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Overeating, Obesity, and Dopamine Receptors

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Abstract

New results in rats show that compulsive overfeeding can lead to deficits in the brain reward circuit. Interestingly, these deficits resemble those that result from drug addiction.

The neurotransmitter dopamine plays a key role in the brain reward circuit. The intake of highly addictive drugs such as cocaine causes an increase in dopamine levels in the limbic brain including the nucleus accumbens of the striatum, which leads to reinforcement of associated behaviors (*1*). Recent studies have also shed light on the involvement of the striatum in feeding in obese humans. Notably, positron emission tomography studies have shown that striatal dopamine D_2 receptors are reduced in obese individuals compared with D_2 receptors from their leaner counterparts (*2*). In addition, it has also been demonstrated that obese individuals tend to overeat to compensate for blunted striatal sensitivity (*3*). Analogous deficiencies in striatal dopamine signaling have also been observed in individuals addicted to drugs. Because pathological overeating is also driven by pleasure and the compulsion to continue despite known negative effects, like drug addiction, it is thought to involve dopamine neurotransmission. However, whether these deficiencies in D_2 receptor signaling drive obesity or whether obese individuals develop deficiencies as a result of reward dysfunction is an open question.

Johnson and Kenny (*4*) set out to understand the physiology of compulsive eating by studying the behavior of rats with easy access to high-fat food. They now find that the brain reward circuit involved in compulsive overfeeding is similar to the circuit associated with drug addiction (*4*).

In the first set of experiments, rats of roughly equal size were prepared for brain stimulation reward procedures. Briefly, stimulating electrodes were implanted in the lateral hypothalami. The rats were allowed to recover from the surgical procedures and baseline levels of electrical stimulation required for rats to turn a wheel were recorded. The amount of stimulation, or stable reward threshold, was virtually identical for all rats. Next, the authors divided the animals into three groups. For 40 days, the first set of rats had access to only standard laboratory chow; the second set had access to chow and one-hour access to palatable, energy-rich "cafeteria-style" food such as bacon, sausage, and cake; and the third set had extended access to both chow and high-fat food. Over time, the rats with extensive access to energy-rich food gained approximately twice as much weight as the rats that had access to only chow or chow and limited amounts of energy-rich food. In addition, rats with greater access to the palatable diet required greater stimulation to turn the wheel, a hallmark of brain reward deficiency that is also associated with forms of drug addiction.

Next, the authors tested whether overeating had any effect on D_2 receptor levels in the striatum. To do this, the authors repeated the feeding experiments without insertion of electrodes. Again, rats were divided into three groups that had access to chow only, chow and limited access to high-fat food, or chow and extensive access to high-fat food. After significant differences in body weight between chow-only and extensive-access rats were noted, they were killed in order to examine levels of D_2 receptors in the striatal complex. Immunoblot analysis revealed that the body weight of rats correlated negatively with the level of D_2 receptors. In other words, the fatter the rat, the lower the density of D_2 receptors in the striatum.

To establish the link between levels of striatal D_2 receptors and brain reward, in a fresh batch of rats, the authors used a viral vector with a short-hairpin interfering RNA to knock down gene expression. Rats with reduced D_2 receptor levels after knockdown had increased reward thresholds that resembled the scenario found in rats on an extended-access energy-rich diet. Interestingly, other recent studies have shown that inherently impulsive rats have reduced D_2/D_3 receptor levels even in the absence of drug exposure (*5*). Conversely, it is feasible that high D_2 receptor levels might offer some protection against drug intake (*2*). An unanswered problem that emerges from these studies is whether spontaneous impulsivity is correlated to overeating through reduced D_2 receptor levels.

In another series of experiments, rats were given access to one of the three diets and, after 40 days, were conditioned to expect a foot shock that corresponded to a light signal (*4*). Rats from all three groups were also allowed to eat the energy-rich food for a brief period. Rats

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with limited earlier access or no access to energy-rich food binged once access to the palatable food was provided. These rats stopped eating when the light signal came on. However, fear of foot shocks could not deter feeding in rats with widespread prior access to palatable food. Again, compulsive overeating resembled drug self-administration in that negative consequences were insufficient deterrents to reward-seeking.

Taken together, these studies strongly argue in favor of the involvement of the brain reward circuit in compulsive overeating. An argument for a direct role in obesity is less compelling. As with all behavioral studies performed on laboratory rodents, extreme caution should be exercised in extrapolating observations to human populations. In humans, the act of eating is profoundly influenced by social, cultural, and emotional factors that may not be observable in other animals (even in other primates). Additionally, feeding behaviors are much more intricate than those associated with drug self-administration. For example, eating a sandwich involves multiple levels of sensory involvement in a way that injecting heroin does not. In addition, drugs activate the brain reward circuit by direct intervention at receptors, while food does so indirectly via numerous chemicals such as hormones, opioids, and cannabinoids. It is also worth bearing in mind that the brain reward circuit is not the only circuit involved in eating behavior; other circuits such as learning and motivation play significant roles in feeding too (*2*). Finally, there are many genetic and metabolic factors that predispose an individual to overeating and influence the propensity for becoming obese. In particular, a great deal of research over the last two decades has focused on leptin and ghrelin, hormones that influence appetite. It is known that leptin influences striatal activity and eating behavior (*6*). How leptin signaling in the hypothalamus and striatal D_2 receptor signaling are coordinated for the regulation of energy homeostasis requires further study (*7*).

Nonetheless, interesting questions emerge. Is there a direct link between drug abuse and compulsive overfeeding? Can one be considered a predisposing factor for the other in the clinic? And finally, will therapeutic agents that combat drug abuse be effective for treating compulsive overeating? No doubt, studies will build on current knowledge to provide a clearer picture.

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