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Mini Review Article

New Insight into the Role of Ghrelin and the FTO Gene in Obesity

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The alarming rise in prevalence of obesity, coupled with undesirable health effects and increase in morbidity as a result of co-occurrence of obesity with other diseases, makes it very important to fully investigate the role of gastrointestinal hormones and related factors, such as genetics. Hormones of the gastro-intestinal tract play important roles in the neuro-endocrine regulation of food intake and satiety after meals, therefore representing a significant part of the complicated process involved in the process of energy regulation. Ghrelin is a gut hormone that is produced by cells within the gastric fundus, and is a major regulator of body weight. Impairment in ghrelin secretion may, therefore be relevant in the pathogenesis of obesity. The recently discovered FTO gene is found to affect ghrelin secretion. In conclusion this paper aims to highlight the connection between ghrelin and the FTO gene in obesity. It reviews new findings on the role of ghrelin in obesity, in connection with the polymorphism in the obesity-related gene.

Key words: *Ghrelin, FTO-gene, Obesity*

INTRODUCTION

Gastrointestinal (GIT) hormones play important roles in neuroendocrine regulation of food intake, and postprandial satiety. These hormones constitute a significant part of the complex regulation of energy balance (Lean and Malkova, 2015). Ghrelin, mainly produced in the stomach, is involved in the long- term regulation of body weight, satiety and meal termination (Mishra *et al*., 2016). Obesity, which is widely defined as an imbalance between energy intake and energy expenditure as a result of overnutrition (Lokuruka, 2013) may, therefore, be affected by impairments in ghrelin secretions. In addition, the newly discovered obesity-related gene, called the FTO gene, is also involved in food intake and obesity. A ghrelin-driven shift in the energy balance to positive values could be hypothesized to promote weight gain in those who carry the fat mass and obesity-associated **(**FTO) gene that has been linked to obesity (Benedict *et al*., 2014). There is a global increase in the prevalence of obesity and its associated comorbidities, and because of the impact of these conditions, research efforts have been focused on better understanding of regulation of metabolism, and the possibilities of preventing and/or treating obesity.

The aetiology of obesity is multifactorial, but mainly involves both genetic and environmental factors. Over the years, treatment and management of obesity that are aimed at maintaining clinically- significant weight loss are inadequate. Modulation of satiety perception through changes of GIT hormone secretion could be a primary approach to prevent and/or treat obesity and its complications (Troke *et al*., 2014). Prevalence of obesity has increased dramatically over the years, with an estimated 857 million overweight and obese adults in 1980, and an alarming increase to 2.1 billion overweight and obese adults in the world, in 2013 (Ng *et al*., 2014). This rate has more than doubled in the last three decades with a current world prevalence of obesity alone estimated at 600 million, and overweight as 1.9 billion (Ng *et al*., 2014; Altabas and Zjačić-Rotkvić, 2015; Mishra *et al*., 2016). In fact, in 1997 the World Health Organization (WHO) formally recognized obesity as a global epidemic (Caballero, 2007). In west Africa, obesity rate is estimated to affect 10 % of the population (Abubakari *et al*., 2008), while in Nigeria, overweight and obesity in the general adult population are approximated at 20.3 % - 35.1 % and 8.1 % - 22.2 % respectively (Chukwuonye *et al*., 2013). There is, therefore, a world- wide obesity pandemic, and this may be partially explained as a result of sensory stimulation related to food (that is, hedonic inputs) and overconsumption of palatable, energy-dense meals that have increased markedly in society, whereas basic homeostatic satiety controls have remained stable (Lean and Malcova, 2015). Furthermore, it has been documented that obese subjects have delayed onset of satiety after meal consumption, which might be due to alterations in hormonal responses to food intake (Hellstrom, 2013).

Obesity is associated with a range of comorbid conditions such as metabolic diseases, cardiovascular diseases and the development and progression of several cancers (Chen and Enriori, 2015). It is also associated with increases in premature mortality, impaired quality of life, large healthcare cost, and presents a real burden for the modern human society (Altabas and Zjačić-Rotkvić, 2015). To prevent the development of obesity it is crucial to understand the mechanisms that regulate food intake and energy expenditure.

What is Ghrelin?

Ghrelin is a 28- amino acid peptide that was initially discovered in 1996 by Kojima and colleagues, but reported in 1999 (Kojima *et al*., 1999). Ghrelin is synthesized by the endocrine X/A-like cells of the fundus mucosa, and secreted by the stomach and duodenum The endocrine X/A- like cells

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represent about 20% of gastric mucosal cells in humans (Delporte, 2013). Ghrelin was initially thought to be the natural ligand for the growth hormone secretagogue (GHSR) receptor, however, recent studies have confirmed ghrelin as a hormone (Sato *et al*., 2014). GHSR was discovered before ghrelin. Circulating ghrelin exist in two major forms: more than 90% as desacyl ghrelin, and less than 10% as acyl ghrelin (Delporte, 2013). The acyl group of ghrelin is essential for binding to its receptor, called the growth hormone secretagogue receptor, (GHSR), which is essential for its actions (Verhulst and Depoortere, 2012; Sato *et al*., 2014). Ghrelin serves a key regulatory function in energy homeostasis. It is the first circulating hormone that has been demonstrated to stimulate food intake in man (Kojima *et al*., 1999; Perez- Tilve *et al*., 2011).

Formation of Ghrelin

The human ghrelin gene is found in chromosome 3, and subsequent transcription and translation within the X/A-like oxyntic cells in the gastric fundus, leads to initial formation of preproghrelin. Preproghrelin is then converted to proghrelin, which is subsequently cleaved by the enzyme ghrelin- O-acetyltransferase (GOAT), to become ghrelin (Equation 1). At an unknown stage in its processing, an acyl group is added to ghrelin, to form acyl-ghrelin, which is believed to be the active form that stimulates ghrelin receptors. Acylghrelin constitutes only about 10% of the circulating ghrelin, majority exist as des-acylghrelin. The acylation of ghrelin is required to activate the GHS-R and to mediate its effects on GH secretion and food intake. Majority is produced by the X/A-like cells in the gastric oxyntic mucosa (Date *et al*., 2002; Sakata *et al*., 2002; Cheung and Wu, 2013; Delporte, 2013). The function of des-acylghrelin has not been fully elucidated, although it is thought to also be involved in feeding through a separate mechanism from acylghrelin (Kojima *et al*., 1999; Toshinai *et al*., 2006).

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GOAT

Preproghrelin- ⟶ Proghrelin ⟶ Ghrelin.
X/A-like cells in gastric fundus - Equation (1).

Ghrelin and Food Intake

When food is ingested, the nutrients stimulate release of a variety of hormones from entero-endocrine cells throughout the gut and pancreas. All these hormones have the potential to modulate food intake. GIT hormones result in three major outcomes:

i. Meal termination
ii. Inhibition of subsequent meal intake
iii. Orexigenic modulation

Ghrelin participates in regulating the complex process of energy homeostasis, which involves both energy input (by adjusting hunger signals), and energy output (by adjusting the proportion of energy that will go to adenosine triphosphate, ATP, production, fat storage, glycogen storage, and short-term heat loss) (O'Connor *et al*., 2016). The arcuate nucleus in the hypothalamus appears to be the main site of action of ghrelin on food intake; ghrelin administration into other hypothalamic sites (including the paraventricular nucleus and lateral hypothalamus), and non-hypothalamic sites (such as the hindbrain) also promote positive energy balance (Nogueiras *et al*., 2010). The physiological mechanisms that are concerned with regulation of food intake are complex; when food is ingested, gastric distensions and nutrients stimulate release of a variety of hormones from entero-endocrine cells throughout the gut and pancreas. These hormones act through the central nervous system (CNS) to regulate energy; a key region in the CNS that is involved in the regulation of appetite is the hypothalamus (Bewick, 2012). Ghrelin induces food intake by stimulating neural pathways in the CNS, including hypothalamus and the hindbrain, mainly through the gut- brain axis, which plays a major role in the regulation of food intake (Perez-Tilve *et al*., 2011; Lean and Malkova, 2015). This is illustrated in the diagram below (Figure 1).

Meal ingestion results in gastric distension and production of peptide hormones by enteroendocrine cells, both of which can promote a feeling of satiety, and a desire to stop eating (Lean and Malkova, 2015). Peptides that are released from multiple sites in the gut in response to ingested food, and the arcuate nucleus is involved in the immediate need for food intake (Konturek *et al*., 2004). The arcuate nucleus coordinates the homeostatic process concerned with food intake, groups of gut hormone receptors that are contained within the arcuate nucleus are responsible for mediation of this action of appetite regulation. These neurons are;

i. The pro-opiomelanocortin (POMC) appetite-inhibiting neurones.
ii. Neuropeptide-Y (NPY) and agouti-related peptide (AgRP) appetite-stimulating neurons.

NPY and AgRP modulate melanocortin receptor to stimulate food intake. Signals from the periphery results in changes in the relative activity of these neuronal populations and the release of their respective neuropeptides, which subsequently influence feeding behaviour and energy expenditure (Perry and Wang, 2012). Ghrelin stimulates the arcuate nucleus to release NPY and AgRP, which act through the paraventricular nucleus, causing a decrease in the membrane excitability of POMC neurones that secrete melanocortin receptor agonist (the α-melanocyte-stimulating hormone, MSH-α). MSH-α suppress food intake, therefore, decreasing membrane excitability of neurones that cause its release, will enhance an increase in food intake (Perez-Tilve *et al*., 2011).

Ghrelin is the only known circulating factor that potently increase food intake (Perez- Tilve *et al*., 2011). The arcuate nucleus in the hypothalamus appears to be the main site of action of ghrelin on food intake; ghrelin administration into other hypothalamic sites (including the paraventricular and lateral hypothalamus) and non-hypothalamic sites such as the hindbrain also promote positive energy balance (Nogueiras *et al*., 2010). The gut-brain axis is the physiological driver of satiation in humans, its continuing role in regulation of food intake and maintenance of body weight is supported by a body of evidence (Lean and Malkova, 2015). For example, mice that lack both NPY and AgRP do not increase their food intake when administered with ghrelin. Likewise, ghrelin does not stimulate food intake in mice that lack melanocortin receptors, therefore, NPY and AgRP are mediators of the orexigenic

effect of circulating ghrelin via inhibition of melanocortin signaling (Perez- Tilve et al., 2011).

The fat mass and obesity-associated (FTO) Gene

The FTO protein is a known alpha-ketoglutarate- dependent dioxygenase. FTO is an enzyme that in humans, is encoded by the FTO gene. It is located on chromosome 16. Certain variants of the FTO gene appear to be associated with obesity in humans (Loos and Yeo, 2014). The risk allele is a cluster of ten single nucleotide polymorphisms (SNP) in the first intron of the FTO gene, coded by rs9939609 (Chu *et al*., 2008). Polymorphisms within the FTO gene are associated with increased body mass index (BMI) and adiposity across different ages and populations (Karra *et al*., 2013). The FTO obesity-risk variant gene has a population frequency of the following:

- 45 % in west/central Europeans
- 52 % in Yoruba's (West-African natives)
- 14 % in Chinese/Japanese.

Accumulated data across several independent studies implicates the FTO gene in humans as having a direct impact on food intake. It has been suggested to play a key role in regulating energy homeostasis, since it is highly expressed in brain regions that control feeding and energy expenditure, such as the hypothalamus. Despite these, the exact physiological function of the FTO gene is not known, however, studies in mice and humans indicate a role in nervous and cardiovascular systems, and also a strong association with BMI, obesity risk, and type-2-diabetes mellitus (Karra *et al*., 2013; Claussinitzer *et al*., 2015).

Previous studies have revealed that a single-letter variation in the genetic code for the FTO gene is linked with an increased risk of obesity. A unique design was used to study healthy male volunteers to examine the 'real- life' effects of the FTO variation in humans. Men with obesity- risk (FTO) gene were matched for bodyweight, fat distribution, and social factors. Levels of ghrelin tested in their blood show that men with high-risk FTO gene variation had higher and felt hungrier after meal than men with low-risk variant of the gene (Batterham *et al*., 2013). This suggests an impairment of ghrelin suppression (which normally occurs after meals) in the group with the FTO high-risk gene variant. The FTO gene is found to enhance ghrelin levels in humans (Benedict *et al*., 2014). A ghrelin-driven shift in the energy balance to positive values is hypothesized to promote weight gain in those who carry the FTO obesity-risk rs9939609 A allele (Chey *et al*., 2013). Furthermore, recent studies show that people with high-risk (FTO) gene have a higher level of the hunger hormone, ghrelin, in their blood after meals (Benedict *et al*., 2014). This means that they start to feel hungry again soon after eating a meal. Real-time brain imaging reveals that the FTO gene variation changes the way the brain responds to ghrelin, and to images of food, in the regions that are linked with the control of eating and reward (Batterham *et al*., 2013).

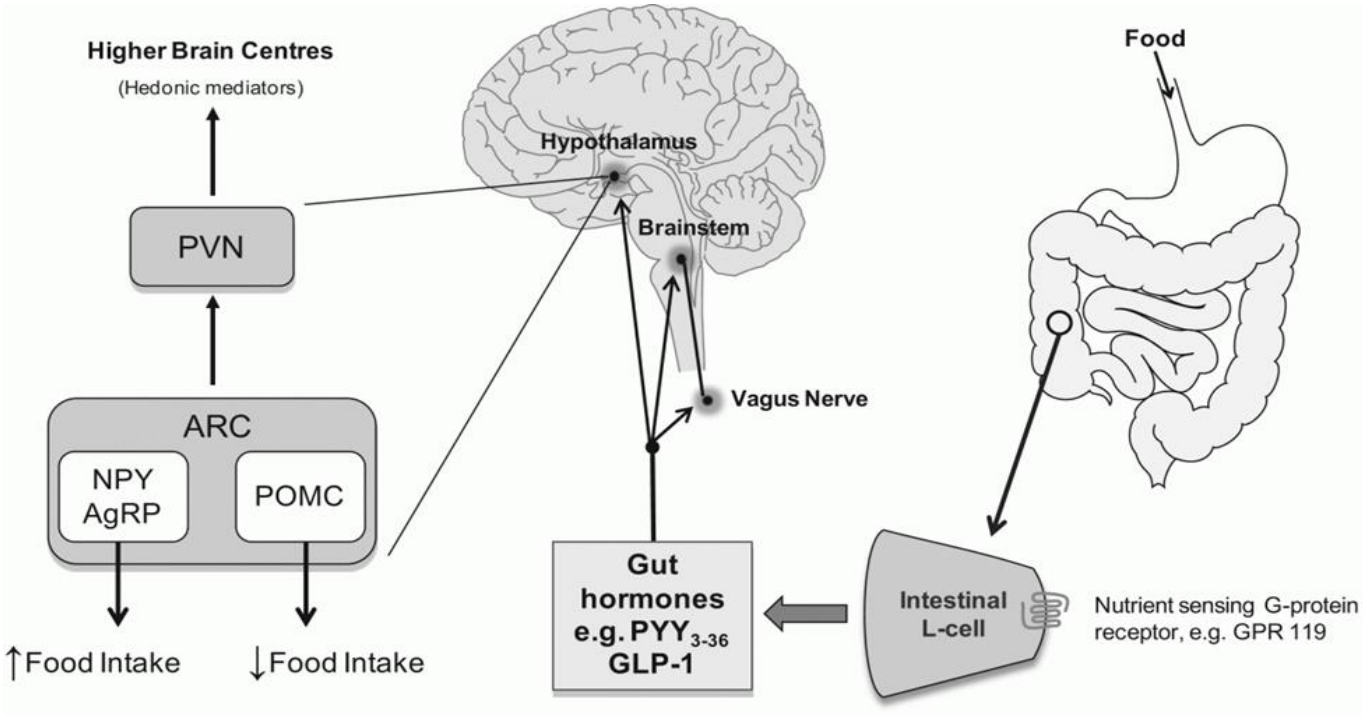

Figure 1: Gut-brain axis regulation of food intake.
PVN- paraventricular nucleus ; PYY- petide YY; ARC- arcuate nucleus GLP- glucagon-like peptide;
NYP- neuropeptide Y; AgRP- agouti-related peptide; POMC- pro-opiomelanocortin nucleus

A proposed mechanism for enhanced ghrelin levels is explained as follows:

In the obesity-associated single nucleotide polymorphism, cytosine is substituted for thymine, and this is involved in the expression of IRX3 and IRX5

genes in human brain. Enhanced expression of IRX3 and IRX5 genes that result from this single nucleotide alteration promotes a shift from energy-dissipating brown adipocytes to energy-storing white adipocytes, and a subsequent reduction in mitochondrial thermogenesis (Smemo *et al*., 2014).

The FTO protein now alters the ghrelin gene by causing methyl chemical groups to be removed, (a so- called epigenetic modification). Removal of the methyl groups has an impact on how many proteins the ghrelin gene produces. The high obesity- risk variant removes more methyl groups from the gene, and this leads to increased levels of the hunger hormone after meals (Benedict *et al*., 2014). In other words, when FTO gene is overexpressed, there is reduced ghrelin mRNA N6-methyladenosine methylation, with a concomitant increase in ghrelin mRNA and peptide levels (Benedict *et al*., 2014).

How is Ghrelin involved in the Pathophysiology of Obesity?

It is a documented fact that ghrelin stimulates food intake, and also aids in sensing the palatability of food. High ghrelin in circulation means more food ingestion, blocking the action of ghrelin can just be an effective treatment for obesity. However, just like so many things in biology and science, it is much more complex than it seems.

If ghrelin stimulates hunger, then why can't a ghrelin antagonist be an effective therapy for obesity? Research is currently underway in developing an anti-ghrelin kind of drug that can be the answer to the menace of obesity. In fact, the Scripps Research Institute in California in 2006 successfully developed an anti-obesity ghrelin vaccine, which is able to slow weight gain and reduce body fat in animals. In addition, ghrelin sensitivity has been found to be more pronounced in obese individuals than in normal weight people, thereby targeting inhibition of circulating ghrelin as a useful therapeutic means of treating obesity (Hepper and Tong, 2014).

In addition, people who lose weight by dieting usually find it difficult to maintain a healthy weight; there seem to be a rebound weight gain afterwards. This may be explained as a result of obesity possibly affecting hypothalamic circuits that regulate appetite and this impact a rebound weight gain after weight loss, this phenomenon is especially seen in diet- induced obesity (Karra *et al*., 2013). Therefore, antagonism of the ghrelin system immediately after diet-induced weight loss may provide protection from rebound weight gain that is usually seen in people who lose weight by dieting. However, inhibition of the ghrelin system by pharmacological antagonism of ghrelin O-acyltransferase, an acyl-ghrelin–specific neutralizing antibody, GHSR antagonism, or ghrelin vaccination to reduce acute weight gain, may also induce negative side effects on numerous ghrelin-regulated behaviors, such as neuroprotection, learning, memory, and motivation (Chen and Enriori, 2015).

Over the past thirty years, GIT hormones have been increasingly understood to play an important role as a regulator of appetite and energy balance in obese individuals (Troke *et al*., 2014), it is now partially clear that gut hormones play a role in the regulation of body weight. Ghrelin, as the 'hunger' hormone, fits with the notion of homeostatic control of body weight; high circulating ghrelin in lean individuals favors increased food intake and positive energy balance. Weight loss, however, in obese people, result in an elevation of ghrelin level, which may contribute to the difficulty in maintaining ideal weight after weight loss. Ghrelin sensitivity has also been found to be more pronounced in obese individuals than in normal weight people, thereby targeting the inhibition of circulating ghrelin as a useful therapeutic means of treating obesity. Nonetheless, the mechanism is still unclear (Patterson *et al*., 2011; Hepper and Tong, 2014).

Some studies have revealed a total lack of postprandial ghrelin suppression in obesity (Hellstrom, 2013) other studies have found normal or incomplete postprandial ghrelin suppression in the obese (Uchida *et al*., 2014). The reduced ghrelin response or its complete insensitivity to meal- induced suppression may contribute to the inability to lose weight in some obese patients (Engstrom *et al*., 2007). Gherlin secretion follows a circadian rhythm, it rises from midnight to dawn in thinner people. This suggests a possible flaw in the circadian rhythm of obese people (Yildiz *et al*., 2004; Fonken *et al*., 2014). Previous studies have shown that ghrelin is increased by lack of sleep, while the same situation of lack of sleep causes a decrease in leptin, which is the satiety hormone that signals a person to stop eating. Therefore, short sleep duration may also lead to obesity through an increase in appetite via hormonal changes. The rise in ghrelin level and fall in leptin which occurs due to lack of sleep has a resultant effect of producing hunger, and probably obesity (Cappuccio *et al*., 2008).

Decrease in ghrelin level occurs after obesity surgery. This is proposed to be involved in the mechanisms that induce sustained weight loss in bariatric surgery when compared with diet- induced weight loss. The surgery procedures reduce weight at least in part, by suppressing ghrelin production and its appetite stimulating effects. However, the mechanism by which gastric bypass leads to a reduction in ghrelin levels is still not fully understood, although it has been suggested that a permanent absence of food in the stomach which results from gastric bypass could cause a continuous stimulatory signal that ultimately suppresses ghrelin production through a process of overriding inhibition (Cummings *et al*., 2004). In sleeve gastrectomy, ghrelin levels are greatly suppressed probably due to resection of the gastric fundus, which

is the most important site of ghrelin production in humans (Nwokolo, 2013).

Concluding Remark

- High circulating ghrelin in lean individuals favors increased food intake and positive energy balance.
- Impairement of ghrelin secretion may contribute to the difficulty in maintaining ideal weight after weight loss.
- High-risk variant of FTO gene, whose exact physiological role is not known, may be the cause of an impairment of ghrelin secretion, which contributes to obesity.

There is a possibility of modification of ghrelin as a therapeutic agent in obesity

REFERENCES

Abubakari, A.R. and Bhopal, R.S. (2008). Systematic review on the prevalence of diabetes, overweight/obesity and physical inactivity in Ghanaians and Nigerians. *Public Health*; 122(2): 173–182.

Altabas, V. and Zjačić-Rotkvić, V. (2015). Anti-ghrelin antibodies in appetite suppression: recent advances in obesity pharmacotherapy. *Immuno Targets and Therapy*, 4: 123- 130.

Batterham, R. L., Magi, R., Manning, S., Yousseif, A., Pucci, A., Santini, F., Karra, E., Querci, G., Pelosini, C., McCarthy, M. I., and Lindgren, C. M. (2013). Contribution of 32 GWAS-Identified Common Variants to Severe Obesity in European Adults Referred for Bariatric Surgery. *PLoS One*, 8(8): e70735.

Benedict, C., Axelsson, T., Söderberg, S., Larsson, A., Ingelsson, E., Lind, L. and Schiöth, H. B. (2014). Fat mass and obesity-associated gene (FTO) is linked to higher plasma levels of the hunger hormone ghrelin and lower serum levels of the satiety hormone leptin in older adults. *Diabetes*, 63(11): 3955-3959.

Bewick, G. A. (2012). Bowels control brain: gut hormones and obesity.*Biochemia medica*, *22*(3), 283-297.

Caballero, B. (2007). The global epidemic of obesity: an overview. *Epidemiology Reviews*, 29: 1-5.

Cappuccio, F. P., Taggart, F. M., Kandala, N. B., Currie, A., Peile, E., Stranges, S., and Miller, M. A. (2008). Meta-analysis of Short Sleep duration and Obesity in Children and Adults. *Sleep*, 31(5): 619–26.

Chen, W., and Enriori, P. J. (2015). Ghrelin: a journey from GH secretagogue to regulator of metabolism. *Translational Gastrointestinal Cancer*, 4(1).

Cheung, C. K., and Wu, J. C. (2013). Role of Ghrelin in the Pathophysiology of Gastrointestinal Disease. *Gut Liver*, 7(5): 505–512.

Chey, W., Fan, S. and Say, Y. (2013). Association of fat mass and obesity-associated (FTO) gene rs9939609 variant with obesity among multi-ethnic Malaysians in Kampar, Perak. *Sains Malaysiana*, 42(3); 365–371.

Chu, X., Erdman, R., Susek, M., Gerst, H., Derr, K., Al-Agha, M., Wood, G. C., Hartman, C., Yeager, S., Blosky, M. A., Krum, W., Stewart, W. F., Carey, D., Benotti, P., Still, C. D., Gerhard, G. S. (2008). Association of morbid Obesity with FTO and INSIG2 allelic variants. *Archives of Surgery*, 143(3): 235–40.

Chukwuonye, I.I., Chuku, A., Onyeonoro, U. U., Okpechi, I. G., Madukwe, O. O., Umeizudike, T. I., and Ogah, O. S. (2013). Prevalence of abdominal obesity in Abia state, Nigeria: results of a population-based house-to-house survey. Diabetes, Metabolic Syndrome and Obesity: *Targets and Therapy*, 6: 285-291.

Claussnitzer, M., Dankel, S. N., Kim, K. H., Quon, G., Meuleman, W., Haugen, C., Glunk, V., Sousa, I. S., Beaudry, J. L., Puviindran, V., Abdennur, N. A., Liu, J., Svensson, P. A., Hsu, Y. H., Drucker, D. J., Mellgren, G., Hui, C. C., Hauner, H., and Kellis, M. (2015). FTO Obesity Variant Circuitry and Adipocyte Browning in Humans. *New England Journal of Medicine*, 373(10): 895-907.

Cummings, D. E., Frayo, R. S., Marmonier, C., Aubert, R., and Chapelot, D. (2004). Plasma ghrelin levels and hunger scores in humans initiating meals voluntarily without time- and food-related cues. *American Journal of Physiology Endocrinology and Metabolism*, 287(2): E297–304.

Date, Y., Murakami, N., Toshinai, K., Matsukura, S., Niijima, A., Matsuo, H., Kangawa, K., and Nakazato, M. (2002). The role of the gastric afferent vagal nerve in ghrelin-induced feeding and growth hormone secretion in rats. *Gastroenterology*, 123; 1120–1128.

Delporte, C. (2013). Structure and Physiological Actions of Ghrelin. *Scientifica*, Article ID 518909, 25 pages.

Engstrom, B.E., Ohrvall, M., Sundbom, M., Lind, L. and Karlsson, F.A. (2007). Meal suppression of circulating ghrelin is normalized in obese individuals following gastric bypass surgery. *Inernational Journal of Obesity*, 31, 476-80. Fonken, L. K., and Nelson, R. J. (2014). The Effects of light at night on Circadian clocks and Metabolism. *Endocrine Reviews*, 35(4): 648–70.

Fonken, L. K., and Nelson, R. J. (2014). The Effects of light at night on Circadian clocks and Metabolism. *Endocrine Reviews*, 35(4): 648–70.

Hellstrom, P.M. (2013). Satiety signals and obesity. *Current Opinions in Gastroenterology*, 29(2): 222-7.

Heppner, K. M., and Tong, J. (2014). Mechanisms in endocrinology: regulation of glucose metabolism by the ghrelin system: multiple players and multiple actions. *European Journal of Endocrinology / European Federation of Endocrine Societies*, 171(1): R21–32.

Karra, E., O'Daly, O. G., Choudhury, A. I., Yousseif, A., Millership, S., Neary, M. T., Scott, W. R., Chandarana, K., Manning, S., Hess, M. E., Iwakura, H., Akamizu, T., Millet, Q., Gelegen, C., Drew, M. E., Rahman, S., Emmanuel, J. J., Williams, S. C., Rüther, U. U., Brüning, J. C., Withers, D. J., Zelaya, F. O., Batterham, R. L. (2013). *Journal of Clinical Investigations*, 123(8): 3539-51.

Kojima, M., Hosoda, H., Date, Y., Nakazato, M., Matsuo, H., and Kangawa, K. (1999). Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature*, 402(6762): 656–60.

Konturek, P.C., Brzozowski, T., Pajdo, R., Nikiforuk, A., Kwiecien, S.,Harsch, I., Drozdowicz, D., Hahn, E. G., and Konturek, S. J. (2004). Ghrelin - A New Gastroprotective Factor in Gastric Mucosa. *Journal Of Physiology and Pharmacology*, 55(2); 325-–336.

Lean, M. E. J. and Malkova, D. (2015). Altered gut and adipose tissue hormones in overweight and obese individuals: cause or consequence? *International Journal*

of Obesity, advance online publication 1 December 2015; doi: 10.1038/ijo.2015.220.

Lokuruka, M. N. I. (2013). A literature review of role of obesity in adult health with reference to Africa. *African Journal of Food, Agriculture, Nutrition and Development*, 13(1).

Loos, R. J. and Yeo, G. S. (2014). The bigger picture of FTO: the first GWAS-identified obesity gene. *Nature Reviews Endocrinology*, 10(1): 51–61.

Mishra, A. K., Dubey, V. and Ghosh, A. R. (2016). Obesity: an overview of possible role(s) of gut hormones, lipid sensing and gut microbiota. *Metabolism*, 65(1): 48-65.

Ng, M., Fleming, T., Robinson, M., Thomson, B., Graetz, N., Margono, C., Mullany, E.C. *et. al.* (2014). Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the global burden of disease study 2013. *Lancet*, 384(9945): 766-781.

Nogueirasa, R., Williams, L. M., and Dieguez, C. (2010). Ghrelin: New Molecular Pathways Modulating Appetite and Adiposity. *Obesity Facts*, 3: 285- 292.

Nwokolo, C.U., Freshwater, D.A., O'Hare, P. and Randeva, H.S. (2003). Plasma ghrelin following cure of Helicobacter pylori. Gut, 52(5): 637–640.

O'Connor, K. L., Scisco, J. L., Smith, T. J., Young, A. J., Montain, S. J., Price, L. L., Lieberman, H. R., and Karl, J. P. (2016). Altered Appetite-Mediating Hormone Concentrations Precede Compensatory Overeating After Severe, Short-Term Energy Deprivation in Healthy Adults. *Journal of Nutrition*, pii: jn217976. [Epub ahead of print].

Patterson M, Bloom S. R, Gardiner J. V. (2011). Ghrelin and appetite control in humans--potential application in the treatment of obesity. *Peptides*, 32(11): 2290-4.

Perez-Tilve, D., Heppner, K., Kirchner, H., Lockie, S. H., Woods, S.C., Smiley, D. L., Tschöp, M., and Pfluger, P. (2011). Ghrelin-induced adiposity is independent of orexigenic effects. *Journal of the Federation of American Societies for Experimental Biology*, 25(8): 2814- 2822.

Perry, B., and Wang, Y. (2012). Appetite regulation and weight control: the role of gut hormones. *Nutrition and Diabetes*, **2**(e26).

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

Sato, T., Ida, T., Nakamura, Y., Shiimura, Y., Kangawa, K., and Kojima, M. (2014). Physiological roles of ghrelin on obesity. *Obesity Research in Clinical Practice*, 8(5): e405-13.

Smemo,S., Tena, J.J., Kim, K.H., Gamazon, E.R., Sakabe, N.J., Gómez-Marín, C., Aneas, I., Credidio, F.L., Sobreira, D.R., Wasserman, N.F., Lee, J.H., Puviindran, V., Tam, D., Shen, M., Son, J.E., Vakili, N.A., Sung, H.K., Naranjo, S., Acemel, R.D., Manzanares, M., Nagy, A., Cox, N.J., Hui, C.C., Gomez-Skarmeta, J.L. and Nóbrega, M.A. (2014). Obesity-associated variants within FTO form long-range

functional connections with IRX3. *Nature*, 507(7492): 371–375.

Toshinai, K., Yamaguchi, H., Sun, Y., Smith, R. G., Yamanaka, A., Sakurai, T., Date, Y., Mondal, M. S., Shimbara, T., Kawagoe, T., Murakami, N., Miyazato,

M.,Kangawa, K., and Nakazato, M. (2006). Des-acyl ghrelin induces food intake by a mechanism independent of the growth hormone secretagogue receptor. *Endocrinology*, 147(5): 2306–14.

Troke, R. C., Tan, T. M. and Bloom, S. R. (2014). The

future role of gut hormones in the treatment of obesity. *Therapeutic Advances in Chronic Diseases*, 5(1): 4–14.

Uchida, A., Zechner, J. F., Mani, B. K., Park, W., Aguirre, V., and Zigman, J. M. (2014). Altered ghrelin secretion in

mice in response to diet-induced obesity and Roux-en-Y gastric bypass. *Molecular Metabolism*, 3(7): 717–730.

Verhulst, P., and Depoortere, I. (2012). Ghrelin's second life: From appetite stimulator to glucose regulator. *World Journal of Gastroenterology*, 18(25): 3183–3195.

Yildiz, B. O., Suchard, M. A., Wong, M. L., McCann, S. M., Licinio, J. (2004). Alterations in the dynamics of circulating Ghrelin, Adiponectin, and Leptin in Human Obesity. *Proceedings of the National Academy of Sciences of the United States of America*, 101(28): 104