REVIEW

Eating Disorders and Depression: Is There a Serotonin Connection?

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Central serotonin pathways modulate eating patterns, and may also participate in the regulation of behavioral impulsivity and mood. Recent studies lend support to the hypothesis that impaired postingestive satiety in bulimia nervosa is associated with reduced hypothalamic serotonergic responsiveness. Serotonin dysregulation has been implicated in major depression, and may play a role in the increased prevalence of depressive episodes in patients with eating disorders. This review compares evidence for alterations in central serotonin regulation in patients with anorexia nervosa, bulimia nervosa, and depression. It is proposed that impaired synaptic transmission in functionally distinct serotonin pathways may result in concurrent or sequential periods of binge eating, behavioral impulsivity, and depression in patients with eating disorders.

Introduction

Over the past decade there has been increasing research on the possible involvement of central nervous system (CNS) serotonin in the pathophysiology of anorexia nervosa and bulimia nervosa. As reviewed by Blundell (1984), Leibowitz (1988), and others, central serotonin pathways, particularly involving the paraventricular nucleus of the hypothalamus, play a major role in mediating postprandial satiety. Thus, lesions or pharmacological antagonism of these serotonin pathways leads to increased meal size with little effect on the latency for onset of eating or the rate of eating. Conversely, interventions that augment the function of hypothalamic serotonin pathways result in behavioral signs of satiety and diminished meal size. These preclinical data have contributed to the hypothesis that impaired hypothalamic serotonin function in bulimic patients creates a vulnerability to recurrent episodes of large binge meals. Results from clinical studies, reviewed below, provide indirect evidence for blunted serotonergic responses in patients with bulimia nervosa.

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Anorexia nervosa is classically a syndrome of abstinence from food. Abnormally potentiated hypothalamic serotonin, with resulting exaggerated satiety responses, could contribute to weight loss in patients with anorexia nervosa. As reviewed below, research efforts to substantiate this proposal in low-weight patients have met with limited success. Approximately half of anorexic patients manifest recurrent episodes of binge eating and behavioral profiles similar to normal-weight bulimic patients (Kassett et al. 1987). Accumulating data indicate that serotonergic responsiveness is decreased in bulimic anorexic patients in comparison to nonbulimic (restrictor) anorexics.

Interest in the relationship between eating disorders and mood disorders grew out of the observation that more than half of patients with anorexia nervosa have a history of a major depressive episode (Gershon et al. 1983; Hudson et al. 1983b; Herzog and Copeland 1985). A similarly high frequency of depression was noted in patients with bulimia (Hudson et al. 1983b; Piran et al. 1985; Walsh et al. 1985; Hudson et al. 1987c; Kassett et al. 1989). Depressive episodes often precede the onset of the eating disorder, indicating that the former are not simply a consequence of the latter. Moreover, family studies have shown that patients with eating disorders, compared to controls, have significantly increased prevalence of depression in first-degree relatives (Hudson et al. 1983a; Gershon et al. 1984; Hudson et al. 1987a; Kassett et al. 1989).

Analyses of the relationship between eating disorders and depression have considered the probable importance of similar developmental experiences, family environment, and psychosocial stressors, as well as biological factors (Swift et al. 1986; Vandereyecken 1987; Hudson and Pope 1987; Laessle et al. 1987). Recent reports, however, have noted significant differences in specific neurobiological test results between the eating disorders and depressive syndromes (e.g., Levy et al. 1989).

This paper reviews evidence that abnormal regulation of CNS serotonin may act as a shared neurobiological vulnerability for eating disorders and depression. The discussion below selectively summarizes related studies in depressed patients (Meltzer 1987). Although beyond the scope of this paper, studies of serotonin function in these patient groups need to be considered in the context of possible alterations in other neurotransmitter and neuropeptide systems.

CSF Metabolite Studies

Studies of the major serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF) provided evidence for decreased CNS serotonin activity in anorexia nervosa (Table 1). In one study that separated low-weight anorexic patients according to bulimic and nonbulimic (restrictor) eating patterns, CSF 5-HIAA levels were not significantly different for these two subgroups (Kaye et al. 1984a). In anorexic patients studied following weight recovery, however, postprobenecid accumulation of 5-HIAA was lower in bulimic than in nonbulimic patients, consistent with an association between bulimia and reduced serotonin activity. Though decreased norepinephrine metabolite levels (e.g., urinary MHPG) in anorexic patients were related to symptoms of depression in some studies (Halmi et al. 1978; Biederman et al. 1984), a similar relationship has not been noted between CSF 5-HIAA concentrations in anorexia nervosa and symptoms of depression. CSF 5-HIAA levels have not, however, been compared among subgroups of anorexic patients identified according to present, past, or family history of major depression, or history of impulsive behaviors. Serotonin metabolite levels return to a normal range relatively promptly when patients regain weight, at a time when psychological symptoms

Table 1. Studies of CSF 5-HIAA in Anorexia Nervosa

Author	No. of subjects		CSF 5-HIAA (% of control)		Clinical correlates: depression, and other symptoms
	Low wt.	Goal wt.	Low wt.	Goal wt.	
Gillberg (1983)	2	—	↓[a]	—	—
Kaye et al. (1984b)	8	8	78	117[b]	—
Gerner et al. (1984)	33	—	88	—	Correlation with depression ratings NS
Kaye et al. (1987)	15	11	65[c]	86[b]	Difference between bulimic and nonbulimic patients NS. Correlation with wt or depression ratings NS

[a]Values lower than range for controls.
[b]Significant increase with weight gain.
[c]$p < 0.01$, patients versus controls.

of anorexia tend to persist, suggesting that decreases in metabolite levels in low-weight patients are nutritionally related. Recent preliminary results indicate that CSF 5-HIAA levels in patients who have maintained stable weight-recovery for at least 6 months are higher than control values (Kaye et al. 1989). Here again, the possible influence of abnormal dietary patterns needs to be evaluated.

As a group, bulimic patients in a normal weight range have normal CSF 5-HIAA levels (Jimerson et al. 1988b; Kaye et al. 1990). Patients with a history of bingeing twice a day had metabolite levels lower than less symptomatic patients and lower than healthy controls (Jimerson et al. 1988b). History of major depression was similar for patients in the low and high binge frequency subgroups.

Studies of major depression do not show a consistent relationship between the severity of current depressive symptoms and CSF 5-HIAA levels (Jimerson and Berrettini 1985; Meltzer 1987). Depressed patients with a history of suicidal or other impulsive aggressive behaviors do have low CSF 5-HIAA levels (Asberg et al. 1976; Brown et al. 1979). Serotonin measures are decreased in other patient groups with a history of impulsive and aggressive behaviors (Coccaro et al. 1989). Thus, an association between impulsive behavior patterns and reduced serotonin function may be more robust than the evidence for decreased CNS serotonin turnover in depression per se (van Praag et al. 1987).

Precursor Availability

Central serotonin synthesis is influenced by the availability of the precursor amino acid L-tryptophan (Fernstrom and Wurtman 1972). The rate of transport of tryptophan from blood to CNS increases with an increase in the ratio of the concentration of tryptophan to other large neutral amino acids, which compete for a shared transport mechanism (T/LNAA ratio). Low tryptophan or low carbohydrate diets can decrease this ratio (Fernstrom and Wurtman 1971; Wurtman and Wurtman 1984). Behavioral consequences of a low T/LNAA ratio might include impaired satiety, depressed mood, and increased impulsiveness.

In an initial study by Coppen et al. (1976), plasma-free and total tryptophan measured after overnight fast were significantly lower in 6 anorexic patients than in healthy controls. Plasma total tryptophan returned to control levels with weight restoration, although levels of the free amino acid remained low. Subsequently, Kaye et al. (1984b) reported normal values for plasma-free tryptophan, plasma total tryptophan, plasma T/LNAA ratio, and CSF tryptophan after overnight fast in 7 anorexic patients. More recently, Goodwin et al. (1989) also described normal fasting plasma tryptophan levels in hospitalized anorexic patients. Lydiard et al. (1988) reported that plasma T/LNAA ratio in normal weight bulimic patients studied after overnight fast was not different from control values.

Basal levels thus appear to be normal in eating disorder patients, but several studies have reported abnormally low postprandial T/LNAA ratios in these patient groups. Thus, anorexic patients showed an exaggerated decrease in the plasma T/LNAA ratio following a protein-rich test meal, and a blunted increase following a carbohydrate-rich test meal (Schweiger et al. 1986). Similarly, bulimic patients showed an abnormally large drop in the T/LNAA ratio after a protein-rich test meal (Broocks et al. 1988). It is not known whether abnormal postprandial levels of plasma amino acids predate or result from chronically abnormal meal patterns in the patients tested. Moreover, it is not clear whether the magnitude and duration of these differences is sufficient to result in behaviorally meaningful decreases in central serotonin synthesis. It is of interest that bulimic patients experiencing less satiety after a large binge meal tended to have relatively smaller increases in the T/LNAA ratio than other patients (Kaye et al. 1988).

Abnormal glucose metabolism in diabetic, obese subjects has been associated with low baseline values for plasma T/LNAA ratio (Ashley et al. 1985). It is of note that the research group reporting low postprandial T/LNAA ratios in bulimia also observed abnormal glucose tolerance test (GTT) results, suggestive of insulin resistance in their bulimic patients (Schweiger et al. 1987). Insulin resistance could potentially contribute to low T/LNAA ratios (Wurtman and Wurtman 1984). Abnormal GTT responses are not observed in all bulimic subjects (Casper et al. 1988), however, suggesting that severity of dietary abnormalities or other clinical characteristics may identify a subgroup of patients with abnormal test meal responses.

Some studies of depressed patients have reported low levels of plasma tryptophan or low plasma T/LNAA ratio (DeMyer et al. 1981; Joseph et al. 1984; Cowen et al. 1989). In healthy volunteers, manipulations that reduce tryptophan availability can produce symptoms of depression (Young et al. 1985). Studies of eating disorder patients during episodes of depression are needed to clarify whether mood changes coincide with periods of significantly reduced plasma T/LNAA ratio.

Neuroendocrine Studies

The magnitude of the increase in plasma prolactin level following administration of a serotonin agonist provides a measure of functional activity in hypothalamic serotonin pathways (Murphy et al. 1986). Patients with anorexia nervosa showed blunted plasma prolactin responses following challenge with the serotonin receptor agonist *m*-chlorophenylpiperazine (*m*-CPP) (Brewerton et al. 1987; Brewerton et al. 1990). Prolactin responses increased only modestly when patients were retested with *m*-CPP several weeks following weight gain. Following intravenous infusion of the serotonin precursor L-tryptophan in hospitalized anorexic patients, increases in plasma prolactin were low in one study (Brewerton et al. 1990), but normal in another (Goodwin et al. 1989). Char-

Table 2. Platelet Measures of Serotonin Function in Patients with Eating Disorders

	Anorexia nervosa	Bulimia
Platelet ^{3}H-IMI binding	↓ [a]	↓ [b]
Platelet 5-HT uptake	N [a,c]	↑ [d]

[a]Weizman et al. 1986.
[b]Marazziti et al. 1988.
[c]Zemishlany et al. 1987.
[d]Goldbloom et al. 1988.

acteristics of the patient populations [e.g., the patients studied by Brewerton et al. (1990) were predominantly bulimic anorexics] may have contributed to differences in study results. It was of note that Goodwin et al. (1989) did find blunted plasma growth hormone responses and attenuated sedative effects for tryptophan in the patient group. Prolactin responses to *m*-CPP were blunted in bulimic patients at normal weight (Brewerton et al. 1990). Plasma prolactin responses to L-tryptophan were blunted only in a subgroup of bulimic patients with symptoms of major depression.

Studies in depressed patients have also shown blunted prolactin responses to intravenous L-tryptophan (Heninger et al. 1984; Cowen and Charig 1987) and to fenfluramine (Siever et al. 1984). It is not known whether patients with concurrent bulimia and depression have lower responses than patients with depression alone. Further studies are needed to assess whether abnormal neuroendocrine responses in depressed patients or in eating disorder patients completely resolve after symptom remission (Coccaro et al. 1989).

Platelet Measures of Serotonin Function

Serotonin uptake in platelets provides a possible model for synaptic reuptake of the neurotransmitter in brain (Da Prada et al. 1988). Though platelet serotonin uptake was reported to be normal in anorexic patients (Weizman et al. 1986; Zemishlany et al. 1987), uptake was increased in patients with bulimia (Goldbloom et al. 1988) (Table 2). If synaptic reuptake in the CNS is increased in bulimia, this could result in decreased availability of serotonin at postsynaptic receptor sites. Platelet samples from patients with depression demonstrate decreased serotonin uptake (Tuomisto et al. 1979; Coppen et al. 1978; Meltzer et al. 1981; Meltzer 1987). These findings raise the possibility that patients with bulimia and patients with depression have opposite changes in synaptic clearance of serotonin. These differing results could, however, reflect changes in blood serotonin levels or variations in platelet population across patient groups.

Platelet imipramine binding was reported to be decreased in initial studies in anorexia nervosa (Weizman et al. 1986) and in bulimia nervosa (Marazziti et al. 1988). In both of these studies, patients with current symptoms of major depression were excluded. Decreased platelet imipramine binding has also been observed in many (Briley et al. 1980; Paul et al. 1981; Wagner et al. 1985) but not all (Kanof et al. 1987) studies in depression. In depressed patients, decreased imipramine binding appears to be a state-related change, as results return to normal levels with remission of depressive symptoms (Suranyi-Cadotte et al. 1982; Langer et al. 1986). Thus, possible past history of depression in eating disorder patients included in the imipramine binding studies should not account for the findings noted above.

Pharmacological Treatment Responses

Evidence that serotonin agonist drugs decreased eating behavior prompted several trials of the serotonin antagonist cyproheptadine in anorexic patients. Cyproheptadine had very modest effects in increasing the rate of weight gain in hospitalized, low-weight anorexic patients (Agras and Kraemer 1984). In a double-blind, inpatient trial with cyproheptadine, nonbulimic patients gained weight more rapidly than bulimic anorexic patients (Halmi et al. 1986). This study provided additional evidence that central serotonin function is diminished in bulimic anorexic patients compared with the nonbulimic subgroup. Double-blind trials with antidepressant drugs, most of which enhance central serotonin neurotransmission (Heninger and Charney 1987; Willner 1985), have shown little effect on weight gain in anorexic patients (Gwirtsman et al. 1984; Agras and Kraemer 1984; Biederman et al. 1985). Even in bulimic anorexic patients where the possibility of decreased CNS serotonin function seems most likely, response to antidepressant medications may be limited by the magnitude of dietary effects on serotonin synthesis, as well as a result of changes in other neurotransmitter and neuropeptide systems (Jimerson et al. 1988a).

In double-blind studies, antidepressant medications substantially decreased binge eating in bulimic patients (Sabine et al. 1983; Pope et al. 1983; Mitchell and Groat 1984; Walsh et al. 1984; Hughes et al. 1986; Agras et al. 1987; Barlow et al. 1988). Initial results with the selective serotonin reuptake blocker fluoxetine were positive (Freeman and Hampson 1987). Reduction in binge frequency with antidepressant treatment appears to be independent of drug-induced decrease in symptoms of depression (Brotman et al. 1984; Mitchell and Groat 1984; Herzog et al. 1987). Pilot studies with the serotonin precursor L-tryptophan showed mixed effects on binge frequency (Krahn and Mitchell 1985; Mira and Abraham 1989). Some bulimic patients showed decreased binge frequency with the serotonin agonist fenfluramine (Blouin et al. 1988), although this appears to be an inconsistent effect (Russell et al. 1988). It is interesting that these results in bulimia are similar to treatment effects in depression, in that the "antidepressant" medications are more consistently efficacious than are serotonin agonist drugs (Murphy et al. 1978).

Discussion

Bulimia Nervosa and Serotonin

The evidence reviewed above suggests decreased central serotonin function in bulimia nervosa. These findings are congruent with preclinical studies linking satiety responses to hypothalamic serotonin activity. The available data do not, however, indicate whether serotonergic abnormalities predate the onset of bulimic symptoms, or whether they result from dietary abnormalities or other psychophysiological concomitants (e.g., stress, anxiety) of the disorder.

Severely symptomatic bulimic patients appear to have decreased presynaptic release of serotonin (as reflected in low CSF 5-HIAA). Chronic dieting patterns in bulimia may lead to decreased presynaptic neuronal serotonin synthesis as a result of decreased precursor availability, as reviewed above. However, bulimic patients also show decreased postsynaptic serotonergic receptor responsiveness (as reflected in blunted prolactin responses to *m*-CPP). This is a different pattern from that observed in dieting studies with healthy volunteers in which diet-induced decrease in presynaptic release of serotonin

resulted in up-regulation of postsynaptic serotonergic responses mediating prolactin secretion (Goodwin et al. 1988; Delgado et al. 1989). We hypothesize that this normal compensatory up-regulation is not observed in bulimic patients because intermittent surges in serotonin synthesis following binge episodes are sufficient to dampen postsynaptic serotonin receptor responses (Jimerson DC et al. in preparation).

Anorexia Nervosa and Serotonin

Studies in low-weight patients with anorexia nervosa have demonstrated decreases in CSF 5-HIAA levels, in neuroendocrine responses to challenges with serotonin agonists, and in platelet imipramine binding sites. Prompt normalization of CSF 5-HIAA levels with weight restoration suggests a major nutritional/dietary component to some of these changes. The impact of dietary-related changes on neuroendocrine responses and platelet measures may also be substantial.

Additional strategies are necessary to assess the overall role of the serotonin system in the pathophysiology of anorexia, including the relationship to specific symptom dimensions. Studies in weight-recovered patients and in low-weight comparison groups would help to clarify whether the predisposition to decreased food intake in anorexia nervosa involves increased serotonergic activity in the hypothalamus.

Serotonin and Psychiatric Symptom Dimensions

The above observations lead us to speculate that patients with relatively severe eating disorder symptoms have impaired regulation of serotonin synaptic function in multiple regions of the CNS. Dysregulation in individual serotonin pathways may occur intermittently, in different regions at different times, resulting in psychiatric symptoms of binge eating, depression, or impulsivity. Based on this model, regulatory instability of serotonergic pathways represents a common link between eating disorder syndromes and depressive illness.

Three dimensions of psychiatric symptomatology have been prominently associated with decreased central serotonin function: decreased satiety, depressed mood, and increased impulsivity. Decreased serotonergic activity in the medial basal hypothalamus may result in blunted satiety responses and consumption of large binge meals in normal-weight bulimic patients. Behavioral disinhibition associated with suicidal and other impulsive/aggressive behaviors may result from decreased serotonin in limbic or cortical areas. Similar serotonergic disinhibition may contribute to the impulse to binge eat, characteristic of normal-weight bulimic patients and bulimic anorexic patients. Depressed mood is likely to reflect decreased serotonin function in rostral brain regions such as the limbic system or cerebral cortex.

In summary, initial studies indicate that severely symptomatic patients with bulimia nervosa have decreases in presynaptic and postsynaptic serotonin function. Analogous results have been reported in patients with anorexia nervosa, although effects of malnutrition complicate interpretation of findings in low-weight patients. Similarities and differences emerge when results of serotonin function in eating disorders and depression are compared. Patients with episodes of an eating disorder and major depression may have intermittent synaptic dysregulation in widely distributed CNS serotonin pathways.

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