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Serotonin alterations in anorexia and bulimia nervosa: New insights from imaging studies

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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, raises the possibility that these symptoms reflect disturbed brain function that contributes to the pathophysiology of this illness. Recent brain imaging studies have identified altered activity in frontal, cingulate, temporal, and parietal cortical regions in AN and BN. Importantly, such disturbances are present when subjects are ill and persist after recovery, suggesting that these may be traits that are independent of the state of the illness. Emerging data point to a dysregulation of serotonin pathways in cortical and limbic structures that may be related to anxiety, behavioral inhibition, and body image distortions. In specific, recent studies using PET with serotonin specific radioligands implicate alterations of 5-HT_{1A} and 5-HT_{2A} receptors and the 5-HT transporter. 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.

Keywords: Anorexia nervosa; Bulimia nervosa; Eating disorders; Serotonin; Brain imaging

1. Introduction

Anorexia nervosa (AN) and bulimia nervosa (BN) are disorders characterized by aberrant patterns of feeding behavior and weight regulation, and disturbances in perceptions of body weight and shape. In AN, there is an inexplicable fear of weight gain and unrelenting obsession with fatness even in the face of increasing cachexia. BN usually emerges after a period of dieting, which may or may not have been associated with weight loss. Binge eating is followed by either self-induced vomiting, or by some other means of compensation for the excess of food ingested. Thus restrained eating behavior and dysfunctional cognitions relating weight and shape to self-concept are *shared* by both AN and BN. Moreover, it is thought that AN and BN share risk and liability factors because these disorders are cross transmitted in families and because many people cross over between AN and BN [1,2]. Individuals with AN and BN are similar in that both tend to be anxious, obsessional, and perfectionistic. Other symptoms, such as impulsivity and behavioral dyscontrol, differentiate AN and BN. Some of these behaviors tend to occur in childhood before the onset of an eating disorder (ED) [3] suggesting they may be susceptibility factors for developing an ED. Moreover, studies [3] have found that perfectionism, inflexible thinking, restraint in emotional

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expression, social introversion, body image disturbances, and obsessions related to symmetry, exactness, and order persist after recovery from an ED.

There is a growing understanding of how genetic and neurobiologically-mediated mechanisms contribute to a susceptibility to develop ED. For example, studies of twins with AN and BN support the hypothesis that a significant genetic contribution to liability for AN [4,5] and BN [1,6] is accounted for by additive genetic factors. These heritability estimates are in line with those found in studies of schizophrenia and bipolar disorder, suggesting that EDs may be as 'genetically-influenced' as disorders traditionally viewed as biological in nature.

Several lines of evidence nominate disturbances of serotonin (5-HT) pathways as playing a role in the pathogenesis and pathophysiology of AN. For example, 5-HT pathways are known to contribute to the modulation of a range of behaviors commonly seen in individuals with AN and BN. That is, 5-HT has been implicated in personality or temperament traits such as harm avoidance [7] or behavioral inhibition [8]. Moreover, 5-HT has been implicated psychiatric symptoms such as obsessionality [9], anxiety and fear, [10] or depression [11], as well as physiological traits such as satiety for food consumption. Second, many studies show disturbances of 5-HT activity in individuals who were ill or recovered from AN and BN. Third, medications that act on 5-HT pathways have some degree of efficacy in individuals with ED.

It is important to emphasize that brain neurotransmitter pathways do not work in isolation. Neurotransmitter systems have complex interactions so that it is likely that multiple systems are involved. In terms of clinical research in humans, we have perhaps more tools for investigating 5-HT activity and more understanding of its function than for other neurotransmitters systems. For that reason, and because of limited space, 5-HT will be the focus of this paper. The past decade has seen the introduction of tools, such as brain imaging and genetics, which hold the promise of being able to characterize complex systems in living humans, and their relationship to behavior. In fact, these tools have rapidly advanced knowledge to the point where we can begin to make educated guesses about the pathophysiology of AN and BN and start to model mechanisms that may be used to test hypotheses.

2. Relationship of symptoms to state and trait

When ill, people with AN and BN commonly have neuroendocrine, autonomic and metabolic disturbances as well as comorbid psychiatric symptoms such as depression, anxiety, and obsessionality. Malnutrition exaggerates these symptoms as there is a reduction, but persistence, of symptoms after nutritional restoration. Determining whether such symptoms are a consequence or a potential cause of pathological feeding behavior or malnutrition is a major methodological issue in the field. It is difficult to study individuals with AN and BN prospectively due to the young age of onset and difficulty in premorbid identification of people who will develop an ED. An alternative strategy is to identify behavioral phenotypes that are independent of the confounding effects of malnutrition by studying women who have recovered from AN and BN. The assumed absence of confounding nutritional influences in women who have recovered from an ED raises a possibility that persistent psychobiological abnormalities might be trait-related and potentially contribute to the pathogenesis of this disorder. While a definition of recovery has not been formalized, investigators tend to include people after they were at a stable and healthy body weight for months or years and had not been malnourished or engaged in pathological eating behavior during that period of recovery. Some investigators include a criterion of normal menstrual cycles and a minimal duration of recovery, such as 1 year.

In fact, studies [12–16] have found that women who were long-term recovered from AN and BN have a persistence of anxiety, perfectionism, and obsessional behaviors (particularly symmetry, exactness, and order). Moreover, long-term recovered AN and BN had continued core ED symptoms, such as ineffectiveness, a drive for thinness, and significant psychopathology related to eating habits. Recent studies [17,18] show that these behaviors often exist premorbidly, in childhood, before the onset of an ED. The presence of these symptoms premorbidly and the persistence of these symptoms after recovery support the possibility that such behaviors are traits that contribute to a susceptibility to develop AN and BN.

3. Serotonin-physiological studies

Several authors have reviewed evidence for 5-HT dysregulation in individuals who were ill with AN and BN [3,19–23]. For example, when underweight, individuals with AN have a significant reduction in basal concentrations of the 5-HT metabolite 5-hydroxyindolacetic acid (5-HIAA) in the cerebrospinal fluid (CSF) compared to healthy controls, as well as blunted plasma prolactin response to drugs with 5-HT activity and reduced 3H-imipramine binding. Considerable evidence also exists for a dysregulation of serotonergic processes in BN. Examples include blunted prolactin response to the 5-HT receptor agonists m-chlorophenylpiperazine (m-CPP), 5-hydroxytrytophan, and dlfenfluramine, and enhanced migrainelike headache response to m-CPP challenge. Acute perturbation of serotonergic tone by dietary depletion of tryptophan has also been linked to increased food intake and mood irritability in individuals with BN compared to healthy controls. Together, these findings suggest altered serotonergic activity. Whether this is caused by reductions in dietary supplies of the 5-HT synthesizing amino acid tryptophan, or by other effects of malnutrition on hormonal or neuro-

transmitter systems remains uncertain. Malnutrition in AN (and to a lesser extent in BN) affects many systems in the body, so it is not surprising that alterations in 5-HT function have been found.

A number of investigators have reported alterations in 5-HT function in individuals who are recovered from AN and BN. While hormones have been used as a reflection of central nervous system (CNS) 5-HT, hormones are altered by malnutrition [24–26] or may be relatively independent of brain 5-HT activity [27]. Thus it is not surprising that hormonal responses to 5-HT specific drugs are normal [15,28–30]. However, considerable evidence, from behavior response to 5-HT challenges [15,29,31–33] have found that depletion of tryptophan (TRP), the precursor of 5-HT or 5-HT-specific agents, alters behavioral responses in individuals who are recovered from AN and BN. Furthermore, CSF concentrations of 5-HIAA were elevated in individuals who were long-term weight recovered from AN [34] and BN [15]. In addition, Steiger et al. [35] found that individuals remitted from bulimia have reduced platelet [3H-] paroxetine binding, which is thought to be a peripheral marker of 5 transporter (5-HTT) activity [36]. Finally some studies have raised the possibility that 5-HT dysfunction may be related to traits, such as borderline personality disorder, rather than the diagnosis of an ED [22,37–39].

Several polymorphisms in genes involved in the serotonergic system have been studied in AN and BN. In general, samples are small, and not all studies have positive findings [40]. For example, some studies have found an association between AN and the −1438G/A polymorphism within the promoter region of the 5-HT_{2A} receptor gene, showing a higher frequency of A allele and AA genotype in individuals with anorexia than in controls. Some studies of a functional polymorphism in the promotor region of the 5-HTT gene (5-HTTLPR), have found increased frequency of the short allele in individuals with BN [41,42] and AN [41–45]. Other studies have linked 5-HT gene variants, in ED patients, to heightened impulsivity and Borderline PD [46,47].

4. Serotonin—medication studies

The efficacy of antidepressant medications in the treatment of BN has been demonstrated in a number of double-blind, placebo-controlled trials [3]. Beneficial effects have been seen across a variety of medication classes, including earlier trials with tricyclic agents and monoamine oxidase inhibitors, and more recent studies with serotonin specific reuptake inhibitors (SSRI). Participants often reported that medication resulted in a significant reduction in binge frequency, when compared to blind-administration of placebo. However, a minority of patients in the medication treatment trials actually achieved full abstinence from binge eating and purging behaviors. While antidepressant administration may contribute to a reduction in symptoms of depression, the reduction in bulimic symptoms does not appear to be correlated with the magnitude of the antidepressant response. A preliminary trial showed a decrease in the frequency of bulimic symptoms in severely symptomatic patients who were treated with the 5-HT3 receptor antagonist ondansetron [48].

The role of medication treatment in low-weight patients with AN has been limited [3]. One agent which appeared to accelerate weight gain in an early trial in AN was cyproheptadine [49], a drug with 5-HT properties. However, the magnitude of this effect was quite small. In contrast to the effectiveness of antidepressant medications in patients with BN, initial studies showed limited benefit with traditional antidepressant agents. Several studies have failed to demonstrate a beneficial effect for the addition of SSRIs in the treatment of hospitalized AN patients [50–52]. AN patients who have achieved weight restoration often have persisting psychological symptomatology accompanied by a significant risk of recurrence of low weight episodes, leading to interest in studies of relapse prevention. A clinically based, prospective longitudinal follow-up study failed to show significant benefit of fluoxetine treatment in comparison to historical controls [53]. However, recent data from a double-blind, placebo-controlled trial in weight-restored patients demonstrated that fluoxetine treatment was associated with reduced relapse rate and reductions in depression, anxiety, and obsessions and compulsions. Results of this study showed that after 1 year, 10 of 16 subjects treated with fluoxetine remained well while only 3 of 19 remained well during placebo treatment [54].

5. Brain imaging studies using 5-HT ligands

New technology using brain imaging with radioligands offers the potential for understanding previously inaccessible brain 5-HT neurotransmitter function and its dynamic relationship with human behaviors. Technologies used to date include single photon emission computed tomography (SPECT) and positron emission tomography (PET) studies. Differences in resolution of imaging technologies, radioligands, characteristics of subject groups, and regions of interest make it difficult to directly compare studies in terms of brain pathways involved. Still, these studies tend to have consistent findings.

5.1. 5-HT_{2A} receptor

The receptor is of interest because it has been implicated in the regulation of feeding, mood, and anxiety, and in antidepressant action [55]. Studies from our group have used PET with [18F]altanserin binding potential (BP) to characterize the $5HT_{2A}$ receptor. Our group [56,57] has found that both REC AN and AN-BN have reduced [18F]altanserin BP in the subgenual cingulate, parietal,

and occipital cortex (Table 1). In addition, REC AN had reduced [18F]altanserin BP of the mesial temporal region and pregenual cingulate [56]. Other studies of ill, underweight AN, which used SPECT with a 5-HT_{2A} receptor antagonist [58], found a significant reduction of 5-HT_{2A} receptor activity in the left frontal cortex, the left and right parietal cortex, and the left and right occipital cortex. It is not certain whether the cingulate regions were investigated or whether ill AN subjects were pure restrictors or included any AN-BN subtypes. Ill BN have been found to have normal 5-HT_{2A} receptor activity [59] while REC BN have reduced [18F]altanserin BP in the medial orbital frontal cortex [60]. These studies are consistent in terms of reporting reduced 5-HT_{2A} activity in cortical regions in AN, and findings are independent of state of illness. It is less certain whether there is a 5-HT_{2A} alteration in BN. It should be noted that samples sizes are relatively small. Moreover, investigators have concentrated on assessment of different regions, and imaging techniques vary in terms of resolution. Thus, much work remains in terms of identifying specific regions and pathways that may be involved in ED.

Bailer [57] found that REC AN-BN subjects showed a positive relationship between [^{18}F]altanserin BP and harm avoidance in the left subgenual cingulate and mesial temporal cortex. Furthermore negative relationships between novelty seeking and [18F]altanserin BP were found in REC AN-BN in the left subgenual cingulate, the pregenual cingulate, and mesial temporal cortex. Finally, REC AN-BN had a negative relationship between the Eating Disorder Inventory - Drive for Thinness (EDI-DT) subscale and [18F]altanserin BP in the right subgenual cingulate, right pregenual cingulate, the lateral temporal cortex, the left parietal cortex, and the prefrontal cortex. No other studies have reported relationships between $5HT_{2A}$ binding and behavior in individuals with ED.

AN and BN are thought to share some common etiologic factors [61]. Still, a number of characteristics distinguish the subgroups, such as extremes of eating behavior and impulse control. The studies described above raise the possibility that anorexic subtypes may share a disturbance of 5-HT_{2A} receptor activity of the subgenual cingulate, whereas regional differences in 5-HT_{2A} receptor activity may distinguish ED subgroups after recovery. The subgenual cingulate is thought to have a role in emotional and autonomic response [62] and a disturbance of this region has been implicated in mood disorders [63–70]. Mood disturbances are common in individual with EDs, although it has been controversial as to whether EDs and mood disorders are independently or commonly transmitted in families [71]. Interestingly, individuals with EDs have disturbances of energy metabolism when ill (see de Zwaan et al. [72] for review) and persistent but mild sympathetic alterations after recovery. Recent demonstration of dense projections from the subgenual cingulate cortex (area 25) to the dorsal raphe raises the tantalizing possibility that the subgenual cortex plays some role in regulating overall serotonergic activity. In fact, in control women (CW) the subgenual cingulate has the highest density of [18F]altanserin binding of any region. Together these data raise the possibility that some factor related to subgenual cingulate function creates a vulnerability for anorexia, perhaps related to mood and autonomic modulation. Alternatively, patterns of receptor activity might correspond to trait variations (that load differently in individuals with AN and BN), rather than to syndromic differences between AN and BN themselves.

The AN studies described above [56–58] have all found alterations in $5HT_{2A}$ activity in the left parietal region. Furthermore, Bailer [57] found negative relationships between [18F]altanserin BP and the a measure of drive for thinness in several regions including the left parietal cortex. A core symptom in AN is the relentless pursuit of thinness and obsessive fear of being fat. These finding raises the speculation that left parietal alterations in REC AN and AN-BN might contribute to body image-distortions. It is well known that lesions in the right parietal cortex may not only result in denial of illness, but may also produce experiences of disorientation of body parts and body image distortion [73]. Mesulam [74] describes a network involving parietal, frontal, cingulate and limbic pathways that modulates spatial attention. The refractory body image distortion in

Table 1
↓ indicates significantly decreased values, ↑ indicates significantly increased values, and nl indicates similar values in ill and REC AN and BN compared to matched controls

Year	Author	Technology	ILL subjects	REC subjects	*n*	Frontal	Cingulate	Temporal	Parietal
2002	Frank	PET $5HT_{2A}$		AN	16	nl	↓	↓	nl
2003	Audenaert	SPECT 5-HT_{2A}	AN		15	↓		nl	
2004	Bailer	PET $5HT_{2A}$		AN–BN	10	nl	↓	↓	↓
2004	Goethals	SPECT 5-HT_{2A}	BN		10	nl	nl	nl	nl
2001	Kaye	PET $5HT_{2A}$		BN	9	↓	nl	nl	nl
In press	Bailer	PET $5HT_{1A}$		AN	13	nl	nl	nl	nl
In press	Bailer	PET $5HT_{1A}$		AN–BN	12	↑	↑	↑	↑
Submitted	Henry	PET $5HT_{1A}$		BN	10	↑	↑	↑	↑
2004	Tiihonen	PET $5HT_{1A}$	BN		8	↑	↑	nl	nl
2001	Tauscher	SPECT 5-HTT	BN		10	decreased subcortical			
Submitted	Bailer	PET 5-HTT		AN–BN	5	decreased dorsal raphe and mesial temporal cortex			
Submitted	Bailer	PET 5-HTT		BN	8	nl			

patients suffering from anorexia nervosa is a central feature of the illness. Other studies, using functional magnetic resonance imaging, support the speculation that left parietal disturbances may contribute to body image distortion [75].

5.2. 5-HT_{1A} receptor

Studies in animals and humans raise the possibility that alterations of the 5-HT_{1A} receptor may play a role in anxiety [76–78], mood and impulse control [79–81], feeding behavior [82–84], as well as SSRI response [55,85].

Our group has used PET imaging with the radioligand [^{11}C]WAY100635 to assess pre- and post-synaptic 5-HT_{1A} receptor function. We found that REC AN-BN [86] had increased [^{11}C]WAY100635 BP in prefrontal, lateral and medial orbital frontal, lateral temporal, parietal, supra- and pregenual cingulate regions as well as in the dorsal raphe, after adjustment for multiple comparisons (Fig. 1). REC AN did not differ significantly from matched CW in any of the assessed regions. Preliminary data in REC BN [87] has also found increased [^{11}C]WAY100635 BP throughout the cortex and in the raphe. In support of this possibility, increased postsynaptic 5-HT_{1A} activity has been reported in ill BN subjects [88] using PET and[11C]WAY100635. Ill BN had increased [11C]WAY100635 in frontal, cingulate, temporal, and raphe regions The most robust differences were observed in the angular gyrus, the medial prefrontal cortex, and the posterior cingulate cortex. Together, these data raise the provocative possibility that increased activity of the 5-HT_{1A} receptor may only be found in individuals with bulimic-type symptoms.

5.3. 5-HT transporter (5HTT)

Our laboratory has used PET with [11C]McN 5652 BP to assess regional 5-HTT activity. Only REC AN-BN had significantly reduced [11C]McN 5652 BP values for the dorsal raphe and mesial temporal cortex (Fig. 1). Others have found reduced 5-HTT activity in imaging studies of individuals when they were ill with bulimia. Tauscher [89] found a reduction in 5-HTT availability in the thalamus and hypothalamus in 10 women who were ill with BN. Two of those individuals had a history of AN but specific imaging data for those 2 individuals were not identified. Kuikka [90] found a reduction of 5-HTT in the midbrain in people who were ill with binge eating disorder (BED). As noted above, some studies of a functional polymorphism in the promotor region of the 5-HTT gene (5-HTTLPR), have found increased frequency of the short allele in individuals with BN [41,42] and AN [41–45]. The short allele, which produces reduced transcriptional efficiency of the 5-HTT promoter, results in decreased 5-HT reuptake [45,91]. This is potentially consistent with reduced [11C]McN 5652 BP on PET imaging.

6. Implications

It is important to emphasize that findings of abnormal 5-HT function in individuals that are recovered from AN and BN are remarkably consistent. As described above, *all studies* of CSF 5-HIAA, behavioral response to 5-HT provocative challenges, and brain imaging with 5-HT ligands. find persistent abnormalities in the REC state. Compared to other behavioral disorders, AN and BN are relatively homogenous. Individuals have relatively similar symptoms, and the course of the illness is gender and age specific. It is likely that this relative homogeneity contributes to these robust findings.

While the etiology of disturbance of 5-HT function is unknown, studies from several groups suggest it is reflected in alterations of 5-HT_{1A} and 5-HT_{2A} receptor activity, the 5-HTT, and CSF 5-HIAA levels. Moreover, other studies raise the possibility of gene polymorphisms in the 5-HT system. Together, these data suggest that many components of the 5-HT neuronal system are involved in individuals with ED.

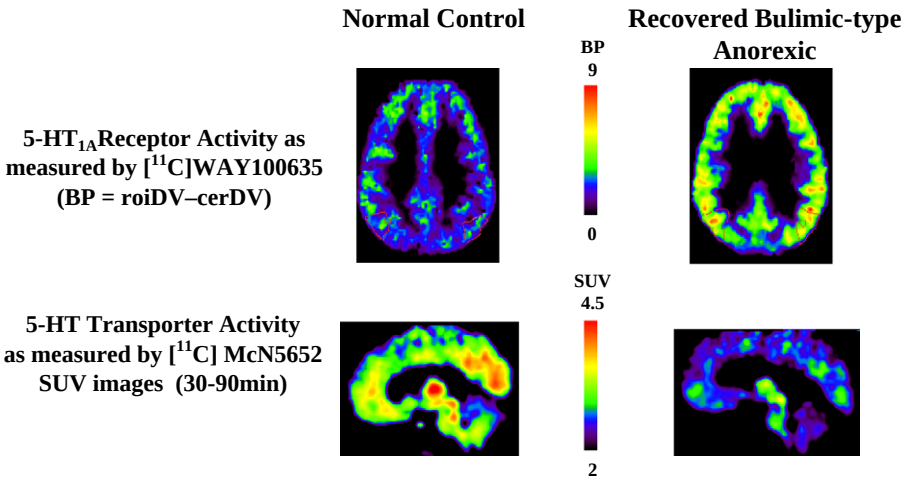

Fig. 1. Representational comparison of PET 5-HT radioligand findings in a women recovered from BAN and a CW.

Thus it is possible that individuals with ED have a dysregulation of the function of neural circuits, perhaps related to disturbances of a number of components of that circuit, such as receptors, or molecules forming the intracellular cascade that translates receptor signals. It is well known that neuronal activity is an integration of many factors such as neuronal firing, synaptic release and reuptake, intracellular mechanisms, and interactions with other neuronal systems. However, limitations of technology have not permitted characterization of the complexities of such systems in studies in humans in vivo. It is likely that in order to understand pathophysiology in humans, we will need to be able to characterize the complexity of brain circuits.

For example, only REC RAN [92] had positive relationships between harm avoidance and postsynaptic [11C]WAY100635 BP in subgenual cingulate, mesial temporal, lateral temporal, medial orbital frontal, and parietal cortex. Such correlations were not found in REC BAN subjects. It is of much interest that other studies from our group [57] found that REC BAN had positive relationships between harm avoidance and [18F]altanserin BP in the left subgenual cingulate, left lateral temporal and mesial temporal cortex. Such relationships were not found in REC RAN [56]. Together, these studies raise the possibility that cingulate and temporal regions may play a role in elevated harm avoidance in people with EDs.

Recent data raise the possibility that the interaction and balance between 5-HT_{1A} and 5-HT_{2A} receptor activity may be important. Postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors are co-localized and interact to mediate, respectively, the direct hyperpolarizing and depolarizing actions of 5-HT on cortical neurons, [93] which in turn project to numerous cortical and subcortical areas. Thus a balance between postsynaptic 5-HT_{1A} and 5-HT_{2A} receptor activity on neurons may modulate the descending excitatory input into limbic and motor structures [94]. While REC RAN and BAN individuals may have differences in 5-HT_{1A} and 5-HT_{2A} receptor activity, the balance between these 2 receptors (e.g. relatively more 5-HT_{1A} than 5-HT_{2A} receptor activity) appears to be similar for RAN and BAN individuals (unpublished data), and this balance may be altered compared to CW. Other data from our laboratory [95] suggest that the balance of postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors contributes to modulating behavior inhibition in healthy women.

Could alterations of 5-HT_{1A} and 5-HT_{2A} receptor interactions in cingulate-temporal regions be related to symptoms of harm avoidance? Harm avoidance is common in AN [96,97]. Moreover most individuals with ED have anxious as well as obsessive-compulsive behaviors, which often start in childhood before the onset of their ED [17,18]. The anterior cingulate, a region that normally serves to inhibit amygdala reactivity [98] also has connections to the periaqueductal gray. 5-HT_{1A} and 5-HT_{2A} in this region contribute to the modulation of escape behavior in rats, a defensive behavior that has been related to panic disorder [99]. The subgenual cingulate is involved in conditioned emotional learning, vocalizations associated with expressing internal states and assigning emotional valence to internal and external stimuli [100–102]. It is thought to have a role in emotional and autonomic response as well as in regulating overall serotonergic activity [62] and has been implicated in depression [65,68–70]. Mood disorders are common in EDs [71], as are disturbances of energy metabolism [72]. The subgenual cingulate has extensive connections with the amygdala, periaqueductal grey, frontal lobes, ventral striatum, and autonomic brainstem nuclei. Mesial temporal regions include the amygdala and related regions which play a pivotal role in anxiety and fear as well the modulation and integration of cognition and mood. The amygdala may enable the individual to initiate adaptive behaviors to threat based upon the nature of the threat and prior experience [103]. Finally, increased 5-HT_{1A} receptor activity may inhibit function of the anterior cingulate, a region that normally serves to inhibit amygdala reactivity [98], thus contributing to heightened amygdala response. In summary, these data could suggest that 5-HT related alterations of subgenual cingulate and amygdala regions contribute to anxious behaviors in AN.

7. Summary

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 ED, 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 adolescent. 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 EDs 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 ED symptoms such as feeding, temperament and personality, body image distortion, cognition, physical exercise, as well as age of onset and gender.

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