Brain imaging of serotonin after recovery from anorexia and bulimia nervosa

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Abstract

Anorexia nervosa (AN) and bulimia nervosa (BN) are related disorders with relatively homogenous presentations such as age of onset and gender distribution. In addition, they share symptoms, such as extremes of food consumption, body image distortion, anxiety and obsessions, and ego-syntonic neglect. Taken together, these observations raise the possibility that these symptoms reflect disturbed brain function, which contributes to the pathophysiology of these illnesses. Several lines of evidence suggest that disturbances of serotonin (5-HT) pathways play a role. First, 5-HT pathways contribute to the modulation of feeding, mood, and impulse control. Second, medications that act on 5-HT pathways have some degree of efficacy in individuals with AN and BN. Third, such disturbances are present when subjects are ill and persist after recovery, suggesting that 5-HT alterations may be traits that are independent of the state of the illness. Positron emission tomography (PET) with radioligands offers an opportunity to directly characterize brain 5-HT pathways and their relationship with behavior. For example, reduced 5-HT2A receptor function occurs in AN whereas increased 5-HT1A receptor function occurs in BN. Moreover, imaging studies correlate altered 5-HT1A and 5-HT2A receptor function with traits often found in individuals with AN and BN, such as harm avoidance. Finally, alteration of these receptors tends to implicate pathways involving frontal, cingulate, temporal, and parietal regions. Alterations of these circuits may affect mood and impulse control as well as the motivating and hedonic aspects of feeding behavior. Such imaging studies may offer insights into new pharmacology and psychotherapy approaches.

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contribute to the pathophysiology of AN [3–5]. First, drugs that act on these systems have some efficacy in the treatment of AN. Second, disturbances in the 5-HT system occur during illness and persist after recovery. Third, 5-HT neuronal systems contribute to the modulation of appetite, motor activity, mood and obsessional behaviors, and impulse control.

New studies using brain imaging with radioligands offer the potential for understanding previously inaccessible brain 5-HT neurotransmitter function and its dynamic relationship with human behaviors. Recovered AN and BN individuals have reduced postsynaptic 5-HT2A receptor activity [6,7] relative to controls in subgenual cingulate, mesial temporal, and parietal cortical regions. Audenaert [8] found that ill AN individuals had reduced 5-HT2A activity in the left frontal, bilateral parietal and occipital cortex. A most puzzling symptom of AN is the severe and intense body image distortion. It is well known that lesions in the right parietal cortex may result in denial of illness and body image distortion [9]. Bailer [7] reported negative relationships between 5-HT2A receptor activity and the Drive for Thinness subscale of the Eating Disorders Inventory in the left parietal cortex and other regions, raising the speculation that left hemisphere disturbances of this pathway contribute to body image distortion in AN.

Recovered bulimic-type AN [10] had increased 5-HT1A postsynaptic activity in the subgenual cingulate and mesial temporal regions, and frontal and other cortical regions, as well as increased presynaptic 5-HT1A autoreceptor activity in the dorsal raphe nucleus. Increased 5-HT1A postsynaptic activity has been reported in ill BN subjects [11]. However, recovered restrictor-type AN have normal 5-HT1A receptor activity [10].

Studies from our group tend to find that when alterations of 5-HT2A and 5-HT1A receptor activity are present, they occur in subgenual cingulate and mesial temporal regions. Other brain imaging studies [3] have found frontal, cingulate, and temporal changes in ill and recovered AN individuals. The subcaudal cingulate is involved in conditioned emotional learning, vocalizations associated with expressing internal states and assigning emotional valence to internal and external stimuli [12]. Mesial temporal regions include the amygdala and related regions which play a pivotal role in anxiety and fear [13] as well as in the modulation and integration of cognition and mood. Together these findings raise the possibility that mesial temporal (amygdala)—cingulate regional dysfunction may be a trait shared by AN and BN. Interestingly, several lines of evidence show that 5-HT1A and 5-HT2A receptors coexist and interact in frontal cortex, amygdala, and hypothalamic regions [14,15] and contribute to the modulation of dopamine or norepinephrine neuronal activity, hormone secretion, and cortical neurons which play a role in working memory, attention, motivation, and concentration. A relative imbalance of 5-HT1A and 5-HT2A receptor interactions in AN and BN may shed light on how alterations of the 5-HT system contribute to the pathophysiology of these illnesses.

It is important to use these findings to generate new hypotheses that can then be tested. We hypothesize that a disturbance of 5-HT neuronal modulation predates the onset of an eating disorder, and contributes to premorbid anxious, obsessional, and perfectionistic childhood traits. Several factors may act on these vulnerabilities to cause AN and BN to begin in adolescence. First, pubertal-related female gonadal steroids or age-related changes may exacerbate 5-HT dysregulation. Second, stress and/or cultural and societal pressures may contribute by activating these systems. With normal dietary intake, this 5-HT disturbance may result in increased 5-HT transmission, which in turn, creates a vulnerability for restricted eating, as well as obsessional behaviors and dysphoric mood states. We hypothesize that people with AN may discover that reduced dietary intake, by reducing plasma tryptophan availability and/or reducing gonadal steroid hormone metabolism, is a means by which they can reduce brain 5-HT functional activity and thus anxious mood. A better understanding of the pathophysiology of ED may lead to a more rational choice of medications, new drug targets, and more specific psychotherapies. In addition, it is now possible to investigate the potential relationship of 5-HT functional activity and stereotypic core symptoms such as feeding, temperament and personality, body image distortion, cognition, physical exercise, as well as age of onset and gender. Thus, we need to ally with basic science colleagues who can model 5-HT function and these domains in animals.

References


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