Title
Can Food Be Addictive? Insights on Obesity from Neuroimaging and Substance Abuse Treatment and Research

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Introduction

"I think it begins with a feeling of emptiness…The moment I become aware of the hole opening inside I'm terrified. I want to fill it. I have to. So I start to eat. I eat and eat- everything, anything I can find to put in my mouth. It doesn't matter what it is, so long as it's food and can be swallowed. It's as if I'm in a race with the emptiness. As it grows, so does my hunger. But it's not really hunger, you see. It's a frenzy, a fit, something automatic and uncontrollable. I want to stop it, but I can't. If I try to, the hole gets bigger, I become idiotic with terror, I feel as if I'm going to become nothing, become the emptiness- get swallowed up by it. So I've got to eat."

This excerpt from a case history by Dr. Robert Linder, PhD (1) exemplifies the patient's experience with the binge eating disorder Bulimia Nervosa.   It is characterized by a loss of control of eating, a feeling that one cannot stop eating or control what or how much one is eating (2). According to recent epidemiological studies, Bulimia Nervosa occurs in about 30% of obese patients attending weight control programs (3).

Background

Obesity has become a major health problem, second only to tobacco in annual associated mortality, with almost 300,000 deaths per year (4). The pathogenesis of obesity is multi- factorial; both genetics and the environment influence the many variables that regulate body weight, metabolism, and eating behavior.   Although, not all obese individuals suffer from binge eating disorder, many can identify with it and therefore may benefit from a better understanding of the neurobiological substrates underlying the behavior. The loss of control associated with obesity is analogous to the compulsive drug taking behavior observed in drug-addicted individuals and the hypothesis of a food addiction was first proposed over 10 years ago by the American Society of Addiction Medicine (ASAM Symposium 1992).

Addiction

Highly palatable and hedonic food can convincingly be considered as a substance of abuse, according to the DSM-IV criteria which include: "a maladaptive pattern of substance use, leading to clinically significant impairment or distress…substance is taken in larger amounts or over a longer period than was intended…there is a persistent desire or unsuccessful efforts to cut down or control substance use…the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance" (2). In particular, the inability to refrain from the compulsive, continued use despite life- threatening health consequences, such as diabetes and hypertension in association with obesity, and despite the psychological impact of changes to lifestyle, social stigma, and prejudice are characteristic of both obesity-overeating and addiction.

The mechanisms of addictive behavior are not well understood. It has long been known that drugs of abuse, including tobacco, cocaine, methamphetamine, and long-term opiates, cause weight loss. This, supported by other evidence, has led to the theory that drugs hijack the brain; in other words, addiction occurs when the unnatural stimuli of drugs misappropriate the brain's reward system, which evolved to reinforce the motivation for natural stimuli such as food. In further support of this theory is the recognition that the treatment of drug addiction and any supervised drug abstinence causes weight gain (5). Analysis of this weight gain leads one to speculate that the removal of the unnatural reward stimuli, the abused drug, led to an increase or compensation in the motivation for the natural reinforcer of food. Numerous studies of Bulimia Nervosa have uncovered a high rate of co-morbid substance abuse, both in patients and their families; this supports a common predisposing factor or mechanism (6). Other researchers have found that in severely obese patients a higher BMI is correlated with a decrease in alcohol intake, suggesting that overeating targets the same reward pathway as alcohol thereby decreasing alcohol's reinforcing effect (7). These clinical observations provide further evidence of a common target for food and addictive drugs in the reward pathway.

Imaging: Addiction and Eating Behavior

Dopamine (DA) has long been implicated as the key neurotransmitter mediating the reward system and consequently regulating eating and addiction behavior.

Although the function of DA in the brain has yet to be fully elucidated, there is extensive research evidence describing how the meso-limbic DA circuit implements the reinforcing effects of the reward system, the motivation to want incentives, both natural stimuli and in drug addiction (8, 9). Although a simplification, reward can be conceptualized as the reinforcing effect of a stimulus dependent on its ability to increase the release of DA in limbic regions of the brain, in particular the nucleus accumbens of the striatum (10, 11). The DA innervation of limbic regions plays an essential role in the reward pathway and can be measured in humans by neuroimaging with Positron Emission Tomography (PET). Neuroimaging studies have shown that upon eating, DA is released in the meso-limbic circuit and this is correlated with the subjective feeling of pleasure (12). DA can be seen as the messenger that enables highly palatable food to be perceived as more reinforcing or rewarding. Drugs of abuse, including nicotine, cocaine, alcohol, amphetamines, marijuana, and opiates, have also been linked with an increase in DA. Imaging studies have shown that the subjective feeling of a high or euphoria associated with certain drugs of abuse is correlated with this DA increase (13, 14). It is the activation of the reward system by DA that mediates the reinforcing effects of food and addictive drugs, and therefore DA dysfunction is likely involved as a common mechanism in pathological eating and drug-taking.

One of the most striking examples of this comes from pharmacology; DA agonists are appetite suppressants, anorexigenic. Their administration leads to a reduction in food intake and inhibition of hyperphagia (15). Many drugs of abuse are DA agonists, and

their effect on eating behavior can be seen as providing the reward without the natural stimulus thus replacing the motivation for food. Correspondingly, DA antagonists are known to enhance meal size and duration of feeding (16). In clinical studies, patients treated with antipsychotic medications, known to block DA receptors, show significant weight gain (17, 18). Antagonism of DA can be interpreted as reducing the sensitivity of the reward system, leading to a compensation or increase in food intake to overcome the block or reduction in reward.

Further evidence of the DA influence comes from neuroimaging of DA receptors by PET, specifically the D2 subtype of the DA receptor, localized in the striatum and known to be the target of antipsychotic medications. Animal studies indicate that the level of DA D2 receptors in the nucleus accumbens mediates the reinforcing response to drugs of abuse (19). In humans, numerous studies have shown significant reductions in the striatum of DA D2 receptors in drug-addicted subjects, cocaine, methamphetamine, alcohol, and heroin (20-22). Recent research has also shown a significant reduction in DA D2 receptors in the striatum of obese subjects, with BMI between 42 and 60 and no current or past psychiatric or other disease that may alter cerebral functioning (23). Moreover in obese subjects, but not in controls, the degree of reduction in DA D2 receptors was significantly associated with BMI.

Reward Deficiency Syndrome

These results, along with extensive research in psychiatric disorders and animal models, have been interpreted to suggest that DA D2 receptors may in part regulate compulsive behavior seen in disorders such as pathological obesity and drug-addiction in a so called Reward Deficiency Syndrome (24, 25). In this theory, the deficit of DA D2 receptors leads to a hypodopaminergic trait causing the brain to seek out DA releasing stimuli in order to feel good. This propensity would put the individual at a higher risk for behaviors such as drug-addiction and pathological eating, behaviors which activate the release of DA to normalize the dysfunction. The lower DA D2 receptor level decreases sensitivity to reward stimuli thereby increasing vulnerability to food intake as a means to temporarily compensate for deficit. This Reward Deficiency Syndrome is a likely a result of many genetic and environmental factors, and whether it serves to predispose a vulnerability or rather is occurs as a result of an environmental stressor or along the pathogenesis of the compulsive behavior is yet to be elucidated.

This hypodopaminergic trait is most apparent in patients diagnosed with Bulimia Nervosa, demonstrated in the opening case history, but may occur to varying degrees in other obese individuals. In addition to their prevalence in weight control programs, Bulimia Nervosa patients also exhibit a higher relapse rate in weight loss studies (26). The severity of the symptoms led researchers to discover a link with the disorder and a reduction in the cerebrospinal fluid of DA and its metobolites (27). Researchers also found a higher prevalence of the Taq I A allele for DA D2 receptor, a polymorphism linked to lower levels of receptor (28-30). This evidence, that low brain DA activity is correlated with dysfunctional eating patterns, supports the theory that those patients with

Bulimia Nervosa display signs consistent with a Reward Deficiency Syndrome; when the brain has a severe dopaminergic deficit behavior is more likely to manifest the compulsive use of substances, such as drugs or food, to increase DA stimulation to a more desirable level.

Future Research

But DA action is not limited to the meso-limbic circuit and the relationship between eating behavior and addiction is more complex than simply sharing a target in the reward pathway. Another prominent place where DA affects food intake is in the brain region the hypothalamus, partly by inhibiting the expression of potent stimulators of eating, peptides such as Neuropeptide-Y and Proopiomelanocortin (31, 32). In this way, DA release in the hypothalamus contributes to a reduction in food consumption and hypophagia (33). Other important messengers involved in modulation of energy homeostasis, body weight, and eating behavior, most notably leptin and insulin, as well as other peptide and steroid hormones have also been shown to modulate DA levels (34). This provides yet another level of complexity through various interactions and cross-talk between different systems.

In addition to the action of DA, substances of abuse and eating behavior modulate other important neurotransmitters, such as GABA, opioids, and serotonin, as well as hormones, second messengers, and neural circuits. The function and dysregulation of these interactions may further elucidate how eating behavior is influenced by variables other than reward such as hunger, satiety, emotion, cognition, environment, and social context. Of particular interest for future research are the conditions of emotional distress or the tendency to eat when exposed to negative emotions and sensitivity to external food-appetitive stimuli because of their likely relationship to stress and environment induced drug addiction relapse.

Summary

Research has provided strong evidence for the relationship between binge-eating obesity, addiction, and the DA reward system. While describing the pathogenesis of these disorders as solely due to DA dysregulation is an oversimplification, the Reward Deficiency Syndrome does provide a model for how researchers in the fields of addiction medicine and obesity are improving the understanding of both disorders. DA is just one of the possible neurobiological substrates where genetic vulnerability and environmental stressors interact to favor food consumption/drug abuse in the individual, and perhaps a future target for pharmacologic therapy. Moreover, this evidence provides hope for patients struggling with obesity, both from the understanding of a neurobiological basis of behavior and the ability to change behavior through the adaptation of successful cognitive-behavioral and psychotherapeutic strategies from addiction medicine to the application of diet and weight control.   Likewise, the possibility of understanding shared

environmental and psychological factors may enable certain individuals to prevent acquiring or reduce the severity of both substance abuse disorders.

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