Physiological mechanisms in the aetiology and maintenance of obesity

UNDURTI N. DAS
UND Life Sciences
13800 Fairhill Road, #321
Shaker Heights, OH 44120, USA

ABSTRACT: Increase in the incidence of obesity and type 2 diabetes mellitus has been attributed to genetic and hypothalamic factors, an increase in the consumption of energy dense food and intestinal microbiota, and lack or decrease in exercise. Obesity and type 2 diabetes mellitus are associated with hypertension, coronary heart disease, and certain forms of cancer. Though consumption of calorie dense diet and lack of adequate exercise are responsible for the initiation of obesity and subsequent development of type 2 diabetes mellitus, it is equally likely that failure of homeostatic mechanisms that regulate appetite, food consumption and energy balance regulated by hypothalamic factors and gut bacteria also play a critical role in the onset of these conditions. Hence, management of obesity and type 2 diabetes mellitus need a comprehensive and multipronged approach.

INTRODUCTION

Lack of exercise and increased consumption of calorie dense food and the resulting positive energy balance is responsible for overweight and obesity and the epidemic of obesity seen. The energy balance is very tightly controlled by hypothalamic factors. Hence, the cross talk between gut hormones and hypothalamic factors is important in the regulation of food intake, energy balance and development of obesity. Since a major portion of digestion and assimilation of digested food occurs in the small intestine, it is likely that bacteria present in the gut could impact energy balance and obesity. Furthermore, genetics may predispose some to develop obesity that could be influenced by environmental factors and hypothalamic dysfunction. Obesity precedes the occurrence of type 2 diabetes mellitus. Hence, both obesity and type 2 diabetes mellitus need to be considered together especially with regard to their aetiology and management.

DEFINITION OF OBESITY

Obesity is an excess of body fat and it occurs when the size or number of fat cells in a person's body increases. For adults, overweight and obesity ranges are determined by using weight and height to calculate a number called the "body mass index" (BMI). BMI is used because, for most people, it correlates with their amount of body fat (BMI = Weight (kg) / Height x Height (in meters)).

- An adult who has a BMI between 25 and 29.9 is considered overweight.
- An adult who has a BMI of 30 or higher is considered obese.

For children and teens, BMI ranges above a normal weight have different labels (at risk of overweight and overweight). Additionally, while defining BMI ranges for children and teens should take into account normal differences in body fat between boys and girls and differences in body fat at various ages.

BMI is just one indicator of potential health risks associated with being overweight or obese. The National Heart, Lung, and Blood Institute guidelines recommend looking at two other predictors:

- The individual's waist circumference (because abdominal fat is a predictor of risk for obesity-related diseases).
- Other risk factors the individual has for diseases and conditions associated with obesity (for example, high blood pressure or physical inactivity).

INCIDENCE OF OBESITY

It is estimated that globally, there are more than 1 billion overweight adults, at least 300 million of them obese. Obesity and overweight pose a major risk for other chronic diseases such as type 2 diabetes, coronary heart disease, hypertension and stroke, and certain forms of cancer. While genes are important in determining a person's susceptibility to weight gain, energy balance is determined by calorie intake and physical activity. Thus societal changes such as economic growth, modernization, urbanization and globalization of food markets are some of the forces that underlie the epidemic. It is interesting to note that children from homes with poor dietary habits, lack of exercise and leisurely lifestyle are much more likely to be overweight or obese when they're adolescents. Children are more likely to become overweight adolescents if their parents are obese (1, 2).

Growth of fast food industry enhanced the incidence of obesity

Increase in the incidence of obesity has been related to the growth of fast-food industry (Figure 1). Several studies showed that fast-food consumption has strong positive associations with weight gain and insulin...
resistance, suggesting that fast food increases the risk of obesity and type 2 diabetes (3-5).

**Obesity increases morbidity and mortality**

Obesity is the second leading cause of preventable death, exceeded only by cigarette smoking (6) and is a major risk factor not only for hypertension, cardiovascular disease, type 2 diabetes mellitus and some cancers in both men and women but also lead to sleep apnea, osteoarthritis, infertility, idiopathic intracranial hypertension, lower extremity venous stasis disease, gastro-esophageal reflux and urinary stress incontinence.

It is estimated that the number of annual deaths attributable to obesity among US adults is approximately 280,000 (7). One-third of all cases of high blood pressure are associated with obesity, and obese individuals are 50 percent more likely to have elevated blood cholesterol levels (8). About 88 to 97 percent of type 2 diabetes cases diagnosed in overweight people are a direct result of obesity. Overweight and obesity also increases the risk of coronary heart disease (9-11).

**CAUSES OF OBESITY**

Development of obesity depends on several genetic and non-genetic factors. They include:

- Resting metabolic rate
- Themic response to food
- Nutrient partitioning
- Energy expenditure associated with physical activity
- Gene knockout and transgenic animals-detail genes involved in obesity
- Exercise
- Hypothalamic factors

There could be individual variations in the factors mentioned above that either predispose he/she to develop obesity. It was reported that there was a significant difference with respect to total energy expenditure (TEE), TEE/BMR (basal metabolic rate), and TEE-BMR divided by weight and TEE-BMR between normal athletes, Pima Indians, people in developing countries and others. Multiple regression analysis showed that fat-free mass and age are the significant variables that can explain 65 percent of the variation in TEE, suggesting that TEE varies dramatically among healthy, free living adults (12). A low rate of non-basal energy expenditure is a permissible factor for obesity. Examination of variation in TEE to variation in uncoupling protein (UCP) led to the observation that TEE was 295 kJ/day lower in African women than in the white women. It was noted that UCP3 exon 5 variant was significantly lower in African American women with the CC genotype than in those with the TT genotype (13). These results coupled with the finding that the exon 8 ins/del polymorphism of UCP2 and UCP2/UCP3 genetic locus are associated with childhood-onset obesity in African American, white, and Asian children (14) supports the concept that genetic markers and energy expenditure influence susceptibility to develop obesity.

In addition, several genes could be either upregulated or down regulated in subjects with obesity (15). Some of the upregulated genes include: vascular endothelial growth factor, fibroblast growth factor, low density lipoprotein receptor, adrenergic beta receptor kinase, glycogen synthase kinase 3 alpha, neuropeptide Y receptor Y1 and Y5 and mitogen activated protein kinases. Genes that are down regulated in obese subjects include: c-fos-induced growth factor, prostaglandin E receptor, insulin receptor substrate 4, natriuretic peptide receptor 4, and adrenergic beta-2 receptor, genes that are involved in the regulation cell growth (c-fos), inflammation (prostaglandin E) and regulation sympathetic nervous system (adrenergic receptor). Thus, altered expression of genes could render a subject to develop obesity by conserving energy.

Fetal nutrition influences the developing neuroendocrine hypothalamus, the integrative control centre for postnatal energy balance regulation (16). Key central components of adult energy balance regulation are present in early gestation, and anorexigenic components were upregulated by elevated glycemia (17) that provides a potential mechanism for the prenatal origins of postnatal energy balance dysregulation and obesity. Thus, prenatal programming of obesity could occur.

**OBESITY AND TYPE 2 DIABETES MELLITUS AS DISORDERS OF THE BRAIN**

In experimental animals, ventromedial hypothalamic (VMH) lesion induces hyperphagia and excessive weight gain, fasting hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and impaired glucose tolerance. Intraventricular administration of antibodies to neuropeptide Y (NPY) abolished hyperphagia in these animals. Streptozotocin-induced diabetic animals showed increase in NPY concentrations in paraventricular, VMH and lateral hypothalamic areas. VMH-lesioned rats showed selectively decreased concentrations of norepinephrine and dopamine in the hypothalamus; whereas long-term infusion of norepinephrine and serotonin into the VMH impaired pancreatic islet cell function. These changes in the hypothalamic neurotransmitters reverted to normal after insulin therapy. This suggests that dysfunction of VMH impairs pancreatic β-cell function and induces metabolic abnormalities that are seen in obesity and type 2 diabetes mellitus (18).

The tone of the parasympathetic nervous system increases after VMH lesion, whereas the sympathetic tone decreases (19). This causes decreased lipolysis that hence obesity. In contrast, radical vagotomies blocked the development of obesity in VMH-lesioned animals. Thus, vagus nerve serves as the neuronal pathway from the hypothalamus to the visceral...
fat and the pancreatic β cells to communicate the messages from VMH that could disturb metabolism leading to obesity in the VMH-lesioned animals (20).

**LIVER-BRAIN CROSS-TALK OCCURS THROUGH THE VAGUS NERVE**

Vagus nerve is also the neuronal pathway in the cross-talk between liver and adipose tissue. In mouse adenovirus-mediated expression of peroxisome proliferative-activated receptor (PPAR)-γ2 in the liver induced acute hepatic steatosis while markedly decreasing peripheral adiposity that is accompanied by increased energy expenditure and improved systemic insulin sensitivity. These animals not only showed increased hepatic PPAR-γ2 expression but also had decreased fasting plasma glucose, insulin, leptin and tumour necrosis factor-α levels indicating markedly improved insulin sensitivity. These animals had decreased glucose output from the liver and showed high tonus of the sympathetic nervous system that could be blocked by resection of the hepatic branch of the vagus nerve (21). Thus, a neuronal pathway consisting of the afferent vagus from the liver and efferent sympathetic nerves to adipose tissues is involved in the regulation of energy expenditure, systemic insulin sensitivity, glucose metabolism and fat distribution between the liver and the peripheral adipose tissues. Liver conveys information regarding energy balance to the VMH neurons of the hypothalamus via the afferent vagus whereas leptin could be the humoral signal to the brain from the adipocytes.

Vagus also conveys messages between liver and pancreatic β cells

Obesity-induced insulin resistance and consequent hyperinsulinemia is initially as a result of pancreatic β cell hyperplasia. Efferent vagal signals to the pancreas modulate insulin secretion and pancreatic β cell mass (22). VMH-lesioned animals not only showed obesity and features of type 2 diabetes mellitus but also had increase in pancreatic weight that was completely inhibited by vagotomy suggesting that vagal hyperactivity produced by VMH lesions stimulated cell proliferation of rat pancreatic β and acinar cells primarily through a cholinergic receptor mechanism (23). This indicates that vagal nerves innervating pancreas are involved in insulin hypersecretion and pancreatic β cell proliferation. Afferent splanchnic and efferent pancreatic vagal nerves play a major role in pancreatic β cell expansion during diet-induced obesity development, in ob/ob and streptozotocin-induced diabetic mice (24).

**THE GUT-BRAIN-LIVER AXIS**

Long-chain fatty acids (such as oleic acid, 18:1 ω-9; linoleic acid, 18:2 ω-6; α-linolenic acid, 18:3 ω-3; arachidonic acid, 20:4 ω-6; eicosapentaenoic acid, 20:5 ω-3; and docosahexaenoic acid, 22:6 ω-3) that are cleaved from triglycerides by the gastrointestinal enzymes when given at calorically insignificant amounts markedly and rapidly increased insulin sensitivity (25). These studies revealed that long-chain fatty acid metabolite called LCFA-CoA (long-chain fatty acid-coenzyme A) is sensed by the intestine that is relayed to the liver such that blood glucose levels are least perturbed due to enhanced secretion of insulin from the pancreatic β cells by the release of incretins and to some extent by the inhibition of gluconeogenesis in the liver. The LCFA-CoA sensed by the gut signals the brain through the vagus nerve, through the hindbrain, and then back down the vagal efferent pathway that terminates in the liver (Figure 2). Intraduodenal perfusion of long chain fatty acids but not medium chain fatty acids reduced calorie intake that could be abolished by inhibition of fat hydrolysis. LCFA perfusion not only resulted in a reduction in calorie intake and food consumption but also a concomitant increase in plasma cholecystokinin (CCK) concentrations. Thus, LCFAs in the duodenum stimulated the release of CCK; CCK then acts on CCK-A receptors present on the abdominal vagus. Another possibility is that leptin present in the gastric fundus (26) is released after food ingestion, an effect that is reproduced by CCK administration. Leptin enhances the satiety inducing effect of CCK suggesting that CCK and leptin could work together to induce satiety and regulate food intake (27). These findings indicate that gut functions as a neuroendocrine organ, produces satiety factors-leptin, CCK and incretins that enhance insulin secretion from pancreatic β cells and sends messages to the brain via the intestine-vagus pathway to modulate the secretion and actions of various hypothalamic neurotransmitters and peptides (28) that ultimately regulate plasma glucose levels. Furthermore, LCFA-CoA molecule in the hypothalamus activates neural pathways that increase insulin sensitivity in the liver that also reduces food intake (29). In contrast, saturated fats and energy-dense foods impair this nutrient-sensing system. Our recent studies revealed that PUFAs can protect pancreatic β cells from chemical-induced apoptosis and thus, prevent the development of diabetes mellitus (30). These PUFAs (LCFAs) also form precursors to various endocannabinoids that have been shown to play a role in the pathobiology of obesity and diabetes mellitus (31). Furthermore, PUFAs are anti-inflammatory whereas saturated fats are pro-inflammatory in nature that could account for low-grade systemic inflammation and insulin resistance seen in obesity and type 2 diabetes mellitus. The gut-brain-liver circuit described also plays a major role in the improvement in insulin sensitivity, amelioration of diabetes, and decrease in food intake and weight loss reported after bariatric surgery since these beneficial effects are seen much before the weight loss is seen. We showed that there are distinct changes in the hypothalamic neurotransmitters and peptides that could account for some of the beneficial actions seen after bariatric surgery (32).

**BDNF IN OBESITY AND TYPE 2 DIABETES MELLITUS**

Brain-derived neurotrophic factor (BDNF) is produced by neuronal cells of the brain that regulates functions of the gut and pancreatic β islet activity in response to plasma levels of

![Figure 2. Statistics showing the prevalence of overweight and obesity by age in USA from 1960 to 2004. Source: CDC/NCHS, Health, United States, 2006.](image-url)
Glucose, protein, fatty acids, insulin and leptin. Systemic administration of BDNF decreased nonfasted blood glucose in obese, non-insulin-dependent diabetic C57BLKS-Lepr(db)/lepr(db) (db/db) mice, with a concomitant decrease in body weight. BDNF reduced the hepatomegaly present in db/db mice and reduced liver glycogen, supporting the involvement of liver in the mechanism of action for BDNF (33). Cao et al. (34) showed that BDNF by gene transfer in mouse models of obesity and type 2 diabetes mellitus produced marked weight loss, alleviated insulin resistance and ameliorated type 2 diabetes mellitus.

**Clinical implications**

Since most of the studies reported above have been performed in experimental animals, it is debatable whether these results are applicable to humans. In this context, it is noteworthy that peripheral leukocytes, macrophages and T cells contain the complete intracellular machinery for the generation, release and inactivation of catecholamines, dopamine, acetylcholine and serotonin, nitric oxide, PUFAs and their various metabolites such as lipoxins, resolvins, protectins and maresins, BDNF, CCK, leptin, ghrelin, all cytokines, and possibly other peptides. Hence, it is possible to measure all these chemicals in the peripheral leukocytes, macrophages and T cells in subjects who are obese and type 2 diabetes mellitus. An alteration in the concentrations of various peptides and catecholamines, acetylcholine and serotonin is expected in these patients. Thus measurement of catecholamines, acetylcholine, serotonin and other peptides and NO, antioxidants, various PUFAs and their metabolites such as lipoxins, resolvins, protectins and maresins in the plasma and peripheral leukocytes could form a simple and reliable method to know how these indices are altered in subjects with obesity and type 2 diabetes mellitus in the light of the result obtained in animal studies.

**GUT BACTERIA IN OBESITY**

Trillions of bacteria collectively termed as the microbiota reside in the human gastrointestinal tract. In majority of individuals, caloric intake exceeds caloric expenditure by less than 1 percent. Even this small difference can accumulate over years that ultimately could lead to increase in body weight. This remarkable capacity of body to match caloric intake with expenditure can be attributed to the brain's capacity to monitor the intake and expenditure of calories and identify and maintain small changes in body fat stores by secreting various circulating hormones and neurotransmitters.

The microbiota of the human gut is dominated by the Firmicutes and Bacteroidetes. Some of the genera in the Firmicutes phyla include: Lactobacillus, Mycoplasma, Bacillus, and Clostridium. Bacteroidetes are obligate anaerobes and are benign inhabitants of the human gut. Bacteroidetes are opportunistic pathogens and can cause disease especially following intestinal surgery or perforation of the gut (35).

In obese humans, the predominant gut bacteria are the Firmicutes. When obese individuals lost weight, the proportion of Firmicutes became more like that of lean individuals (36). The Firmicutes contain enzymes that break down hard to digest dietary polysaccharides and this lead to better digestion and absorption and so the host could become obese. When microbiota from the obese animals was transferred to the lean, mice given the microbiota from obese mice extracted more calories from their food and gained weight, suggesting that gut microbiota play a role in the development of obesity (37).

Gut free (GF) mice are protected against obesity induced by western-style, high-fat, and sugar-rich diet. When adult GF mice were conventionalized (i.e. the cecal content of 8-week old conventionally-raised mouse that contain their microbiota were given to 7-10 week old GF mouse) showed 60 percent increase in body fat, insulin resistance and hyperleptinemia within 14 days of conventionalization, suggesting that gut microbiota does influence the development of obesity (38).

One mechanism by which gut bacteria could influence the development of obesity includes the expression of Gpr41, A G protein-coupled receptor expressed by a subset of enteroendocrine cells in the gut epithelium. Short chain fatty acids and their products formed as a result of microbial fermentation of dietary polysaccharides interact with Gpr41 that lead to an increase in the production of enteroendocrine cell-derived hormones such as PYF that increases absorption of short chain fatty acids which are used as substrates for lipogenesis in the liver that ultimately leads to obesity (39).

In a study of 1015 subjects, a positive correlation was observed between plasma LPS concentration and fat and energy intakes. Mice fed a high-energy diet showed an increase in plasma lipopolysaccharide (LPS) and the increase in LPS. Since, fat is a more efficient transporter of bacterial LPS from the gut lumen into the bloodstream (40), these results indicate that high-fat diet enhances LPS absorption from the gut in to the plasma that, in turn, stimulates macrophages and lymphocytes to secrete inflammatory cytokines such as TNF-α, IL-6. These cytokines are known to produce insulin resistance seen in obesity and type 2 diabetes mellitus.

Following gastric bypass that is performed for subjects who are extremely obese and have type 2 diabetes mellitus.
diabetes mellitus, a large shift in the bacterial population of the gut was noted. Firmicutes were dominant in normal-weight and obese individuals but significantly decreased in post-gastric-bypass individuals (41). Microarray analysis of the preoperative and day 2 specimens identified a 20-gene signature that correlated with the surgical approach. These data suggest that obesity and its treatment produces changes in the gut microbiota and immune response and immunocytes. Thus, a close relationship exists between genes, brain, gut and gut bacteria and hormones, and immunocytes in the pathobiology of obesity (43).

CONCLUSIONS

It is evident from the preceding discussion that peripheral tissues (such as muscle, adipose cells, pancreas and liver) and hypothalamic neurons communicate with each other to maintain energy homeostasis. Immediately after food intake, many gut peptides are secreted such as ghrelin, cholecystokinin (CCK), and incretins etc., which interact with hypothalamic neurons and signal hunger and satiety sensations. Gut CCK reduces food intake by acting at CCK-1 receptors on vagal afferent neurons. The presence of significant amounts of BDNF in the duodenum, ileum, colon, liver and pancreas (43) and its ability to interact with PUFAs indicates that dietary fatty acids could bind with BDNF (since fatty acids bind easily with protein) and this may influence insulin secretion, production of pro-inflammatory cytokines, and glucose homeostasis, through vagus. It is noteworthy that pro-inflammatory cytokine production is regulated by the efferent vagus nerve: the "cholinergic anti-inflammatory pathway" mediated by acetylcholine (ACh) (44). Since, ACh sensitivity (47), it is clear that there is a complex network of interaction between all these molecules in the regulation of energy homeostasis.

Since obesity and type 2 diabetes mellitus could be managed by specifically delivering BDNF to the hypothalamus with or without complexed with unsaturated fatty acids at least in experimental animals, it remains to be seen whether this knowledge can be extrapolated to humans. Local delivery of unsaturated fatty acids to the hypothalamus, altering the gut microbiota, gastric bypass surgery to restrict food intake and absorption of digested food, increasing exercise and reducing energy dense food intake could form other modes of managing obesity and type 2 diabetes mellitus. Obviously, more studies are needed before these measures could be employed in the clinic.

REFERENCES AND NOTES

34. L.Cao, E.J.D. Lin et al., Nat. Med., in press.

Readers interested in a complete list of references are kindly invited to write to the author at undurti@gmail.com.