Volume 2, April 2020, 701814

GUHES

Journal of Gazi University Health Sciences Institute

journal homepage: https://dergipark.org.tr/tr/pub/guhes

The Effects of Acyl and Desacyl Forms of The Ghrelin Hormone on The Body

Emine Elibol[1], Yasemin Akdevelioğlu[2]

[1] Departments of Nutrition and Dietetic, Ankara Yıldırım Beyazıt University, Ankara, Turkey

[2] Departments of Nutrition and Dietetic, Gazi University, Ankara, Turkey

Article info:

Received: 10.03.2020

Accepted: 30.04.2020

Keywords:

appetite,
disease,
hormone,
ghrelin

Abstract

Discovered as the endogenous ligand of the growth hormone secretagogue receptor, the ghrelin hormone is a small 28-amino acid peptide. This hormone is produced by certain tissues of the stomach, the brain, the liver, the kidneys, the pancreas, the pituitary gland, and adipose tissue. Major forms of ghrelin in plasma are acyl and desacyl ghrelin. While decacyl ghrelin was first thought to be an intermediate or degradation product of acyl ghrelin, today it has been found that desacyl ghrelin has metabolic effects on the body as a separate hormone. For this reason, this review was made to evaluate the effects of acyl and desacyl ghrelin on the body. Ghrelin causes a biological effect by binding to the growth hormone secretogogue receptors in the body. Only the acyl ghrelin hormone can bind to the growth hormone secretagogue receptor 1a. Des acyl cannot bind. As a result of studies, it has been determined that acyl ghrelin has an effect on appetite increase, growth hormone release, in addition to body weight and insulin resistance. Desacyl ghrelin has an effect on appetite decreas, body weight, as well as increase in insulin sensitivity. Moreover, it has been emphasized in recent years that desacyl ghrelin may be a strong inhibitor of the acyl ghrelin hormone. However, the effects of these two hormones in some patients are not fully understood. Therefore, studies investigating the effects of these hormones on different diseases should be conducted in the future.

1. Introduction

Appetite and nutritional behavior are not only regulated by different mechanisms in the central nervous system (CNS), but also in hormones such as ghrelin and leptin. It also plays a role in the regulation of appetite (Kojima & Kangawa, 2002). The hormone ghrelin, first described by a scientist named Kojima in 1999, contains 28 amino acids (Barazzoni et al., 2007; Kojima et al., 1999). Ghrelin is synthesized by endocrine X/A-like cells of the fundus mucosa in the stomach (Delporte, 2013). This hormone is also released from some tissues of the brain, the kidneys, the pancreas, the liver, adipose tissue, and the pituitary gland (Pacifico et al., 2009; Yoshimoto et al., 2002). There are 4 forms of the ghrelin hormone in the body which are octanoylated (acyl ghrelin) (C8: 0), nonacylated (des-acyl ghrelin), decanoylated (C10: 0), and decenoylated (C10: 1) (Hosoda, Kojima, & Kangawa, 2006). All forms are produced by the precursor of the same ghrelin form. The Ghrelin molecule is acylated by the Ghrelin O Acyl Transferase (GOAT) enzyme (Ozcan et al., 2014). The most common forms of ghrelin in plasma are acyl and desacyl ghrelin. When desacyl ghrelin was discovered, it was thought to appear when the acyl ghrelin was still ineffective (Hosoda et al., 2006). In a study by Yang et al. (2008) it was emphasized that desacil ghrelin is not an intermediate metabolite of acyl ghrelin.

Zhu et al. (2006) also supports this conclusion. Therefore, it has not yet been clearly determined how desacil ghrelin is formed (Yang et al., 2008). Nowadays, it is emphasized that acyl and desacyl ghrelin are different hormones. Moreover, desacil ghrelin is thought to have a specific receptor (Delhanty, Neggers, & van der Lely, 2013). Ghrelin forms are known to have different physiological functions in the body (Schmidt et al., 2004). Initially, while desacyl ghrelin was thought to be inactive, today it has been found to have significant endocrine activity in the body (Kojima & Kangawa, 2005). Acyl ghrelin has an impact on appetite increase, growth hormone release, body weight, and insulin resistance. Desacyl ghrelin triggers an effect ondecrease in appetite and body weight as well as increase in insulin sensitivity (Delhanty, Neggers, & van der Lely, 2012; Yoshimoto et al., 2002). In addition, it has recently been pointed outthat desacyl ghrelin can act as a significant functional obstacle to acyl ghrelin (Delhanty et al., 2013).

Researches mostly focus on total ghrelin. However, total ghrelin contains both acyl and desacil ghrelin. Also, these two forms have different effects on the body. For this reason, there is a need for studies which investigate the effects of these two forms and not the total ghrelinseparately. Therefore, this study was conducted to evaluate the metabolic effects of acyl and desacyl ghrelin hormones in the body.

2. The Effects of Ghrelin on Growth Hormone Release

There are two Growth Hormone Secretogogue Receptors (GHS-R) in the body. These are GHS-R 1a and GHS-R 1b, which are found in the pituitary gland and in other specific organs. GHS-R1a affects growth hormone (GH) release as well as endocrine activity (Inhoff, Wiedenmann, Klapp, Mönnikes, & Kobelt, 2009). The ghrelin molecule can bind to the GHS receptor and show biological effects

***Corresponding author:** Emine Elibol
e-mail address: eelibol@ybu.edu.tr

(Nikolopoulos, Theocharis, & Kouraklis, 2010). The Acyl ghrelin hormone can bind to GHS-R1a, while desacyl ghrelin cannot (Inhoff et al., 2009). The growth hormone releasing hormone (GHRH) stimulates the growth hormone releasing hormone receptor (GHRH-R), thereby increasing cyclic adenosine monophosphate (cAMP) to release the growth hormone. The acyl ghrelin hormone then plays a role in growth hormone release by stimulating the ghrelin hormone releasing receptor, increasing intracellular Ca^{+2} (Nagaya, & Kangawa, 2003).

3. The Ghrelin Hormone and Diseases

Ghrelin, which has drawn attention in recent years, has been shown to have an effect on many diseases such as obesity and diabetes as well as sleep, memory, in addition to liver defects. According to the results of research, the metabolic effects of acyl and desacyl ghrelin hormones are shown in Table 1.

3.1. Obesity

Appetite hormones such as ghrelin and leptin also play a role in the pathophysiology of obesity, which is affected by genetic and environmental factors (DelParigi et al., 2002). Adipogenesis is controlled by specific transcription factors such as peroxisome proliferator-activated receptor PP (PPARγ) and sterolregulatory element binding protein-1 (SREBP1). In literature, acyl ghrelin has been shown to play a role in the increase of adipose tissue in the body as well as the stimulation of GH release and appetite (Yang et al., 2008). Despite contradictory studies on this subject, acyl ghrelin, which has anorexigenic effects in obese individuals, has been shown to have high or normal levels, while anorexiagenic desacyl ghrelin has been determined to have low levels. Therefore, it has been emphasized that desacyl ghrelin may be effective on obesity (Nonogaki, Nozue, & Oka, 2006; Barazzoni et al., 2007; Longo et al., 2008; Pacifico et al., 2009). In studies on the acyl ghrelin hormone, the hormone has been shown to increases adiposity in rats by increasing the expression of fat storage enzymes such as lipoprotein lipase, acetyl-CoA carboxylase, fatty acid synthase, and stearoyl-CoA desaturase-1 (Choi et al., 2003; Giovambattista et al., 2007; Thompson et al., 2004). In a study, 8 healthy men received 240 min of intraarterial acyl ghrelin infusion. As a result, it was emphasized that the acyl ghrelin hormone can promote lipolysis directly in skeletal muscles due to the increase in serum free fatty acids and palmitate levels (Vestergaard et al., 2011). In the study, Allas et al. infused 23 patients with desacyl ghrelin and 24 patients with placebo for 14 days. Decrease in appetite was detected only in patients who received desacil ghrelin. Body weight did not change in both groups. A significant reduction in waist circumference and fat mass was observed in the group which received desacyl ghrelin (Allas et al., 2018).

The hormone ghrelin plays an important role in the regulation of appetite metabolism, which is crucial in the pathogenesis of obesity. Plasma ghrelin levels and gene expression change according to food intake. In healthy individuals, the level of plasma acyl ghrelin is high before food intake. However, it decreases after food consumption. While the level of plasma acyl ghrelin does not change in prolonged fasting, an increase in the level of desacyl ghrelin is observed. Ghrelin, commonly known as the hunger hormone, has two hormone forms and these forms

***Corresponding author:** Emine Elibol
e-mail address: eelibol@ybu.edu.tr

Table 1. Effects of hormone acyl and desacyl ghrelin hormones on the body

Acyl Ghrelin	**Desacyl Ghrelin**
Appetite ↑ (Akamizu et al., 2008; Chen et al., 2005; Hotta et al., 2004)	Appetite ↓ (Asakawa et al., 2005; Chen et al., 2005; Hotta et al., 2004)
Adipogenesis ↑ (Choi et al., 2003; Giovambattista, Gaillard, & Spinedi, 2007; Thompson et al., 2004).	Adipogenesis ↑↓ (Allas et al., 2018; Thompson et al., 2004)
Hepatic steatosis ↑ (Dallak, 2018; Liu, Lin, Cheng, Hu, & Lu, 2009).	Hepatic steatosis ↓(Dallak, 2018).
Insulin resistance ↑ (Vestergaard, Jessen, Møller, & Jørgensen, 2017).	Postprandial glucose ↓ (Ozcan et al., 2014). Insulin secretion ↔ (Zorrilla et al., 2006).
Luteinizing Hormone ↓ and Follicle Stimulating Hormone ↓ (Martini et al., 2006).	Luteinizing Hormone ↓ and Follicle Stimulating Hormone ↓ (Martini et al., 2006).

LH: Luteinizing Hormone, FSH: Follicle Stimulating Hormone

have different effects on metabolism. While acyl ghrelin is known to cause anorexigenic effects, desacyl ghrelin is known to cause anorexigenic effect (Churm, Davies, Stephens, & Prior, 2017).

The acyl ghrelin hormone alters the appetite depending on several mechanisms. Firstly, acyl ghrelin can increase appetite by activating Neuropeptide Y (NPY) neurons and agouti-related peptides (AGRP). In addition, this hormone stimulates the hypothalamus by inducing the vagal afferent nerve and increasing GHS-R expression (Churm et al., 2017). The effects of desicil ghrelin on appetite have not clearly been found. Some studies have shown that desacil ghrelin causes increased expression of c-Fos in arcuate nucleus (ARC) and paraventricular nucleus (PVN) of the hypothalamus by crossing the blood-brain barrier bytransmembrane diffusion. Thus, desacil ghrelin is thought to be effective in the synthesis of anorexigenic hypothalamic mediators by providing an increase in neuronal activity (Asakawa et al., 2005; Banks, Tschöp, Robinson, & Heiman, 2002; Chen et al., 2005; Inhoff et al., 2009). Thirty anorexia nervosa (AN) patients and 16 healthy individuals were included in the study. In the study, plasma acyl ghrelin levels (34.7±3.2 pmol/L) of AN patients were similar to that of the control group (29.9±3.1 pmol/L), while desacyl ghrelin levels (223.5±37.3 pmol/L) were significantly higher than that of the healthy individuals (94.1±7.5 pmol/L). Moreover, the ratio of desacil ghrelin to acyl ghrelin was found to be 6.14 ± 0.44 in anorexia patients and 3.34 ± 0.24 in healthy individuals (Hotta et al., 2004). In the study conducted by Inhoff et al., rats were injected with ip simultaneously with ghrelin (13 μg/kg) plus vehicle (n=12), vehicle plus vehicle (n=13), ghrelin (13 μg/kg) plus 64 μg/kg or127 μg/kg desacyl ghrelin (n =12/group), and 127 μg/kg desacyl ghrelin (n=10) or vehicle plus 64 μg/kg (n=13). As a result, it was found that desacyl ghrelin suppresses ghrelin-induced food intake (Inhoff et al., 2008). In a other study rats were divided into three groups which were vehicle (5nmol), acyl ghrelin (5nmol), and desacyl ghrelin (5nmol) groupsto evaluate the effects of acyl and desacyl ghrelin on food intake. The results suggested that desacyl ghrelin decreases food intake and acyl ghrelin increases food intake (Chen et al.,

***Corresponding author:** Emine Elibol
e-mail address: eelibol@ybu.edu.tr

2005). In a study, it was emphasized that excessive expression of desacil ghrelin can decrease body weight due to the decrease in food intake without increasing energy expenditure (Asakawa et al., 2005).

3.2. Non-Alcoholıc Fatty Liver Disease

Non-alcoholıc fatty liver disease (NAFLD) is a common public health problem in both developed and developing countries. It is characterized by a wide spectrum of liver defects ranging from simple steatosis to non-alcoholic steatohepatitis. Increased de novo synthesis and triglyceride (TG) accumulation in hepatocytes occur in non-alcoholic fatty liver disease cases (Dallak, 2018). Diacyl glycerol is one of the pathways responsible for TG synthesis in the liver. Diacyl glycerol regulates protein kinase C activation (Harvey, & Ferrier, 2015). In recent years, intestinal hormones have been shown to play an important role in preventing the formation of hepatic steatosis and hepatic insulin resistance in NAFLD (Delhanty, 2012).

It has been suggested that the acyl and desacil ghrelin hormones have different effects on fatty liver (Dallak, 2018). However, its mechanism has not been fully explained. In the study, it was found that short-term acyl ghrelin administration (200 ng/kg/day, twice/day) for 4 days increased hepatic lipid accumulation by inhibiting fat oxidation by means of AMP-activated protein kinase (AMPK) (Barazzoni et al., 2005).

In another study, it has been shown that administration of acyl ghrelin (11 nmol/kg/day for 14 days) induces hepatic steatosis and hepatic insulin resistance by activating the signal of rapamycin mammalian target (mTOR) and the peroxisome proliferator-active receptor-γ (PPARγ) (Li et al., 2014). In a study on rats, it was found that acyl ghrelin increased hepatic steatosis and desacyl ghrelin reduced hepatic steatosis. Moreover, decacyl ghrelin was found to decrease hepatic insulin resistance while acyl ghrelin increased it (Dallak, 2018).

3.3. Diabetes

The ghrelin hormone is thought to play a role in insulin hemoastasis due to the expression of ghrelin and GHS-R1α RNAs in the pancreas and β-cells. Acyl ghrelin plays a role in glucose metabolism and acts on diabetes. The effects of desacil ghrelin on glucose metabolism is not fully understood. Intravenous administration of desacyl ghrelin has been shown to have a positive effect on glucose metabolism, insulin sensitivity, and inhibition of lipolysis (Benso et al., 2012; Churm et al., 2017).

Dezaki et al. (2004) reported that administration of endogenous acyl ghrelin suppresses insulin release by reducing glucose-induced calcium concentration in pancreatic cells of mice and rats. In addition, DiGruccio et al. (2016) stated that the presence of GHS-R1 in pancreatic cells can be effective in the suppressionof insulin secretion.

In a study, desacil ghrelin levels in patients with metabolic syndrome were found to be lower than in non- metabolic syndrome patients. Moreover, HOMA-IR levels were found to have a negative correlation with desacil ghrelin. Also, there was no relationship between acyl ghrelin and HOMA-IR (Lee, & Cho, 2015). In another study, acyl ghrelin injection was shown to increase insulin resistance in

***Corresponding author:** Emine Elibol
e-mail address: eelibol@ybu.edu.tr

8 adult hypopituitary patients (Vestergaard et al., 2017). In the study conducted by Ozcan et al., (2014) 8 individuals were given 3 or 10 mg/kg desacil ghrelin.Desacil ghrelin decreased postprandial glucose levels and acyl ghrelin. However, in a study conducted by Zorilla et al., (2006) an effect of desacil ghrelin on insulin secretion was not found.

In studies conducted, it was found that the rate of acyl/desacyl ghrelin in obese individuals with insulin resistance was higher than in those with non- insulin resistant obesity (Barazzoni et al., 2007; Rodríguez et al., 2010; St-Pierre et al., 2007). These findings show that different forms of the ghrelin hormone can trigger different effects in maintaining glycemic control.

3.4. Cardiovascular diseases

The prevalence of the ghrelin hormone and receptor in cardiovascular tissues indicates that the cardiovascular system is a target for ghrelin (Zhang et al., 2010). Ghrelin is an important autocrine/paracrine factor of cardiovascular tissues and has various effects such as increased myocardial contractility, vasodilation, and anti-inflammation (Li et al., 2006). Acyl as well as desacil ghrelin may have different effects on the cardiovascular system (Zhang et al., 2010). In a study, it was found that as acyl ghrelin increased in patients with metabolic syndrome, systolic blood pressure increased (Rodríguez et al., 2010).

In the study conducted by Yano et al., (2013) 590 hypertensive patients were monitored for 3 years and 42 of these patients had cardiovascular problems. The study found that individuals with cardiovascular disease have low basal desacil ghrelin levels. As a result, it was emphasized that desacil ghrelin may have protective effects on cardiovascular diseases.

3.5. Reproductive Health

The physiological role of the hormone Ghrelin in regulating gonadotropin secretion is not fully known. However, it appears to be effective on reproductive health. It is known that acyl ghrelin can have a negative effect on the gonadotropic axis (Martini et al., 2006). In a study investigating the effects of desicil ghrelin on gonadotropin secretion, decacyl ghrelin decreased the luteinizing hormone (LH) release similarly as acyl ghrelin and acyl ghrelin increased the follicle stimulating hormone (FSH) (Martini et al., 2006). Studies have shown that ghrelin suppresses the secretion of LH (Fernández-Fernández, Tena-Sempere, Aguilar, & Pinilla, 2004; Furuta, Funabashi, & Kimura, 2001; Iqbal, Kurose, Canny, & Clarke, 2006; Vulliémoz et al., 2004).

In the study carried out by Broglio et al., (2004) 6 women were given placebo, acyl ghrelin, desacil ghrelin or acyl, and desacil ghrelin. As a result, it was found that acyl ghrelin was effective in increasing prolactin, the adrenocorticotropic hormone, and cortisol levels. The effects of desacil ghrelin were similar to that of plesabo. When the findings were evaluated, it was determined that acyl and desacil ghrelin had contradictory results on reproductive health. Also, its mechanism was not fully understood.

3.6. Cancer

It has been reported that acyl and desacyl ghrelin may differ according to cancer types, although the effect on cancer cell proliferation is not yet fully

***Corresponding author:** Emine Elibol
e-mail address: eelibol@ybu.edu.tr

understood (Lin & Hsiao, 2017). In recent years, it has been reported that ghrelin induces cell proliferation in colon cancer through the GHS-R/Ras/PI3K/Akt/mTOR axis (Lien, Lin, Yang, Wu, & Chen, 2016).

In addition, ghrelin has been found to increase cell proliferation in oral cancer through modulation of Glucose transporter 1 (GLUT1) expression (Kraus et al., 2016). In another study, ghrelin in addition to desacil ghrelin were found to inhibit DU-145 prostate carcinoma cell proliferation and have no effect on LNCaP cells (Cassoni et al., 2004). Desacyl ghrelin has been shown to inhibit cell proliferation in H345 lung cancer cells(Cassoni et al., 2006). However, it has been shown to pose the opposite effect in SW-13 and NCI-H295R adrenocortical cancer cells (Delhanty et al., 2007). As a result, acyl and desacil ghrelin are thought to have similar effects on cancer. However, the mechanism is not fully understood (Lin & Hsiao, 2017).

3.7. Other Diseases

Sleep and nutrition have similar pathways in metabolism. Many hypothalamic areas, such as the suprachiasmatic nucleus, the lateral hypothalamus, and the ventromedial hypothalamic nucleus, play a role in regulating both sleep as well as metabolism/nutrient intake. In recent years, preproghrelin gene products have been shown to be effective on nutrition and sleep (Conn, 2012). In a study, it was found that the administration of intravenous ghrelin to rats increases alertness and decreases Non-REM (Tolle et al., 2002).

Bone metabolism is known to play a role in energy metabolism through the integration of the hormones such as leptin and ghrelin. Ghrelin has been shown to modulate osteoblast differentiation and function directly or through growth hormone in addition to insulin-like growth factor. However, in recent years, it has been found that ghrelin plays a role in conjunction with leptin in modulating bone structure (Delhanty, van der Eerden, & van Leeuwen, 2014).

Nowadays, the effects of ghrelin on neurobiological behavior have been looked into. This hormone has been shown to improve mitochondrial function and increase neuronal survival by reducing apoptosis, inflammation, and oxidative stress in cells. In addition, ghrelin stimulates the proliferation and differentiation of neural stem/progenitor cells. Moreover, ghrelin benefits in the restoration of memory, mood, and cognitive dysfunction after a stroke or traumatic brain injury (Jiao et al., 2017).

4. Conclusion

The hormone mostly released from the stomach and containing 28 amino acids has four different forms of hormones (especially acyl and desacyl) in the body. Acyl and desacyl ghrelin have been shown to have different metabolic effects on the body. Acyl ghrelin can increase insulin resistance, obesity, and fatty liver cases. Desaçil ghrelin can reduce insulin resistance, obesity, in addition to fatty liver. Morever, it may play a protective role in cardiovascular diseases. However, the effects of these two hormones on metabolic diseases in the body is not yet fully understood. It is thought that knowing the effects of acyl and desacyl ghrelin on metabolism will play an important role in the treatment of diseases. Therefore, more comprehensive studies are needed to evaluate the effects of acyl and desacil ghrelin on diseases in the

***Corresponding author:** Emine Elibol
e-mail address: eelibol@ybu.edu.tr

future. In particular, human and animal studies should focus on the mechanisms of action of these hormones on appetite. In particular, researchers should focus on the mechanisms of action of acyl and des acyl ghrelin. The datas to be obtained in future studies will play an important role in the treatment of diseases such as non-alcoholic fatty liver, anorexia neurosis and hemodialysis, and will shed light on the literature as an example of future studies.

Conflicts of interest

No conflict of interest was declared by the authors.

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***Corresponding author:** Emine Elibol
e-mail address: eelibol@ybu.edu.tr

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***Corresponding author:** Emine Elibol
e-mail address: eelibol@ybu.edu.tr