Nutrition, Serotonin and Behavior in Anorexia and Bulimia nervosa

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Introduction

Anorexia nervosa (AN) and bulimia nervosa (BN) are disorders characterized by aberrant patterns of feeding behavior and weight regulation, and disturbances in attitudes toward weight and shape and the perception of body shape. In AN, there is an inexplicable fear of weight gain and unrelenting obsession with fatness even in the face of increasing cachexia. BN usually emerges after a period of dieting, which may or may not have been associated with weight loss. Binge eating is followed either by self-induced vomiting or some other means of compensation for the excess of food ingested. The majority of people with BN have irregular feeding patterns and satiety may be impaired. Although abnormally low body weight is an exclusion for the diagnosis of BN, some 25–30% of patients with BN who present to treatment centers have a prior history of AN; however, all individuals with BN have pathological concern with weight and shape. Common to individuals with AN or BN are low self-esteem, depression, and anxiety.

In certain respects, both diagnostic labels are misleading. Individuals affected with AN rarely have complete suppression of appetite, but rather exhibit a volitional, and, more often than not, ego syntonic resistance to feeding drives while eventually becoming preoccupied with food and eating rituals to the point of obsession. Similarly, BN may not be associated with a primary, pathological drive to overeat; rather, like individuals with AN, those
with BN have a seemingly relentless drive to restrain their food intake, an extreme fear of weight gain, and often have a distorted view of their actual body shape. Loss of control with overeating usually occurs intermittently and typically only some time after the onset of dieting behavior. Episodes of binge eating ultimately develop in a significant proportion of people with AN [1], whereas some 5% of those with BN will eventually develop AN [2]. Because restrained eating behavior and dysfunctional cognitions relating weight and shape to self-concept are shared by patients with both these syndromes, and transitions between syndromes occur in many, it has been argued that [3] AN and BN share at least some risk and liability factors in common.

The etiology of AN and BN is presumed to be complex and multiply influenced by developmental, social, and biological processes [4, 5]. However, the exact nature of these interactive processes remains incompletely understood. While cultural attitudes toward standards of physical attractiveness have relevance to the psychopathology of eating disorders, it is unlikely that cultural attitudes have a major influence. That is because dieting behavior and the drive toward thinness are quite commonplace in industrialized countries throughout the world, yet AN and BN affect only an estimated 0.3–0.7% and 1.7–2.5%, respectively, of females in the general population. Moreover, the fact that numerous clear descriptions of AN date from the middle of the 19th century [5] suggests that factors other than our current culture play an etiologic role. Second, both syndromes, AN in particular, have a relatively stereotypic clinical presentation, sex distribution, and age-of-onset, supporting the possibility of some biological vulnerability. In fact, emerging evidence suggests that both AN and BN are familial and that clustering of the disorder in families may arise partly from genetic transmission of risk [6, 7]. Moreover, studies in twins [8, 9] suggest some sharing of familial risk and liability factors between AN and BN.

The reasons that people with AN and BN engage in extremes of eating behavior remain obscure. Accumulating evidence raises the possibility that disturbed appetitive behaviors may, in part, be a consequence of disturbed modulation of brain serotonin (5-HT) pathways, a system well known to contribute to modulation of feeding behavior. In addition, altered 5-HT activity may contribute to unpleasant disturbances of mood. Recent evidence suggests, in turn, that altered feeding behavior may have effects on tryptophan, an essential amino acid that is the precursor of 5-HT. People with eating disorders may find that extremes of nutrition may, through effects on 5-HT, briefly reverse uncomfortable mood states. Thus they may enter a vicious cycle and spiral out of control. This paper will review some of the new evidence suggesting that heritable biological phenomena strongly contribute to the pathogenesis of AN and BN and studies supporting the contention of a 5-HT link between eating behavior and mood in these illnesses.
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Persistent Psychological Disturbances after Recovery from AN and BN

People who have an eating disorder (ED) often have a variety of symptoms aside from pathological eating behaviors. Physiological symptoms include an abundance of neuroendocrine, autonomic, and metabolic disturbances. Psychological symptoms include depression, anxiety, substance abuse, and personality disorders. Determining whether such symptoms are a consequence or a potential cause of pathological feeding behavior or malnutrition is a major methodological issue in the study of eating disorders. It is impractical to study EDs prospectively due to the young age of onset and difficulty in premorbid identification of people who will develop an ED. However, subjects can be studied after long-term recovery from an ED. The assumed absence of confounding nutritional influences in recovered ED women raises a possibility that persistent psychobiological abnormalities might be trait-related and potentially contribute to the pathogenesis of this disorder.

Investigators [10–13] have found that women who were long-term recovered from AN had a persistence of obsessional behaviors as well inflexible thinking, restraint in emotional expression, and a high degree of self- and impulse-control. In addition, they have social introversion, overly compliant behavior, and limited social spontaneity as well as greater risk avoidance and harm avoidance. Moreover, individuals who are long-term recovered from AN had continued core eating disorder symptoms, such as ineffectiveness, a drive for thinness, and significant psychopathology related to eating habits. Similarly, people who have recovered from BN continue to be overconcerned with body shape and weight, abnormal eating behaviors, and dysphoric mood [14–18]. Recovered AN and BN women had increased perfectionism and their most common obsessional target symptoms were the need for symmetry and ordering/arranging. Considered together, these residual behaviors can be characterized as overconcerns with body image and thinness, obsessiallity with symmetry, exactness, and perfectionism, and dysphoric/negative affect. In general, pathologic eating behavior and malnutrition appears to exaggerate the magnitude of these concerns. Thus, the intensity of these symptoms is less after recovery but the content of these concerns remains unchanged. The persistence of these symptoms after recovery raises a question of whether disturbances of such behaviors are premorbid traits that contribute to the pathogenesis of AN and BN.

Studies of Neurotransmitters

The role of biology in the etiology of AN has been proposed for the past 60 years. Earlier theories raised the question of whether people with AN had a pituitary or hypothalamic disturbance. More recently, a growing
understanding of neurotransmitter modulation of appetitive behaviors has raised the question of whether some disturbance of neurotransmitter function causes AN and/or BN [19–21]. It is possible that disturbances of brain neuropeptides and/or monoamines could contribute to other symptoms and behaviors, such as neuroendocrine or autonomic abnormalities, or alterations of mood and behavior, in people with AN or BN. It is important to emphasize that monoamine or neuropeptide disturbances could be a consequence of dietary abnormalities or premorbid traits that contribute to a vulnerability to develop AN or BN. One way to tease apart cause and effect is to study people with AN or BN at various stages in their illness, that is, while symptomatic and after recovery.

**5-HT Neuronal Activity**

There has been considerable interest in the role that 5-HT may play in AN and BN, because 5-HT pathways play an important role in postprandial satiety. Treatments that increase intrasynaptic 5-HT, or directly activate 5-HT receptors, tend to reduce food consumption whereas interventions that dampen serotonergic neurotransmission or block receptor activation reportedly increase food consumption and promote weight gain [19, 22]. Moreover, central nervous system (CNS) 5-HT pathways have been implicated in the modulation of mood, impulse regulation and behavioral constraint, and obsessionality. They also affect a variety of neuroendocrine systems.

When underweight, patients with AN have a significant reduction in basal concentrations of the 5-HT metabolite 5-hydroxyindolacetic acid (5-HIAA) in the CSF compared to healthy controls [23], as well as blunted plasma prolactin response to drugs with 5-HT activity [24] and reduced $^3$H-imipramine binding [25]. Together, these findings suggest reduced serotonergic activity, which could be secondary to a diet-induced reduction of availability of the amino acid, tryptophan, the precursor of 5-HT. In contrast, CSF concentrations of 5-HIAA are reported to be elevated [26] and neuroendocrine responses to 5-HT-stimulating drugs are normalized [11] in women who are long-term weight recovered from AN. These contrasting findings of reduced and heightened serotonergic activity in acutely ill and long-term recovered AN individuals, respectively, may seem counterintuitive; however, since dieting lowers plasma tryptophan levels in otherwise healthy women [27], resumption of normal eating in AN may unmask intrinsic abnormalities in serotonergic systems that mediate certain core behavioral or temperamental underpinnings of risk and vulnerability.

Considerable evidence also exists of dysregulation of serotonergic processes in people who are ill with BN. This includes blunted prolactin response
to the 5-HT receptor agonists *m*-chlorophenylpiperazine (*m*-CPP) [28, 29], 5-hydroxytryptophan [30], and *d*,*l*-fenfluramine [31, 32], increased platelet 5-HT uptake [33], reduced platelet imipramine binding capacity [34] and enhanced migraine-like headache response to *m*-CPP challenge [35]. Moreover, acute perturbation of serotonergic tone by dietary depletion of tryptophan has also been linked to increased food intake and mood irritability in women with BN compared to healthy controls [36]. While ill BN have normal CSF 5-HIAA levels, women who are long-term recovered from BN have elevated concentrations of 5-HIAA in the CSF [17] and a dysphoric response to tryptophan depletion [37].

Together, these data show that both recovered AN and BN women have elevated CSF 5-HIAA concentrations. It has been found that low levels of CSF 5-HIAA are associated with impulsive and non-premeditated aggressive behaviors, which cut across traditional diagnostic boundaries. Behaviors found after recovery from AN and BN, such as obsessions with symmetry, exactness, and perfectionism, and negative affect, tend to be opposite in character to behaviors displayed by people with low 5-HIAA levels. Together, data support the hypothesis [38] that increased 5-HT activity may be associated with exaggerated anticipatory overconcern with negative consequences, while the lack of such concerns may explain impulsive, aggressive acts that are associated with reduced 5-HT activity.

These data raise the possibility that a disturbance of 5-HT activity may create a vulnerability for the expression of a cluster of symptoms that are common to both AN and BN. That is, 5-HT has been postulated to contribute to temperament or personality traits, such as harm avoidance [39] or behavioral inhibition [40] or to categorical dimensions such as obsessive compulsive disorder (OCD) [41], anxiety and fear [42] or depression [43] as well as satiety for food consumption. Importantly, these symptoms persist in AN and BN after recovery.

The possibility of a common vulnerability for AN and BN may seem puzzling given well-recognized differences in behavior in these disorders. However, recent studies suggest that AN and BN have a shared etiologic vulnerability [8]. Other factors, that are independent of a vulnerability for the development an eating disorder, may contribute to the development of eating disorder subgroups. For example, people with restricting-type AN have extraordinary self-restraint and self-control. The risk for obsessive-compulsive personality disorder is elevated only in this subgroup and in their families and shows a shared transmission with restricting-type AN [6]. In other words, an additional vulnerability for behavioral overcontrol and rigid and inflexible mood states, combined with a vulnerability for an eating disorder, may result in restricting-type AN.
The Role of Diet and Its Relationship to 5-HT Activity in AN and BN

Considered together, when ill, AN and BN subjects may have a relatively diminished 5-HT activity. With refeeding, 5-HT activity increases and elevated 5-HT activity may emerge after long-term recovery. Self-starvation is not conducive to homeostatic adaptation and survival, and in most people food restriction is not an inherently reinforcing behavior. However, persistent dieting to the point of starvation raises the speculation that food restriction might have some benefit for people with AN and/or BN.

Experimental data may most clearly support this hypothesis in people with AN. People with AN may have a trait-related increased 5-HT neuronal transmission that occurs in the premorbid state and persists after recovery. Increased 5-HT neurotransmission in turn contributes to uncomfortable core symptoms such as obsessionality, perfectionism, harm avoidance and anxiety. We hypothesize that people with AN starve themselves in order to reduce 5-HT neuronal activity and thus reduce a dysphoric behavioral state.

It is well known that diet can influence brain 5-HT neurotransmission. Tryptophan (TRP), an essential amino acid only available in the diet, is the precursor of 5-HT. Meal consumption, depending on the proportion of carbohydrate and protein, can enhance brain 5-HT release [44, 45], thereby affecting appetite regulation. In brief, carbohydrate consumption causes an insulin-mediated fall in plasma levels of the large neutral amino acids (LNAA, tyrosine, phenylalanine, valine, leucine, isoleucine) which compete with TRP for uptake into the brain. This elevates the plasma TRP/LNAA ratio, and thus brain TRP, which rapidly accelerates brain 5-HT synthesis and release. Dietary proteins tend to block these effects by contributing large amounts of LNAA to the bloodstream. Considerable amounts of evidence in animals and healthy humans [27, 44–50] show that a restricted diet significantly lowers plasma TRP, resulting in a decreased plasma ratio of TRP to neutral amino acids, and, in turn, a reduction in the availability of TRP to the brain. Thus, restricted diet (and experimentally reduced TRP) decreases brain 5-HT synthesis, down-regulates the density of 5-HT transporters [51], and produces a compensatory supersensitivity of postsynaptic receptors in response to reduced 5-HT turnover [52]. Limited data show that malnourished and emaciated AN women have a reduction of plasma TRP availability [53].

We tested the hypothesis that AN patients have a trait-related increase of 5-HT neurotransmission that could contribute to dysphoric mood symptoms by administering substances that decreased and increased 5-HT neurotransmission. On one day, subjects were deprived of TRP (acute tryptophan depletion, ATD), which reduces plasma TRP availability [54] and decreases brain 5-HT concentrations [55]. We found that the ATD challenge was associated with a reduction in negative mood. In contrast, when AN subjects were administered
d-fenfluramine (d-FF), a drug that increases 5-HT release from nerve terminals and inhibits 5-HT reuptake [56], they had an increase in negative affective symptoms. On the day subjects were given ‘placebo’, there was no change in mood.

In comparison, studies [17, 36] show ill patients with BN, after TRP depletion, have an increase in labile and dysphoric mood and overeat compared to control women, supporting the possibility that women with BN have a fragile and dysregulated 5-HT system that is vulnerable to dietary manipulations. While Oldman et al. [57] found no significant effects of TRP depletion on mood, appetite, or food intake in women with BN who were abstinent from binge eating and purging, Smith et al. [37] found that dysphoric response to ATD persisted in remitted BN women. These data suggest that women with BN are vulnerable to the mood-lowering effects of TRP depletion. This corroborates results from other studies that have shown that individuals predisposed to other, possibly serotonergically-mediated psychiatric disorders, are particularly susceptible to the depressant effects of TRP depletion [54, 58, 59]. In summary, these studies may help understand why starvation is reinforcing in people with AN, but not in people with BN.

**Pharmacotherapy**

The results of most double-blind, placebo-controlled randomized trials reported to date indicate that antidepressants show at least some superiority over placebo in reducing the frequency of binge eating episodes [60]. In addition, some studies show a reduction in intensity of some other symptoms commonly seen in BN, such as preoccupation with food and depression [61].

People with AN have responded less effectively to treatment [62]. Extended hospitalizations can be lifesaving because such treatment can restore weight to emaciated people, which, in turn, reverses medical complications. However, hospitalizations can be lengthy and expensive and the rate of relapse after hospitalization has been high [63]. The evaluation of the efficacy of medications in augmenting weight gain in AN is limited, because most trials have been conducted in outpatients or inpatients participating in behavioral and nutritional ED programs, which are themselves efficient in the short run. Nevertheless, in these settings controlled trials have not provided consistent evidence for the efficacy of antidepressant medications in the treatment of AN [64–66].

Recent studies that have focused on preventing relapse show more promise. Our group has found in separate open and double-blind placebo-controlled studies that fluoxetine improved outcome and reduced relapse after weight restoration [67, 68]. That is, fluoxetine, when given after weight restoration, significantly reduces the extremely high rate of relapse normally seen in...
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AN perhaps because it reduces core ED symptoms, depression, anxiety, and obsessions and compulsions. In contrast, several studies [69, 70] have found that SSRIs are not useful when people with AN are malnourished and underweight. As noted by Tollefson [71], SSRIs are dependent on neuronal release of 5-HT for their action. If the release of 5-HT from presynaptic neuronal storage sites was substantially compromised, and net synaptic 5-HT concentration was negligible, a clinically meaningful response to an SSRI might not occur.

This link between dietary intake and SSRI efficacy is supported by data which have repeatedly shown that dieting in healthy normal weight and obese women reduces TRP availability and thereby limits potential serotonergic production [27, 31, 72–74]. Moreover, studies in animals show that food restriction decreases 5-HT and its synthesis rate in the brain [48] and down-regulates the density of 5-HT transporters [51]. Finally, depletion of TRP, the precursor of 5-HT, reverses the effects of SSRI antidepressants in depressed patients [75, 76]. In AN, weight restoration normalizes nutrition and CSF 5-HIAA concentrations become elevated [26]. These changes in nutrients and 5-HT activity may explain why individuals with AN may become responsive to fluoxetine after weight restoration.

Other Potential Effects of Nutrition on 5-HT Activity and SSRI Efficacy

Impaired 5-HT functional activity could also be a consequence of nutrients other than TRP, which are essential to normal 5-HT synthesis and function, and are reduced in underweight AN patients [77–81]. These nutritional factors include insulin activity, essential fatty acids, zinc and pyridoxine (vitamin B6). Insulin mediates the increased brain uptake of TRP and 5-HT synthesis following carbohydrate ingestion. The low basal and postingestive insulin concentrations observed in underweight AN patients [82] may hamper this process. Very low fat diets, as typically consumed by women with AN, have been found to diminish neuronal 5-HT activity in animal studies [83]. In addition, the type of dietary fat consumed determines the biophysical properties of cell membranes and hence influences neurotransmitter receptor function. Specifically, it has been hypothesized that an inadequate n-3 fatty acid intake adversely affects serotonergic function [84].

Zinc also influences membrane stability to the extent that zinc deficiency increases membrane fluidity, causing the loss of receptor function [77]. Poor zinc status has been observed in individuals with AN [80], which may contribute to the ineffectiveness of SSRIs during the acute stage of the illness. The B vitamins are also involved in metabolic pathways influencing 5-HT availability. Vitamin B12 and folate are required for the formation of
tetrahydrobiopterin which is a hydroxylase cofactor in the rate-limiting step of 5-HT synthesis [85]. Vitamin B₆, in the form of pyridoxal-5-phosphate, is a cofactor required in the reaction that converts 5-hydroxytryptophan to 5-HT [86, 87]. Dietary deficiency and lowered biochemical activity of these B vitamins in some patients with AN [78–81] may therefore compromise the ability of SSRIs to facilitate serotonergic function.

An alternative possibility is that reduced serotonergic activity in dieting women and women underweight with AN is mediated through low levels of gonadal steroids that are observed in malnourished states [88, 89]. Estrogen has been found to stimulate significant increases in the density of central 5HT2A binding sites [93] and 5-HT transporter binding sites [90], to inhibit monoamine oxidase activity [91] and to be positively correlated to platelet 5-HT content [92]. A deficiency of estrogen in malnutrition may, therefore, thwart the functional activity of the serotonergic system and the potential responsiveness to SSRI medication.

In summary, AN is a condition in which inadequate nutrition appears to impair SSRI efficacy. It has also been shown that people with BN show signs of starvation when bingeing and purging [88, 93]. While not as well studied, it is possible that malnutrition could also compromise SSRI efficacy in individuals with BN. These data raise the possibility that nutritional factors may affect SSRI response in depression, OCD, or other conditions characterized by disturbances in serotonergic pathways. When patients do not respond to one SSRI medication, physicians often switch to another SSRI medication. Another strategy would be to assess nutritional status. Better nutrition might serve to improve SSRI efficacy. The possibility that suboptimal nutrition status is responsible for nonresponse to SSRI treatment in depression or OCD remains to be determined.

References

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Discussion

*Dr. Fernstrom:* If fenfluramine causes increased anxiety in these people, then in recurrent anorexics why would an SSRI (serotonin-selective reuptake inhibitor) work? Secondly, wouldn’t serotonin antagonists be expected to work in this disease?

*Dr. Kaye:* When you give people SSRIs they tend to make them more anxious in the first week or so. You have to tell them that they have to get through the anxiety for the drug to work. This has been well described in the OCD (obsessive-compulsive disorder) literature. So probably what is happening is that you are exaggerating the hyperserotonergic function, but there are well-described secondary and long-term consequences in terms of changes in postsynaptic and presynaptic receptors. The modulatory function of the serotonergic system is probably working very erratically in people with depression and eating disorders, and these drugs appear to make the system work more efficiently, so that there is a better signal-to-noise ratio.

The other question is whether postsynaptic antagonists really are effective. We’re doing some studies now with alanzapine, which is a postsynaptic antagonist of the serotonin-2 receptors. We find that in some people with anorexia nervosa this is a very useful drug and reduces anxiety. The other thing that alanzapine and the other atypical SSRIs do is to stimulate weight gain. I had one patient who had an incredibly dramatic response—a woman with an anorexic-like disorder for many years. Her weight increased from about 36 to 73 kg and for the first time in her life she just ate.
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what she wanted. Not everybody with anorexia responds in that way of course, but we
have had some reasonable responses in other patients. We’ve just published two case
reports on this.

Dr. Uauy: Is there any role of adjusting the composition of the diet to optimize
brain serotonin?

Dr. Kaye: All the years that we’ve been feeding people with anorexia nervosa,
no-one has really asked the question of what is an optimal diet for these patients. There
are no studies, but it’s a very important question and something we ought really to do
some research on.

Dr. Fernstrom: If I could just comment on that. My understanding is that you
simply try to treat people with anorexia to get them up to ideal body weight as quickly
as possible and that you don’t take into account any considerations of diet quality. The
fact is that these women are very fat-averse and yet what they’re given to eat has a high
fat content, and they’re also given dietary instructions that do not take into account
what their dietary aversions are.

Dr. Kaye: Also we give them animal fat, which is the last thing that people with
anorexia nervosa are going to eat when they’re at home! Yet I have done this also, and
I don’t know what would be better at this point.

Dr. Langhans: As I understand it, hyperactivity is one of the major symptoms. Is
anything known about the effects of exercise or hyperactivity on brain serotonergic
activity?

Dr. Kaye: Anorexics have a kind of stereotyptic motor activity. They do certain kinds
of activities – they walk, they jog, and if you keep them from doing that they fidget;
they’re always moving around or doing calisthenics. Maybe Dr. Fernstrom knows about
the effects on serotonin?

Dr. Fernstrom: There have been studies in rats on the effects of exercise on
serotonin production, and it seems to increased it. Different mechanisms are proposed,
some having to do with tryptophan and some not. The other side of the coin is that
when you starve rats and take them well below their normal body weight, they become
hyperactive. In that situation, hyperactivity is associated with less serotonin, so you
have two opposing situations.

Dr. Kaye: The other thing that we find with anorexia is that they have low levels
of CSF dopamine activity – about half the level of other groups of patients used as control.
This suggests that there is some disturbance of dopamine activity, which makes sense
in terms of motor activity, though what it means is less clear.

Dr. Bunout: The personality profile you find for people with anorexia nervosa is
just the opposite of the personality profile of people with addictive behaviors. I was
wondering whether you have any idea what happens to 5-HIAA in the CSF in people
with addictive behavior or alcoholism? The other side of the coin is that people who are
prone to anorexia nervosa should not have addictive behaviors. Is there any information
on that?

Dr. Kaye: My recollection is that 5-HIAA is not abnormal in alcoholics. There is a
substantial literature on addiction and eating disorders, and not surprisingly people
with anorexia tend not to use drugs or alcohol. They don’t tend to have family members
who use drugs or alcohol either. In fact the rates of drug and alcohol use in family
members tend to be less than in the normal population. Our studies and others show
that substance abuse and eating disorders are independently transmitted, so these are
different disorders in terms of genetic and familial transmission.

Dr. Arroyo: Along with these pharmacological approaches, have you tried any
psychotherapeutic approaches, and what is the effect of this combination of treatments?

Dr. Kaye: The literature on the long-term outcome of anorexia is pretty grim. There
have been some treatment trials, both of drugs and less often of psychotherapeutic
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treatment, and I should say the treatment trials don’t seem to make much difference to outcome. More recently in the last 5 or 10 years, there have been several small-scale trials looking at various kinds of psychotherapy in terms of reducing relapse, which to my mind is a much more promising way to go about things. These studies show some modest effects in some populations, but it’s not very powerful.

Dr. Cole: Could you comment on the relation between sex steroids and this disease, given that it occurs in females after puberty?

Dr. Kaye: I’m interested in this issue, because these are disorders that occur around puberty, and that is so stereotypic that you have to assume that there’s some relation with the sex steroids. My understanding of the literature is that female gonadal steroids have effects on serotonergic activity that are different from those of the male. My theoretical assumption is that there’s something about puberty that’s activating the serotonergic system.

Dr. Cole: I think there has to be some connection there, because the arcuate nucleus and the hypothalamic centers that are involved in satiety are so loaded down with estrogen receptors, it must make sense. I assume there have been studies on estrogens and biogenic amines and the regulation of gonadotropins and everything else in the arcuate nucleus, and that they might influence the receptors or other aspects of 5-HT metabolism.

Dr. Møller: Migraine also has its highest incidence in females around 14–16 years, about the same age as anorexia nervosa. Do you know of any connection between these two conditions? Migraine is definitely associated with malfunction of the serotonin system.

Dr. Kaye: Several studies in humans have found a strong inverse relation between age and serotonergic activity. There is also a high correlation between age and binding of the 2A receptor in the brain in normal people. In people with bulimia nervosa this relationship with age is not present. I suspect that in people with eating disorders something happens at puberty that activates the serotonergic system which then becomes unresponsive to the normal modulatory effects, whatever they are. To go back to your question, in the teenage years there may be relatively more serotonergic activity and as you get older the serotonergic activity diminishes, so people with migraine may be more susceptible for various reasons when they’re in their teenage years but later, as the serotonergic system changes its functional activity, they are no longer so susceptible.

Dr. Woods: Are you suggesting that when millions of young women diet, only those who seem to get a special kind of reinforcement, or reward perhaps, because of the serotonin system are likely to keep doing it to the point of becoming anorexic?

Dr. Kaye: Exactly. It has to reduce anxiety appreciably. People with anorexia do get hungry. They’ll tell you they’re hungry. They cook for others. They often go into food businesses. They’ll window-shop in supermarkets. They think about food all the time. But they don’t eat. There must be something going on that makes eating so unrewarding that they don’t do it.

Dr. Fernstrom: Why wouldn’t they search around for other ways to reduce anxiety, like alcohol for example.

Dr. Kaye: That’s exactly what happens. Data from twin studies show that if one identical twin gets anorexia nervosa, the other does not necessarily get it as well, but does have an anxiety disorder. Genetically it appears that there is some kind of susceptibility factor which then has to be coped with in different kinds of ways, depending on the culture or the environment. So if you have an anxiety disorder you could develop anorexia, but you could cope in other ways, such as overexercise or extreme involvement in religion and so on. There are lots of ways of dealing with anxiety; however, alcohol doesn’t seem to be one for them.
Dr. Arrayo: As there is a very well-defined metabolic pathway for serotonin metabolism, I wonder whether the search for candidate genes has produced any new information on the genetics of these conditions.

Dr. Kaye: There does seem to be a 2A receptor variant that is associated with anorexia or obsessive-compulsive behaviors, but it’s not present in all cases. Basically, there haven’t been enough candidate genes yet to look at, and the populations haven’t really been large enough to look at the ones there are. A multicenter study looking at the genetics of anorexia and bulimia nervosa is under way and by the end of next year we’ll have a sample size of 2,000 people with anorexia and bulimia.