

Chapter 18

Disturbances in Brain Neurotransmitter Systems in Anorexia Nervosa: A Review of CSF Studies

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INTRODUCTION

Patients with anorexia appear to have characteristic disturbances of appetite, neuroendocrine function, motor activity, and mood. Since CNS neurotransmitters modulate these systems, it is logical to try to determine whether disturbances of brain chemistry occur in anorexia nervosa. Two major problems, however, have limited progress in investigating brain neurochemistry in anorexia nervosa. First, the technology available to explore brain neurochemistry in living human subjects is limited. Perhaps the best available method is to measure concentrations of brain neurochemicals in CSF. It is difficult, however, to correlate CSF neurochemical values with disturbances of specific brain pathways. Second, while abnormalities of CSF neurochemicals have been found in underweight anorectics, these abnormalities may be secondary to malnutrition or contribute to weight loss and aberrant behavior. Studying anorectics after weight recovery may be one way of circumventing such problems and identifying possible trait disturbances. Despite these problems, a number of CSF studies have been carried out, and in fact, offer some insights into pathophysiological processes in anorexia nervosa. This chapter will review CSF studies to date in anorexia nervosa and discuss the implications of these findings.

BACKGROUND

The possibility of neurotransmitter disturbance in the brains of patients with anorexia nervosa has been argued for the past decade. Mawson [1] hypothesized that central catecholamine pathways might be involved in anorexia nervosa. Barry and Klawans [2] suggested that increased activity of dopamine might theoretically account for much of the pathophysiology of this disorder, while Redmond et al [3] suggested that excessive norepinephrine activity might be contributory. Other authors [4,5] have reviewed the possibility of brain dysfunction in anorexia nervosa.

The inaccessibility of the brain to clinical investigations has made it difficult to prove or disprove theories. Measuring levels of neurochemicals in the CSF is one of the few techniques available for looking directly at brain neurotransmitter metabolism. A major difficulty with CSF studies is that measurements of neurochemicals in CSF are thought to reflect the sum contributions of various brain and spinal cord regions. There is no method presently available to relate changes in CSF neurochemical concentrations to specific brain regions, but CSF studies remain the best available technique to estimate brain neurotransmitter activity.

The past decade of research has generated an immense amount of data about physiologic disturbances

in underweight patients with anorexia nervosa. Abnormalities exist in practically every endocrine system measured; these include the cortisol [6-8], gonadotropic [9-12], thyroid [13-15], growth hormone [16,17], and water regulation [18,19] systems. These disturbances are not due to primary pituitary dysfunction, but appear to reflect hypothalamic dysregulation. Many of the neurochemicals discussed in this paper have been implicated in the hypothalamic regulation of one or more of the neuroendocrine abnormalities mentioned. The neurochemistry of endocrine regulation is complex, and interested readers are referred to reviews [20,21].

Disturbances of mood have been described in anorexia nervosa [22], as well as in their family members [23]. The relationship of severity of dysphoria to anorexia nervosa, however, is not clear, as it is not certain whether dysphoria is primarily associated with malnutrition or whether there is an underlying trait-related mood disorder. The monoamines, as well as certain neuropeptides such as the opiates, have been implicated in mood regulation in humans. Whether disturbances of these systems do, in fact, contribute to alterations of mood in anorexia nervosa, seems a reasonable hypothesis, but is not proved.

Patients with anorexia nervosa manifest a paradoxical attitude toward food. Anorectics are often obsessed with food, have an appetite, and a desire to eat. They are, however, at the same time, terrified of eating and gaining weight. Little is known about the neurochemistry of appetite regulation in anorexia nervosa and whether disturbances of the neurochemistry modulating appetite produce these ambivalent food-related behaviors. The past decade has produced some understanding of the neurotransmitter systems that modulate appetite in animals. Again, the monoamines, the opiates, and a number of other neuropeptides have been implicated in appetite regulation [24].

Several groups have now found that underweight anorectics have a decrease in sympathetic nervous system (SNS) activity as measured by decreased plasma norepinephrine and decreased urinary MHPG. The CNS regulates the SNS and contributes some proportion of MHPG to the pool of peripheral MHPG, CSF norepinephrine and MHPG values often correlate with peripheral measures of norepinephrine and MHPG. Overall, it would seem reasonable to expect underweight anorectics to also have decreased CSF, norepinephrine, and MHPG, although this has not occurred in the few studies published.

Neurochemical abnormalities could be caused by weight loss or be the cause of weight loss in anorexia nervosa. The options available to determine cause and effect of neurochemical abnormalities in anorexia ner-

vosa are limited. Prospective investigations of the neurochemistry of a population at risk for anorexia are not feasible because of the low prevalence of the illness. Studies of acutely ill anorectics are complicated by the quagmire of cause and effect. Even though CSF neurochemical abnormalities in this group may not answer the question of cause and effect, they certainly suggest abnormal brain function. These findings give clues as to which systems are most disturbed during weight loss and malnutrition. Specific disturbances can be further characterized by new generations of pharmacologic challenge studies designed to explore individual neurotransmitter systems.

Another option is to study anorectics after long-term weight recovery. If some system continued to be disturbed after weight recovery, this might serve as a clue to trait-related abnormalities in anorexia nervosa. We have found disturbances of norepinephrine and serotonin (5-HT) in anorectics studied months after weight restoration. Whether these findings are related to continued symptoms or whether recovery depends on alterations in specific systems occurring is unclear.

CSF studies remain a rather controversial and relatively infrequently performed procedure, particularly as a research tool in anorexia nervosa. These studies have proved to be safe in our patients. There have been no harmful side-effects aside from a 15% incident of post-lumbar headache, rarely lasting more than two or three days and responding to bed rest.

CNS MONAMINE DISTURBANCES

Methodologic difficulties exist with measuring monoamines in CSF. The monoamines serotonin and dopamine cannot be reliably measured in CSF. Rather, investigators measure concentrations of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA) and of the dopamine metabolite, homovanillic acid (HVA) in CSF. These metabolites are thought to reflect the turnover of serotonin and dopamine respectively in brain [25].

Both norepinephrine and its major metabolite, MHPG, can be measured in CSF. Since a substantial portion of free MHPG in human CSF is derived from plasma [26], CSF MHPG is not an accurate reflection of brain norepinephrine turnover. It is unclear whether CSF norepinephrine concentrations adequately reflect brain norepinephrine metabolism because of rapid reuptake of norepinephrine by brain neurons [27,28] and because brainstem norepinephrine centers contribute disproportionately large amounts of norepinephrine to lumbar CSF [29]. All monoamine systems have multiple pathways in the brain so that if alterations are found

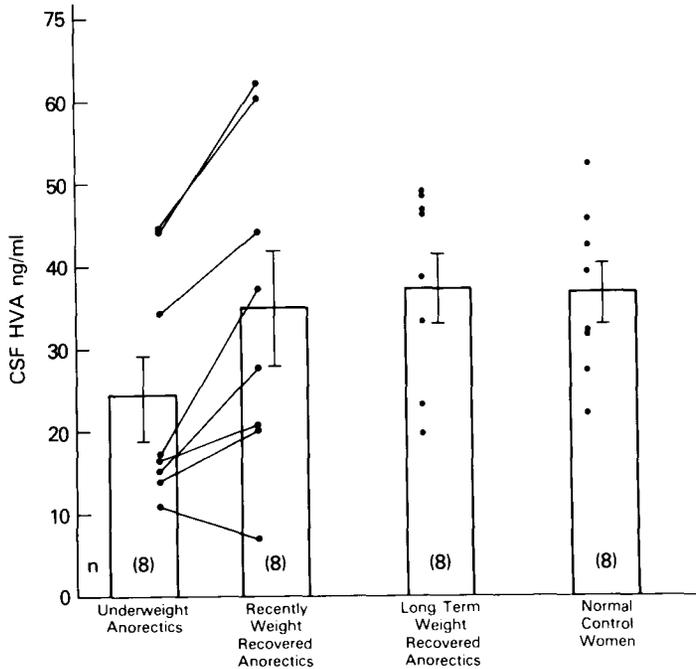


Figure 18.1 Mean (\pm SEM) concentrations of HVA in CSF for each group of anorectics and normal controls. Underweight anorectics had a significant increase ($t = 3.77$, $p < .01$) in CSF HVA after weight restoration.

in CSF measurements, the source(s) of these disturbances are uncertain.

Monoamine Precursors

All of the monoamines are derived from neutral amino acid precursors. Tryptophan is the precursor of 5-HT, and tyrosine is the precursor of dopamine and norepinephrine. It is thought that all neutral amino acids compete for one transport site at the blood brain barrier [30], therefore, the uptake of any one neutral amino acid depends on the concentration in blood of the other neutral amino acids.

Several groups have found that underweight anorectics had normal concentrations of monoamine precursor amino acids in their blood [31,32]. The ratios of the amino acid precursors to the other neutral amino acids are also normal in underweight anorectics [31]. Others, however, have found that underweight anorectics have decreased concentrations of amino acid precursors. In underweight anorectics, Copen et al [33] found low total and free plasma tryptophan, and Gerner et al [34] found significantly lower concentrations of CSF tyrosine than controls. Because of these conflicting findings, it remains unclear whether decreased availability of monoamine precursors contribute to CSF monoamine disturbances in underweight anorectics.

Brain Serotonin and Dopamine Metabolism: Basal CSF Concentrations

Only two studies [31,34] report basal CSF concentrations of 5-HIAA and HVA in underweight anorectics. Both groups found that underweight anorectics had basal concentrations of 5-HIAA and HVA that were similar to healthy controls. Gerner and associates [34] only measured these metabolites in underweight anorectics and controls. Our laboratory [31] measured these metabolites in underweight anorectics, and again in the same patients after weight restoration. We found that seven of eight patients studied as underweight anorectics showed an increase in CSF HVA (figure 1) and 5-HIAA (Figure 2) after weight recovery. Because of the small number of subjects and the large variance, it is only apparent that CSF HVA and 5-HIAA were decreased in underweight anorectics when the same subjects were compared while underweight and after weight recovery. We also measured these metabolites in a group of anorectics who had been weight recovered for a mean of 20 months and found that this group had values of CSF 5-HIAA and HVA that was also similar to controls.

Underweight anorectics have neuroendocrine disturbances that tend to normalize with weight recovery. CSF concentrations of dopamine and 5-HT metabolites have a similar pattern. Could abnormalities in CNS

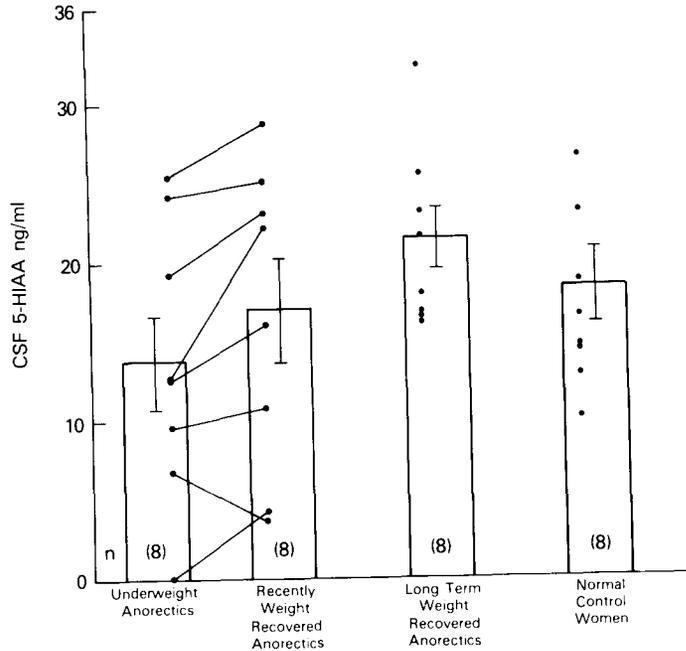


Figure 18.2 Mean (\pm SEM) concentrations of 5-HIAA in CSF for each group of anorexics and normal controls. Underweight anorexics had a significant increase ($t = 2.42$, $p < .05$) in CSF 5-HIAA with recent weight recovery. Long-term weight recovered anorexics had significantly elevated CSF 5-HIAA concentrations compared with the underweight anorexics ($t = 2.58$, $p = .02$).

dopamine and 5-HT pathways account for then neuroendocrine disturbances found in underweight anorexics? Central 5-HT and dopamine pathways modulate some of the neuroendocrine systems that are disturbed in underweight anorexics. For example, there is considerable pharmacological evidence that the central release of 5-HT stimulates corticotrophin-releasing hormone (CRH) secretion [20] and that hypothalamic dopamine transmission appears to participate in regulating LH secretion [35]. The evidence for an effect of central dopamine and 5-HT pathways on other neuroendocrine systems is less conclusive. Disturbances in central dopamine or 5-HT function may contribute to neuroendocrine abnormalities in underweight anorexics. However, more specific conclusions will only be possible when further studies are done.

Chronic low weight and caloric deprivation might account for changes in monoamine metabolism. Studies in animals show that short-term caloric deprivation produces a mixture of changes in brain monoamine concentrations [35-43]. A possibility also exists that some disturbance in monoamine function drives weight loss, since animal studies support the concept that hypothalamic monoamine systems regulate appetitive behavior. It appears that monoamine metabolism is inti-

mately linked with control of appetite and weight and that changes in one affect the other. An association between brain monoamine metabolism, appetitive behavior, and weight loss in anorexia nervosa appears feasible, although the causal relationship remains unknown.

ACCUMULATION OF CSF HVA AND 5-HIAA AFTER PROBENECID

Two methods are available to estimate brain dopamine and serotonin metabolism. The first method is to measure basal level of the serotonin metabolite, 5-HIAA, and of the dopamine metabolite, in CSF. The second method is to measure the accumulation of CSF 5-HIAA and HVA by blocking their transport from CSF to blood by the administration of probenecid.

Only one study [44] reports on accumulation of HVA and 5-HIAA after probenecid administration. This study found that after probenecid administration, a difference existed in accumulation of the serotonin metabolite, 5-HIAA, in CSF between anorexics that fasted and those that binged. This difference in serotonin metabolism between fasters and bingers was present only in weight-recovered anorexics, but not in the

underweight anorectics. In contrast, CSF accumulation of the dopamine metabolite after probenecid was not different between weight-recovered fasters and bingers.

Patients with anorexia nervosa can be subdivided into two groups by appetitive behavior: those that fast and those that binge [45-48]. These subgroups of anorectics differ in other clinical dimensions, such as characterologic style, mood, and impulse control. These behavioral and appetitive differences between fasters and bingers are consistent with other data, suggesting specific influences of serotonin on mood and feeding. Alterations in brain serotonin metabolism have been found in other psychiatric populations. Decreased brain serotonin metabolism has been related to depression [49], suicide [50], and aggressive behavior [51]. Disturbances in brain serotonin pathways may serve to permit dysphoric or impulsive behavior to occur.

In animal studies, brain serotonin has been implicated in appetite suppression, particularly of carbohydrate intake [52,53]. Carbohydrate intake selectively increases tryptophan uptake by the brain, and consequently increases brain serotonin. Our data are consistent with this proposed carbohydrate/serotonin mechanism. Fasters have greater CSF 5-HIAA turnover after probenecid, and decreased appetites. Bulimics have lower 5-HIAA turnover after probenecid. Whether low 5-HIAA is responsible for carbohydrate craving is speculative, but may have heuristic value in suggesting new treatments. Possibly, bingeing on carbohydrates in an attempt to enhance brain serotonin and, in this manner, serves as a form of self-medication.

Alterations in serotonin metabolism may be a trait-related phenomenon, because it appears after weight recovery. Further investigations of brain serotonin metabolism in a larger sample are needed to answer questions raised by this preliminary study.

BRAIN NOREPINEPHRINE METABOLISM

As mentioned norepinephrine and MHPG are decreased in plasma and urine in all studies of underweight anorectics [8,54-60]. In contrast, two groups [31,34] have found that underweight anorectics have concentrations of CSF norepinephrine and MHPG that are similar to normal controls. Since there is usually a good correlation between peripheral and central values of norepinephrine and MHPG, this finding in underweight anorectics was surprising.

One explanation for this discrepancy may be that concentrations of norepinephrine or MHPG in underweight anorectics may relate to the nutritional state. A review of the anorexia nervosa literature suggests that investigations that reported decreased concentrations

of urinary MHPG or plasma norepinephrine in underweight anorectics had studied their subjects soon after admission [8,54,56]. Studies completed after some degree of nutritional rehabilitation had norepinephrine and MHPG values that were in the normal range [31,34]. Abraham [57] found a positive correlation between weight gain and urinary MHPG. Together these studies suggest that norepinephrine turnover decreases during starvation and increases with nutritional rehabilitation. A pattern of decrease in norepinephrine turnover with food restriction, and an increase of norepinephrine turnover with feeding is known to occur in animals and humans.

Of the brain monoamine systems investigated, brain norepinephrine pathways appear to demonstrate the clearest role in the normal regulation of each of the neuroendocrine systems that become disturbed in underweight anorectics. Norepinephrine appears to exert an excitatory influence on gonadotropin release [20,61], perhaps by stimulating the tonic secretion of the LH-releasing system [62,63]. Release of norepinephrine in the hypothalamus decreases CRH secretion [20] and appears to have an excitatory effect on the hypothalamic control of TSH secretion [64,65]. Central norepinephrine activity seems to inhibit vasopressin release [66], although some studies suggest norepinephrine stimulates vasopressin release [66]. Brain norepinephrine and opiate systems are intimately linked [68,69].

We have been interested in investigating anorectics who are weight recovered. Studies of long-term outcome find that many anorectics who return to a normal weight continue to have concerns with their weight and have appetite disturbances [70-75]. Since these women are at normal weight, if they have neurochemical disturbances, such disturbances might be trait related. We found [31,76] that anorectics who had been weight recovered for a mean of 20 months had decreased concentrations of CSF norepinephrine (figure 3), CSF and plasma MHPG, and plasma norepinephrine compared with healthy control women.

The decrease in norepinephrine and MHPG in long-term weight recovered anorectics suggests several interpretations. A decrease in norepinephrine activity might occur during the transition from recent weight recovery to long-term weight maintenance. Another possibility is that anorectics able to gain and maintain weight have a difference in SNS function compared with anorectics with a poor outcome. If decreases in norepinephrine activity occur in the interval between weight recovery and long-term weight maintenance, what might be the purpose? Other systems also slowly change during the transition from short- to long-term weight recovery. These include multiple neuroendocrine systems, physical activity, and caloric efficiency [77]. Since noradrenergic

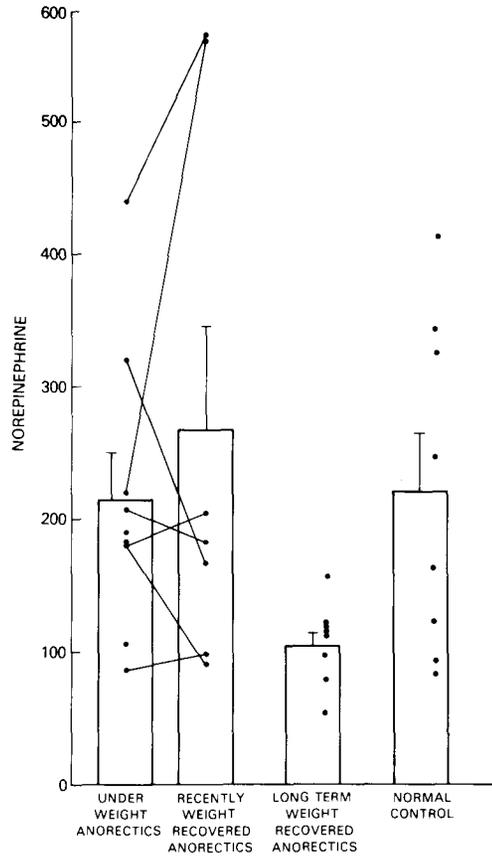


Figure 18.3 CSF norepinephrine concentrations demonstrated no consistent pattern of change between underweight anorectics and the same patients after weight recovery. Long-term weight recovered patients had significantly lower concentrations of CSF NE than normal controls ($t = 2.60, p < .05$) and underweight anorectics ($t = 3.01, p < .02$).

pathways contribute to regulating energy balance, perhaps altered norepinephrine metabolism in long-term weight recovered anorectics is one biologic adaptation that facilitates the maintenance of a relatively normal weight. It is also possible that some portion of continued symptoms in long-term weight-recovered anorectics are attributable to trait-dependent neurotransmitter alterations that may have been obscured by state-related changes while underweight or immediately after weight recovery.

CNS NEUROPEPTIDE METABOLISM

CSF Opiate Activity

Most data concerning endogenous opioids and appetite regulation [78-81] suggests that opioid agonists stimulate eating and antagonists diminish eating. Opiates are thought to influence other systems known to be disturbed in anorexia nervosa. Opiates, of course, have

been implicated in modulation of mood. Opiates regulate and are regulated by monoamines and appear to influence some neuroendocrine systems, such as gonadotropins.

Two studies have measured CSF opiate concentrations in anorexia nervosa, but by quite different methodologies. Gerner and Sharp [82] found underweight anorectics had normal concentrations of CSF beta-endorphin-immunoreactivity. In contrast, our group [83] used a radioreceptor assay that measured total activity of all opiate compounds in CSF. We found the mean level of CSF opioid activity in beta-endorphin equivalents was significantly higher in the underweight anorectics than in the same patients after weight restoration or the long-term weight recovered anorectics.

In recent years a variety of opiates have been found in the brain. Thus, it is not surprising that there is a discrepancy between the measurement of one specific opiate, and all opiates together. It is unknown whether

increased opiate activity at minimum weight reflects a specific opioid appetite stimulation that is a consequence of diminished weight or a stress effect that might serve as a biologic protective response to help the body decrease metabolic requirements when weight is lost. The peripheral endorphinergic system [84] may aid survival in famine by conserving nutrients and water and decreasing energy-expending activities.

CSF and Plasma Vasopressin Concentrations

Abnormalities of water balance in anorexia nervosa have been suggested by earlier work [18,19]. One important component of the regulation of water balance is arginine vasopressin (AVP), a peptide manufactured in the hypothalamus and released by the posterior pituitary to regulate free water. Underweight anorexics [85] have an abnormal release of AVP in response to an osmotic stimuli such as hypertonic saline. This defect takes two forms. The least common is a subnormal rise in AVP relative to the strength of the stimuli. The more common defect is erratic or osmotically uncontrolled AVP release. This pattern contrasts markedly to healthy adults who invariably show a smooth, progressive rise in plasma AVP that correlates closely with the rise in plasma sodium during the infusion of hypertonic saline. AVP osmoregulation returned to normal in most of the long-term weight recovered anorexics.

In healthy adults, daytime concentrations of CSF AVP ranges from 0.5 to 2.0 pg/ml [86]. In addition, the CSF levels tend to parallel but are almost always lower than those in plasma. In anorexia nervosa, some anorexics at any stage had elevated CSF AVP levels, and many anorexics had an abnormal ratio of CSF AVP to plasma AVP.

The pathophysiologic consequences of AVP disturbances in anorexia nervosa remain to be fully defined. We did find most subjects had increased urine output, but this finding is difficult to explain in patients who show erratic secretion without obvious deficiency of vasopressin. The possible significance of CSF abnormalities is speculative, because we do not know what role AVP plays in brain function.

CSF Somatostatin

The growth hormone release-inhibiting factor, somatostatin, has been found in multiple regions throughout the brain [87]. Malnourished anorexics have high basal plasma concentrations of growth hormone that normalize with nutritional rehabilitation without weight gain [16,17]. High levels of growth hormone could be due to decreased brain SRIF. Gerner and Yamada [88] found decreased CSF somatotropin-release inhibition factor (SRIF)-like immunoreactivity in underweight anorexics compared with controls. Whether SRIF alterations

are responsible for growth hormone or other disturbances in anorexia nervosa is an interesting question requiring further investigation.

OTHER CSF NEUROCHEMICALS

GABA

GABA is an inhibitory neurotransmitter [89] that has been implicated in Huntington's Disease [90,91] and epilepsy [92]. Animal studies suggest that GABA may have some modulatory effect on appetite [93]. Gerner and Hare [94] found underweight anorexics and normal control women had similar CSF levels of GABA. Since CSF GABA seems to adequately reflect brain GABA [95,96], this finding suggests that not all neurotransmitters are uniformly disturbed during low weight in anorexia nervosa.

Cortisol

In the underweight state, patients with anorexia nervosa have increased plasma cortisol secretion and non-suppression to dexamethaxone [8]. Cortisol metabolism is disturbed in depression [9], and some investigators [98,99] have reported elevated CSF cortisol in depression. Gerner and Wilkins [100] found underweight anorexics had elevated CSF cortisol values. Depressed and nondepressed anorexics had similar CSF cortisol elevations. While elevated CSF cortisol may not be related to mood in anorexia nervosa, cortisol has a number of effects on catecholamine metabolism [101] and is, in turn, thought to be partially modulated by norepinephrine pathways. Thus, elevated cortisol may produce, or reflect, disturbances in other brain systems.

CONCLUSIONS

The questions we tried to answer in the studies reviewed in this chapter were: (1) Were abnormalities in brain neurotransmitters present in patients with anorexia nervosa, and if so (2) would abnormalities in brain neurotransmitters explain behavioral or physiologic disturbances in anorexia nervosa?

These studies have demonstrated that a number of changes occur in neurotransmitter and neuromodulator systems in anorexia nervosa. Whether any of these changes is a primary etiological event that occurs early in the illness or triggers the illness remains an open question. Some of the changes appear to occur predictably in each individual when underweight, such as the decrease in basal brain dopamine, serotonin, and somatostatin metabolism, and the increase in CSF cortisol and opioid activity. Some changes, such as those in vasopressin function, are prolonged and may last months

after weight recovery. Some disturbances, such as in CSF norepinephrine in long-term weight recovered subjects, suggest that alterations in norepinephrine function may be necessary for sustaining weight restoration. Weight recovered fasting and bulimic anorectics appear to have differences in serotonin metabolism, data that is consistent with what is known about serotonergic influences on appetite and mood.

The past decade has produced a wealth of data about neuroendocrine disturbances in anorexia nervosa. These neuroendocrine studies have focused on peripheral hormonal systems. In general, these peripheral hormonal studies implicated disturbances of hypothalamic regulatory systems, which are in part regulated by the same neurotransmitters that are disturbed in anorexia nervosa. Furthermore, these neurotransmitter abnormalities could contribute to the disturbances of appetite, mood, motor activity, and metabolism described in anorexia nervosa. It is likely that there are other neurotransmitter system disturbances in anorexia nervosa. For example, many gastrointestinal peptides are also present in the brain [102]. The relationship of these peptides to appetite regulation needs to be elucidated. Our technology now permits more direct exploration of brain pathways and neurochemical dysfunction in anorexia nervosa and allows us to build on the foundation laid by previous investigators.

The discovery of neurochemical disturbances in anorexia nervosa may be most useful as a means of suggesting new neuropharmacologic treatments for this disease. At present there is no medication "magic bullet" that enhances weight restoration or weight maintenance. The possibility that there are trait-related disturbances of serotonin or norepinephrine metabolism in anorexia nervosa might suggest trials of specific agents.

In summary, we have come to accept that there are systematic disturbances of specific neuroendocrine systems in anorexia nervosa. Abnormalities in neurotransmitter metabolism are also part of the neurobiological syndrome of anorexia nervosa and may contribute to the characteristic changes in behavior and physiology.

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