Neuroscience of Obesity: Pathogenesis of a Disease Influenced by the Environment

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Abstract

Over the last several decades, worldwide obesity rates have been increasing at an alarming rate. Obesity is a complex multifaceted disease that can increase one's risk of developing Type 2 diabetes, cardiovascular disease, and atherosclerosis. While it is understood that energy balance from the laws of physics dictate fluctuations in weight gain, more attention has been given to the drivers behind obesity from a neuroscience perspective in recent years. The current food environment provides a venue of hyperpalatable, cheap, and accessible foods to populations that are particularly in areas of low socioeconomic status. Sugar-sweetened beverages (SSBs) compose a majority of added sugars and excess calories in the American diet and present health concerns such as non-alcoholic fatty liver disease. The composition of items in this obesogenic food environment can notably play a role in altering subcortical activity related to pleasure associated with food. Key modulators in this phenomenon include leptin, ghrelin, cortisol, and the hypothalamic-pituitary-adrenal (HPA) axis. Additionally, chronic stress and mental illness are important to address as they can further disrupt the key modulators mentioned. Disruption in these hormones is associated with increased obesity through various epidemiological research. Despite the three macronutrients carbohydrates, fat, and protein, which each distinctly impact the brain, a substantial number of randomized controlled trials (RCTs) exist showing that when total energy intake is accounted for, weight loss is produced. As a result, obesity drugs on the market that facilitate weight loss work on the brain to help control total energy intake. Understanding the subcortical and environmental impacts of the obesity crisis can help physicians, registered dietitians, and the layperson navigate evidence-based methods to slow down the drastic rise in adiposity seen in contemporary society.

Introduction

Obesity is a complex multifactorial disease that is characterized by excess adiposity that can promote metabolic health issues. Since 1975, worldwide obesity rates have nearly tripled and by 2050, it is estimated that 60% and 50% of male and female adults, respectively, will develop obesity (1, 2). Currently, obesity is screened for using body mass index (BMI), a useful tool at the population level to recognize BMI patterns. BMI is simply an individual's mass in kilograms divided by their height in meters. While a good tool at the population level, BMI has its limitations. Factors such as waist-to-height ratio, location of adiposity, and race/ethnicity must be considered. For instance, visceral fat located abdominally around vital organs can increase one's risk of developing Type 2 diabetes, atherosclerosis, and cardiovascular disease (3). Additionally, South Asians have a greater risk of developing obesity-related complications at a lower BMI compared to other ethnicities (4). Due to this, it is critical to appreciate the intricacies and the multifaceted nature of obesity.

Recently, more attention has been given to the drivers behind obesity from a neuroscientific lens. It has been established that the principle of energy balance as a law of physics dictates weight gain and weight loss (5). This fundamental principle states that a net positive energy balance will result in accumulation of weight, while a net negative energy balance will result in weight loss because energy must be conserved. However, recent literature has aimed to expand on this principle by examining the biological drivers of weight gain. The energy balance model of obesity proposes that the brain is the primary organ responsible for body weight regulation through complex interactions with the food environment and external signals (6). When discussing excess food intake, socioeconomic constraints must also be addressed. An obesogenic food environment that consists of cheap, accessible, hyperpalatable foods can be seen as one explanation for the obesity epidemic (7–10). These environments tend to be abundant in areas with low socioeconomic status and can contribute to excess energy intake through the presence of more unhealthy foods. The food environment is simply the composition of food that is accessible and available in a particular area. Residing in an area with deprived socioeconomic status is a factor that is associated with many obesogenic behaviors (7). The food environment is speculated to play a role in the brain and obesity as well through the human reward system; the mechanism at play here results in increased food intake and circulating fuels (6). In adolescents, consistent exposure to television advertisements of food commercials affects the striatum (11) and these commercials also results in greater neural activation in the nucleus accumbens and caudate nucleus, predicting an increased consumption of calories (12). After a one-year follow-up, there was an increase in BMI, suggesting that the food environment can play a subcortical role in driving the increase in obesity rates.

Moreover, the purpose of this review was to highlight several neurobiological factors in humans that are contributing to the advancement of obesity in modern society. The current food environment, along with other factors, plays a role on our energy intake over time. Additionally, this review sought to address controversies surrounding macronutrient distribution impacting weight loss. This review examined the sophisticated nature of factors that influence obesity, including but not limited to the environment, hedonic feeding, subcortical effects, and mental health. Ultimately, this paper can benefit those working with patients in a healthcare setting as well as the average person trying to improve their health. The reason for this

proposed benefit is due to taking a detailed view into the many pathologies and causes of obesity that can present differently depending on the person.

Methods

A comprehensive literature search was completed exclusively through PubMed to locate literature related to obesity and neuroscience. A combination of terms including obesity, neuroscience, BMI, brain, environment, hedonic feeding, subcortical, and reward were utilized with the Boolean operators "AND" and "OR." Additionally, references of selected articles were examined to ensure a thorough representation of the literature.

Discussion

Sugar-sweetened beverages

The World Health Organization (WHO) has an adamant stance on reducing the consumption of added sugar in the diet. The WHO strongly recommends that total energy intake from free sugars be less than 10% in adults and children (13). This means for someone consuming a 2,500-calorie diet, free sugar intake should be no more than 250 calories daily. Sugar-sweetened beverages (SSBs) are very accessible and heavily marketed in the current food environment and come in forms such as soft drinks and fruit juices (14). Since SSBs are devoid of fiber, offer little nutritive value, and are easily overconsumed, there is discussion about the role of these products in society. SSBs are the leading source of added sugars in the United States (15). The overconsumption of these products is strongly associated with poor metabolic outcomes such as cardiovascular disease, non-alcoholic fatty liver disease, and cancer (16–18). Because metabolic disease is such a pervasive public health issue, recent efforts have been made to utilize a "tax" on these products to deter frequent consumption and have been successful (19).

It is clear that besides contributing to excess caloric intake, SSBs also play a role in the brain. For instance, a randomized controlled trial (RCT) assigned one arm of the study to consume SSBs for 21 days and measured functional magnetic resonance imaging (fMRI) scans of the brain as well as behaviors related to hedonic feeding (20). There was an increase in oxygen utilization by the striatum shown in the fMRI readings as well as reports of pleasure. This pleasurable feeling can potentially explain why individuals are drawn to hyperpalatable foods due to the strong reward response produced (21). In the striatum, the main function of neurons is to participate in movement and reward (22). There have been several documented cases of increased striatum activation in individuals with obesity compared to those without (11, 23–25). The interaction is just one of many brain interactions related to the food environment that can explain why individuals are likely to overeat.

SSBs are associated with poor health outcomes (16–18); therefore, there has been a recent push to urge consumers to switch to using non-nutritive sweeteners (NNS). NNS have little to no energy content and are much sweeter than regular table sugar (26). As a result, it is believed that substituting NNS in place of SSBs can help reduce the intake of added sugar in the diet. There is controversy surrounding NNS, also commonly known as artificial sweeteners (AS). Some evidence suggests that intake of one particular AS, aspartame, can induce neurobiological impairments and gut dysbiosis (27); however, the overwhelming evidence suggests AS are safe and valuable to consume when trying to reduce sugar intake (28–31). From a mechanistic point of view, this reasoning is sound, as swapping SSB for NNS can help one lower their overall energy intake, therefore avoiding the metabolic consequences of added sugars. A counterpoint supporting the consumption of AS suggests that the human outcomes associated with AS far outweigh the plausible mechanisms related to the neuroendocrine control of appetite, satiety, and cravings (32). While AS correlate with obesity and other adiposity-based chronic diseases, this is more so a result of confounding variables incorrectly blaming AS for the increase in obesity (32). Ultimately, the health outcomes from reducing sugar intake can go a long way. Primarily, this is accomplished by reduction of calories aiding in maintaining weight loss.

How chronic stress can impact obesity

Physical and psychological stress is a normal aspect of life (33). It is normal to experience a degree of stress in events which will activate the sympathetic nervous system. The human body will compensate by releasing the catecholamines epinephrine and norepinephrine; epinephrine specifically can provide glucose in the bloodstream in this stressful scenario for defensive action (34). While acute stress is normal and vital to life, chronic stress can trigger neurobiological actions that contribute to alterations in the hypothalamic-pituitary-adrenal (HPA) axis (35). There is compelling evidence that suggests chronic stress can contribute to enhanced interest in fatty and sweet foods (36). Hyperpalatable foods tend to be high in both fat and carbohydrates; as a result, stress can influence an individual's tendency to be in a state of positive energy balance. It is believed these foods alter the mesolimbic dopamine reward system by increasing glucocorticoids in the body (36–38). One important glucocorticoid related to obesity and involved in the stress response is cortisol (39). In adult men with visceral obesity, elevated morning cortisol has been identified, further suggesting that the HPA axis is a critical component in the stress response and obesity (40). While morning cortisol is normally highest according to the circadian rhythm, subjects in the study with less visceral fat did not show comparable awakening cortisol levels. This points to the strong impact of visceral adiposity. It is important to remember that visceral adiposity is harmful to internal organs and has also been shown to be a strong predictor of insulin resistance (3, 41–45). Chronic stress can also result in disrupted sleep patterns which independently elevate cortisol levels (46). Stressful situations such as low socioeconomic class are shown to deprive sleep and impair regular function of the HPA axis (47). As a direct result, neuroendocrine regulation can be impaired because of a drastic chronic state of increased cortisol. Furthermore, recent literature substantiates the hypothesis between poor sleep and obesity (48). It was noted that individuals with better sleep health had greater associations with decreased obesity in this particular investigation.

Ghrelin is colloquially referred to as the hunger hormone; however, it has several intricate functions in food intake, growth hormone release, and adipose deposition (49). This hormone is related to energy balance and is elevated during acute

and chronic stress (50). The properties of ghrelin have been explored in the brain relating to food reward, the HPA axis, and regulation of appetite related to dopamine (51–54). Specifically, in the brain, ghrelin increases food intake by stimulating the synthesis of neuropeptide Y and agouti-related protein (55). Several studies have examined the role of ghrelin in mice and have found ghrelin resistance in obese mice (56–58); however, rodent data is often inapplicable to humans. In overweight humans, higher levels of ghrelin were linearly associated with increased caloric intake (59). This suggests that these individuals have stronger cravings for hyperpalatable foods and have greater tendencies to display hedonic behaviors toward food. Additionally, there has been replication of higher ghrelin in individuals who consume food products high in fat and carbohydrate; however, it is notable that in these subjects there were lower levels of leptin (60). Leptin is a hormone that is related to long-term energy balance (61). When there are low levels of leptin, our body gets a signal that invokes a feeling of hunger, further contributing to excess energy intake (62–63). Leptin and ghrelin together have been found to increase food cue reactivity which is related to physiological responses to the activation of human reward systems (64). The current food environment that is rich in hyperpalatable foods can contribute to the fluctuating levels of leptin and ghrelin in humans (7–10). The role of these hormones in obesity at a cellular level is still under investigation (65).

Mental health and obesity

An individual's mental health can be shaped by social, environmental, and economic conditions (66–68). Notably, people who suffer from poor mental health and intellectual disabilities experience excess mortality compared to the general population (69). Additionally, excess adiposity is one risk factor for all-cause mortality (70). Recently in the United Kingdom, a sample of 3.6 million adults demonstrated a J-shaped association between increased BMI and excess mortality (71). Therefore, the relationship between mental health and obesity is an important consideration when examining the obesity epidemic.

Depression, also known as major depressive disorder (MDD) is a mental health disorder that affects 350 million people globally (72). The mechanisms of MDD can be further clarified through neuroscience literature. Neuroscience has become a pivotal resource for scientists and researchers to understand the connection between depression and obesity (73). When it comes to body weight regulation, the brain has neural circuits that have been shown to control energy intake in response to food environments (5). One can think of these circuits as ways to control food intake through different responses to several hormones including dopamine. Hall and colleagues acknowledge the concept of brain circuits is novel and that different responses in these circuits are being evaluated in mouse models (6). For instance, the brain circuits will be used to test the intervention of a high-fat diet compared to a high-carbohydrate diet. There is also data that show the neural adaptations in these circuits can explain associations between depression and obesity (74–75). Furthermore, it can be hypothesized that there are subcortical effects in obesity and depression that are similar. In fact, depression has been linked to decreased gray volume in regions such as the left precentral gyrus, hippocampus, insula, and cerebellum (76–79). Similarly, obesity is associated with a loss of gray matter (80). Gray matter makes up the outer layer of the brain, constitutes the greatest number of neural cells in the cerebellum, and plays a crucial role in everyday function in humans (81–82). Dysfunction and atrophy in this area can possibly explain the relationship between obesity and depression. The alteration in critical brain regions may also explain hedonic eating patterns, or eating simply for pleasure. Higher gray matter volume is shown to increase one's ability to moderate and control food intake (83). When conditions such as obesity and depression deteriorate gray matter in the brain, the ability to moderate food intake is diminished and there is an inclination toward foods that are more palatable and elicit a potent reward response (21). This subcortical alteration can ultimately drive an individual to consume excess calories over time, which will result in a positive energy balance, contributing to weight gain.

The question that naturally arises from this discussion is "How can I prevent mental illness to improve the quality of my life?" That being said, there are no current data that show mental-health–related complications can be entirely prevented or cured, even with contemporary pharmacological therapies (84). Therefore, the best option is to manage these symptoms through a combination of effective medical therapies as well as lifestyle interventions. It should be noted that regardless of these types of interventions, there is a chance that these mental illnesses cannot be prevented due to hereditary components. Recent systematic reviews and meta-analyses show strong evidence for aerobic and resistance exercise in managing mild depression and depressive symptoms in adolescents and adults (85–86). There are several plausible mechanisms that are at play here. One outcome of resistance training is the increase in gray matter thickness and cognition in those who resistance trained twice a week for 26 weeks (87). While the human outcome data show positive benefit from resistance training, the mechanisms are not completely understood but most likely exert their effect through cellular and molecular interactions with lactate, tumor necrosis factor alpha, brain-derived neutrophic factor, and insulin-like growth factor-1 (88). Like resistance training, aerobic exercise is also shown to increase white and gray matter in the brain (89). One mechanism related to the benefits of exercise can be seen through the release of myokines, notably interleukin-6 in rodents (90). Further research is needed to fully understand how exercise contributes to positive health outcomes from a mechanistic and molecular standpoint; however, there is a clear benefit shown from exercise to combat depressive symptoms in the human outcome data.

Ultimately, the best option to combat mental illness and obesity could be through guided stress-management programs. A randomized controlled trial looking at outcomes related to BMI, depression, and stress showed significant decreases in stress and depression as well as the adoption of a healthier dietary pattern (91). Similar programs conducted both in person and online showed comparable benefits (92-95). The crossover between depression and obesity is complex and must be addressed from a subcortical perspective to be effectively targeted.

Macronutrient impact on the brain

The three common macronutrients are protein, carbohydrates, and fat. These nutrients go through various metabolic pathways to provide our body with energy. Dietary fat provides nine calories per gram while protein and carbohydrates each provide four calories per gram (96). The impact of these macronutrients on human and in vivo systems has been meticulously studied from the perspective of the brain. It should be noted that there are different forms of dietary fat, such as saturated, polyunsaturated, monounsaturated, and trans, each of which have unique health implications in the literature. For instance, a diet rich in saturated fat has been shown to increase low-density lipoprotein (LDL) cholesterol and reductions in LDL cholesterol are paramount in reducing combined cardiovascular events (97). Additionally, LDL cholesterol has been shown in mendelian randomization trials to be a strong predictor of cardiovascular disease (98). This controlled data even allows for causality to be inferred, which cannot be done through various epidemiological studies. Animal models show that the intake of high dietary fat, particularly saturated fat, can alter brain neurochemistry in the hypothalamus (99–102). The hypothalamus has a main function in controlling appetite and maintaining homeostasis; hence, it is plausible that higher dietary intake of fat can affect this system to drive one to hyper-consume calories.

Carbohydrates serve as the brain's preferred source of energy. When discussing carbohydrates, specificity is required, as there are multiple types of carbohydrates such as readily digestible refined carbohydrates compared to fiber, which the body cannot metabolize. Refined carbohydrates tend to be processed and stripped of vital nutrients and are associated with altering the serotonin pathway in mice which can contribute to hedonic feeding patterns (103). In humans, excessive refined carbohydrate consumption is linked to poor hippocampal function and disruption of the mesolimbic and prefrontal reward pathways (104). However, it is unclear whether reverse causality is at play here. Refined carbohydrates tend to be hyperpalatable and are packaged in foods that also contain a large quantity of fat, therefore making the item more rewarding. The excess consumption of total energy may better explain the alterations in reward processing; however, further research is needed. On the other hand, fiber is a carbohydrate that cannot be broken down and moves food through the digestive system. Fiber has arguably the strongest evidence supporting its consumption through several meta-analyses and cohort studies associating fiber consumption with reduced all-cause mortality in a dose dependent manner (105–109). Epidemiological research shows that fiber is associated with a lower overall body weight (110). This can potentially be attributed to the satiety

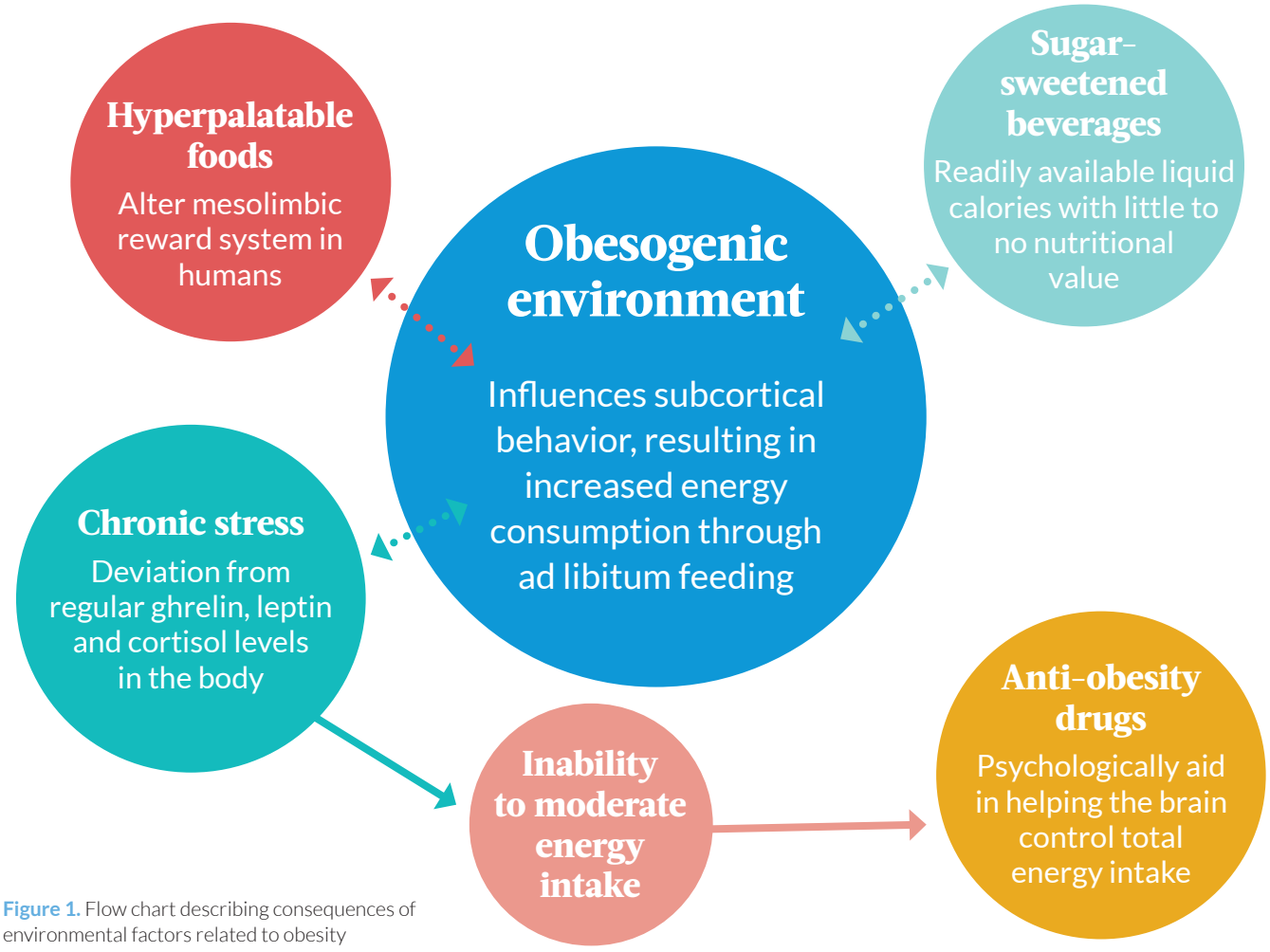

Figure 1. Flow chart describing consequences of environmental factors related to obesity

effect it provides. While the mechanisms for fiber's positive effects are still being studied, it is suspected that there is a relationship to the gut-brain axis and fermentative metabolism (111).

Protein is an important molecule and is involved in several processes in the body. In hypocaloric diets, the increased consumption of protein helps individuals with obesity maintain weight loss (112). This can potentially be attributed to the thermic effect of food protein provides, although this impact is relatively small. Additionally, higher-protein diets are more readily accepted into normal food culture, which can make these diets easier to adhere to (113). Protein signaling is believed to operate through the vagal nerve and include gastric hormones (114). While additional research is needed on the significance of protein mechanistically, there are a few things certain regarding macronutrients as a whole. Energy balance will dictate weight gain or weight loss (5), which is seen in closely controlled trials. Regardless of the macronutrient composition, a net energy deficit will result in weight loss. In a meta-analysis of 53 RCTs, there was no evidence that showed significant changes in body weight in the long term when total energy is controlled for (115). This trial included dietary patterns that were higher in fat as well as dietary patterns that were lower in fat and various macronutrients. It is worth acknowledging that subcortical effects related to feeding can make this process more difficult as shown by the neuroscientific research (11–12, 21–23, 35, 36)

Conclusion

Obesity is a disease that is driven by a chronic shift in energy balance. The current food environment makes hyperpalatable foods readily available that can work on the brain to drive overconsumption. As the rates of obesity continue to rise, it is imperative to find evidence-based solutions to combat the epidemic. The human reward system can be shifted specifically through leptin and ghrelin as a result of the obesogenic food environment (64). Within this environment, SSBs continue to pose problems to metabolic health. In addition to provoking behaviors associated with hedonic feeding (20), SSBs continue to be the leading source of added sugars in the United States (15). Replacing these beverages with NNS and focusing on overall dietary patterns that provide satiety can help reduce overconsumption of calories. Socioeconomic status must also be acknowledged. Low socioeconomic status is associated with impairing the HPA axis (47). This can make it more difficult for an individual to control energy intake because of internal hormonal cues. The low socioeconomic status can also result in periods of chronic stress which disrupt healthy sleep patterns (46). A major concern for areas that have a high proportion of individuals with low socioeconomic status is the presence of food deserts, which limit access to healthy foods in these communities (116). As expected, this will result in more hyperpalatable foods that are cheap, accessible, and easily overconsumed.

Contemporary medicine has produced anti-obesity drugs that have shown promise. One example of a drug that is commonly prescribed to patients with obesity is semaglutide. Semaglutide has been demonstrated to result in lower ad libitum caloric intake compared to placebo in the literature (117). The mechanisms of semaglutide seem to work in the brain by decreasing preference for energy-dense foods that provide low satiety (117). This can be an effective way in reducing overall energy intake and fighting the obesity epidemic. A recent genome-wide association study has shown that food-liking and preference can largely be influenced by genetic variations and biology (118). While more research needs to be completed, the cutting-edge research in genetics will potentially advance our understanding of the impact the food environment has on the brain in the future.

In closing, the relationship between hedonic feeding in the obesity epidemic is largely environmentally driven and complex in nature. This can be seen in Figure 1. Major issues that must be addressed include the obesogenic food environment and mental illness that can manifest in stress. The stigma behind obesity can also hurt an individual's psychological and physical well-being and must be addressed (119). Efforts made toward combating these issues will be promising and can change the tide of the ongoing obesity crisis across the globe.

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