Understanding the Neural Circuitry of Appetitive Regulation in Eating Disorders

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There has been much confusion and speculation about the reasons for abnormal eating behaviors and other symptoms in anorexia nervosa (AN) and bulimia nervosa (BN) (1). For example, individuals with AN dramatically restrict their caloric consumption and achieve severe emaciation yet are often preoccupied with food or cook for others. Moreover, food, or even the anticipation of eating, tends to be anxiogenic, whereas avoiding eating often reduces these uncomfortable feelings. Individuals with BN tend to alternate between restrictive eating and overeating with loss of self-control, followed by purging behaviors. They may use bingeing and purging behaviors to suppress negative mood states. In this issue of *Biological Psychiatry*, Gérard *et al.* (2) contribute new insights to an emerging literature that characterizes the neurochemistry contributing to altered feeding, reward, and mood symptoms in AN and BN.

The development of more effective treatments for AN and BN has been stymied, in part, because there is so little known about the pathophysiology of these disorders. Although AN and BN are characterized as eating disorders (EDs), it remains unknown whether there is a primary disturbance of pathways that modulate feeding or whether disturbed appetite is secondary to other phenomena, such as anxiety or obsessional preoccupation with weight gain. In part, this dilemma arises because the regulation of appetite and feeding are complex phenomenon, involving peripheral and central pathways.

In theory, disturbances anywhere within this circuit could contribute to abnormal eating behaviors. Individuals with AN and BN have behaviors suggestive of altered reward, mood, and impulse control. Thus, there has been great interest in the question of whether there is involvement of higher-order cortical-limbic systems (1), which encode the rewarding, emotional, and cognitive aspects of food ingestion and which can override hypothalamic homeostatic signals of energy balance (3). For example, for those who overeat, it is possible that the rewarding aspects of palatable foods can drive overconsumption, even in the presence of replete energy stores.

When considering neural systems that may regulate the rewarding aspects of food, there is evidence that the endogenous endocannabinoid system has an important role in signaling rewarding events. As noted by Solinas *et al.* (4) type 1 cannabinoid (CB1) receptors are found in brain areas involved in reward processes, such as the dopaminergic mesolimbic system. Activation of CB1 receptors by plant-derived, synthetic, or endogenous CB1 receptor agonists increases rewarding effects of abused drugs and food.

In addition, CB1 receptors show high specific binding in the cerebral cortex, cerebellum, caudate/putamen, globus pallidus, substantial nigra, and hippocampus (5).

In this issue of *Biological Psychiatry*, Gérard *et al.* (2) have published the first study to investigate the CB1 receptor in ill AN and BN patients. The investigators used positron emission tomography and the selective CB1 receptor ligand [18F]MK-9470. The authors compared 16 BN, 14 AN, and 19 age-matched control women. Statistical parametric mapping and volume-of-interest analyses of CB1 receptor availability were performed. The authors found that global CB1 receptor availability was significantly increased in cortical and subcortical brain areas in AN patients compared with healthy control subjects. Importantly, regional CB1 receptor availability was increased in the insula in both AN and BN patients and in the inferior frontal and temporal cortex in AN patients.

The discovery of altered function of neural processes in AN and BN invariably raises the question of whether such findings are cause or a consequence of symptoms. When malnourished and emaciated, individuals with AN, and to a lesser degree BN, have widespread alterations of brain and peripheral organ function. Thus, determining whether symptoms and neural changes are a consequence or a potential cause of pathologic feeding behavior or malnutrition is a major methodologic problem in the field. In this study, statistical parametric mapping analysis showed that ill AN patients had a whole-brain gray matter increase in CB1 receptor availability of 24.5% compared with controls. The most parsimonious explanation is that abnormal CB1 receptor function is one of many malnutrition-induced compensatory responses in ill AN individuals, presumably to drive eating and weight restoration.

Interestingly and importantly, a regional analysis showed increased CB1 receptor binding in AN and BN in the insular cortex in comparison with healthy controls and altered inferior frontal and temporal cortex binding in AN. Research in the past decade has implicated abnormal insula and reward function in a range of EDs. For example, brain-imaging studies, using other technologies, show altered insula and often frontal response and striatal responses to pictures or tastes of food in AN individuals (6) and BN individuals (7) as well as obese subjects or obese binge eating subjects (8).

What role does the insula play in the modulation of appetite? In humans, the primary gustatory cortex is comprised of the frontal operculum and the anterior insula (AI). As Small (9) notes, the insula, as well as the overlying operculum and orbital frontal cortex, are regions of the brain that represent the sensory components of food such as taste, flavor, and oral texture, as well as hunger and insulin levels, and may also respond to its rewarding properties (6). These regions are thought to code hunger and satiety.

Brain-imaging studies have consistently shown that food deprivation (compared with having been fed) in healthy individuals activates the insula and the orbital frontal cortex (10). It is important to note that the AI, in general, is critically involved in interoceptive processing (11). Interoception includes a range of sensations beyond taste (e.g., pain, temperature, sensual touch, muscle tension, air hunger, stomach pH, and intestinal tension). Integration of these internal feelings provides a synthesized sense of the physiologic condition of the entire body and is important for the instantiation of the self because it provides the link between cognitive and affective processes and the current body state (11).

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There is an anatomical link between the AI and ventromedial putamen (12) that is thought to translate sensory-interoceptive-hedonic aspects of feeding into motivated motor behavior (approach or avoidance) of highly palatable foods (13).

In summary, these findings suggest that the AI response to palatable foods codes a biosignal related to the sensory-interoceptive aspects of appetitive behaviors and translates this signal into the motivation to eat.

The study by Gérard et al. (2) supports the possibility that endocannabinoid pathways contribute to abnormal hedonic input into sensory/interoceptive/motivation signals in AN and BN. It is important to mention that considerable data show that ill AN and BN patients have disturbances of a number of neuropeptides related to hypothalamic function; disturbances of serotonin, dopamine, and other neuromodulatory systems; and brain imaging evidence of dysregulation of higher cortical function (1).

Although speculative, the mixed symptoms of food restriction and anxiety, yet obsessive interest in food, raises the possibility of confusing and dysregulated interactions of converging signals regarding energy balance and the rewarding, emotional, cognitive, and homeostatic aspects of eating. For example, for AN, hypothalamic signals about the body being starved and in negative energy balance may work in concert with top-down signals regarding the rewarding aspects of palatable food consumption to drive an obsessive interest in food. But food intake may be inhibited by signals that miscode food consumption as anxiogenic or by an overdrive from inhibitory dorsal executive circuits.

Because the interactions of such signals are difficult to disentangle in a cross-sectional study during the ill state, it remains unknown whether altered CB1 receptor binding in the insula is a compensatory response to chronic malnutrition or contributes to the pathogenesis of this illness. Still, such findings may have important therapeutic implications, that is, to serve to identify new targets for medications that may help reverse emaciation in AN or help blunt overconsumption in BN.

Studies involving ill AN and BN patients are particularly challenging. It is often difficult to get subject cooperation in ill AN individuals, especially when drug administration is necessary. Thus, studies often consist of only small groups of subjects. In addition, substantial malnutrition, which results in metabolic, structural, and body composition abnormalities, creates methodological problems rarely experienced in other behavioral disorders. Little research has been done on developing methods to correct for such effects of malnutrition. For example, because many studies find AN, and to some extend BN, individuals have reduced brain volume, the authors tested for voxel based morphometry differences, although they found none. The AN patients had significantly lower weight than BN individuals and healthy controls. The authors attempted to control for this possible confounding factor by correcting for injected dose and the subject's body weight when modeling CB1 receptor availability.

In summary, this is an important new insight that supports the possibility that disturbances of components of the reward or hedonic systems contribute to ED behaviors. Studies in those recovered from an ED are warranted. If such findings persist after recovery, this would support the likelihood that abnormal CB1 receptor binding is a trait, although a scar from years of chronic malnutrition is also a possibility.

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