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Sarah Picciotto
Touro College

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Regulation of Ghrelin a Possible Treatment Option for Obesity and Diabetes

Sarah Picciotto

Sarah will graduate in June 2015 with a B.S. in Biology and will attend SUNY Downstate P.A. program.

Abstract

Obesity is a mounting problem in America today. One major concern about obesity is that it is a risk factor for type 2 diabetes, a disease that impairs insulin sensitivity and secretion. This interferes with blood glucose levels and can cause hyperglycemia, which is when there is too much circulating glucose in the blood. Ghrelin, an amino acid peptide responsible for appetite stimulation and energy balance, plays a direct role in insulin secretion and glucose metabolism. In many experiments, elevated ghrelin levels are associated with decreased insulin secretion from pancreatic islet cells. Although ghrelin concentration is decreased in obese individuals and diabetics, researchers attempt to use the ghrelin system as a treatment option for these people. It seeks to accomplish this by regulating the ghrelin produced by the body, diminishing its activity, affecting its receptor, the growth hormone secretagogue receptor (GHS-R1a), and by targeting ghrelin directly. Studies observed these methods' effects on insulin secretion and sensitivity as well as blood glucose concentration. The octanoylation of ghrelin, which activates it, is catalyzed by ghrelin Oacyltransferase (GOAT). Therefore GOAT inhibitors are one way of minimizing ghrelin's effects on metabolism. Additionally, cAMP concentrations decrease in islet cells of the pancreas in the presence of ghrelin. Using cAMP analogs can counter ghrelin's consequences as well. On the other hand, targeting the GHS-R1a receptor with an antagonist can also help enhance insulin secretion. Another research option entails using immunoneutralization to build antibodies against endogenous ghrelin. Lastly, studies have examined ghrelin knockout models in mice, by deleting the ghrelin gene, to examine the results that the lack of ghrelin has on insulin-glucose metabolism. Each of these methods has been proven to affect insulin and glucose metabolism. Further advances in the clinical application of these methods may lead to viable treatment options for obesity and diabetes.

Introduction

A big problem facing the world today is the rise of obesity. According to the CDC, approximately one third of the American adult population is obese. Obesity is characterized by a Body Mass Index (BMI), of 30 or higher, while healthy weight BMI is in the range of 18.5-24.9 (CDC, 2012). One possible consequence of obesity is the development of type 2 diabetes. Diabetes is a disease characterized by elevated glucose levels as a result of insufficient insulin production or a malfunctioning insulin system. Of the American population 29.1 million or 9.3%, had diabetes in 2012. This number was an increase from 2010 when the statistics were 25.8 million and 8.3% (American Diabetes Association, 2014). In type 1 diabetes mellitus, the β cells of the pancreas that are responsible for producing insulin are destroyed. In the absence of insulin, these individuals are at risk for hyperglycemia, or dangerously elevated blood glucose levels. Type 2 diabetes usually has a later onset. People with type 2 diabetes experience insulin resistance so that the insulin does not help glucose enter the body cells. Eventually the body stops producing insulin altogether (CDC, 2014). Most cases of diabetes, 90-95% are type 2 diabetes. Statistics show that 90% of cases of type 2 diabetes in western countries can be attributed to excess weight gain or obesity. Improving glucose tolerance while losing weight is the aim of new treatments for diabetes. Examining the effects the hormone ghrelin has on glucose metabolism can be a valuable therapeutic option (Rudolph, et al. 2007). Ghrelin is a 28 amino acid peptide hormone that plays a role in many different body functions. It is the endogenous ligand for the growth hormone secretagogue receptor (GHS-R) and has been proven to increase growth hormone secretion. Additionally, ghrelin is known as an orexigenic, or appetite-stimulating hormone, and is also responsible for energy balance. It is produced predominantly in the stomach but is also

produced in other places including the pancreas. One important function ghrelin serves is the ability to control insulin release from β cells of the pancreas. In the presence of ghrelin, insulin secretion is reduced, and blood glucose concentration increases. Research shows the effect of ghrelin on pancreatic islet β -cells. Ghrelin suppresses insulin secretion from β -cells by interfering with the K and Ca^{2+} channels that are stimulated by glucose metabolism. Obese individuals and diabetics have lower levels of plasma ghrelin than lean individuals. It is reasonable to suggest that this may be a regulated response in order to minimize the ghrelin activity that reinforces obesity. Subsequent research implicated possible regulation of ghrelin to treat obesity and diabetes. Since insulin levels are decreased in the presence of ghrelin, investigation of techniques to reduce or diminish the effects of ghrelin is in effect. Various treatment options that have undergone research and experimentation show positive outcomes in regard to treating diabetes and obesity. Many techniques that influence ghrelin's role in decreased insulin secretion are still in the experimental phase but may eventually be effective to treat diabetes and obesity. Ghrelin's effects on insulin sensitivity are also being explored. Can regulation of ghrelin serve as a possible treatment option for diabetes and obesity?

Methods

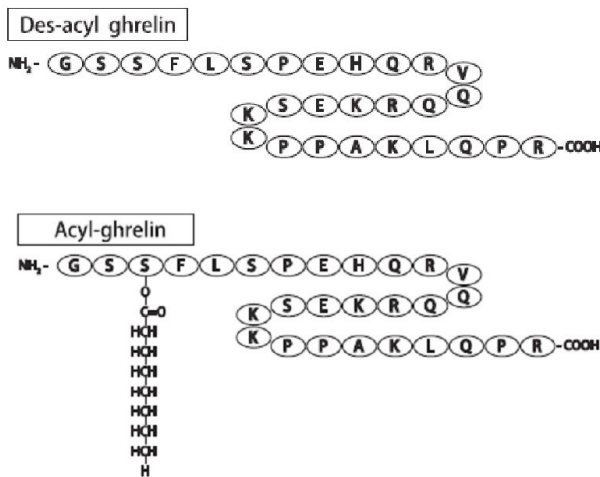
The research obtained about ghrelin's effects on the metabolism of diabetics and obese individuals was collected from a variety of sources. The majority of articles were collected using Touro's library to access databases such as Pubmed, ProQuest and more. Additionally, other articles were found by searching Google scholar for relevant journals on the topic. After reviewing numerous articles on ghrelin's effects on obesity and diabetes, evidence was compiled to answer the research question.

Discussion

Ghrelin and its forms:

Ghrelin is a 28-peptide amino acid that is produced mainly in the stomach. This hormone is responsible for signaling hunger and maintaining an energy balance. Acylated ghrelin, or acyl ghrelin, the active form of ghrelin consists of noctanoylation on the third serine. This form of ghrelin is able to bind to the GHS-R1a, enabling it to have a biological effect in areas such as growth hormone secretion and glucose metabolism. However, most of our plasma circulating ghrelin is unacylated ghrelin, or des acyl ghrelin, which has been discovered to have biological effects as well (Kiewiet, et al. 2009).

Figure 1



The effects of each form of ghrelin on insulin concentration and sensitivity has been studied. Acylated ghrelin (AG), the active form of ghrelin has been found to be responsible for decreased insulin levels, while unacylated ghrelin's (UAG) affects are being studied. It has been noted that ghrelin levels have a preprandial increase and a postprandial decrease indicating its role as an appetite stimulant (Kiewiet, et al. 2009). The hormone insulin acts in the opposite way, so investigators seek to explain the relationship between the two. Some studies examined the effects of AG and UAG on the insulin metabolism. Findings were that AG stimulated glucose release by hepatocytes, while UAG inhibited these effects. In addition, in an experiment done with adult-onset growth hormone-deficient patients, AG was found to decrease insulin sensitivity, and coinjection of UAG countered the effect. Thus, the circulating plasma ghrelin's two forms act in contrasting ways (Ukkola, 2009). An experiment was conducted in order to isolate the actions of AG and UAG. Subjects were administered a combination of AG and UAG and then each form of ghrelin on its own. The subject group consisted of 8 morbidly obese female Caucasians. The mean age was 45.4± 10.3 in the range of 28-62 years old. The average BMI of the subjects was 42.4± 4.8 kg/m².

This experiment was a repeated measures design in which each of the 8 subjects received all the experimental conditions with a two-week break in between. Ghrelin was administered after overnight fasting conditions after a saline infusion. The three experiments were: administration of 200 µg of UAG on its own, administration of 100 µg of AG together with 100 µg UAG, and a placebo. Subjects were then given a 595 kcal breakfast, a similar lunch three hours later, and then they were free to eat what they pleased until midnight. Blood samples were collected to measure the total ghrelin, glucose, and insulin concentrations. After the first hour of administration, while subjects were fasting, administration of UAG on its own did not change insulin levels or glucose concentrations, nor did it differ from the placebo. Receiving the combination of UAG and AG resulted in significantly decreased insulin levels as compared to UAG administration alone and the placebo (58.2 ± 6.3% insulin concentration when AG and UAG were administered combined, compared to 91.8 ± 3.0%, the insulin concentration when UAG was administered alone). This experiment tested for insulin sensitivity using the glucose to insulin ratio. The results indicated an almost 50% decrease in insulin levels and almost no change in glucose concentration. This demonstrated the effect of UAG to improve insulin sensitivity when administered along with the AG that lowered the insulin levels. Also, subjects with a smaller AG:UAG ratio possessed increased insulin sensitivity indicating the combination effect of coinjection of AG and UAG. This may lead to a possible treatment for diabetes for many diabetics have problems with insulin sensitivity. However, further research is needed to exactly determine insulin sensitivity, for the glucose-insulin ratio does not consider secretion, distribution and degradation of insulin (Kiewiet, et al. 2009).

However, a recent study tested the effect of AG in combination with UAG on insulin and glucose metabolism. Healthy volunteers were given pharmacological doses of AG and UAG as a bolus and at 210-minute intervals under fasting conditions and intravenous glucose administration. However, The UAG did nothing to plasma insulin levels after AG decreased them. This study did not examine but encourages further study on insulin sensitivity following AG and UAG administration (Barazzoni, 2014). Previous research tested the effects of ghrelin on insulin sensitivity by using the insulin-glucose ratio. Although the insulin levels stayed the same, the glucose levels decreased indicating greater insulin sensitivity (Kiewiet, et al. 2009). Although this may not give the most reliable results because it does not consider other factors that can contribute to insulin sensitivity, it is a start in observing the effect that UAG has on insulin sensitivity. Nevertheless, further research is needed to confirm this relationship.

Insulin Sensitivity

Although it may be hypothesized that obese individuals have

elevated ghrelin levels contributing to their obesity, on the contrary, obese individuals have lower ghrelin concentrations than normal. According to a study obese patients' plasma active ghrelin levels compared to lean subjects were 180 ± 18 vs. 411 ± 57 pg/ml. Serum total ghrelin levels differed from 3650 ± 408 in obese patients and 5263 ± 643 pg/ml in lean subjects. Ghrelin levels were correlated with insulin resistance that was calculated using the HOMA approach which is: $\text{insulin (micro-units/milliliter)} \times \text{blood glucose (millimoles/liter)} / 22.5$ (Marzullo, et al. 2003).

Similarly, in a different study, lower ghrelin levels were found in obese subjects. This study, shows the correlation between body fat and circulating ghrelin levels after obese and lean subjects were fed a weight maintaining diet and abstained from exercise two days. The results indicated that the obese subjects' ghrelin levels were 32% lower than the lean subjects'. Additionally, a negative correlation was found between ghrelin concentration and body fat ($r = -.45$). Insulin was also negatively correlated to ghrelin concentration ($r = -.45$) (Tscöp, et al. 2001). Since ghrelin is responsible for energy balance and homeostasis, this study is consistent with present knowledge. Obese individuals have stable energy levels so the body lowers the ghrelin response. However, although the circulating ghrelin levels are minimized, its effects on insulin and body fat are still present.

Studying children with type I diabetes mellitus (T1DM) indicated lower levels of total ghrelin in comparison to healthy subjects. Also, higher levels of AG contributed to lower insulin levels and greater insulin resistance. Therefore, a possible way the body protects diabetics from hyperglycemia can be the decreased concentration of circulating ghrelin. Insulin therapy after four months elevated ghrelin levels in twenty children with T1DM (Ukkola, 2009). This can indicate the body considering lower ghrelin levels unnecessary due to the insulin therapy.

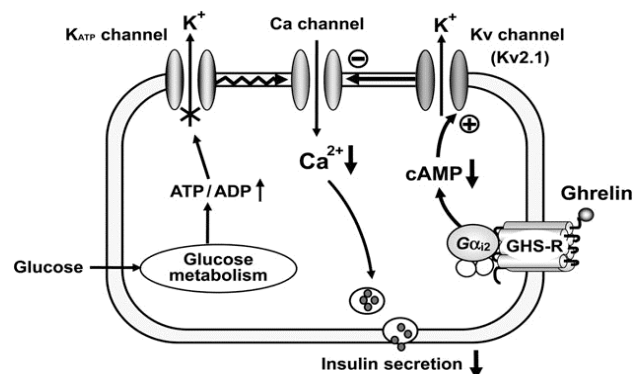
Although we can understand how insulin resistance is a problem in diabetic patients, obesity can contribute to insulin resistance as well. One way in which obesity contributes to insulin resistance is through the immune system's activation by obesity. Adipose tissue macrophages produce pro-inflammatory cytokines that can lead to insulin resistance by blocking insulin action in adipose tissue, skeletal muscle, and liver. Therefore, ghrelin as a possible therapeutic option can improve both diabetics and obese individuals' health (Ota, 2014).

Ghrelin's Metabolic Effects

An experiment examined ghrelin levels in lean, obese, diabetic and nondiabetic subjects. Blood samples were collected after overnight fasting and again after monitored eating. Compared to normal weight subjects, mean plasma ghrelin concentrations were 225% for those with anorexia nervosa and 68% for obese

subjects. A negative correlation exists between BMI and plasma ghrelin concentration. The body maintains homeostasis by decreasing ghrelin levels in the presence of positive energy balance. When the body has excess energy from nutrition, the ghrelin levels are decreased to postpone hunger. This justifies the postprandial, or after eating a meal, decrease of ghrelin levels (Shiyya, et al. 2002). Ghrelin's effects on feeding and energy balance refer to the ghrelin produced in the stomach; however, the pancreas also produces ghrelin contributing to glucose metabolism. Ghrelin is an insulinostatic hormone, meaning it controls the release of insulin. Ghrelin levels were compared from the pancreatic vein that leaves the pancreas and the pancreatic artery that brings new blood to the pancreas. Results showed 8 times the amount of ghrelin levels in the pancreatic vein, indicating the pancreas produces that ghrelin (Yada, et al. 2014). The GHS-R1a, the ghrelin receptor, is located on pancreatic islet cells. Ghrelin binds to the receptor and decreases insulin release from the cell and elevates blood glucose concentrations. When glucose concentrations rise from 2.8 mM to 8.3 mM, insulin release from β cells is stimulated. The intensification of Ca^{2+} concentrations, stimulated by glucose metabolism is a crucial step in insulin secretion. However, insulin release is weakened when ghrelin is exogenously administered at a high concentration of 10 nM. Ghrelin suppresses the peaks of Ca^{2+} by increasing amplitudes of K^+ currents that block the influx of Ca^{2+} ions into the cell thereby slowing down the process of glucose-induced insulin release (Yada, et al. 2008).

Figure 2



The binding of ghrelin to GHS-R reduces cAMP expression and increases the K^+ current. This slows down the influx of Ca^{2+} into the cell, leading to a decreased insulin secretion response to glucose metabolism. (Yada, et al. 2014)

Research has proven that ghrelin's effect on the K^+ channels result from decreased cAMP levels. cAMP, cyclic AMP (adenosine monophosphate) signaling plays one of the most vital roles in insulin secretion from beta cells (Kashima, et al. 2001). Ghrelin uses G-protein $\text{G}\alpha_{i2}$ to obstruct the cAMP response to glucose metabolism. cAMP activates PKA, protein-kinase-A, and suppresses K^+ currents in islet cells. Since the insulinostatic effect of ghrelin

occurs through the cAMP pathway, one possible way to minimize it is by presenting cAMP analogues along with ghrelin. One molecule used in testing the effects of cAMP analogs on insulin secretion is 6-Phe-cAMP. In the presence of cAMP analogs, ghrelin has no effect on insulin secretion. Hence, by reinstating the cAMP activation pathway in the presence of ghrelin, diabetics can experience enhanced insulin secretion (Dezaki, et al. 2011). This study demonstrates a new remedial approach to reducing ghrelin's effects. cAMP analogs may aid diabetes by enhancing insulin secretion in pancreas islet.

Ghrelin Antagonism

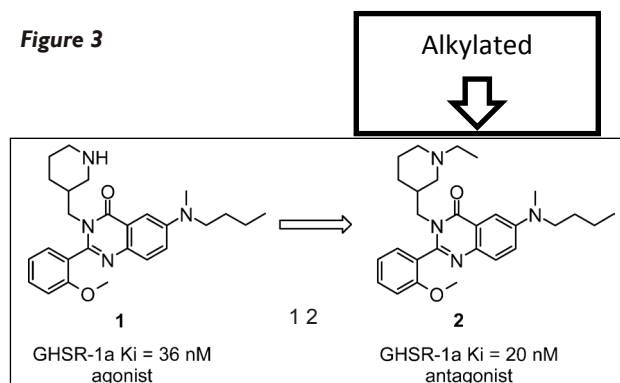
Since type 2 diabetics do not have enough insulin, anti-ghrelin treatments can enhance insulin secretion. In obesity, insulin resistance is a problem, so eliminating ghrelin can produce a positive effect on hyperglycemia. Ghrelin's affects on insulin and glucose metabolism, food intake, and body weight all need to be assessed in order to determine if antagonism of ghrelin can relieve symptoms of diabetics and obese individuals. One popular method used to remove ghrelin's affects is by antagonism of the GHS-R. If the receptor does not accept ghrelin, it has no effect on the pancreatic islets. In an experiment using fasted mice, ghrelin receptor antagonists [D-Lys3]-GHRP-6 enhanced insulin secretion and lowered blood glucose levels. This research indicated that a ghrelin blockade increases insulin release to help maintain normal glucose concentrations (Yada, et al. 2008). Experiments done with gastrectomized mice, that lack stomach-derived ghrelin, show the role of pancreatic ghrelin in the insulin response. After GHS-R antagonist was administered, both groups of mice showed the same increased insulin response. This proves that the pancreatic ghrelin is responsible for these effects. Therefore, targeting the GHS-R can be a therapeutic approach in enhancing insulin secretion (Dezaki, et al. 2006). Administering intra-peritoneal ghrelin antagonist to mice also decreased food consumption (Asakawa, et al. 2003). These findings can be beneficial in aiding obese individuals control their food intake.

Additionally, an experiment done on mice implied ghrelin's effects on body weight, insulin levels, and blood glucose concentrations. Injection of ghrelin twice a day for five days increased body weight in mice compared to the control. Depending on the diet and whether the mouse received ghrelin or saline, determined the increase in body weight. For example, one group of mice were fed a high fat diet and given saline. These mice exhibited a .60 g/day increase in body weight, while those fed a high fat diet with ghrelin had a .92 g/day increase. Serum cholesterol and insulin levels increased and glucose concentration increased as well. The same experiment tested how ghrelin antagonist, [D-Lys3]-GHRP-6, affected the same factors. After 7 days of administration to obese mice, weight gain, fat pad mass, and blood glucose concentrations decreased (Asakawa, et al. 2003). This study does

not seem to be consistent with other research that has linked elevated ghrelin to decreased plasma insulin secretion; but a moderate increase in glucose concentration was observed. This can indicate a case of insulin resistance instigated by an increase in free fatty acids (FFA) that are known to contribute to insulin resistance. GHS-R antagonists increased insulin sensitivity and reduced glucose levels. In addition, it simultaneously decreased FFA concentration aiding in fostering insulin sensitivity (Asakawa, et al. 2003).

One class of drugs that is being studied as possible ghrelin receptor antagonists are quinazolinone derivatives. In the lab, quinazolinone derivative 1 was discovered to have affinity to GHS-R1a. Yet, it was found that the molecule had agonistic binding to the receptor rather than the desired antagonistic affect. Alkylation of the N group on the molecule altered its functionality by transforming it into a GHS-R1a antagonist. Piperidine-substituted quinazolinone derivatives that are phenyl or phenoxy substituted were found to act as GHS-R antagonists (Del-porte, 2011).

Figure 3



In a structure-activity relationship study, many derivatives of the compound were tested for their effects in vivo. Two quinazolinone compounds that were used for study were compounds 26 and 43. These antagonists were administered at doses 3, 10, and 30 mg/kg. While compound 26 lowered body weight at the 10 mg/kg dose, compound 43 only was effective at 30 mg/kg. Compound 26 at 30 mg/kg is known as the first orally administered GHS-R antagonist possible to induce weight loss in animals. This renders it a feasible way to treat obesity, a leading cause of diabetes. Compound 26 administered at the highest dose had similar effects to an anti-obesity drug that is still under evaluation by the FDA, CBI antagonist rimonabant, 5-(4-choophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide. This study also tested glucose tolerance. Both compounds decreased glucose excursion by around 20%. However, the cause behind these decreased blood glucose levels, was not tested for. The study would like to go further in confirming that this result from the GHS-R antagonist stemmed from an enhanced insulin secretion (Rudolph, et al. 2007). This research

brings practical application of a drug that may be available to help treat obesity and diabetes. As a receptor antagonist, it minimizes ghrelin's insulino-static effects and enhances glucose metabolism.

Immunoneutralization

Immunoneutralization of ghrelin also is a potential method of enhancing insulin secretion. Creating a vaccine to stimulate antibody production against acylated ghrelin may be a viable treatment for obese individuals. However, when a trial was conducted using a CYT-009 Ghr Qb vaccine, antibodies were developed, but weight stayed the same (Delporte, 2011). In another instance, mice were immunized against ghrelin to produce an antibody response. After being fed identical diets, the rats with more ghrelin-specific antibodies gained less weight per calorie ingested. Since their food intake did not vary from other control mice, this experiment shows that ghrelin produces a metabolic change rather than feeding changes. However, ghrelin has been known to increase feeding in a high-fat diet, these mice were given low-fat, less appetizing meals. This could be a factor that might have influenced the ghrelin-vaccinated mice's feeding habits, so the reliability of their conclusion is questionable. Additionally, there can be possible draw-backs to this course of treatment. Long-term or other side effects of eliminating ghrelin are unclear. It may have possible ramifications on energy balance that is regulated by ghrelin. The absoluteness of inactivating ghrelin by use of antibodies is also irreversible, unlike ghrelin receptor antagonism that can be stopped when undesired effects occur. Another obstacle that we may be facing with immunoneutralization is the negative feedback loop of the body producing more ghrelin to compensate for lack of ghrelin signals. Although the immediate results of an anti-ghrelin vaccine may look promising, further research is needed to confirm the safety and reliability of this method to reduce body weight. Controlling the immune response can keep ghrelin antibodies from getting out of hand (Carlson, Cummings, 2006). However, until research can safely develop and monitor such a vaccine, it would be best to put this method on hold.

Ghrelin Knockout

An alternative to a ghrelin vaccine is the ghrelin knockout model. The ghrelin gene is deleted from rats and they are then monitored for feeding habits, metabolism, weight gain, and glucose concentration. One point to remember is the unknown effects of ghrelin's complete absence from the body. In one experiment, ghrelin's effects on insulin secretion were tested using ghrelin knockout mice. In particular, glucose-induced insulin release was higher in knockout mice. On the contrary, basal insulin levels remained the same in knockout and wild-type mice. Therefore, ghrelin knockout mice had improved insulin responses to glucose. Afterwards, an insulin tolerance test (ITT) was given to both groups of mice. No significant differences were found between them. The experiment advanced to testing the effects of a high-fat

diet, known to increase glucose concentrations. When fed a high fat diet, blood glucose levels increased in wild-type mice, and no increase was identified in the knockout mice. This can be attributed to enhanced insulin secretion in response to elevated glucose levels. After the wild-type mice did a glucose tolerance test (GTT), mice with a high-fat diet showed higher glucose concentration levels compared to a control diet, implicating glucose intolerance. On the other hand, the ghrelin knockout mice exhibited no difference in glucose tolerance between the high-fat diet and the control group. However, there was an increased insulin response in the mice fed a high-fat diet (Dezaki, et al. 2006). This research shows ghrelin's role in glucose-insulin metabolism. In the absence of ghrelin, increased insulin levels and improved glucose tolerance were found. Although ghrelin knockout cannot be done to humans, it serves as an indication of ghrelin's metabolic effects. Regulating ghrelin levels in obese people can possibly improve their body weight and glucose tolerance.

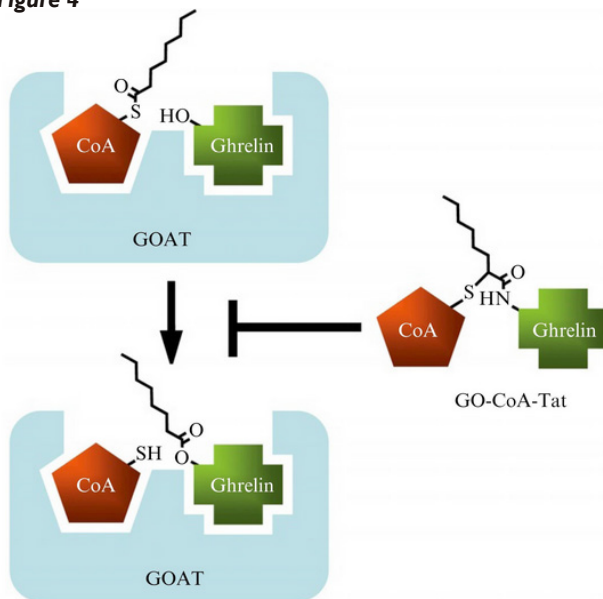
GOAT

Ghrelin O-acyltransferase is a membrane-bound O-acyltransferase. It catalyzes the octanoylation of ghrelin allowing it to be acylated and able to connect with the GHS-R1a receptor. Since it catalyzes ghrelin to be in its active form, one idea is to target GOAT to slow the process of the body producing acylated ghrelin. In GOAT knockout models, there is no acylated ghrelin found circulating (Pulkinen, et al. 2010). As discussed earlier, studies show that unacylated ghrelin counteracts acylated ghrelin's effect on insulin, and did nothing to insulin metabolism when administered on its own (Kiewiet, et al. 2009). So, inhibiting GOAT action can minimize the effects that acylated ghrelin has on insulin and glucose metabolism.

One method studied to inhibit GOAT is the administration of GO-CoA-Tat in mice. The GHS-R binding property of ghrelin is determined by the octanoylation on serine 3, making it acyl ghrelin. This inhibitor was found to be most active in binding to GOAT. After administering GO-CoA-Tat to mice at a 40 mg/kg dose, acyl ghrelin levels decreased while des acyl ghrelin levels remained unchanged. Additionally, after 1 month, weight gain due to decreased fat mass was assessed in the treated mice. Interestingly, no difference in weight was found compared to ghrelin knockout mice. This indicates that GOAT inhibition may have similar effects to ghrelin knockout. The mice's response to glucose was measured to observe the effects of GO-CoA-Tat. The insulin response was increased and blood glucose levels subsequently decreased. This did not occur in ghrelin knockout mice thereby reinforcing the mechanism of GOAT inhibition to prevent ghrelin's acylation (Taylor, et al. 2012). Additionally, use of this GOAT inhibitor may be a better option than using a ghrelin antagonist. Some advantages that a study done by Barnett et al. in 2010 explains that GO-CoA-Tat does not need to cross the

blood brain barrier unlike the GHS-R antagonist which targets receptors in the brain as well. Additionally, there is no feedback of the body trying to compensate by producing extra acylated ghrelin to bind to the receptors. Another reason given is that targeting an enzyme like GOAT may be safer than targeting a widespread receptor (Barnett, et al. 2010). However, GOAT is still being studied and its use in treatment is not yet confirmed. Further experimentation would need to be done to examine the viability of such a method of treatment in humans, and the possible negative side effects of a drug using this mechanism.

Figure 4



This simple diagram shows the catalytic activity of GOAT on ghrelin. Additionally, the inhibitor GO-CoA-Tat is shown to demonstrate interference with the GOAT mechanism.

In conclusion, currently research is in the process of determining the possibilities of using the ghrelin system to treat or cure diabetes and obesity. No definite answer can be given about its viability in human subjects as most experimentation is done in mice. However, the facts have been proven. Ghrelin's influences on insulin secretion, blood glucose concentration, weight-gain, and fat mass have been assessed in various studies. The regulation of ghrelin by reducing its impact on pancreatic islets or by eliminating it altogether have been found to enhance insulin secretion and lead to less weight gain. Therefore, further research on the pharmacological effects of drugs used to regulate ghrelin's effects may lead to a more certain conclusion.

Legend

AG: Acylated ghrelin UAG: Unacylated ghrelin

GHS-R: Growth hormone secretagogue receptor

GOAT: Ghrelin O-acyltransferase

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