REVIEW PAPER

Eating Disorder and Obsessive-Compulsive Disorder: Neurochemical and Phenomenological Commonalities

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This paper explores a possible connection between neurochemistry and cognitions in eating disorders (ED). Cognitions play an important role in ED. However, a possible neurochemical origin of these cognitions has not been explored. Obsessive-compulsive disorder (OCD) is known as a disorder of thinking. Extensive neurochemical research conducted on this disorder indicates a connection between serotonin (5-HT) dysregulation and cognitions in OCD. This study used research done on OCD as a template to interpret the available research findings in ED and their possible meaning in terms of neurochemical origin of cognitions in ED. This paper suggests that the neurochemical and behavioral expression of both ED and OCD occur on a continuum. At one end of the continuum, ED and OCD are expressed through constrained behaviors of an avoidant quality. This pole is also characterized by high levels of serotonin markers. At the other end, both disorders are characterized by disinhibited approach behavior. This end of the continuum is characterized by low levels of 5-HT markers. It is suggested that these levels of 5-HT generate cognitions that may in turn promote specific behaviors.

Key Words: eating disorders, obsessive-compulsive disorders, serotonin, cognitions

INTRODUCTION

In spite of extensive research, the motivation underlying severe dieting in anorexia nervosa and chaotic eating in bulimia nervosa is still poorly understood. The clinical literature indicates that persistent irrational beliefs play a major role in the development and maintenance of eating disorders (ED) (Garner and Bemis 1985). Cognitions could be causal in the development of ED. However, the origin of these cognitions is unknown. Neurochemical imbalances have also been identified in ED (Fava et al 1989), but the possible connection between these neurochemical anomalies and the distorted cognitive style found in ED has been left largely unexplored. The hypothesis that the distorted cognitive pattern seen in ED may be an expression of neurochemical imbalances is plausible, and could open new avenues in the treatment of ED. However, exploring a possible neurochemical origin of cognitions in ED is difficult, mainly because of the limited access to these patients for physiological research.

Few psychological disorders are known to be primarily disorders of thinking. In the neurotic range, only obsessive-compulsive disorder (OCD) is known as such. Extensive

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research has been conducted to explore the possible neurochemical basis of the cognitive style in OCD, and a large body of results is now available on that topic. This is particularly relevant to the understanding of the relationship between cognitions and neurochemistry in ED, since several phenomenological and neurochemical similarities have been found between ED patients and OCD patients. It has even been suggested that EDs are a modern variant of OCD (Rothenberg 1986, 1988). Thus, in this paper, the research performed on OCD is intended to be used as a template to explore the link between cognitions and neurochemistry in ED.

Although these 2 disorders have often been associated phenomenologically and neurochemically (Hsu et al 1993; Kaye et al 1993), this paper suggests that both ED and OCD occur along a continuum. One end of this continuum is characterized by avoidance-oriented behaviors and the other end is characterized by high approach behavior. For example, at the avoidant end of the continuum, the individual suffering from OCD engages in repeated attempts to avoid contamination, by compulsive washing, or catastrophic consequences of forgetfulness, by checking. At the other end of the continuum, behavior is characterized by a high level of approach to the environment. Here, the individual's goal is to engage in extreme levels of contact with the environment such as in recurrent sexual and violent fantasies. The same polarity is present in ED. At the avoidant end, the individual avoids food and engages in restriction. At the approach end, the individual engages in extreme contact with food and ingests large amounts. At the avoidant end of the continuum, ED and OCD have similar neurochemical profiles generally characterized by high levels of serotonin. At the approach end, ED and OCD are generally characterized by low levels of serotonin. Our working model further suggests that the behavioral expression of ED may be driven by specific cognitive patterns, as seems to be the case in OCD. Such parallels would raise the possibility that, as in OCD, the cognitive style typical of ED has a biological basis. In this paper, the position that cognitions are precursors of behavior has been adopted.

The first part of this paper considers the psychometric relationships between ED and OCD to determine whether or not ED and OCD are, in fact, phenomenologically related. In the second part, the extent to which ED and OCD share neurochemical features is examined to determine whether or not there is a similar neurochemistry in these 2 disorders. Through such an exploration, the authors hope to clarify the possible contribution of neurochemistry to the cognitive style of ED.

PSYCHOMETRIC STUDIES OF ED AND OCD

Generally, psychometric studies comparing ED and OCD proceed either by assessing the prevalence of comorbidity between these 2 groups, or by looking at overall psychological profiles on general diagnostic instruments such as the Minnesota Multiphasic Personality Inventory (MMPI) (Hathaway and McKinley 1951) and the SCL-90-R (Derogatis 1983).

Comorbidity

Studies of comorbidity have found a high prevalence of lifetime diagnosis of OCD in ED, ranging from 15% (Laessle et al 1987) to 69% (Hudson et al 1983) in anorexia nervosa restrictive subtype; and from 8% (Laessle et al 1987) to 33% in bulimia nervosa (Hudson et al 1987). The wide range in the prevalence of OCD in anorexia nervosa across studies may be attributable to the National Institute of Mental Health Diagnostic Interview Schedule (DIS), the diagnostic instrument used in these studies. This instrument relies somewhat on the subjectivity of the interviewer, which may have influenced the outcome of the interview to show high rates of OCD in the Hudson et al (1983) study or low levels in the Laessle et al (1987) study.

Nevertheless, as bulimic symptomatology increases in ED, OCD prevalence appears to diminish. Hudson et al (1983) examined 3 categories of ED patients: anorexia nervosa of the restrictive type, anorexia nervosa with bulimia, and bulimia nervosa. The lifetime prevalence rate of OCD in the restrictive group was 3 times that of the bulimic group. The lifetime diagnosis of OCD in patients suffering from anorexia with bulimic symptoms fell half way between that of the restrictive and the bulimic group. Laessle et al (1987) also found lower rates of OCD in patients with bulimia, than in patients with anorexia and patients suffering from anorexia with bulimia. This finding suggests a stronger connection between OCD and anorexia than between OCD and bulimia.

Studies have also been conducted on the prevalence of ED symptoms in OCD. Pigott et al (1991) found that patients with OCD had significantly elevated scores on the Eating Disorder Inventory (Garner et al 1983) in comparison with those of a healthy control group, although these scores were also significantly lower than those of patients with eating disorders patients. However, Joffe and Swinson (1987) found no differences between the Eating Attitude Test (Garner and Garfinkel 1980) scores of obsessive-compulsive patients and those of normal control subjects. The difference between these 2 studies cannot be attributed to differential gender representation. In both studies, male and female subjects were approximately equally represented. However, this difference might be attributable to the use of different scales (EDI versus EAT), or to the fact that the sample used in Pigott et al (1991) included about 20% of patients whose obsession or compulsion were directly related to their body shape and appearance. No such patients were included in the study conducted by Joffe and Swinson (1987). In any case, the number of studies conducted assessing the prevalence of ED in OCD is still too small to allow one to establish whether the correspondence between OCD and ED is bidirectional or unidirectional. Evidence collected so far suggests that OCD

is common in ED but there is still insufficient evidence to conclude that the reciprocal proposition is also true.

Studies of comorbidity (Hudson et al 1983; Hudson et al 1987; Laessle et al 1987) have also found a higher prevalence of affective disorders in ED than of any other concurrent disorders. Generally, OCD is the second most prevalent comorbid disorder for anorexia nervosa restrictive type (Hudson et al 1983; Laessle et al 1987), and the third for both anorexia nervosa with bulimia, and bulimia (Hudson et al 1983; Hudson et al 1987; Laessle et al 1987). While this finding may seem to indicate a stronger association between affective disorders and ED than between OCD and ED, it should be noted that affective disorders are also more prevalent than OCD in the general population. The prevalence of lifetime diagnosis of affective disorders in the general population is approximately 13% (DSM-IV 1994) compared to 70% (Hudson et al 1983, 1987; Laessle et al 1987) in ED. Affective disorders are thus approximately 7 times more prevalent in ED than in the general population. However, the lifetime prevalence of OCD in the general population has been estimated to be 2.5% to 3% (Robins et al 1984; Bland et al 1988; Karno et al 1988), without exclusion criteria. Rates with hierarchical exclusions are consistently two-thirds the rates without exclusions (Robins et al 1984). Therefore, the lifetime prevalence of OCD can safely be assumed to be approximately 2% in the general population compared to 30% (Hudson et al 1983, 1987; Laessle et al 1987) in ED, a 15-fold increase. Thus, compared to rates found in the general population, rates of OCD in ED are more elevated than rates of affective disorders in ED.

It is reasonable to argue that the presence of obsessive-compulsive symptoms in ED are secondary to starvation and chaotic eating rather than primary. However, studies comparing the personality and psychological functioning of ED patients before and after treatment show that, although obsessive-compulsive symptoms improve after treatment, recovered patients still display high levels of obsessive-compulsive traits and symptoms. Using the Middlesex Hospital Questionnaire (Crown and Crisp 1966), Stonehill and Crisp (1977) found patients with anorexia before treatment to have significantly higher obsessional scores than healthy controls. Although these scores improved somewhat after restoration of body weight, they were not significantly different from pretreatment scores. At follow-up, 4 to 7 years later, obsessional scores returned to pretreatment levels although these results are difficult to interpret because approximately half of the patients were symptomatic at that point. In a retrospective study of patients with anorexia to determine premorbid personality traits, Beumont et al (1976) found that 76% of the patients with anorexia with restrictive features had premorbid obsessional traits compared to 57% of patients suffering from anorexia with bulimic features. Strober (1980) compared the pretreatment Leyton Obsessional Inventory (Cooper 1970) scores of patients suffering from anorexia with and without bulimia with those of depressed patients and patients with personality disorders. Patients with anorexia had significantly higher obsessional symptoms and character traits than these other 2 groups of patients. Post-treatment obsessional symptomatology was significantly lower but changes in trait obsessionality after treatment were negligible and not significant.

Although these data may suffer from many methodological problems, including the retrospective nature of the reports, they do provide convergent evidence of an elevated prevalence of obsessive-compulsive traits and symptoms in ED, and particularly in anorexia. Despite the fact that obsessive-compulsive traits and symptoms do not refer to the same diagnostic entity and are not always convergent (Joffe et al 1988; Black et al 1989; Baer et al 1990; Mavissakalian et al 1990), there is some evidence that traits and symptoms are highly correlated and that individuals with obsessive-compulsive personality disorder are more likely to have OCD and vice versa (Rasmussen and Tsuang 1984, 1986; Lenane et al 1990; Baer and Jenike 1992; Black et al 1993). It is, thus, reasonable to suggest that, although starvation and dietary chaos may contribute to the expression of obsessive-compulsive symptoms, ED patients are predisposed to OCD because of their premorbid obsessive-compulsive personality style.

Psychometric profile

Studies of psychometric profiles have found OCD and ED patients to have many similarities. OCD and ED patients have very similar MMPI profiles (Bulik et al 1992) and are similar on instruments assessing depression (Solyom et al 1982). In addition, OCD and ED patients are comparable in their level of general anxiety and obsessive-compulsive symptoms (Pigott et al 1991; Solyom et al 1982), and are similar on the anxiety-related items of the SCL-90-R (obsessive-compulsive symptoms, anxiety, and phobic anxiety) but not on items unrelated to anxiety such as psychotism and interpersonal sensitivity (Bulik et al 1992). These findings suggest that OCD and ED share common dysfunctions which may render such patients more susceptible to anxiety symptoms.

STUDIES OF SEROTONIN IN OCD AND ED

Neurochemical studies of OCD have revealed a dysregulation of serotonin functions which is believed to be an important contributor to the disorder (Barr et al 1992). Because OCD is primarily a disorder of thinking, this dysregulation suggests that the cognitive style characteristic of OCD could be caused by a 5-HT dysregulation. ED patients have also been shown to have dysregulated 5-HT functions (Leibowitz 1990). Although these data have generally been approached from the point of view of the relevance of 5-HT to mood disorders and eating behavior itself (Anderson and Kennedy 1992), there might also be a connection between 5-HT functions and unusual thinking patterns in ED. To

investigate this possibility, studies of serotonergic functions in OCD will first be reviewed, followed by studies of the same functions in ED.

Serotonin studies in OCD

Three main methods have been used to study 5-HT functions in OCD: 1. drug response data; 2. peripheral markers of 5-HT functions; and 3. neuroendocrine and behavioral responses to pharmacologic challenges. Nonserotonin selective antidepressant treatments for OCD have been tried in the past but met with very limited success (Thorén et al 1980; Ananth et al 1981; Insel et al 1983; Zohar et al 1987; Leonard et al 1988). However, potent and selective 5-HT reuptake inhibitors yielded positive results, stirring a new interest in a possible serotonin basis of OCD (Goodman et al 1990). Thus, drug response studies preceded the assessment of 5-HT functions in OCD. The latter were done in order to clarify the mechanism of action of serotonergic antidepressants in OCD.

Drug response data in OCD

The efficacy of serotonin reuptake inhibitors (SRIs) in the treatment of OCD has been extensively demonstrated. Clomipramine (CMI) has been studied the most, and has consistently yielded positive results, suggesting an involvement of 5-HT in OCD. However, the metabolism of CMI to desmethylclomipramine raised doubts about the primary involvement of 5-HT in OCD, since this metabolite has noradrenergic reuptake properties (Barr et al 1992). But selective SRIs such as fluvoxamine, fluoxetine, and sertraline also proved to be of high efficacy in the treatment of OCD (Greist et al 1995), supporting the central role of 5-HT reuptake inhibition in clomipramine's antiobsessional effects. Furthermore, desipramine, a noradrenergic reuptake inhibitor, was also tested to verify any involvement of norepinephrine in OCD. In all studies (Zohar and Insel 1987; Leonard et al 1988; Goodman et al 1990), desipramine was found to be inferior to 5-HT agents with only 10% of patients responding to the drug, compared to 52% of patients responding to fluvoxamine, for example (Goodman et al 1990). Finally, preliminary reports showed that patients resistant to treatment with 5-HT reuptake inhibitors improved after fenfluramine augmentation (Hollander et al 1990), and in a case report, Rasmussen (1984), showed that one patient improved after tryptophan augmentation.

Drug response data supporting an involvement of 5-HT in OCD were also collected through an animal model of OCD: canine acral lick. When affected with this condition, dogs compulsively lick their front paws and flanks, inflicting injuries upon themselves that are sometimes serious enough to require euthanasia. This condition is notoriously resistant to treatment. Clomipramine and fluoxetine were found to be of equivalent efficacy in the treatment of this disorder, while sertraline was slightly less effective (Rapoport et al 1992). This model has specific interest, since the dogs' response to the drugs was very similar to that of humans. The doses per kilogram, percentage of improvement (as rated by owners), and latency of response to treatment in dogs was equivalent to that found in the treatment of human patients (Rapoport et al 1992).

It could be argued that the efficacy of SRIs in the treatment of OCD is mediated by the alleviation of depression rather than through a neurological mechanism specific to OCD. However, that the beneficial effect of 5-HT antidepressants in OCD is distinct from their antidepressant effect is demonstrated by the fact that obsessive-compulsive symptoms improve in OCD patients taking these drugs, whether or not they had depression when treatment was initiated (Katz and DeVeaugh-Geis 1990; Goodman et al 1992). In addition, the profile of action of these drugs in these 2 disorders is different. The action of antidepressants in OCD takes much longer than in depression: 4 to 6 weeks in depression versus 8 to 12 weeks in OCD (Goodman et al 1992). The therapeutic doses to treat OCD are much higher than in depression. For example, it is generally agreed that, for depression, the optimal fluoxetine dose is 20 mg per day (Altamura et al 1988). However, the optimal fluoxetine dose for OCD is 60 mg per day (Greist et al 1995). Similarly, paroxetine 10 mg to 50 mg per day is used in depression (Nemeroff 1994), whereas 60 mg per day is preferred for OCD (Kaye and Dancu 1994). The maximum sertraline dose for depression is 200 mg per day (Chouinard et al 1990), whereas this dose is optimal for OCD (Greist et al 1995).

Furthermore, the effect of antidepressants in OCD is not as profound as in depression; there is a graded response in OCD, where patients show some improvement but do not become completely free of symptoms (Goodman et al 1990). The rate of response is lower in OCD than in depression: 40% to 60% of patients are responders in OCD (Goodman et al 1992). The rate of relapse in OCD can be as high as 90% within 2 months after discontinuation of treatment (Pato et al 1988), which is much higher than in depression. Substitution of CMI for desipramine yields a similar relapse rate (Leonard et al 1991).

In summary, drug response data suggest a definitive but complex involvement of the serotonergic system in OCD. Many aspects of the action of SRIs in OCD remain to be clarified. For example, the physiological effects of SRIs at the cellular level are visible within hours after initiation of the medication (Barr et al 1992), but the behavioral effects take weeks to appear. Although a variety of neurochemical changes may underlie this effect, downregulation of 5-HT receptors has been proposed as a mechanism of action. For example, chronic treatment with fluoxetine has been shown to cause an overall downregulation of 5-HT_1 and 5-HT_2 receptors in several areas of the brain (Wamsley et al 1987), and to downregulate presynaptic terminal autoreceptors in the hippocampus (Blier et al 1988). Long-term treatment with fluoxetine has also been found to downregulate

somatodendritic receptors in the nucleus raphe dorsalis without affecting 5-HT_{1A} receptors density in postsynaptic regions (Welner et al 1989). The evidence concerning fluoxetine is consistent with several studies showing that citalopram, indalpine, and zimelidine induce a desensitization of 5-HT_{1A} autoreceptors in the nucleus raphe dorsalis (Blier and de Montigny 1983; Blier et al 1984; Chaput et al 1986). Another explanation for the delayed behavioral effects of SRIs is that the effects of these medications are not limited to the serotonergic system, but rather depend on the integration of downstream modifications in a variety of neurochemical systems. This integration may require more time than the modification of one single system, thus explaining the delayed behavioral effect.

Peripheral markers in OCD

The investigation of peripheral markers of serotonergic functions in OCD patients can be roughly divided into cerebrospinal fluid (CSF) studies and blood platelet studies. CSF studies will be reviewed first.

Cerebrospinal fluid studies in OCD: The measurement of CSF 5-HT is pertinent to the study of serotonergic functions in that it is believed to reflect central levels of serotonin. Because CSF levels of 5-HT are too low to be meaningfully measured, studies of serotonin activity via the CSF usually assess the concentration of 5-HIAA, a major metabolite of 5-HT. The studies reviewed here were conducted with patients who had been free of drugs for a minimum of 3 weeks to 4 weeks. Two studies have shown significantly elevated CSF levels of 5-HIAA in OCD patients compared to controls (Insel et al 1985; Kruesi et al 1990). One study found elevated 5-HIAA in OCD patients compared to controls but this difference was not significant (Thorén et al 1980). Another study found no differences (Lydiard et al 1990), and one study of 2 patients who had violent obsessive thoughts found lower levels of 5-HIAA than normal (Leckman et al 1990).

The number of studies reported above is small, and their findings may appear contradictory. However, careful examination reveals an interesting pattern. While the classic OCD shows a tedious thinking process and behavior oriented towards avoidance, and is associated with high levels of CSF 5-HIAA, recurrent desire to or fear of losing control is associated with low levels of this metabolite. This finding is consistent with the fact that serotonin depletion promotes approach behavior in animals, and serotonin enhancement results in increased behavioral avoidance (Spoont 1992). It may be that high levels of serotonin are associated with avoidant behaviors such as in classic symptoms of OCD while low levels of this neurotransmitter would be associated with disinhibited approach behavior such as in violent obsessive thoughts. Low levels of CSF 5-HIAA have also been found in violent and impulsive patients (Linnoila et al 1983; van Praag 1983; Virkkunen et al 1987; Virkkunen et al 1994). In normal volunteers, Roy et al (1988) found a significant negative correlation between CSF levels of 5-HIAA and scores on the "urge to act out hostility" subscale of the Hostility and Direction of Hostility Questionnaire (HDHQ) (Foulds 1965). The converging sources of evidence indicate an association between low levels of 5-HT and disinhibited approach behavior. This evidence suggests that subcategories of OCD may have different physiologies in which high levels of 5-HT are associated with avoidance-oriented behavior and low levels are associated with approach behavior.

Further evidence indicating a relationship between levels of 5-HT, as measured through 5-HIAA, and OCD comes from the fact that, after treatment with CMI, CSF levels of 5-HIAA are significantly decreased (Altemus et al 1994). Improvement in OCD symptoms has been found to be significantly and negatively correlated with decreasing levels of CSF 5-HIAA (Thorén et al 1980).

Blood platelet studies in OCD: The rationale for the studies of blood platelets in OCD is that platelets model central 5-HT activity. Blood platelets also store and release 5-HT and are considered to be a modulator of 5-HT uptake (Barr et al 1992). [^{3}H]-imipramine binding may serve as a model for serotonergic functions (Murphy et al 1989b). The studies reviewed here were conducted with patients who had been free of drugs for a minimum of 4 weeks. Only one study had an abstinence period of 2 weeks (Black et al 1990), and in another study, subjects had never received any psychotropic medication (Marazziti et al 1992). Compared to normal subjects, some studies show fewer [^{3}H]-imipramine binding sites (B_{max}) in OCD (Weizman et al 1986; Bastani et al 1991; Marazziti et al 1992), and others found no differences (Insel et al 1985; Black et al 1990; Kim et al 1991; Vitiello et al 1991; Won Kim et al 1991). Lower affinity for 5-HT uptake (K_m) was found in only one study (Bastani et al 1991) and was normal in the others (Marazziti et al 1992; Weizman et al 1986a). No differences were found in the affinity for [^{3}H]-imipramine binding (K_d). Vitiello et al (1991) found increased uptake velocity of 5-HT (V_{max}) in OCD patients compared to controls.

The evidence provided by the study of blood platelets is inconclusive. Reduced [^{3}H]-imipramine binding sites are indicative of reduced 5-HT activity (Bastani et al 1991; Marazziti et al 1992). However, increased uptake velocity of 5-HT (V_{max}) in OCD patients is indicative of a possibly hyperactive serotonergic system (Vitiello et al 1991). These contradictory results might be clarified by the fact that depressed patients also exhibit reduced density of [^{3}H]-imipramine binding sites (B_{max}). Therefore, findings showing reduced 5-HT activity may be attributable to differing prevalence of concurrent depression between samples of OCD patients (Barr et al 1992). Close examination of the above-mentioned studies shows that inclusion criteria for patient groups were more lenient in studies that have found lower B_{max} values in OCD patients than in control groups (Weizman et al 1986; Bastani et al 1991; Marazziti et al 1992). These studies may have included more patients with a history of depression or actual low levels of depression.

Blood platelet studies are inconclusive. However, except for one study which did not find a difference between OCD patients and normal subjects (Lydiard et al 1990), cerebrospinal fluid studies have shown OCD patients with classic symptoms to have clearly elevated levels of CSF 5-HIAA (Insel et al 1985; Kruesi et al 1990), or to show a trend in this direction (Thorén et al 1980). If indeed CSF levels of this metabolite reflect brain levels of 5-HT, these results would indicate that OCD patients with classic symptoms have high levels of central serotonin. The possibility that these patients have high levels of central 5-HT activity has much intuitive appeal in view of the avoidant quality of their behavior.

Pharmacologic challenges in OCD

Pharmacologic challenges in OCD are conducted in an effort to identify more precisely what neurochemical systems are implicated in the positive response of these patients to SRIs. The most widely used compound in pharmacologic challenge in OCD is *m*-chlorophenylpiperazine (*m*-CPP), a trazodone metabolite. *m*-CPP is mostly an agonist of 5-HT receptors at both pre- and postsynaptic sites. Its greatest affinity is for the 5-HT_{1C} receptors (now denoted 5-HT_{2C} receptors, Hoyer et al 1994), for which it is an agonist, and 5-HT_3 receptors, for which it is an antagonist, but it also interacts with several other 5-HT receptors (Hollander et al 1992). In normal subjects, *m*-CPP induces an increase in body temperature and an elevation in serum prolactin and cortisol (Mueller et al 1985a; Mueller et al 1985b). That these physiological responses are mediated by the 5-HT system has been demonstrated by the fact that administration of the 5-HT antagonist metergoline blocks them (Mueller et al 1986). *m*-CPP also produces behavioral effects in normal subjects, as evidenced by increased anxiety with intravenous infusion (Mueller et al 1986) but not with oral doses (Kahn et al 1990).

Investigation of behavioral responses to *m*-CPP in OCD patients has yielded fairly consistent results. OCD patients experience an increase in obsessive-compulsive symptoms in responses to oral doses of *m*-CPP (Zohar and Insel 1987; Zohar et al 1987; Hollander et al 1991; Pigott et al 1991; Hollander et al 1992), but fail to show the same response with intravenous doses (Charney et al 1988). Although the reason for this sensitivity to route of administration is unclear, these results suggest serotonergic hypersensitivity in OCD patients. The involvement of the 5-HT system in the response of OCD patients to *m*-CPP is further confirmed by the fact that the behavioral effects of *m*-CPP in OCD patients are blocked after pretreatment with CMI (Zohar et al 1988), fluoxetine (Hollander et al 1991), and metergoline (Pigott et al 1991).

The behavioral effects of *m*-CPP suggest that some receptors activated by this compound are hyper-responsive in OCD patients. The fact that this response is curtailed by pretreatment with SRIs further suggests that SRI medications down-regulate some receptors specifically associated with OCD.

Summary of serotonin disturbances in OCD

The evidence provided by the investigation of peripheral markers of 5-HT functions, and from pharmacologic challenges, converges to indicate elevated 5-HT functions in classic symptoms of OCD (Thorén et al 1980; Insel et al 1985; Zohar et al 1988; Kruesi et al 1990), and lowered serotonin functions in OCD characterized by urges of an impulsive nature (Leckman et al 1990). Since OCD is primarily a disorder of thinking, dysregulations of the 5-HT system could contribute to a cognitive style which in turn would induce behaviors typical of the 2 poles of the disorder. At one end, hyperserotonergic functions could be associated with cognitions resulting in avoidance behavior. At the other end, hyposerotonergic functions could be associated with cognitions resulting in high approach behavior.

Serotonin studies in ED

Several neurotransmitters have been implicated in the control of feeding and are believed to play a role in ED. Since serotonin has been shown to mediate and possibly control satiety (Leibowitz 1990), it has been explored for a possible contribution to ED. Three main methods are used to study 5-HT functions: 1. measures of concentration of neurotransmitter and metabolites in the CSF; 2. studies of blood platelets; and 3. pharmacologic challenge studies. In all studies of peripheral markers of serotonin in ED, subjects were ordinarily abstinent from drugs for at least 4 weeks, except in one study where subjects were abstinent from drugs for only one week (Gerner et al 1984), and in 4 studies in which drug abstinence was not specified (Kaye et al 1984a; Kaye et al 1984b; Hallman et al 1990; Hassanyeh and Marshall 1991).

Peripheral markers in ED

Cerebrospinal fluid studies in anorexia nervosa: A complete understanding of the investigation of 5-HIAA in anorexia nervosa relies on the distinction between stages of the disorder (before and after weight recovery) and the extent of the presence of bulimic symptoms. Kaye et al (1984b) found levels of 5-HIAA to be low in underweight patients with anorexia, but to return to normal with weight recovery. More detailed investigation of the same patients showed that, after weight recovery, patients with anorexia of the restrictive type had levels of 5-HIAA that were higher than those of normal subjects (Kaye et al 1984a). Kaye et al (1988) also found that underweight patients with anorexia had levels of CSF 5-HIAA that were lower than those of normals but that, after recent weight restoration, these patients had CSF 5-HIAA values that were similar to those of normal subjects. Gerner et al (1984) found no differences in CSF levels of 5-HIAA between patients with anorexia and normal control subjects. However, patients in this study had already undergone some degree of refeeding and weight gain, which renders these results compatible with the finding of normalization of CSF 5-HIAA after refeeding. Finally, patients with anorexia

whose weight had been restored for at least 6 months were found to have CSF 5-HIAA levels that were significantly higher than those of normal subjects (Kaye et al 1991). This result indicates elevated serotonin activity (Kaye and Weltzin 1991), and is of particular interest since, after long-term weight restoration, any disturbance found in monoaminergic activity could be trait related rather than caused by poor nutrition or weight loss (Kaye et al 1991). Finally, weight-restored patients with anorexia of the restrictive type were found to have CSF 5-HIAA values that were higher than those of weight-restored patients suffering from anorexia with bulimia (Kaye et al 1984a). In summary, underweight patients with anorexia show lower levels of 5-HIAA than those of normal subjects. Newly weight-restored patients with anorexia have normal levels of 5-HIAA. However, long-term weight-restored patients with anorexia show elevated levels of 5-HIAA compared to weight-restored patients suffering from anorexia with bulimia and normal subjects. These findings suggest that patients with anorexia of the restrictive type may have had elevated premorbid serotonergic activity.

Cerebrospinal fluid studies in bulimia nervosa: A relatively consistent pattern emerges from the study of CSF 5-HIAA in bulimia nervosa. One study found weight-restored anorexics with bulimia to have significantly lower levels of 5-HIAA than weight-restored patients with anorexia of the restrictive type and normal subjects (Kaye et al 1984a). One study found only nonsignificantly lower levels of 5-HIAA in patients with bulimia compared to healthy control subjects (Kaye et al 1990).

Within patients with bulimia, lower levels of 5-HIAA are associated with a more severe symptomatology (Jimerson et al 1988). Jimerson et al (1988) found that patients having more than 14 binge episodes per week (high binge frequency) had 5-HIAA levels that were significantly lower than those of normal subjects and of patients who had 14 or fewer binge episodes per week (low binge frequency). It is thus possible that the Kaye et al (1990) study included a majority of patients with low binge frequency. Despite this slight inconsistency, studies of CSF 5-HIAA indicate that low serotonergic activity is related to bulimic symptomatology while high serotonergic activity appears related to a restrictive eating style.

Blood platelets in ED: Platelet serotonin uptake has been found to be comparable between patients with anorexa and normal subjects (Weizman et al 1986b; Zemishlany et al 1987), although one study reported low [^{3}H]-imipramine binding (B_{max}) in patients suffering from anorexia with weight loss (Weizman et al 1986b). Whole blood 5-HT has been found to be higher in patients with anorexia nervosa compared with normal subjects (Hassanyeh and Marshall 1991), which is compatible with the possibility of hyperserotonergic functions in anorexia nervosa (Hassanyeh and Marshall 1991). Patients with bulimia were shown to have an increase in platelet serotonin uptake (Goldbloom et al 1990), which is consistent with decreased availability of brain 5-HT for neurotransmission (Goldbloom and Garfinkel 1990). One study found no differences between patients with bulimia and normal subjects in platelet serotonin uptake (Hallman et al 1990). However, the results of this last study are difficult to interpret because of the lack of information provided on the composition of the patient group. Another study found fewer [^{3}H]-imipramine binding sites (B_{max}) in patients with bulimia compared to normal subjects (Marazziti et al 1988), which is also compatible with reduced 5-HT activity.

Pharmacologic challenges in ED

To date, there is only one published study examining the effects of *m*-CPP on food intake in humans (Brewerton et al 1994). This study showed a decreased food intake in normal subjects, and a quasi significant trend for patients with bulimia to decrease their food intake after *m*-CPP. There was also an intriguing trend for patients with bulimia, but not for control subjects, to diminish their protein consumption after *m*-CPP. In addition, normal subjects reduced their fat intake after *m*-CPP, but patients with bulimia failed to do so. Although patients with bulimia and control subjects reacted similarly to *m*-CPP for the most part, the decreased food intake in patients with bulimia is consistent with the suggestion that this group has lower serotonergic functions than normal subjects.

Summary of serotonin disturbances in ED

Studies of 5-HT functions in ED are sparse, particularly studies of patients with anorexia of the restrictive type. However, the evidence available indicates that, after long-term weight restoration, these patients have higher levels of 5-HT markers than weight-restored patients suffering from anorexia with bulimia, patients with symptoms of bulimia, and normal subjects. This physiological difference is accompanied by consistent food avoidance in the active phase of anorexia of the restrictive type. Conversely, patients with bulimic features such as anorexics with bulimia are characterized by episodes of disinhibited eating and have low indicators of 5-HT, both in periods of remission and in the active phase of the disorder. Patients with bulimia who are symptomatic are found to have slightly lower levels of 5-HIAA than normal subjects. In summary, patients of the restrictive and the bulimic groups have CSF levels of 5-HIAA that differ from the normal population, with the restrictive group having higher levels and the bulimic group having lower levels. To the extent that weight-restored patients are behaviorally normalized, these data suggest that the differences found between them may be trait related rather than exclusively state driven. Furthermore, the eating behavior of these 2 populations closely follows what would be expected of their respective neurochemistry. High levels of CSF 5-HIAA in the restrictive group correspond to food avoidance and low levels in the bulimic group are accompanied by episodes of disinhibited eating. Intermediate levels of 5-HT markers correspond to an intermediate eating style in the normal

population when compared to the style of the restrictive and the bulimic groups. Clearly, dysregulated 5-HT functions, that is, elevated and lowered 5-HT functions, are involved in ED.

Despite the coherence of behavioral and physiological observations in ED, the direction of causality is still unclear. High methodological constraints are imposed on studies of ED patients. Given the difficulties of prospectively studying anorexia and bulimia to investigate premorbid or symptom-free periods, patients are studied either while symptomatic or when briefly or partially recovered. It is not possible to evaluate the extent to which the recovered ED patient is physiologically similar to her premorbid state. Symptomatic phases may have lasting impacts and the physiology of these patients, once recovered, may not be completely comparable to their premorbid physiology. It is, thus, not possible to establish a causal link by which high or low levels of 5-HT would contribute to the onset of either anorexia or bulimia. However, this typical neurochemistry, whether a cause or an effect, could have an impact on the cognitive and behavioral style of the patients and could contribute to the promotion of either food approach or avoidance.

DISCUSSION

This review suggests that serotonin plays a role in both OCD and ED. The evidence for serotonin in OCD comes from drug response data, the results of studies of peripheral markers, and pharmacologic challenges. Overall, indicators of 5-HT functions are elevated in OCD involving avoidance-oriented behavior such as washing and checking. In contrast, indicators of 5-HT functions are lower than normal in OCD involving disinhibited approach behaviors such as recurrent violent or inappropriate thoughts. Paralleling these findings, a similar trend is observed in ED. Indicators of 5-HT functions are elevated in ED associated with food avoidance, as in anorexia restrictive type. In contrast, these markers are lower than normal in ED characterized by episodes of impulsive and disinhibited eating behavior, as in bulimia. This pattern is further confirmed by the fact that, within anorexia, the presence of bulimic symptoms is associated with CSF levels of 5-HIAA that are lower than in the absence of bulimic symptoms. Furthermore, the severity of bulimic symptoms is negatively associated with CSF levels of 5-HIAA; more frequent binges are associated with lower CSF 5-HIAA. Patients with anorexia also tend to have more obsessive-compulsive features than patients with bulimia who are generally more disinhibited and impulsive than normal (Johnson et al 1988).

These parallels suggest that both OCD and ED can be placed on a continuum where at one end, the syndromes are characterized by avoidance (e.g., of food or contamination) and at the other end, they are characterized by insufficient inhibition and high approach (e.g., binge eating or violent and socially inappropriate thoughts). For both disorders, each end of this continuum is associated with abnormal serotonin functions: elevated for the avoidant end, and lowered for the approach end. Thus, even though ED and OCD are distinct disorders, they may share a common 5-HT dysregulation with high levels of 5-HT associated with anorexia nervosa of the restrictive type and classical symptoms of OCD such as checking and washing, and low levels associated with bulimia and a subcategory of OCD marked by feelings of impulsivity and lack of inhibition. This paper further raises the possibility that dysregulated 5-HT functions mediate specific cognitive styles such that, in ED and OCD, high 5-HT activity generates cognitions leading to avoidance behavior, and low 5-HT activity generates cognitions resulting in high approach behavior.

One important question is: why should the neurochemical imbalance described above lead to disturbed eating patterns as in the case of ED, or to disturbed behavioral control as in the case of OCD? Part of the answer could lie in the fact that, although OCD and ED have common 5-HT dysregulations, the full neurochemical profiles of these 2 disorders are different. EDs are characterized by many other neurochemical imbalances that are relevant to feeding (Fava et al 1989) and are not necessarily present in OCD. These other neurochemical imbalances may lead individuals with 5-HT dysregulation to develop eating symptomatology rather than OC symptoms. Thus, although ED and OCD may overlap with regard to serotonergic dysregulations, the neurochemical network underlying these 2 disorders is apparently different enough to result in distinct disorders.

While there appears to be a connection between 5-HT, OCD, and ED, the nature of this connection is complicated by the numerous receptors in the 5-HT system (Hoyer et al 1994). OCD is classified within the anxiety disorder family (DSM-IV). Both eating and anxiety involve multiple and common receptors. Appetite is regulated by 5-HT_{1A}, 5-HT_{1B} (ID in humans), and 5-HT_2 (Montgomery and Fineberg 1989). Anxiety involves 5-HT_{1A} and 5-HT_2 receptors (Charney et al 1990; Eison and Eison 1994), and there is preliminary evidence for an involvement of 5-HT_3 receptors in animals (Eison 1994) and in humans (Lecrubier et al 1990). The way these receptors interact with each other has yet to be clarified. It is possible that, in ED, a specific integration of anxiety and appetite-related receptors occurs, accounting for the presence of OC and eating symptoms within one family of disorders.

Similar patterns of response to drugs which influence 5-HT availability could help to clarify the connection between OCD and ED. While SRIs are not systematically used as an exploratory tool of 5-HT functions in ED, they have been studied as a possible alternative to traditional antidepressant treatment because they cause fewer adverse side effects (Gwirtsman et al 1990; Fluoxetine bulimia nervosa collaborative group 1992). Some understanding of 5-HT functions in ED can be drawn from these studies. Patients with anorexia who were treated with CMI did not gain more

weight or gain it more rapidly than patients who were treated with placebo. However, these patients had better post-treatment weight maintenance than patients who received placebo (Lacey and Crisp 1980). This result may indicate lowered obsessive preoccupations with thinness. In addition, patients with anorexia of the restrictive type were found to have a better response to drugs with serotonergic properties (cyproheptadine and fluoxetine) than patients suffering from anorexia with bulimia or patients with bulimia (Halmi et al 1986; Kaye et al 1991). These findings are interesting in that they parallel drug response data in OCD. Both anorexia of the restrictive type and classic OCD appear to have elevated 5-HT functions, and both respond favorably to serotonin-enhancing drugs.

With respect to bulimia, antidepressants in general are effective, regardless of their specific target monoamine (Bond et al 1986; Fluoxetine bulimia nervosa collaborative group 1992). This may occur because, among other effects, they elevate central 5-HT levels. The administration of 5-HT antagonists concurrently with tricyclic or MAO antidepressants could help clarify this question. For example, the administration of metergoline concurrently with clomipramine in OCD patients has been shown to worsen OC symptoms (Benkelfat et al 1989), which supports the involvement of 5-HT in this disorder. Similarly, the effect of a 5-HT antagonist on bulimia nervosa symptomatology in patients receiving antidepressant medication could also contribute to clarify the role of 5-HT in this disorder.

In summary, a serotonin connection between OCD and ED may exist as shown by the pattern of 5-HT functions at both ends of these disorders; avoidance-oriented OCD and anorexia of the restrictive type have high 5-HT functions, and high approach OCD and bulimia have low 5-HT functions. The thinking patterns at both ends of the 5-HT continuum are opposite in terms of degree of intended avoidance, and may be driven by serotonergic functions. Further study of this question is important since, for both OCD and ED, cognitions appear to be a major determinant of behavior.

Some specific hypotheses can be derived from the above reasoning and serve as guides to the exploration of serotonergic functions in OCD and ED. For example, if, in fact, low levels of 5-HT are associated with cognitions and behaviors characterized by disinhibited approach, the obsessive-compulsive symptoms of patients with bulimia should not be avoidance-oriented as much as those of patients with anorexia of the restrictive type. Patients with bulimia should have obsessive-compulsive symptoms similar to those found in OCD patients with low peripheral indices of 5-HT, that is, explosive, disinhibited thoughts rather than symptoms such as washing and checking. In other words, the specific phenomenology of the OC symptoms of patients with bulimia should differ from that of patients with anorexia of the restrictive type and more specifically, be less avoidance-oriented.

Finally, the results of the studies reviewed above are not always perfectly consistent (as can be seen, for example, in the studies of CSF 5-HIAA in OCD). Conclusions are drawn despite these imperfections. The goal of this paper is to suggest a possible new understanding of OCD and ED based on elements of the literature that may still be tentative at this point. We have attempted to develop a working model to generate new hypotheses and research in this field. Through such research, some of these inconsistencies may be resolved to reveal findings that may further our understanding of ED and OCD. For example, our working model suggests that studies failing to find differences in the levels of CSF 5-HIAA between OCD patients and normal subjects could have included OCD patients experiencing violent fantasies. Such patients with low levels of 5-HIAA may mask the differences between normal subjects and OCD patients with classic symptoms of OCD who display high levels of this metabolite. To explore these questions, research explicitly differentiating OCD patients on the basis of the phenomenology of their obsessions is needed.

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