Dopamine D2 Receptor Deficiency as a Cause of Obesity

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'Of all human frailties, obesity is, perhaps, the most perverse.' So says psychologist Stanley Schachter in his 1974 book Obese Humans and Rats (1, p.1). Schachter wonders, as have many others, why obesity persists when our society has such severe consequences for it and the solution should be so simple. A dopamine D2 receptor deficiency may be the answer.

Obese persons are subject to discrimination, social isolation and a myriad of health issues. In spite of this, obesity rates are increasing dramatically in the United States. This is because obesity is a more complex disorder than originally thought. It was assumed that obesity was controlled by an energy-in versus energy-out equation and that healthy diet and exercise would correct the problem. However, obesity appears to be a physical addiction to food stemming from a lack of dopamine D2 receptors (which is both a cause and consequence of obesity) and an over-activity of certain areas of the parietal cortex. Treatment for obesity is more complex than a diet and daily job. A healthy lifestyle must be combined with treatment of the neurological causes. This treatment might include twelve-step programs, long term restricted caloric intake, and newly developed drugs.

Obese individuals have a body mass index (weight in lbs divided by height in meters squared) of over 30 (2), and are the target of bias and stigmas. According to the Obesity Society, negative attitudes towards the obese begin developing at age three; the obese face discrimination and social isolation beginning as early as preschool. In the workplace, the obese are ascribed negative stereotypes (including lazy, undisciplined,

incompetent and disagreeable) and receive fewer promotions and raises. It seems peers of the obese do not feel guilty about this discrimination, placing the blame on the individual and believing they simply need to 'eat less.' Adverse social reactions to their appearances lead to higher rates of depression, anxiety, low self-esteem, self blame and suicidal behavior among obese individuals. (3)

These social problems are matched by physiological complications. According to the CDC, the obese are at an increased risk for coronary heart disease, type 2 diabetes, hypertension, stroke, osteoarthritis, gynecological problems, liver and gallbladder disease, sleep apnea, respiratory problems and certain types of cancer (2). Though obese individuals obviously need more medical attention, medical professionals often cling to the same stereotypes as the general populous, blaming the obese for their health issues and viewing them as overindulgent and lazy. This, unfortunately, means that obese individuals are more likely to avoid medical attention and preventative care. (3)

However, despite the aforementioned laundry list of negative consequences and the apparent simplicity of the solution, obesity is on the rise in America. In 1997, only three states had an obesity rate over 20%. Ten years later, in 2007, only one state had an obesity rate under 20% and most were approaching 30% (2). Why is something that seems so easy to correct effecting so many?

Dopamine (DA), a neurotransmitter which reinforces behavior by causing pleasant or satisfying feelings, plays a large role in addiction. Nora Volkow discovered that drug addicts displayed a DA D2 receptor deficiency. She postulated that addicts were compensating for this insensitivity to DA by using drugs that cause a DA flood in the brain. Food also causes a flood of DA. Volkow repeated her study on obese versus

normal weight participants and found an identical lack of DA D2 receptors in obese subjects. "These people were compulsively driven to eat as if food were their stimulus of choice," she said. Because both food and drugs cause an abnormally large release of DA, the brain synthesizes less of it to try and maintain homeostasis. This increases the individual's perceived need for the substance and may lead to substance abuse, dependence and addiction. (4, p 155)

To determine if a DA D2 receptor deficiency was a cause or consequence of obesity, Jennifer Temple studied the DNA of obese and normal subjects; half of each group had a gene linked to a DA receptor deficiency. Participants were given food rewards for completing tasks and received more food for working harder. Temple found that obese subjects with this gene variation worked much harder than either normal weight subjects with the deficiency gene or subjects without it. Temple deduced that a DA D2 deficient genotype drives individuals to seek excess rewards, but that the type of reward desired varies. Those with the genotype who are of normal weight may engage in physical activity, drug use, gambling or other dopamine releasing behaviors instead of eating. Temple's study indicates that DA D2 deficits in the obese are at least partially genetic in nature, and part of the cause of obesity. Overeating to compensate for a genetic receptor deficit may itself decrease receptor numbers over time. Hence, the DA D2 receptor deficit is most likely both a cause and a consequence of obesity. (5)

Though addiction and obesity seem to rely on the same dopaminergic pathways, Gene-Jack Wang felt there must be a neurological difference between the obese individual and the addict. Wang used positron emission topography (PET) scans to map brain activity after administration of a sugar solution to participants after 16 hours of

fasting. The PET scans showed that specific areas of the parietal cortex corresponding to sensory input from the tongue, lips and mouth were overactive in obese subjects, but not in normal weight subjects or in drug addicts. (4, P. 156)

Combine a genetic insensitivity to dopamine, an increased need for dopamine stimulation and an overactive response to oral sensation and it is not hard to understand what might trigger compulsive eating in spite of any external or internal consequences.

Twelve-step programs, modeled after other addiction support groups, help individuals feel in control by setting out guidelines for recovery. The group setting eases feelings of isolation and stress. This can increase motivation and self efficacy, but will not address the underlying physical and neurological causes. Relapses are extremely common after an obese individual sheds excess weight. (4, p. 155)

Long term restriction of caloric intake can increase the number of DA receptors in the brain. One study restricted the food intake of half of a group of rats (containing obese and average weight individuals) while the other half received unlimited food. PET scans showed increased numbers of receptors in rats with restricted diets and fewer DA D2 receptors in obese rats (as expected). Researchers felt that increasing receptor numbers and sensitivity to other types of reward may help prevent overeating. The restricted diet even helped attenuate normal declines in dopamine sensitivity due to aging. (7)

Psychoactive drugs including Narcan, an available form of Naloxone, and Rimonabant show promise in treating obesity. Naloxone, an opiate antagonist, was demonstrated to reduce food cravings in rats in a study conducted by Jeffery Grimm at Western Washington University. Researchers felt Naloxone could be used to help obese patients deal with their food cravings. While weight loss by the obese is not uncommon,

keeping the weight off is. Naloxone could help the obese maintain a healthy weight and lifestyle where it would otherwise be extremely difficult. (6, p. 544)

Rimonabant decreases activity of the endocannabinoid system, which increases dopamine availability. Separate studies have indicated that Rimonabant aids in weightloss and cessation of addiction to cigarettes. This is good news for smokers concerned with gaining weight after quitting. In one study, smokers receiving 20 mg of Rimonabant per day over 15 days lost an average of a half a pound (one third quit smoking). Those receiving a placebo gained 2.4 pounds and only one-fifth quit during the 15 days. (4, p. 156)

These are exciting advances in the understanding and treatment of obesity. Obese individuals now have a greater opportunity to maintain a healthy weight and lifestyle in spite of their DA D2 receptor deficiencies and parietal cortex abnormalities. Obesity is an emotionally and physically taxing disorder and is as hard to overcome as any other physical addiction, but there is a better chance of recovery now than ever before. There is now considerable hope for this 'most perverse' of human frailties.

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