, whereas leptin is regarded nociceptive. [426] How could ghrelin be involved in pain in functional disorders? In general, conditions of increased motility are associated with an increase of total ghrelin and regarded an anti-nociceptive agent. Could this increase contribute to an increased motility of the upper GI-tract, and replace sensation of satiety with pain?

Furthermore, Guneli et al. point out that ghrelin might be involved in the endogenous antinociceptive system of the brain, also by way of

mediators such as beta-endorphin and endogenous opioids.[426]

A trial by Ang et al., evaluating the effect on postprandial gastric tone and satiety after exogenous ghrelin administration, finds that ghrelin inhibits gastric accommodation, and decreases the ventricular volume after meals. [409] The studies by Cremonini et al. discovered that a ghrelin infusion significantly, but only with marginal difference, reduced the intra-gastric volume. [408]

Ghrelin in functional disorders

Functional Gastrointestinal Disorders are defined by the ROME criteria as *a variable combination of chronic or recurrent gastrointestinal symptoms not explained by structural or biochemical abnormalities.* [427]

Symptoms of functional disorders may be provoked as a consequence of eating, which might be an example of signalling between the stomach and colon by local nervous systems, as well as local hormones.[1] Processes of cognitive and behavioural origin can exacerbate symptoms of functional disorders, mediated by complex pathways, and behavioural therapy has been successful in treating some patients. [13]

When it comes to associations between ghrelin and functional disorders, it appears that they vary with the different conditions. In general, literature concludes that higher levels of ghrelin are correlated with symptoms of pain in patients with motility type of functional disorders. [428, 232] Some concludes with lower values of ghrelin. [229]

Shinomiya et al. report a positive correlation with symptoms of dysmotility and plasma ghrelin, and a negative correlation with des-acyl ghrelin. [428] Their conclusion was that acyl ghrelin might be

related to the pathophysiology of functional disease. [428] Several groups have also shown either a significant association [229, 228] or a trend towards an association between reduced ghrelin and delayed emptying of the stomach. [230] In other words; conditions with reduced motilty is characterized by a reduction of ghrelin, and vice versa.

In patients with functional bowel syndromes of unknown origin, postprandial distress and symptoms of nausea and bloating might replace the sensation of satiety satisfaction after a meal. [429] Sjolund et al., examined patients with the irritable bowel syndrome, and they concluded that ghrelin and motilin have a significant co-variation in IBS, and that this might contribute to the syndrome and accelerate gut motility. [430] El-Sahly et al reported that in patients with IBS dominated by constipation, ghrelin density in the gut mucosa was reduced. [431]

When it comes to ghrelin involvement in functional disorders, one needs to consider that this is only one component of the gut-brain axis. In a condition with a pathological increase in ghrelin, one could expect also an increased motility, which could possibly explain pain, but also an increased food intake. Does obesity, associated with an increased acyl: des-acyl ghrelin ratio, induce a pathological perception of gut motility as hunger? Does reduction of acyl ghrelin, reduced gastric motility and MMC-frequency, induce a pathological perception of pain after food ingestion, again leading to a reduction of food intake?

A Mediator of Inflammation?

T-cells, B-cells and polymorphonuclear cells are all producers of endogenous ghrelin [432] and the GHS-R1a-receptor has been described in human lymphocytes, monocytes and polymorphonuclear cells. [152, 432] The receptor is also expressed in cells of the spleen [83] and colonic mucosa. [18]

Ghrelin is among the first hormones to rise after an injection with LPS (E.Coli bacterial endotoxin), and ghrelin peaks correspond with levels of IL-6, GH and ACTH. [433] Intestinal inflammation apparently increases ghrelin secretion. [434] Acyl ghrelin is associated with inflammation, as measured by CRP, [179] while des-acyl, and thereby the main component of total ghrelin, is regarded anti-inflammatory.

The general opinion in literature is that ghrelin works through influencing different cytokines. Two research groups claim that ghrelin in general suppresses cytokines, [152, 435] while one study claims that acyl ghrelin regulates pro-inflammatory cytokines in the T-cells. [436] From literature, a negative correlation between ghrelin and TNF-alfa [437] and IL-6 is reported, [433, 437] while higher levels of IL-beta is associated with lower values of ghrelin. [438] However, there is also one study not demonstrating any change in neither IL-6 nor TNF-alfa by repeated administration of ghrelin, [316] and one study demonstrating a positive correlation.[233]

Several mechanisms have been suggested to be involved in the integration of ghrelin in the immune response, among them activation of Toll-Like receptors and NOD-like receptors in the gastric cells, [433] by way of the NFkappaB mediated pathway, inducing IL-8 activity in the colonic epithelium, [439] and modulation of cell function by way of triggering activation of the PPAR-gamma.[440]

Chronic inflammation of mucosa is known to withdraw the function of ghrelin producing cells in the stomach. [441] Inflammatory bowel disease (IBD) is a condition of inflammation associated with changes in ghrelin levels. The main conclusion in litterature is that ghrelin is increased in patients with active disease, compared with controls. [442, 233, 234] This increase is independent on body weight. [233] Patients whose disease were in remission phase had no significant changes

in ghrelin. [442], [233].

Aydin et al. discuss how des-acyl ghrelin would be of greater interest in IBD than acyl ghrelin. Des-acyl ghrelin is, according to Aydin et al., proven to stimulate cell proliferation, and IBD is characterized by an increased epithelial proliferation. [443]

Ghrelin mRNA and GHS-R1a are reported by Hosomi et al. to be significantly elevated in the colonic mucosa of patients with Mb. Crohn, the highest in patients with active disease. [444] The authors further suggest that ghrelin might regulate the inflammatory response through increased amount of T-cells. [444] They discovered that ghrelin appeared to direct the T-cell response towards the Th2-response, by inducing cytokines like IL-4 and IL-13, while inhibiting IFN-gamma in healthy controls. [444] Furthermore, they claim that in patients with Mb.Crohn, ghrelin did not increase the Th2-cytokines, which is interpreted as a distortion in the T-cell reactivity toward ghrelin. [444] An interesting co-finding of one study investigating the effects from administration of the TNF-alfa inhibitor Infliximab to patients with Mb.Crohn, is the significant reduction of total and acyl ghrelin, as well as reversion back to a normal meal-related profile. [445] These findings also indicate that ghrelin is a measure of inflammatory activity of Crohn's disease. [445]

Inflammation of obesity - immunological function from a metabolic window?

Not only is increased acyl-ghrelin and decreased total ghrelin associated with the state of as well as the development of obesity; acyl-ghrelin is also associated with inflammation as measured by CRP [179] and oxidative stress. [446] Is inflammation another aspect of the suppression of total ghrelin and increase of acyl ghrelin seen in obesity? Obese subjects have a lower total level of ghrelin with a higher level of TNF-a.[350]

There is also a significant association between a lower total ghrelin, lack of ghrelin suppression and the metabolic syndrome, as pointed out by Suematsu et al. [446] This group suggests that a higher relative component of acyl ghrelin might contribute to accelerate the process of atherosclerosis. [446]

There is also a significant correlation between metabolic syndrome and level of TNF-alpha, IL-beta and IL-6. [447, 176] The correlation of ghrelin and inflammatory markers has also been reproduced in children. Okamatsu et al. reported higher levels of anti-bodies, CRP and cytokines (interleukins) in obese children. [448] St.-Pierre et al. ask whether there could be a two-way mediating effect from ghrelin, activating the TNFa-system, thus increasing obesity-related conditions. [176]

Dixit et al report that ghrelin significantly inhibits the leptin-induced inflammatory response in the lymphocytes. [152] Their suggestion is that this might induce pathology such as the metabolic syndrome seen in states of obesity. [152] It would be plausible to suggest that the increase of the pro-inflammatory leptin and the reduction of the anti-inflammatory total ghrelin associated with the leptin resistance of chronic obesity initiates a state of chronic inflammatory disease. [449]

Ghrelin distortion causing pain in obesity?

Guneli et al. discuss an interesting theory, combining the findings from ghrelin in functional disorders and obesity. [426] They refer earlier reports, and claim that it appears to be a reverse correlation of body weight and treshold of the nociceptive reflex. [426]

Guneli et al. launch endocrine changes as a possible mechanism how pain treshold might be affected in states of obesity. [426] They suggest that suppression of ghrelin in obesity leads to an increased

susceptibility of pain. [426] Guneli et al. also refer to Kojima et al., finding that ghrelin receptors are expressed in areas of the brain controlling pain transmission. [37] However, they also point out the possibility that ghrelin influences nociceptive signalling by its involvement in the endocannabinoid system. [426]

Obesity is associated with an increase in acyl ghrelin, which is again associated with a higher extent of motility. Could endocrine influence on pain treshold, along with changes in motility patterns and hunger/satiety regulation lead to a sensation of pain in obese subjects, replacing a normal sensation of hunger? Are these distortions in ghrelin and other endocrine components of the gut-brain axis an inducer of a sensation of pain, interpreted as hunger in obese subjects? The mechanisms for this are not outlined in literature investigated by this paper.

Main points

* It should be remarked that these conditions are influenced by several other endrocrine and neurological components within the gut-brain axis. Ghrelin could be understood as an example of how several such components within the gut-brain axis are changed in states of pathology

* Ghrelin levels are correlated with symptoms in patients with motility type of functional disease

* Ghrelin is regarded a natural promoter of gut motility, and its precursor is transcribed from the same gene as motilin.

* Literature is inconclusive on whether ghrelin is dependent on vagal connections or not in order to increase gastric motiltiy.

* How ghrelin is actually involved nociceptive transmission in humans is not answered, and functional disorders are not explained by ghrelin dysregulation only.

* Acyl-ghrelin is also associated with inflammation, and is increased compared to des-acyl ghrelin in obesity and the metabolic syndrome.

* Ghrelin is increased in inflammatory conditions

* Ghrelin is produced in, and the receptor GHS-R1a expressed in lymphocytes as well as polymorphonuclear cells.

Concluding remarks

This paper attempted to answer four central questions about how the neuro-hormone ghrelin is integrated into the gut-brain axis, its effects on central processes within this common physiological axis. As stated in the introduction, this paper understands "the common physiological spectrum" as how the different sensations of hunger, satiety and pain are controlled within the mechanisms of the gut-brain axis. This is the basis for the holistic understanding of how different conditions of pathology, obesity, functional disorders and inflammation are seen with dysregulation of this axis.

Ghrelin is a part of the gut-brain axis, both as a neuro-endocrine and paracrine mediator of functions. Its actions is regulated by way of endocrine signalling, vagal connections as well as by other molecular components within the GI-tract.

This paper wishes to point out that a discussion of ghrelin effects on metabolic functions is pointless without considering that it is one among 20 known endocrine mediators within the GI-tract. In order to investigate the different aspects of weight, hunger and eating

behavior, one needs to consider a wide range of other mediators as well. Ghrelin cannot, at any point, explain the entire picture, neither in weight regulation, hunger, satiety nor pain.

A major weakness in current litterature is that a major component does not differ between the two molecular forms acyl- and des-acyl ghrelin. Not only do they execute different functions, the relationship between them is also important: the ratio acyl: des-acyl ghrelin. In the years to come, research groups should be aware of this issue.

Ghrelin mediates appetite, hunger and satiety mainly through activation of neurones of the hypothalamus. However, signals are transmitted both by way of endocrine and neurological mechanisms. Apparently, ghrelin is influenced by several components of The Gut Brain Axis, and shows an association with both insulin and several other endocrine components. Dysregulation of ghrelin is associated with dysmotility and symptoms in functional disorders of the GI-tract. Ghrelin is also associated with inflammatory conditions, and there are indications also of an association between pain and dysregulation of ghrelin.

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APPENDIX 1

For bibliography, see paper Ghrelin in The Hunger, The Brain and The Pain

THE HUNGER

	Subjects	**Controls**		**Schmid et al., 2005**
n	9	9		
Subject characteristics	Healthy male and female subjects	Cross-over, same subjects given placebo		
Dose of ghrelin administrated	100	Placebo	ug	
VAS score after intervention	6.2	0.9	cm	
SD	3.2	1.5	cm	
p	< 0.05			
	Subjects	**Controls**		**Huda et al., 2009**
n	9	9		
BMI	51.4	22.3		
SD	3.4	0.9		
Subject characteristics	Obese subjects	Lean		
Basal plasma total ghrelin	414.4	762.1	pmol/ kg^-1	
SD	86.3	71.1	pmol/ kg^-1	
p	< 0.05	< 0.05		
Dose of ghrelin administrated	5	5	pmol/ kg^-1/ min^-1	
Food intake after ghrelin	+ 35	+ 41 (lean)	%	
SD	14	14 (lean)	%	
p			0.008	
VAS score	Flattened hunger profile Pre-prandial rise Post-prandial fall	Pre-prandial rise Post-prandial fall	cm	
	Subjects	**Controls**		**Druce et al., 2005**
n	12	12		
BMI	31.9	20.5		
SD	3.5	0.6		
Subject characteristics	Obese subjects	Lean controls		

Basal plasma total ghrelin	441.7	459.6	pmol/L	
SD	171.0	156.6	pmol/L	
p			0.78	
Dose of ghrelin administrated	5.0 pmol/kg/min			
Food intake after ghrelin	+ 70.1	+ 20.1	%	
SD	15.5	10.6	%	
p		< 0.01		
VAS-score after ghrelin	+21.3	Not significant	%	
p			< 0.05	
	Subjects			**Wren et al., 2001**
n	9			
BMI	23.2			
SD	0.7			
Dose of ghrelin administrated	Infusion commenced at 0.2 - rate then doubled every 20 min. to max 25.6		pmol/kg/min	
Subject characteristics	Lean, healthy subjects			
Energy intake	+ 28		%	
SD	3.9		%	
Increase in hunger score after ghrelin infusion	+ 10 (meal 1) + 20 (meal 2)		%	
p			< 0.05	
	Subjects	**Controls**		**Akamizu et al., 2004**
n	12	6		
Subject characteristics	Healthy male subjects randomized to either high or low dose of ghrelin	Healthy male subjects randomized to placebo		
Basal plasma ghrelin (acyl and total)	20.7 (acyl, high dose group) 188.0 (total, high dose group) 12.0 (acyl, low dose group) 20.7 (total, low dose group)	18.3 (acyl) 221.6 (total)	fmol/ml	
SD	10.1 (acyl high dose) 62.6 (total high dose) 5,3 (acyl	5.4 (acyl) 46.3 (total)	fmol/ml	

	low dose) 66.8 (total low dose)			
p	Significant	Significant		
Dose of ghrelin administrated	1 (low dose) 5 (high dose)	Placebo	ug/kg	
VAS score post-prandial	No significant change	No significant change		
Plasma ghrelin post-prandial (acyl and total) concentration max.	3454.0 (acyl, high dose) 6597.9 (total, high dose) 447.2 (acyl, low dose) 1058.7 (total low dose)	23.8 (acyl) 230.7 (total)	fmol/ml	

Table 3: Effects from ghrelin infusion on VAS-score for hunger/ food intake [123, 124, 125, 66, 126]

	Obese	**Lean**		**Misra et al., 2009**
n	13	13		
Fasting p acyl-ghrelin	39.7	55.5	pmol/L	
SD	17.7	18.1	pmol/L	
p	0.04			
	Obese			**Ikezaki et al., 2002**
n	49			
Fasting p-ghrelin	157.8 (boys) 137.7 (girls)		fmol/L	
Range	69.1 - 369.8 (boys) 77.8 - 202.2 (girls)		fmol/L	
p	Significant			
	Obese	**Lean**		**Soriano-Guillen et al., 2004**
n	26	41		
Fasting p-ghrelin	420	796 (Tanner 1) 355 (Tanner 5)	pg/ml	
SD	29	61 (Tanner 1) 26 (Tanner 5)	pg/ml	
p	< 0.05			
	Obese	**Lean**		**Bacha et al., 2005**
n	23	36		
Fasting p-ghrelin	445.9 (male) 312.8 (female)	605.7 (male) 598.9 (female)	pmol/L	
SD	54.8 (male) 36.5 (female)	132.6 (male) 55.6 (female)	pmol/L	
p (negative correlation with BMI)	0.001			

Table 4: Fasting ghrelin in obese children/adolescents [127, 128, 129, 130]

	Obese	**Lean**		**Tschoep et al., 2001**
n	8	7		
Fasting p-ghrelin	106	155	pmol/L	
SD	25	23		
p			< 0.01	
	Obese	**Lean**		**Shiiya et al., 2002**
n	11	28		
Fasting p-ghrelin	0.68	1		*Obese subjects had 68 % of ghrelin values in lean controls*
p			< 0.05	
	Obese	**Lean**		**Vicennati et al., 2007**
n	20	12		
Fasting p-ghrelin	Lower than controls			
p	< 0.033			
	Obese	**Lean**		**Druce et al. 2005**
n	12	12		
Fasting p-ghrelin	441.7	449.6	mg/mL	
SD	171.0	156.6		
p			0.78 (not significant)	
	Obese			**Holdstock, 2003**
n	66			*Subjects are not compared to lean controls*
Fasting S-ghrelin	86.9		pmol/L	
SD	40.2			
p			Not found	
	Obese	**Lean**		**Bellone et al., 2002**
n	36	29		
Fasting ghrelin p-ghrelin	229.5	426.0	pg/ml	
25th and 75th centile	162.5 - 339.5	183.0 - 618.0	pg/ml	
p	< 0.03			
	Obese	**Lean**		**Sondergaard et al., 2009**
n	10 (upper-body obese) 10 (lower body obese)	10		
Fasting S-ghrelin	0.60 (upper-body obese) 0.69 (lower body obese)	0.85	ug/L	

SD	0.16(upper-body obese) 0.22 (lower body obese)	00.22	ug/L	
p		00.33 not significant		
	Obese	**Lean**		**English et al., 2002**
n	10	13		
Basal ghrelin, total	325	857	pmol/L	
95 % CI	204-519	627-1171	pmol/L	
p	< 0.0001			
	Obese	**Lean**		**Carlson et al., 2009**
n	13	10		
Basal P-ghrelin	1087	1418	pg/ml	
SD	187	232	pg/ml	
p	< 0.05			

Table 5: Ghrelin in obese subjects compared to lean controls 90, 98, 64, 125, 131, 250, 78, 133, 132

	Obese	**Lean**		**English et al.., 2002**
n	10	13		
BMI	42.8	22.5		
SD	3.8	0.7		
Basal ghrelin, total	325	857	pmol/L	
95 % CI	204-519	627-1171	pmol/L	
p	< 0.0001			
Post-prandial ghrelin suppression %	No significant change	39.5	%	
Test meal	714/515 kcal man/woman 11 % protein 15 % fat 76 % carb.			
	Obese	**Lean**		**Greenman et al., 2004**
n	24			
BMI	29 (male) 29.4 (female)			
SD	1.5 (male) 3 (female)			
Basal fasting plasma total ghrelin	397 (male) 794 (female)		pg/mL	
SD	72 (male) 198 (female)		pg/mL	
End post-prandial ghrelin suppression meal 1	Reduced suppression			
End post-prandial	Reduced suppression			

ghrelin suppression meal 2				
End post-prandial ghrelin suppression meal 3	Reduced suppression			
Test meal 1	300 (100 % carb).			
Test meal 2	400 4.5 % protein 91 % fat 5.5 % carb.			
Test meal 3	240 84 % protein 11 % fat 5 % carb.			
	Obese	**Lean**		**Marzullo et al., 2006**
n	10	6		
BMI	43.4	21.8		
SD	0.8	1.4		
Post-prandial ghrelin suppression meal 1	Significant	Significant		
Post-prandial ghrelin suppression meal 2	Significant	Significant		
Post-prandial ghrelin suppression meal 3	Significant	Significant		
Test meal 1	500 17 % protein 30 % fat 53 % carb.			
Test meal 2	500 17 % protein 55 % fat 28 % carb.			
Test meal 3	500 30 % protein 25 % fat 40 % carb.			
	Obese	**Lean**		**Carlson et al., 2009**
n	13	10		
BMI	44.5	23.1		
SD	7.1	1.3		
p	< 0.05			
Basal P-ghrelin	1087	1418	pg/ml	
SD	187	232	pg/ml	
p	< 0.05			
Ghrelin post-prandial	Significant decrease, but later than lean			

	controls			
Test meal	60 % carbohydrate, 20 % protein, 20 % fat	60 % carbohydrate, 20 % protein, 20 % fat		

Table 6: Post-prandial suppression of ghrelin is reduced in obesity compared with healthy controls. 133, 122, 132

	Subjects	**Controls**		Morpurgo et al., 2003
n	10			
Intervention time period	3 weeks program 1200-1800 kcal/day 21% protein, 53 % carb, 26 % fat.			
BMI	45.2			
SD	10.6			
Start post-prandial ghrelin suppression	No suppression observed			
Start fasting plasma ghrelin	110.8	352.4	pmol/L	
SD	69.7	176.7	pmol/L	
BMI end	Significantly lowered			
End fasting plasma ghrelin	91.8	199.0	pmol/L	
SD	70.2	105.2	pmol/L	
p	NS	< 0.01		
Post-prandial ghrelin suppression	No significant change			
Test meal	550 kcal 19 % protein 33 % fat 48 % carb.			
	Subjects			**Romon et al., 2006**
n	17			
Intervention time period	7 weeks intervention program, 800 kcal/day, 20 % carb, 50 % protein, 30 % fat			
BMI	37.6			
SD	5			
Basal plasma total ghrelin	1.86		ng/ml	
SD	1.05		ng/ml	
End BMI	33.1			

SD	4.5			
Fasting plasma total ghrelin	2.28		ng/ml	
SD	1.48		ng/ml	
p	0.05			
End post-prandial ghrelin suppression meal 1	No change in suppression			
End post-prandial ghrelin suppression meal 2	Bigger suppression observed			
Test meal 1	813 20 % protein 809 % fat			
Test meal 2	813 20 % protein 80 % carb.			

Table 7: Post-prandial suppression in obese subjects after dietary intervention 263, 135

	Subjects	**Controls**		**Gil-Campos et al., 2010**
n	34	20		
Age	9.4	9.8		
SD	04	04		
BMI Z-score	4.05	- 0.99		
SD	0.30	0.39		
Fasting plasma total ghrelin	231.6 (boys) 300.5 (girls)	243.9 (boys) 325.1 (girls)	pg/mL	
SD	29.5 (boys) 63.1(girls)	43.2 (boys) 48.0 (girls)	pg/mL	
P-ghrelin 1 hour	181.5 (boys) 240.6 (girls)	157.7 (boys) 228.4(girls)	pg/mL	
SD	16.6 (boys) 54.6 (girls)	79.4 (boys) 27.1(girls)	pg/mL	
P-ghrelin 2 hours	180.0 (boys) 238.2(girls)	196.4 (boys) 224.8(girls)	pg/mL	
SD	43.5 (boys) 58.0(girls)	21.5 (boys) 31.5(girls)	pg/mL	
P-ghrelin 3 hours	216.4 (boys) 287.9(girls)	183.4 (boys) 245.5(girls)	pg/mL	
SD	32.9 (boys) 63.1(girls)	34.7 (boys) 27.5(girls)	pg/mL	
p (difference in post-prandial ghrelin suppression)	< 0.012			
Test meal	Mixed breakfast 430 kcal			
	Subjects			**Maffeis et al., 2006**
n	10			
Age	11.4			
SEM	0.5			

BMI-SD	2.4			
SEM	0.2			
Fasting S-total ghrelin	701		pg/mL	
SD	66.9		pg/mL	
S-ghrelin 30 min	- 7.0		%	
S-ghrelin 60 min	- 15		%	
p	< 0.005			
Total suppression	27.3		%	
SD	2.7		%	
Test meal	Mixed compositions but high fat, 40 % of daily need			
	Subjects	**Controls**		**Lomenick et al., 2008**
n	12	20		
Age	9.4	10.2		
SD	0.4	0.3		
BMI Z-score	2.34	0.2		
SEM	0.17	0.11		
p	< 0.001			
Fasting P-total ghrelin	743	965	pg/mL	
SD	55	130	pg/mL	
p			0.13	
Ghrelin suppression meal 1	No significant	No significant		
Ghrelin suppression meal 2	No significant	Significant		
Test meal	400 kcal meal 1, 600 kcal meal 2, 60 % carbohydrate, 10 % protein, 30 % fat			
	Subjects	**Controls**		**Mittelman et al., 2010**
n	10	70		
Age	12.8	12.8		
SD	0.4	0.4		
BMI adjusted for percentile	36.3	19.7		
SD	2.5	0.6		
p	not significant		< 0.001	
Fasting P-total ghrelin before test meal 1	1407	1441	pg/mL	
SD	67	128	pg/mL	
p			0.835	
Acyl ghrelin before test meal 1	123.3	80.7	pg/mL	
SD	25.7	16.0	pg/mL	

p			0.175	
Test meal 1	Large meal providing 62.5 % of daily energy need, 50 % carbohydrates, 30 % fat, 20 % protein			
Total ghrelin after test meal 1	1490	1439	pg/mL	
SD	138	167	pg/mL	
p			0.822	
Acyl ghrelin after test meal 1	83.8	66.9	pg/mL	
SD	19.3	12.4	pg/mL	
p			0.463	
Test meal 2	Small meal providing 25 % of daily energy need, 50 % carbohydrates, 30 % fat, 20 % protein			
Fasting ghrelin before test meal 2	1400	1393	pg/mL	
SD	73	176	pg/mL	
p			0.977	
Acyl ghrelin before test meal 2	121.4	81.5	pg/mL	
SD	25.1	13.6	pg/mL	
p			0.174	
Total ghrelin after test meal 2	1490	1439	pg/mL	
SD	138	167	pg/mL	
p			0.822	
Acyl ghrelin after test meal 2	83.8	66.9	pg/mL	
SD	19.3	12.4	pg/mL	
p			0.463	

Table 7: Post-prandial suppression of ghrelin in children [136, 137, 139, 138]

	Before weight loss	**After weight loss**		**Foster-Schubert et al., 2005**
n	87			
Weight	81.7	- 1.4	kg	
SD	1.4	0.4	kg	
p		< 0.05		
Fasting ghrelin	599	+ 32	pg/ml	
SD	38	16	pg/ml	
p		< 0.05		
Intervention time			12 months	
	Before weight loss	**After weight loss**		**Garcia et al. 2006**
n	25	25		
BMI	37.7	34.4		

		(after 6 months) 33.9 (after 12 months)		
SD	1.7	1.5 (after 6 months) 1.4 (after 12 months)		
p			< 0.05	
Fasting ghrelin	589	704 (after 6 months) 541 (after 12 months)	pg/ml	
SD	52	64 (after 6 months) 45 (after 12 months)	pg/ml	
p			< 0.01	
Intervention time			12 months	
	Before weight loss	**After weight loss**		**Cummings et al. 2002**
n	13	13		
Weight loss		17.4	%	
SD		1.5	%	
Fasting ghrelin		+ 24	%	
p		< 0.001		
Intervention time			6 months	
	Before weight loss	**After weight loss**		**Hansen et al., 2002**
n	8	8		
Weight	95.6	90.6	kg	
SD	5.6	5.3	kg	
p			<0.02	
Fasting ghrelin	114	128	fmol/ml	
SD	17	16	fmol/ml	
p			<0.01	
Intervention time			6 months	
	Before weight loss	**After weight loss**		**Zahorska-Markiewicz et al., 2004**
n	35	35		
Weight	96.5	87.8	kg	
SD	16.5	15.2	kg	
Fasting ghrelin	66.3	73.7	pmol/L	
SD	13.7	14.8	pmol/L	
p			0.002	
Intervention time			3 months	
	Before weight	**After weight**		**Moran, 2007**

	loss	loss		
n	14	14		
BMI	35.3	34.4		
SD	1.3	1.7		
p		< 0.05		
Fasting ghrelin	935	912	mmol/L/ 180 min	*Expressed as Area Under Curve*
SD	31	35	mmol/L/ 180 min	"
p		NS		
Intervention time			8 weeks	
	Before weight loss	**After weight loss**		**Olszanecka-Glinianowicz, 2008**
n	22	22		
BMI	37.2	33.7		
SD	4.6	4.6		
p		< 0.001		
Fasting ghrelin	63,5	72,8	pg/ml	
SD	13,0	15,1	pg/ml	
p		< 0.01		
Intervention time			3 months	
	Before weight loss	**After weight loss**		**Romon, 2006**
n	17	17		
BMI	37.3	33.5		
SD	4.8	4.6		
p		< 0.0001		
Fasting ghrelin	1.86	2.28	ng/ml	
SD	1.05	1.48	ng/ml	
p		< 0.05		
Intervention time			7 weeks	
	Before weight loss	**After weight loss**		**Crujeiras et al., 2010**
n	104	104		
BMI	30.7	29.0		
SD	2.4	2.2		
p		< 0.001		
Fasting ghrelin	952	964	pg/ml	
SD	326	343	pg/ml	
p		0.461		
Intervention time			8 weeks	
	Before weight loss	**After weight loss**		**Kotidis et al., 2006**
n	14	14		
BMI	38.6	35.11		
SD	6.83	6.32		
p		0.001		
P- total ghrelin (fasting)	1.97	3.59	ng/ml	
SD	0.77	0.88		
p	0.002			
Intervention			6 months	

time				

Table 8: Effects from weight loss on fasting ghrelin, 141, 142, 144, 143, 145, 146, 147, 135, 148, 149

	Before weight loss	**After weight loss**		**Reinehr et al., 2008**
n	44	31	*31 children had weight loss*	
Age	11.2		Years	
SDS-BMI	2.2	1.5		
SD	0.4	0.4		
p		< 0.05		
Ghrelin	1080	1209	pg/ml	
SD	(899-2278)	(902-2294)	pg/ml	
p		Not significant		
Intervention time			12 months	
	Before weight loss	**After weight loss**		**Krohn et al., 2006**
n	23	23		
Age	10-16			
BMI-SDS	2.85	2.47		
Range	2.27 - 3.85	1.79 - 3.64		
p		< 0.001		
Fasting ghrelin	25.3	31.8	ng * min/mL	*Area under curve*
SD	1.7	2.3	ng * min/mL	*"*
p		< 0.001		

Table 9: Effects from weight loss on fasting ghrelin in children. 151, 150

	Subjects given ghrelin infusion		**Broglio et al., 2001**
Dose	1.0	mg/kg	
n	7		
GH	5452.4	ug/min/L	
SD	904.9	ug/min/L	
p	< 0.01		
	Subjects given ghrelin infusion		**Di Vito et al., 2002**
Dose	1.0	ug/kg	
n	7		
GH 15 min	2695	ug/min/L	
SD	492.6	ug/min/L	
p	< 0.01		
	Subjects given ghrelin infusion		**Arosio et al., 2004**
Dose	3.3	ug/kg	
n	8		
GH 30 min	53	ug/L	
SD	23	ug/L	
p	< 0.01		

	Subjects given ghrelin infusion		Popovic et al., 2003
Dose	1	ug/kg	
n	9		
GH peak	75.1	ug/L	
SD	16	ug/L	
p	< 0.001		
	Subjects given ghrelin infusion		**Takeno et al., 2004**
Dose	0.2	ug/kg	
n	6		
GH peak	29.9	ng/mL	
SD	23.1	ng/mL	
p	< 0.05		
	Subjects given ghrelin infusion		**Alvarez-Castro et al, 2006**
Dose ***obese group***	1	ug/kg	
n ***obese group***	6		
GH peak ***obese group***	24.4	ug/L	
range ***obese group***	7.4-85.0	ug/L	
p ***obese group***	< 0.05		
Dose ***normal weight group***	1 ug/kg		
n ***normal weight group***	6		
GH ***normal weight group***	68.5	ug/L	
range ***normal weight group***	22.5-119-5	ug/L	
p ***normal weight group***	< 0.05		
	Subjects given ghrelin infusion		**Hataya et al., 2001**
Dose 1	0.08	ug/kg	
n	4		
GH peak	5.5	ng/ml	
SD	2.2	ng/ml	
p	< 0.01		
Dose 2	0.2	ug/kg	
n	5		
GH peak	39.8	ng/ml	
SD	5.8	ng/ml	

p	< 0.01		
Dose 3	1.0	ug/kg	
n	5		
GH peak	79	ng/ml	
SD	10.3	ng/ml	
p	< 0.01		
Dose 4	5.0	ug/kg	
n	4		
GH peak	109.8	ng/ml	
SD	11.7	ng/ml	
p	< 0.01		
	Subjects given ghrelin infusion		**Lucidi et al., 2005**
Dose 1	7.5	pmol/kg^-1	*Subjects are given acyl ghrelin infusion*
n	8		
GH	Significant increase		
p	< 0.01		
Dose 2	15	pmol/kg^-1	
n	8		
GH	Significant increase		
p	< 0.01		
	Subjects given ghrelin infusion		**Peino et al., 2000**
Dose 1	0.25	ug/kg	*Subjects are given acyl ghrelin infusion*
n	6		
GH	0.5	ug/L	
SD	0.007	ug/L	
p	NS		
Dose 2	0.5	ug/kg	
n	6		
GH	0.6	ug/L	
SD	0.09	ug/L	
p	NS		
Dose 3	1.0	ug/kg	
n	6		
GH	6.5	ug/L	
SD	2.6	ug/L	
p	NS		
Dose 4	3.3	ug/kg	
n	12		
GH	69.8	ug/L	
SD	9.2	ug/L	
p	< 0.005		
Dose 5	6.6	ug/kg	
n	12		
GH	90.0	ug/L	
SD	16.9	ug/L	
p	< 0.005		

Table 10: Effects from infusion of ghrelin on GH-secretion [160, 161, 162, 50, 164, 163, 165, 166, 450]

	Subjects	**Old controls**	**Young**		**Sturm et al.,**

			controls		2003
n	8	8	8		
Mean age	80.4	77	22	Years	
SD	2.6	0.9	1.3		
BMI	16.9	23.7	20.5		
SD	0.57	0.8	0.4		
Basal p-ghrelin	1320	552	664	pg/ml	
SD	348	132	83	pg/ml	
p				< 0.1	
VAS score pre-prandial	Significantly lower for hunger and higher for satiety in the subjects than in controls				
p				0.006	
VAS score post-prandial	Significantly lower for hunger and higher for satiety in the subjects than in controls				
p				0.008	
Ghrelin suppression	361	134	176	pg/ml	
SD	126	39	59	pg/ml	
p				0.15	
Test meal	A 280 kcal test meal + ad libitum meal				
	Subjects		**Young controls**		(Di Francesco, 2008)
n	12		12		
Mean age	75.2		28.2	Years	
SD	2		2	Years	
VAS score post-prandial	Significantly lower		Significantly higher		
p	< 0.05		< 0.05		
Ghrelin post-prandial	A lower acyl: des-acyl ratio in the high-fat meal				
p				< 0.05	
Test meal 1	800 kcal, 20 % fat				
Test meal 2	800 kcal, 40 % fat				
	Subjects	**Old controls**	**Young controls**		**Serra-Prat et al., 2009**
n	15	10	17	Frail subjects compared to non-frail and young controls	
Mean age	83.0	80.01	39.17		
SD	7.3	8.4	9.8		
BMI	28.7	26.7	25.2		
SD	6.6	3.0	3.3		
Basal plasma total ghrelin	734.6	1074	950.4	pg/ml	
VAS score pre-prandial	3.1		7.3		
p				< 0.001	
VAS score 1 hour post-prandial	1.1		2.2		
p		*No significant difference from subjects*	0.026		
VAS score 3 hours post-prandial	1.8		3.8		

p		*No significant difference from subjects*	0.020		
Post-prandial p- ghrelin 90/120 min.	697.6	917	848.5	pg/ml	
p	0.394	0.017	0.028		
Post-prandial plasma total ghrelin 4 hours	798.4	948.9	1192.0	pg/ml	
p	0.027	0.445	< 0.001		
Test meal	380 kcal				
	Subjects	**Old controls**	**Young controls**		Bauer et al., 2010
n	19		15		
Mean age	80.7		35.4		
SD	5.6		6.4		
BMI	26.4		25.3		
SD	5.6		5.1		
Acyl ghrelin profile	Significantly lower		Significantly higher		
VAS-profile	Significantly lower		Significantly higher		
Test meal 1	285 kcal, mixed energy content				
Test meal 2	420 kcal, mixed energy content				

Table 11: Effects on ghrelin and VAS-score after a test meal in undernourished older subjects compared with well-nourished old and young controls. 167, 168, 169, 174

	Subjects	**Controls**		**Lundholm et al., 2010**
n	12	10		
Characteristics	Anorexia of cancer	Anorexia of cancer		
Basal BMI	21.0	22.0		
SD	0.8	1.2		
Body fat free mass	44.8	44.3	kg	
SD	2.9	2.2	kg	
VAS score before intervention	5.6	3.9	cm	
SD	9.4	3.0	kcal/kg/day	
S-total ghrelin basal	563	3418	ng/L	
SD	90	2570	ng/L	
S-acyl ghrelin basal	96	604	ng/L	
SD	30	336	ng/L	
Dose of ghrelin administrated	13	0.7	ug/kg/day	
Intervention time period	8	8	weeks	
Body fat free mass after	47.8	45.1	kg	

intervention				
SD	2.9	2.8	kg	
p	< 0.3	< 0.3		
VAS score after intervention	6.8	4.0	cm	
SD	0.7	1.1	cm	
p	< 0.02	< 0.02		
Food intake after intervention	No significant increase			
S-total ghrelin after intervention	1229	3817	ng/L	
SD	501	2997	ng/L	
p	Not significant			
S-acyl ghrelin after intervention	178	543	ng/L	
SD	72	338	ng/L	
p	Not significant			
	Subjects			**Neary et al., 2004**
n	7			
Subject characteristics	Cancer patients with impaired appetite			
Basal ghrelin (total)	538		pmol/L	
CI	433 - 643		pmol/L	
Dose of ghrelin administrated	5		pmol/kg/min	
Energy intake after ghrelin	+ 31		%	
CI	14 - 49			
p	0.005			
Ghrelin 60 min.	1718		pmol/L	
95 % CI	1303 - 2132		pmol/L	
	Subjects			**Nagaya et al., 2001**
n	10			
Subject characteristics	Patients with chronic heart failure			
Dose of ghrelin administrated	2		ug/kg/day	
Intervention time period	3 weeks			
Energy intake after ghrelin	Significantly increased			

Table 12: Effects from administrating ghrelin to patients with anorexia from different aetiologies 312, 309, 451, 173

	Subjects	**Control group 1**	**Control group 2**	**Nagaya et al., 2001**

n	28	46	12	
Subject characteristics	Chronic heart failure + cachexia	Chronic heart failure		
Basal plasma total ghrelin	237	147	1400	fmol/ml
SD	18	10	14	fmol/ml
p		*< 0.001*	*No significant difference from subjects*	
	Subjects	**Controls**		**Yoshimoto et al., 2002**
n	30	11		
Subject characteristics	Mild to severe renal disease	Normal renal function		
Basal p-total ghrelin	Increased, correlated with creatinine value	147	fmol/ml	
SD		27	fmol/ml	
Basal p-acyl ghrelin	Increased, but not correlated with creatinine value	9.1	fmol/ml	
SD		2.3	fmol/ml	
	Subjects			**Neary et al., 2004**
n	7			
Subject characteristics	Cancer patients with impaired appetite			
Basal p-total ghrelin	538		pmol/L	
CI	433 - 643		pmol/L	
	Subjects	**Controls**		**Tacke et al., 2003**
n	105	97		
Subject characteristics	Patients with chronic liver disease			
P-ghrelin total basal	230	210	pmol/L	
Range	94 - 719	138 - 319	pmol/L	
p	< 0.041			
	Subjects	**Controls**		**Marchesini et al., 2004**
n	43	50		
Subject characteristics	Patients with chronic liver disease			
P-ghrelin total basal	414	398	pmol/L	
Range	164	142	pmol/L	
p	Not significant			
	Subjects	**Controls**		**Itoh et al., 2004**
n	50	13		
Subject characteristics	Patients with COPD and anorexia			
Basal p-total	237	157	fmol/ml	

ghrelin	(195 normal weight) (272 underweight)			
SD	135 (11 normal weight (20 underweight)	10	fmol/ml	
p	< 0.01			
	Subjects	**Controls**		**Shimizu et al., 2003**
n	21	21		
Subject characteristics	Patients with cachexia of lung cancer			
Basal p-total ghrelin	180	132	fmol/ml	
CI	17	8	fmol/ml	
p	*Subjects are only compared to other patinents with cancer without cachexia, but results are significant p = 0.011*			
	Subjects	**Controls**		**Xin et al., 2009**
n	22	15		
Subject characteristics	Cachexia from heart failure	Healthy		
BMI	18.4	22.6	kg/m2	
SD	0.8	0.5		
Basal p-total ghrelin	1237.8	985.5	pg/mL	
SD	47.9	64.2	pg/mL	
p	Not significant			

Table 13: Ghrelin levels in subjects with cachexia 173, 172, 171, 452, 170, 71, 309

	Subjects	**Controls**		**Broglio et al., 2001**
n	11	11		*Subjects serve as their own controls when given placebo*
Dose of ghrelin	1	0	ug/kg	
Glucose peak measured	15 minutes			
Glucose peak value	93.9	No significant change	mg/dl	
SD	7.1		mg/dl	
p	< 0.01			
Insulin nadir measured	45 minutes			
Insulin nadir	10.0	No significant change	mU/l	
SD	0.6		mU/l	
p	< 0.1			
	Subjects	**Controls**		**Arosio et al., 2003**
n	8	8		*Subjects serve as their own controls when*

				given placebo
Dose of ghrelin	3.3		ug/kg	
Glucose peak measured	30 minutes			
Glucose peak	5.1	4.7	mmol/L	
SD	0.3	0.2	mmol/L	
p	< 0.05			
Insulin nadir measured	60 minutes			
Insulin nadir	24.4	No significant change	pmol/L	
SD	13.6		pmol/L	
p	< 0.05			
	Subjects	**Controls**		**Akamizu et al., 2004)**
n	6	6		*Subjects serve as their own controls when given placebo*
Dose 1 of ghrelin	1	0	ug/kg	
Glucose AUC change from basal 0-90 min	152.5	84.8	mg/dl	
SD	187.2	7.1	mg/dl	
p	Not significant			
Insulin AUC change from basal 0-90 min	- 26.5	3.4	U/ml	
SD	54.5	3.0	U/ml	
p	Not significant			
Dose 2 of ghrelin	5	0	ug/kg	
Glucose AUC change from basal 0-90 min	166.25	78.7	mg/dl	
SD	455.8	6.6	mg/dl	
p	Not significant			
Insulin AUC change from basal 0-90 min	- 85.3	4.3	U/ml	
SD	81.4	1.2	U/ml	
p	Not significant			
	Subjects	**Controls**		**Tong et al., 2010**
n	12	12		*Subjects serve as their own controls when given placebo*
Dose 1 of ghrelin	0.3	0	nmol/kg/h	
Fasting p-glucose	4.9	4.9	mmol/L	
SD	0.2	0.2	mmol/L	
Fasting p-insulin	37.8	37.8	pmol/L	
SD	6.2	6.2	pmol/L	
Insulin at steady state of	30.4	36.5	pmol/L	

ghrelin				
SD	5.0	5.8	pmol/L	
p	Not significant			
Dose 2 of ghrelin	0.9		nmol/kg/h	
Insulin at steady state of ghrelin	36.1 (dose 2)	36.5	pmol/L	
SD	6.9 (dose 2)		pmol/L	
p	Not significant			
Dose 3 of ghrelin	1.5		nmol/kg/h	
Insulin at steady state ghrelin	25.6 (dose 3)	36.5	pmol/L	
SD	3.9 (dose 3)		pmol/L	
p	Not significant			

Table 14: Effects from administrating ghrelin on insulin 160, 162, 126, 323

	Subjects	**Controls**		**McLaughlin et al., 2004**
n	20	20		
Subject characteristics	Reduced insulin sensitivity	Normal insulin sensitivity		
BMI	32.5	32.0		
SD	0.4	0.4		
p		Not significant		
Fasting p-total ghrelin	252	412	pg/mL	
SD	19	35	pg/mL	
p		<0.001		
Fasting p-insulin	19.5	7.4	mU/ML	
p		<0.001		
	Subjects	**Controls**		**Anderwald et al., 2003**
n	6	6		
Subject characteristics	Reduced insulin sensitivity	Normal insulin sensitivity		
BMI	29	26		
SD	20	1		
p	<0.05			
Fasting p-total ghrelin	211	242	pmol/L	
SD	14	53	pmol/L	
p	<0.05			
Fasting p-insulin	9	7	mU/L	
SD	1	1	mU/L	
p	<0.05			
	Subjects (obese)	**Controls (non-obese)**		**Katsuki et al., 2004**
n	18	18		
BMI	28.4	21.4		
SD	0.6	0.6		
p	< 0.01			
Fasting p-acyl ghrelin	20.4	14.5	fmol/mL	

SD	1.7	1.1	fmol/mL	
p	< 0.01			
Fasting s-insulin	68.8	38.7	pmol/L	
SD	6.2	5.8	pmol/L	
p	< 0.01			
	Subjects (moderately obese	**Subjects (morbidly obese)**	**Controls**	**Zwirska-Korczala et al., 2007**
n	12	17	8	
Fasting p-total ghrelin	555	701	850	pg/mL
SD	67	78	86	pg/mL
p	< 0.05			
Fasting p-acyl ghrelin	108	194	199	pg/mL
SD	12	27	23	pg/mL
p	< 0.05			
P-insulin (fasting)	21.18	26.8	16.1	uU/mL
SD	4.8	2.2	1.5	uU/mL
p	< 0.05			
BMI	34.9	46.9	23.2	
SD	0.9	1.6	0.7	
p	< 0.05			
	Subjects	**Controls**		**Marzullo et al., 2004**
n	20	20		
BMI	41.3	22.4		
SD	1.1	0.6		
p	< 0.001			
Fasting p-total ghrelin	3651	5668	pg/ml	
SD	408	644	pg/ml	
p	< 0.05			
Fasting p-acyl ghrelin	180.4	411.8	pg/ml	
SD	18.5	57.4	pg/ml	
p	< 0.001			
Fasting p-insulin	13.7	9.5	uU/ml	
SD	1.3	1.3	uU/ml	
p	< 0.05			
	Subjects (Type 2 diabetes + obesity)	**Subjects 2 (Obese + normal glucose tolerance)**	**Controls (lean)**	**Rodriguez et al., 2009**
n	19	20	21	
Fasting p-acyl ghrelin	8.4	4.8	3.4	pmol/L
SD	1.1	0.8	0.6	pmol/L
p			< 0.01	
Fasting p-insulin	11.9	7.5	3.7	uU/ml
SD	1.1	0.9	0.6	uU/ml
p	< 0.05			
BMI	33.4	32.5	23.1	
SD	0.6	0.5	0.3	

p	< 0.05			
	Subjects	**Controls**		**Barazzoni et al. 2007**
n	45			
BMI	32			
SD	0.7			
Fasting p-total ghrelin	907		pg/ml	
SD	48		pg/ml	
Fasting p-acyl ghrelin	75		pg/ml	
SD	6		pg/ml	
Fasting p-des-acyl ghrelin	414		pg/ml	
SD	36		pg/ml	
p-acyl: des-acyl ghrelin	24.6		%	
SD	3.6		%	
Fasting p-insulin	23		uU/ml	
SD	2		uU/ml	
	Subjects (obese + insulin resistance)	**Controls (obese + normal insulin sensitivity)**		**St-Pierre et al., 2007**
n	31	29		
BMI	33.63	32.62		
SD	4.23	4.31		
Fasting p-total ghrelin	1063	1246	pg/ml	
SD	399	369	pg/ml	
p	< 0.08			
Fasting p-acyl ghrelin	114	98	pg/ml	
SD	57	47	pg/ml	
Fasting p-des-acyl ghrelin	971	1156	pg/ml	
SD	395	359	pg/ml	
p-acyl: des-acyl ghrelin	0.13	0.08	%	
SD	0.11	0.03	%	
p	< 0.01			
Fasting S-insulin	19.50	12.58	uU/ml	
SD	7.70	4.48	uU/ml	
p	< 0.05			

Table 15: Fasting ghrelin and insulin in subjects with reduced insulin sensitivity/ type 2 diabetes and healthy controls. 184, 183, 79, 182, 181, 77, 180, 179

	Insulin	Ghrelin	Ghrelin basal
Flanagan et al., 2003	444,48 pmol/L	569,86 pg/ml	770,04 pg/ml
Leonetti et al. 2004	1040,36 pmol/L	179,03 pg/ml	205,53 pg/ml
Schaller et al., 2003	1602 pmol/L	122 pg/ml	246 pg/ml
Caixas et al., 2002	370 pmol/L	358,4 pg/ml	358,4 pg/ml
Saad et al., 2002	564 pmol/L	61 pg/ml	85 pg/ml

Table 16: Results from euglycemic hyperinsulinemic clamp testing. 117, 116, 331, 330, 118

	Subjects		Lin et al., 2004
n	34		
Subject characteristics	Obese subjects treated with RYGBP		
Intervention time period	Only within the surgical procedure		
BMI before	47.0		
SD	0.7		
p	< 0.01		
Ghrelin before	355	pg/ml	
SEM	20	pg/ml	
Ghrelin immediately post-operative	246	pg/ml	
SEM	13	pg/ml	
p	< 0.001		
	Subjects		**Fruhbeck et al., 2004**
n	6		
Intervention time period	6.1 +/- 0.4	months	
BMI before	42.6		
SD	1.6		
Ghrelin before	355.7	pg/ml	
SD	11.4	pg/ml	
BMI after surgery	32.5		
SD	3.6		
Ghrelin after surgery	117	pg/ml	
SD	34	pg/ml	
p	< 0.05		
	Subjects		**Foschi et al., 2008**
n	10	days	
Intervention time period	131 +/- 6		
BMI before	44.1		
SD	1.8		
Ghrelin before	92.1	pg/ml	

SD	5.44	pg/ml	
BMI after surgery	35		
SD	1.6		
Ghrelin after surgery	73	pg/ml	
SD	6.36	pg/ml	
p	< 0.0009		
	Subjects		**Cummings D. E. et al., 2002**
n	5		
Intervention time period	6 months		
BMI before	68.0		
SE	7.8		
BMI after 6 months.	43.5		
SD	6.0		
Ghrelin after 6 months (AUC 24 hours)	3058	pg/day/ml	
SD (AUC 24 hours)	718	pg/day/ml	
p	< 0.001		
	Subjects		**Dadan et al., 2009**
n	7		
Intervention time period	12 months		
BMI before	44.3		
SD	3.7		
P-ghrelin before	81.2	pg/ml	
SD	21.9	pg/ml	
P-ghrelin 1 day after	37.4	pg/ml	
SD	16.4	pg/ml	
p	< 0.001		
P-ghrelin 7 days after	66.6	pg/ml	
SD	31.8	pg/ml	
P-ghrelin 1 month after	92.8	pg/ml	
SD	38.9	pg/ml	
p	Not found, publication reported decrease		
P-ghrelin 3 months after	80.2	pg/ml	
SD	27.6	pg/ml	
BMI after 3 months	42.91		
p	Not found, publication reported decrease		
	Subjects		**Morinigo et al., 2004**

n	8		
Intervention time period	9-15 months		
BMI before	43.5 - 59.1		
BMI after 9-15 months	- 10.3	%	
SD	1.5	%	
Ghrelin after 3 months	Decreased		
p	< 0.05		
	Subjects		**Roth et al., 2009**
n	18		
Intervention time period	24 months		
BMI before	47.4		
BMI after 24 months.	32.0		
SD	6.2		
p	< 0.001		
Ghrelin after 24 months	Decreased		
p	0.002		

Table 17: Studies finding a decrease in ghrelin after Roux-en-Y; non-randomized trials. 188, 182, 186, 144, 185, 184, 187

	Subjects		**Faraj et al., 2003**
n	25		
Intervention time period	15 months		
BMI before	52.0		
SD	9.3		
Ghrelin before	Decreased		
BMI after	32.6		
SD	6.6		
Ghrelin after	No significant change		
	Subjects		**Couce M. E. et al., 2006**
n	49		
Intervention time period	6 months		
BMI before	50.0		
SD	5.3		
Ghrelin before	932.4	pg/mL	
SD	52.2	pg/mL	
BMI after 6 months	39.8		
SD	1.5		
n	11		*Only 11 subjects, reason not described*

p	< 0.01		
Ghrelin after 6 months	622.7	pg/mL	
SD	59.4	pg/mL	
p	< 0.08		
	Subjects		**Liou et al., 2008**
n	68		
Intervention time period	12 months		
BMI before	39.7		
SD	7.2		
Fasting p-total ghrelin before	18.7	pmol/L	
SD	7.9	pmol/L	
BMI after 6 months	30.2		
SD	5.7		
p	< 0.001		
Fasting p-total ghrelin after 6 months	18.1	pmol/L	
SD	5.9	pmol/L	
p	NS		
BMI after 12 months	27.45		
SD	4.8		
p	< 0.001		
Fasting p-total ghrelin after 12 months	17.2	pmol/L	
SD	5.5	pmol/L	
p	Not significant		
	Subjects		**Mancini et al., 2006**
n	10		
Intervention time period	12 months		
P-ghrelin before	742		
SD	174		
P-ghrelin after	765	pg/mL	
SD	258	pg/mL	
p	0.82		
	Subjects		**Morinigo et al., 2008**
n	10		
Intervention time period	1 year		
BMI before	49.2		
SD	2.0		
P-ghrelin before	863.1	pg/ml	
SD	56.0	pg/ml	
BMI 6 weeks	43.3		
SD	1.8		
Ghrelin 6 weeks	728.0	pg/ml	
SD	46.1	pg/ml	

BMI 52 weeks	34.5		
SD	1.2		
p	< 0.01		
Ghrelin 52 weeks	862.5	pg/ml	
SD	83.5	pg/ml	
p	< 0.05		

Table 18: Studies finding no change in ghrelin after Roux-en-Y; non-randomized [302, 354, 453, 454, 455]

	Subjects		**Holdstock et al., 2003**
n	66		
Intervention time period	12 months		
BMI before	44.8		
SD	6.4		
Fasting p-total ghrelin before	86.9	pmol/L	
SD	40.2	pmol/L	
BMI after 6 months.	34.8		
SD	5.7		
p	<0.05		
Ghrelin after 6 months	125	pmol/L	
SD	71.2	pmol/L	
p	<0.05		
BMI after 12 months.	31.5		
SD	6.1		
p	<0.05		
Ghrelin after 12 months	141	pmol/L	
SD	70.2	pmol/L	
p	< 0.05		
	Subjects		**Stoeckli et al., 2004**
n	5		
Intervention time period	24 months		
BMI before	43.6		
SD	2.0		
p	<0.05		
Ghrelin before	240.4	pg/mL	
SD	47.4	pg/mL	
p	< 0.05		
BMI after 24 months.	32.9		
SD	3.0		
p	< 0.001		
Ghrelin after 24 months.	408.0	pg/mL	
SD	147.8	pg/mL	
p	NS		
	Subjects		**Borg et al., 2006**

n	6		
Intervention time period	6 months		
BMI before	48.3		
SD	1.4		
Ghrelin before	232	pmol/L	
SD	72	pmol/L	
BMI after 6 months.	36.4		
SD	1.5		
p	< 0.001		
Ghrelin after 6 months	331	pmol/L	
SD	95	pmol/L	
p	Not significant		
	Subjects		**Stratis et al., 2006**
n	20		
Intervention time period	3 months		
BMI before	58.5		
SD	2.0		
p			
Ghrelin before	633	pg/mL	
SD	43	pg/mL	
BMI after 3 months	46.1		
SD	1.4		
p	< 0.001		
Ghrelin after 3 months	675	pg/mL	
SD	39	pg/mL	
p	0.435		
	Subjects		**Karamanakos et al., 2008**
n	16		
Intervention time period	12 months		
BMI before	46.6		
SD	3.7		
p	< 0.0001		
Ghrelin before	638	pg/mL	
SD	189	pg/mL	
BMI after 12 months.	31.5		
SD	3.4		
p	< 0.001		
Ghrelin after 12 months	714	pg/mL	
SD	230	pg/mL	
p	0.19		
	Subjects		**Sundbom et al., 2007**
n	15		
Intervention time period	12 months		

BMI before	45		
Ghrelin before	814	pg/mL	
Range	735-904	pg/mL	
Ghrelin after 1 day	436	pg/mL	
Range	397-478	pg/mL	
p	<0.05		
BMI after 12 months	30		
p	<0.05		
Ghrelin after 12 months	1114	pg/mL	
Range	964-1288	pg/mL	
p	<0.05		
	Subjects		**Garcia-Fuentes et al., 2008**
n	13		
Intervention time period	7 months		
BMI before	53.0		
SD	9.1		
p	< 0.001		
Ghrelin before	734.3	pg/mL	
SD	286.1	pg/mL	
p	< 0.01		
BMI after surgery	34.4		
SD	5.9		
p	< 0.001		
Ghrelin after surgery	1137.6	pg/mL	
SD	316.1	pg/mL	
p	< 0.01		
	Subjects		**Ybarra et al., 2009**
n	41		
Intervention time period	12 months		
BMI before	44.1		
SD	0.4		
Ghrelin before	324	pg/mL	
SD	12	pg/mL	
BMI after 6 months.	43.3		
SD	0.5		
n	7		
Ghrelin after 6 months	270	pg/mL	
SD	33	pg/mL	
BMI after 12 months.	42.4		
SD	0.6		
p	<0.04		
n	4		
Ghrelin after 12 months	266	pg/mL	
SD	52	pg/mL	

p	< 0.005		
	Subjects		**Pardina et al. , 2009**
n	34		
Intervention time period	12 months		
BMI before			
SD	0.9		
Ghrelin before	46 % lower than normal		
BMI after 1 month	42.3		
SD	1.6		
Ghrelin after 1 month	Increased from basal		
BMI after 12 months.	30.9		
SD	0.9		
Ghrelin after 12 months	Complete recovery to normal weight values		
p	Not found		

Table 19: Studies finding an increase in ghrelin after Roux-en-Y; non-randomized clinical trials + 1 prospective RCT (Karamanakos). 131, 348, 349, 347, 202, 352, 456, 446, 365

	Subjects		**Langer et al., 2005**
n	10		
Intervention time period	6 months		
S-Ghrelin before	109.6	fmol/mL	
SD	32.6	fmol/mL	
BMI after 6 months	- 61	%	
SD	13	%	
S- Ghrelin after 6 months	35.8	fmol/mL	
SD	12.3	fmol/mL	
p	0.005		
	Subjects		**Cohen et al., 2005**
n	4		
Intervention time period	6 months		
BMI before	65.5		
SD	01.05		
S-Ghrelin before	781	pg/ml	
SD	96	pg/ml	
BMI after	- 16.3	Units	
S- Ghrelin after	589	pg/ml	
SD	61	pg/ml	
	Subjects		**Karamanakos et al., 2008**
n	16		
Intervention time	12 months		

period			
BMI before	45.1		
SD	3.6		
Ghrelin before	605	pg/mL	
SD	185	pg/mL	
BMI after 1 month	41		
SD	3.5		
p	< 0.001		
Ghrelin after 1 month	364	pg/mL	
SD	83	pg/mL	
p	< 0.001		
BMI after 3 months	36.8		
SD	2.9		
p	< 0.001		
Ghrelin after 3 months	399	pg/mL	
SD	135	pg/mL	
p	< 0.001		
BMI after 6 months.	32		
SD	3.9		
p	< 0.0001		
Ghrelin after 6 months	398	pg/mL	
SD	100	pg/mL	
BMI after 12 months	28.9		
SD	3.6		
p	< 0.001		
Ghrelin after 12 months	399	pg/mL	
SD	97	pg/mL	
p	< 0.001		
	Subjects		**Bohdjalian et al., 2010**
n	26		
Intervention time period	5 years		
Excess weight loss	55	%	
SD	6.0		
Before P-total ghrelin	593	pg/ml	
SD	52	pg/ml	
12 months P-total ghrelin	593	pg/ml	
SD	52	pg/ml	
5 years P-total ghrelin	219	pg/ml	
SD	23	pg/ml	
	Subjects		**Wang et al., 2009**
n	10		
Fasting p-ghrelin	447.3	pg/ml	
SD	71.2	pg/ml	
BMI	39.4		
SD	3.8		
Intervention time	2 years		

period			
Excess weight loss 24 months	60	%	
SD	12	%	
P-ghrelin after 24 months	319.7	pg/ml	
SD	91.9	pg/ml	

Table 20: Effects from sleeve gastrectomy on ghrelin [201, 355, 202, 359, 200]

	Subjects		**Valera Mora et al., 2007**
n	11		
Intervention time period	18 months		
BMI before	48.6		
SD	2.4		
Ghrelin before	573	pg/mL	
SD	77.9	pg/mL	
BMI after 18 months	33.4		
SD	1.2		
Ghrelin after	574.1	pg/mL	
SD	32.7	pg/mL	
p	Not significant		
	Subjects		**Garcia-Fuentes et al., 2008**
n	38		
Intervention time period	7 months		
BMI before	54.0		
SD	5.9		
p	< 0.001		
Ghrelin before	740.2	pg/mL	
SD	220.2	pg/mL	
p	< 0.05		
BMI after	38.4		
SD	4.7		
p	< 0.05		
Ghrelin after	779.0	pg/mL	
SD	210.7	pg/mL	
p	< 0.01		
	Subjects		**Fruhbeck et al. 2004**
n	3		
Intervention time period	4.4 +/- 0.8	months	
BMI before	60.5		
SD	7.3		
Ghrelin before	306.5	pg/mL	
SD	43.5	pg/mL	
BMI after	37.5		
SD	4.0		

Ghrelin after	406	pg/mL	
SD	86	pg/mL	
p	0.020		
	Subjects		**Kotidis et al., 2006**
n	13		
Intervention time period	18 months		
BMI before	59.15		
SD	15.82		
Ghrelin before	1.44	ng/mL	
SD	0.77	ng/mL	
p	0.001		
BMI after	32.91		
SD	6.46		
Ghrelin after	0.99	ng/mL	
SD	0.35	ng/mL	
p	0.019		
	Subjects		**Mingrone et al., 2006**
n	6		
Intervention time period	14 months		
BMI before	58.98		
SD	10.12		
Ghrelin before	164.47	ug/L	
SD	29.19	ug/L	
BMI after 14 months	28.78		
SD	176		
p	< 0.0001		
Ghrelin after	204.64	ug/L	
SD	28.51	ug/L	
p	< 0.01		
	Subjects		**Garcia-Unzueta et al., 2005**
n	30		
Intervention time period	12 months		
BMI before	48		
SD	7		
Ghrelin before	277	pg/mL	
SD	206	pg/mL	
BMI after 1 month	43		
SD	6		
Ghrelin after 1 month	313	pg/mL	
SD	195	pg/mL	
p	Significant		
BMI after 3 months	39		
SD	6		
Ghrelin after 3	327	pg/mL	

months			
SD	212	pg/mL	
BMI after 12 months	33		
SD	5		
Ghrelin after 12 months	375	pg/mL	
SD	190	pg/mL	
p	Significant		

Table 21: Studies investigating effects on ghrelin from the Biliopancreatic Diversion [457, 456, 182, 149, 206]

	Subjects		**Schindler et al., 2004**
n	23		
Intervention time period	6 months		
BMI before	44.8		
SD	1.0		
Ghrelin before	100.39	fmol/mL	
SD	12.90	fmol/mL	
BMI after	39.2		
SD	1.0		
p	< 0.0001		
Ghrelin after	149	fmol/mL	
SD	26.08	fmol/mL	
p	0.12		
	Subjects		**Fruhbeck et al., 2004**
n	7		
Intervention time period	7 +/- 0.6	months	
BMI before	45.6		
SD	1.8		
Ghrelin before	362.2	pg/ml	
SD	19.3	pg/ml	
BMI after	34.8		
SD	1.9		
Ghrelin after	480	pg/ml	
SD	78	pg/ml	
p	0.02		
	Subjects		**Leonetti et al., 2003**
n	10		
Intervention time period	3 months		
BMI before	42.09		
SD	4.32		
Ghrelin before	407.3	pg/ml	
SD	21.6	pg/ml	
p	< 0.01		
BMI after	36.3		
SD	5.47		
p	< 0.01		
Ghrelin after	314.2	pg/ml	

SD	84.3	pg/ml	
p	0.04		
	Subjects		**Langer et al., 2005**
n	20		
Intervention time period	6 months		
Ghrelin before	73.7	fmol/mL	
SD	24.8	fmol/mL	
BMI after	-29	%	
SD	11	%	
p	< 0.0001		
Ghrelin after 6 months	104.9	fmol/mL	
SD	51.1	fmol/mL	
p	0.012		
	Subjects		**Hanusch-Enserer et al., 2004**
n	18		
Intervention time period	12 months		
BMI before	45.3		
SD	5.3		
Ghrelin before	234	pmol/L	
SD	53	pmol/L	
BMI after 6 months	37.2		
SD	5.3		
p	< 0.0001		
Ghrelin after 6 months	232	pmol/L	
SD	53	pmol/L	
p	Not significant		
BMI after 12 months	33.6		
SD	5.5		
p	< 0.0001		
Ghrelin after 12 months	261	pmol/L	
SD	72	pmol/L	
p	0.05		
	Subjects		**Cohen et al., 2005**
n	15		
Intervention time period	18 months		
BMI before	44.7		
SD	0.9		
Ghrelin before	1062.9	pg/mL	
SD	116.7	pg/mL	
BMI after	- 3-13	units	
Ghrelin after	1225.1	pg/mL	
SD	619	pg/mL	
p	0.04		
	Subjects (diabetic)	**Subjects (non-diabetic)**	**Geloneze et al., 2003**
n	14	14	
Intervention time period	12 months		
BMI before	56.3		
SD	10.2		

BMI after	- 66.8	- 68.1	%
SD	13.4	13.7	%
p	No significant difference between groups Significant change from pre-surgery		
Ghrelin after	213 (non diabetics) 240 (diabetics)		pg/ml
SD	67 (non-diabetics) 23 (diabetics)		pg/ml
p	< 0.01 pre-surgery No significant difference between groups		
	Subjects		**Foschi et al., 2005**
n	12		
Intervention time period	119 +/ 5.8	days	
BMI before	42.9		
SD	1.6		
Ghrelin before	92.1	pg/ml	
SD	5.44	pg/ml	
BMI after	34.1		
SD	1.1		
Ghrelin after	172	pg/ml	
SD	26	pg/ml	
p	< 0.0003		
	Subjects		**Dadan et al., 2009**
n	11		
Intervention time period	12 months		
BMI before	54.5		
SD	6.72		
P-ghrelin before	94.2	pg/ml	
SD	52.9	pg/ml	
P-ghrelin +1 day	42.42	pg/ml	
SD	12.3	pg/ml	
p	< 0.05		
P-ghrelin +7 days	87.17	pg/ml	
SD	24.4	pg/ml	
p			
P-ghrelin +1 month	79.55	pg/ml	
SD	21.8	pg/ml	
p			
P-ghrelin +3 months	140.6	pg/ml	
SD	49.2	pg/ml	
p	< 0.05		
BMI +3 months	35.95		
	Subjects		**Nijhuis et al., 2004**
n	17		
Intervention time period	24	months (average)	
BMI before	47.5		
SD	6.2		
Fasting ghrelin before	742	pg/ml	

SD	246	pg/ml	
BMI after	33.2		
SD	5.8		
p	< 0.001		
Fasting ghrelin after 24 months	904	pg/ml	
SD	127	pg/ml	
p	< 0.05		

Table 22: Studies investigating effects from gastric banding on ghrelin; 362, 182, 192, 201, 458, 196, 301, 186, 185, 208

THE BRAIN

	Subjects		**Tolle et al., 2003**
n	8		
BMI	14.6		
SD	0.4		
Fasting ghrelin	491	ng/L	
SD	68	ng/L	
p	< 0.01		
	Subjects		**Tanaka et al., 2003**
n	19		
BMI	13.6		
SD	1.5		
Fasting ghrelin	Elevated		
p	< 0.01		
	Subjects		**Nedvidkova et al., 2003**
n	5		
BMI	15.21		
SD	1.54		
Fasting ghrelin	1800.6	pg/mL	
SD	47	pg/mL	
p	< 0.001		
	Subjects		**Monteleone et al., 2008**
n	20		
BMI	16.6		
SD	1.6		
Fasting ghrelin	370.6	pg/mL	
SD	163.8	pg/mL	
p	< 0.0016		
	Subjects (restrictive type AN)	**Subjects (binge/purge type AN)**	**Germain et al., 2010**
n	22	10	
BMI	15.2	15.4	
SD	1.6	1.4	
Fasting ghrelin	Increased	Decreased	
	Subjects		**Nakai et al.,, 2003**
n	5		
BMI	13.9		
SD	1.0		
Fasting acyl ghrelin	52.1	fmol/mL	
SD	10.5	fmol/mL	
	Subjects (restrictive type AN)	**Subjects (binge/purge type AN)**	**Tanaka et al., 2003**
n	19	20	

BMI	13.6	13.7	
SD	1.5	1.9	
Fasting ghrelin	Significantly higher in binge/purge type. Elevated from normal in both groups		
p	< 0.01		
	Subjects		**Broglio et al., 2004**
n	9		
BMI	14.7		
SD	0.4		
Fasting ghrelin	643.6	ng/L	
p	21.3	ng/L	
	Subjects		**Hotta et al., 2004**
n	30		
BMI	15.54		
SD	2.62		
Fasting ghrelin (acylated)	34.7	pmol/L	
SD	3.2	pmol/L	
Fasting ghrelin (des-acyl)	223.5	pmol/L	
SD	37.3	pmol/L	
	Subjects (restrictive type AN)	**Subjects (binge/purge type AN)**	**Otto et al., 2004**
n	19	17	
BMI	14.7	15.3	
SD	0.4	0.2	
Fasting ghrelin (total)	1036	1194	pg/mL
SD	160	194	pg/mL
p	No significant difference between groups		
	Subjects		**Misra et al., 2009**
n	22		
BMI	16.6		
SD	1.2		
Fasting ghrelin (total) mean value	618.7	pg/mL	
SD	180,9	pg/mL	
p	0.002		
	Subjects		**Harada et al., 2008**
n	10		
BMI	13.43		
SD	0.29		
p	< 0.01		
Fasting des-acyl ghrelin	340.1	pg/mL	
SD	38.76	pg/mL	
p	< 0.05		
Fasting acyl ghrelin	28.60	pg/mL	
SD	2.10	pg/mL	
p	0.05		

Table 23: Observation studies investigating fasting ghrelin in subjects with anorexia nervosa [220, 223, 218, 217, 216, 62, 223, 213, 210, 127, 158]

	Subjects (low weight)	Subjects (recovering)	Controls	Miljic et al., 2006
n	9	6	10	
BMI	12.0	17.2	17.6	
SD	0.4	1.3	0.4	
p	< 0.01			
Plasma ghrelin (total)	985.3	685.2	443.7	pg(ml
SD	165.4	78.0	78.7	pg(ml
p	Significantly higher ghrelin for patients with anorexia nervosa			
Insulin	11.85	11.03	8.10	U
	2.30	3.43	3.20	U
	Subjects	**Controls**		**Germain et al., 2007**
n	10	10		
BMI	15.2	15.7		
SD	0.4	0.2		
Plasma ghrelin (total)	701	324	pmol/L	
p	Significantly higher ghrelin in subjects			
SD	50	24	pmol/L	
	Subjects	**Controls (low weight)**	**Controls (normal weight)**	**Germain et al., 2009**
n	15	9	10	
BMI	14.8	16.1	20.5	
SD	0.1	0.1	0.4	
p	< 0.05	< 0.05		
Plasma ghrelin (total)	4181	3518	2998	pg(ml
SD	533	536	223	pg(ml
p	< 0.05	< 0.05		
Plasma ghrelin (acyl)	1123	781	838	pg(ml
SD	209	167	85	pg(ml
p	< 0.05	< 0.05		

Table 24: Basal ghrelin in patients with anorexia nervosa compared with controls [390, 459, 460]

	Subjects	Controls	Koyama et al., 2010
n	5	10	
Intervention period	8 weeks cognitive behaviour treatment + nutritional rehab.		
Start BMI	12.17	20.97	
SD	2.07	1.90	
Start Des-Acyl Ghrelin	503.20	281.50	pg/mL
SD	19.60	144.20	pg/mL
Start Acyl ghrelin	34.60	24.4	pg/mL
SD	11.59	16.04	pg/mL
End BMI	13.93		pg/mL

SD	2.09				pg/mL
p	< 0.001				
End Des-Acyl Ghrelin	281.80				pg/mL
SD	138.58				pg/mL
p	0.029				
End Acyl Ghrelin	37.60				pg/mL
SD	12.22				pg/mL
p	Not significant				
	Subjects (Emergency)	**Subjects (Restrictive)**	**Subjects (Binge/ purge)**	**Controls**	**Tanaka et al., 2004**
n	7	14	9	24	
Intervention period	42-117				days
Start BMI	11.1	13.1	14.5	21.5	
SD	0.3	0.2	0.3	0.4	
Start Plasma total ghrelin	520.7	254.3	346.7	132.9	pmol/L
SD	27.8	25.9	21.8	20.0	pmol/L
p					< 0.05
End BMI	13.9	15.1	16.2	21.5	
SD	0.4	0.3	0.3	0.4	
End Plasma total ghrelin	250.8	208.2	238.0	132.9	pmol/L
SD	29.1	25.6	22.4	20.0	pmol/L
p					< 0.05
	Subjects	**Controls**			**Janas-Kozik et al., 2007**
n	30	20			
Intervention period	6 months CBT + normo-caloric diet				
Start BMI	15.1	21.4			
SD	1.4	2.1			
	< 0.001				
Start plasma ghrelin total	Higher than controls				
p	0.002				
BMI 3 months	17.2				
SD	1.1				
p	< 0.001		%		
Plasma total ghrelin after 3 months	Lower than controls				
p	0.015		%		
BMI 6 months	17.7				
SD	1.8				
p	< 0.001				
Plasma total ghrelin after 6 months	Lower than controls				
p	< 0.001				
	Subjects	**Controls**			**Nakahara et al., 2007**
n	14	12			
Intervention period	Not given				

Start BMI	12.4	22.3		
SD	1.7	2.2		
Start plasma total ghrelin t	433.1	215.6	pmol/L	
SD	124.8	90.7	pmol/L	
p	< 0.001			
BMI after intervention	16.8		%	
SD	2.1			
p			%	
Plasma total ghrelin after intervention	320.6		pmol/L	
SD	90.6		pmol/L	
p	< 0.0001			

Table 25: Effects from renutrition on ghrelin in patients with anorexia nervosa [393, 213, 222, 221]

	Subjects		**Tanaka et al., 2003**
n	15		
BMI	20.0		
SD	2.9		
Fasting plasma total ghrelin	298.4	pmol/L	
SD	135.8	pmol/L	
p	< 0.0005		
	Subjects		**Kojima et al., 2005**
n	10		
BMI	20.0		
SD	0.6		
Fasting plasma total ghrelin	265.0	pmol/L	
SD	25.5	pmol/L	
p	< 0.05		
	Subjects		**Germain et al., 2010**
n	16		
BMI	21.9		
SD	2.2		
Fasting plasma total ghrelin	Decreased		
p	< 0.001		
	Subjects		**Tanaka et al., 2006**
n	24		
BMI	18.5		
SD	0.4		
Fasting plasma total ghrelin	301.7	pmol/L	
SD	18.9		
p	< 0.05		
	Subjects		**Monteleone et al., 2008**
n	21.9		
BMI	21.4		
SD	3.3		
Fasting plasma total ghrelin	217.4	pg/mL	
SD	111.8	pg/mL	

	Subjects		**Tanaka et al., 2002**
n	18		
BMI	20.0		
SD	2.1		
Fasting plasma total ghrelin	286.9	pM	
SD	146.4	pM	
p	< 0.05		
	Subjects		**Fassino et al., 2005**
n	20		
BMI	20.3		
SD	0.5		
Fasting plasma total ghrelin	560.2	pg/ml	
SD	97.2	pg/ml	
p	< 0.05		

Table 26: Fasting plasma ghrelin in patients with bulimia nervosa
221, 227, 216, 225, 217, 226, 224

	Subjects		**Munsch et al., 2009**
n	18		
BMI	32.4		
SD	54		
Fasting plasma total ghrelin	139176	AUC 120 min pg min/mL	
SD	1713	AUC 120 min pg min/mL	
p	0.021		
	Subjects		**Geliebter et al., 2008**
n	10		
BMI	36.6		
SD	6.2		
Fasting plasma ghrelin	350	ng/L	
SD	36.6	ng/L	
p	0.02		
	Subjects		**Monteleone et al. , 2005**
n	34		
BMI	39.8		
SD	4.9		
Fasting plasma total ghrelin	Decreased		
p	< 0.001		

Table 27: Fasting plasma ghrelin in subjects with binge eating disorder
461, 384, 402

THE PAIN

Study/year	Finding	Functional disease
Shinomiya et al. 2005	Correlation between symptom score and elevation in p - acyl ghrelin	Dysmotility type (14) and ulcer type (4)

Lanzini et al. 2006	p - total ghrelin elevated *	Functional dyspepsia (32) and ulcer-like disease (7)
Takamori et al. 2007	Lower fasting p-desacyl ghrelin Lower p-total ghrelin Lower ratio desacyl: acyl ghrelin in fasting state No difference in p-acyl ghrelin No post-prandial difference from controls No correlation of ghrelin with dysmotility	Dysmotility syndrome (16)
Shindo et al. 2009	Lower p - acyl ghrelin in PDS and NERD patients Correlation between acyl ghrelin and the T.max of gastric emptying for PDS-patients. No such correlation in EPS or NERD.	Post-prandial distress syndrome (76) Epigastric pain syndrome (36) Non-erosive reflux disease (39)
El-Sahly et al. 2009	Normal p-acyl ghrelin Normal p- total ghrelin Increased density of ghrelin cells in oxyntic mucosa	Irritable Bowe Syndrome
Lee et al. 2009 (Cochrane)	Lower pre-prandial p-ghrelin Normal post-prandial p-ghrelin No correlation with dysmotility Correlation between acyl ghrelin and delayed gastric emptying in the patient group with abnormal low levels of ghrelin.	Functional dyspepsia
Akamizu et al. 2008	Authors report des-acyl and acyl ghrelin to be within normal values, considering BMI and age	Functional anorexia, including functional dyspepsia

Table 28: Overview of results from studies investigating ghrelin in IBS and functional dyspepsia [428, 232, 230, 229, 431, 228, 462]

	Subjects (active IBD)	**Subjects (remission IBD)**	**Controls**	**Peracchi et al., 2003**
n	42	54	203.0	
Ghrelin	323.6		81.1	pmol/L
SD	119.2	217.4		pmol/L
p	<0.001	64.9		
Correlation	Not significant			

ghrelin: BMI				
BMI	22.1	0.29		
SD	3.4			
	Subjects (active IBD)	Subjects (remission IBD)	Controls	Ates et al., 2008
n	Ulcerous Colitis: 16 Crohn's disease: 10	Ulcerous Colitis: 18 Crohn's disease: 15	32	
Ghrelin	Ulcerous Colitis: 108 Crohn's disease: 110	Ulcerous Colitis: 72 Crohn's disease: 75	84	pg/ml
SD	Ulcerous Colitis: 11 Crohn's disease: 10	Ulcerous Colitis: 13 Crohn's disease: 15	14	pg/ml
p				<0.001
Correlation ghrelin: BMI	Significant both groups	Not significant		

Table 31: Ghrelin in different stages of [233, 234]

	Subjects	Controls/Placebo	Binn et al., 2006
n	5 (+1 vagotomized subject)		
Dose	1-4		ug/kg
T-lag for test meal	33	65	min
SD	5	14	min
p		< 0.01	
T-1/2 for test meal	119	173	
SD	6	38	
p		< 0.001	
	Subjects	Controls/Placebo	Tack et al., 2005
n	6	6	
Dose	40	ug/30 min	
T-1/2 for solid test meal	144	98	min
SD	45	15	min
p		NS	
T-1/2 for liquid test meal	86	53	
SD	7	6	
p		0.02	

Table 32: Effects from ghrelin injection on emptying time after test meal in patients with gastroparesis. [421, 82.]

Study/ Year	Main Finding	Patient group
Murray et al. 2005	Ghrelin infusion (5 pmol/kg/min) increases gastric emptying significantly	Subjects with diabetic gastroparesis (10)
Tack et al. 2006	Ghrelin infusion induces	Healthy, fasting subjects

	MMC	
Cremonini et al. 2006	Ghrelin infusion increases motility of the fundus No change in gastric emptying	Obese subjects
Levin et al. 2006	Ghrelin infusion increases gastric emptying and hunger	Obese subjects
Bisschops et al. 2008	Ghrelin infusion induces MMC	Healthy, fasting subjects
Ang et al. 2009	Ghrelin infusion (40 ug/ 30 minutes) increases motility of the fundus and the gastric accommodation.	Healthy, fasting subjects (10)
Binn et al. 2006	Ghrelin infusion increases gastric emptying	Subjects with diabetic gastroparesis and vagotomy
Sallam et al. 2010	The TZP-101 ghrelin agonist increases gastric emptying	Subjects with gastroparesis

Table 33: effects of ghrelin infusion on gastric motility, accommodation or emptying. 419, 408, 407, 412, 465, 409, 421, 464