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The role of serotonin in human mood and social interaction Insight from altered tryptophan levels

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Abstract

Alterations in brain tryptophan levels cause changes in brain serotonin synthesis, and this has been used to study the implication of altered serotonin levels in humans. In the acute tryptophan depletion (ATD) technique, subjects ingest a mixture of amino acids devoid of tryptophan. This results in a transient decline in tissue tryptophan and in brain serotonin. ATD can result in lower mood and increase in irritability or aggressive responding. The magnitude of the effect varies greatly depending on the susceptibility of the subject to lowered mood or aggressivity. Unlike ATD, tryptophan can be given chronically. Tryptophan is an antidepressant in mild to moderate depression and a small body of data suggests that it can also decrease aggression. Preliminary data indicate that tryptophan also increases dominant behavior during social interactions. Overall, studies manipulating tryptophan levels support the idea that low serotonin can predispose subjects to mood and impulse control disorders. Higher levels of serotonin may help to promote more constructive social interactions by decreasing aggression and increasing dominance.

Keywords: Tryptophan; Serotonin; Depression; Aggression; Dominance; Social interaction

1. Introduction

Over the past four decades, advances have been made in understanding the role of serotonin in the control of mood and behavior and in the etiology of psychopathology. Given the complexity of the problem, a variety of different experimental approaches have been needed, each with their own particular advantages and disadvantages. Studies that look at measures related to serotonin function in patients may demonstrate an alteration, but such associations do not necessarily imply anything about cause and effect. Studies that look at the mechanism of action of treatments provide information on the role of serotonin in the treatment of symptoms, but systems involved in therapy are not necessarily those involved in etiology. Altering levels of the serotonin precursor tryptophan can provide information both on the results of low serotonin levels and also on whether increasing serotonin levels can be therapeutic. In such studies, cause and effect are quite clear, but as discussed below, such studies have their own disadvantages.

Tryptophan hydroxylase, the rate-limiting enzyme on the pathway from tryptophan to serotonin, is not normally saturated with tryptophan. In humans, increasing tryptophan levels can increase serotonin synthesis as much as twofold (Young and Gauthier, 1981), while decreasing tryptophan availability can cause a substantial decline in serotonin synthesis and turnover (Nishizawa et al., 1997; Carpenter et al., 1998). When tryptophan is given to increase serotonin synthesis, a dose of 6 g (about six times the normal daily dietary intake; Sainio et al., 1996), is enough to saturate tryptophan hydroxylase and double the rate of serotonin synthesis (Young and Gauthier, 1981). In clinical studies, lower doses are sometimes used, e.g., 1 g TID (Young, 1986). While giving tryptophan can be done chronically, lowering tryptophan levels can only be done acutely.

In the acute tryptophan depletion (ATD) technique, subjects ingest a mixture of amino acids that contains no tryptophan (Young et al., 1985; Moore et al., 2000). This induces protein synthesis (Moja et al., 1991), and as tryptophan is incorporated into proteins, its level in blood and tissues declines markedly. This results in a decline in serotonin synthesis in both animal (Gessa et al., 1974) and human brain (Nishizawa et al., 1997). In animal studies, alterations in serotonin synthesis lead, in some circum-

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stances, to a change in serotonin release (Stancampiano et al., 1997; Bel and Artigas, 1996; Heslop et al., 1991; Schwartz et al., 1990; Westerink and De Vries, 1991; Sharp et al., 1992). ATD attenuates the prolactin response to D-fenfluramine challenge in healthy human subjects, indicating that there is a decline of serotonin levels in the releasable pool of serotonin (Coccaro et al., 1998). However, the evidence for a decline in serotonin release after ATD in humans in the absence of fenfluramine treatment is circumstantial. It is presumed to occur when the consequences of ATD or tryptophan loading are consistent with what is know about the role of serotonin in humans.

The advantage of the tryptophan depletion and loading techniques is that the relation between cause and effect in any experiment is clear, but they have several limitations. First, as noted above, there is no direct evidence that brain serotonin release is altered in humans. Second, altered tryptophan levels may influence the levels of compounds other than serotonin. ATD at night lowers plasma melatonin (Zimmermann et al., 1993), while tryptophan supplementation increases plasma melatonin (Huether et al., 1992). Other potentially psychoactive tryptophan metabolites that might be altered include tryptamine, quinolinic acid and kynurenic acid. Tryptophan supplementation has been shown to increase human CNS tryptamine synthesis (Young and Gauthier, 1981), but the functional implications of this are not known. A third limitation of the ATD method is related to the imbalanced mixture of amino acids ingested. Tryptophan has a special role to play in the regulation of protein synthesis (Sidransky et al., 1968). While tryptophan supplements may increase protein synthesis in the brain (Jorgensen and Majumdar, 1976), tryptophan deficiency could possibly decrease brain protein synthesis. Furthermore, an extensive animal literature exists on the effects of amino acid imbalance, and a tryptophan-deficient amino acid mixture is an example of a diet causing amino acid imbalance. In rats, an amino acid imbalance causes a rapid decline in food intake (Harper et al., 1970). Conditioned place aversion probably plays a role in this decline in food intake, and the effect may be mediated by serotonin, as serotonin$_3$ receptor antagonists block both taste aversion and the decline in intake of an amino acid imbalanced diet (Terry-Nathan et al., 1995). It is important to note that this effect occurs with any amino imbalanced diet, not just one with deficiency of tryptophan. Thus, the involvement of serotonin in the anorexia is not mediated via altered tryptophan availability. However, ATD does not lower food intake in humans (Young et al., 1988; Oldman et al., 1994, 1995; Weltzin et al., 1995). This may reflect a difference between humans and rats rather than demonstrating that humans are not sensitive to the effects of amino acid imbalance. If amino acid imbalance can alter one aspect of brain function, food intake, via an unknown mechanism, it might mediate changes in mood or behavior in ATD studies by the same mechanism. Thus, an appropriate control would be to look at the effect of amino acid mixtures deficient in amino acids other than tryptophan, to see if they have the same effect as T-amino acid mixtures. This was done by Klaassen et al. (1999a) who compared the effect of ATD and acute lysine depletion in healthy subjects with a family history of depression. Consistent with previous work, ATD caused a modest but significant lowering of mood (Benkelfat et al., 1994). However, depletion of the essential amino acid lysine had no effect on mood. Lysine is not a neurotransmitter precursor and, like other amino acids, is degraded to provide energy. It is also a precursor of carnitine, but this is not relevant to the control of mood. Thus, nonspecific effects related to amino acid imbalance are unlikely to account for the effects on mood. Confirmation of this result with other amino acid mixtures deficient in other essential amino acids would reinforce this conclusion.

A fourth limitation of the ATD technique is the relatively short duration of the biochemical changes. Obviously, the effects of chronic low brain serotonin on, for example, mood may be different both quantitatively and qualitatively from the effects of a few hours of low brain serotonin produced by tryptophan depletion. This is not a limitation of tryptophan supplementation studies.

2. Mood

2.1. Tryptophan depletion

A transient lowering of mood was the first reported behavioral effect of ATD in humans (Young et al., 1985). As noted above, recent results confirm that this is unlikely to be a nonspecific effect of amino acid imbalance. Acute lysine depletion has no effect on mood even in individuals who respond to ATD (Klaassen et al., 1999a). Acute depletion of the catecholamine precursors, phenylalanine and tyrosine, also lowers mood, but the effect is qualitatively different from that produced by ATD, the latter associated with irritability and the former with self-reported boredom and decreased interest in rewards (Leyton et al., 2000b,c).

Mood-lowering responses following ATD have been reported in approximately half of the published studies in healthy volunteers. This variability in response to ATD appears to reflect characteristics of the individual being tested. Women report a mood-lowering effect more often than men (Ellenbogen et al., 1996). This does not appear to be due to women being more likely to articulate a mild change in mood. Preliminary results suggest that women are not more likely than men to report mood lowering following cathecholamine depletion (Moreno et al., 1999b). Women, compared to men, also have a superior treatment response to SSRI antidepressants but not to noradrenergic tricyclics (Kornstein et al., 2001). This, along with evidence from other sources (e.g., Young et al., 1980; Biver et al., 1996; Okazawa et al., 2001), raises the possibility that a sex-

related difference in response to ATD might reflect differences in serotonin function.

People at elevated genetic risk for mood disorders are also more likely to display a transient mood-lowering response to ATD. In a sample of carefully screened healthy men, with or without a multigenerational family history of mood disorders, only the high-risk males exhibited mood lowering following ATD. This effect of family history has been replicated and, to date, has been seen in three of four reported studies (Benkelfat et al., 1994; Ellenbogen et al., 1999; Klaassen et al., 1999b; Quintin et al., 2001). A mood-lowering response to ATD might be a phenotypic marker of vulnerability to depression (Benkelfat et al., 1994).

The mood lowering seen following ATD in healthy subjects is in the subclinical range. In comparison, larger changes have been reported to occur in those with a personal history of mood disorders. As in healthy subjects, there appears to be considerable individual variability among former patients in susceptibility to ATD-related mood lowering. A transient reappearance of depressive symptoms in some remitted, treatment-free subjects with a history of clinical depression has been reported in four studies (Smith et al., 1997; Neumeister et al., 1998b; Moreno et al., 1999a; Leyton et al., 2000a) but not in three others (Miller et al., 1996; Lam et al., 2000; Leyton et al., 1997). Preliminary attempts to identify factors that might account for the marked individual differences in mood-lowering response to ATD among former patients implicate sex (Moreno et al., 2001), a history of self-injury/suicidal behavior (Smith et al., 1999; Leyton et al., 1997, 2000a), elevated genetic risk for impulsive aggressive behavior (Leyton et al., 2000a), relapse during the following 12 months (Neumeister et al., 1999; Moreno et al., 2000) and, possibly, inherited polymorphisms of the gene encoding for the 5-HT transporter (Moreno et al., 2001, but see also Lenzinger et al., 1999). Two positron emission tomography studies suggest that, in remitted patients, reinstatement of depressive symptoms following ATD is associated with decreased metabolic activity in the orbitofrontal cortex and striatum (Bremner et al., 1997; Smith et al., 1999). Intriguingly, ATD does not exacerbate depressive symptoms in currently ill untreated patients with major depressive disorder (Delgado et al., 1994), possibly due to a ceiling effect.

The largest mood-lowering responses to ATD have been reported to occur in remitted patients still receiving antidepressant treatment. Here, too, considerable variability in effect size exists, and this seems to be related to treatment modality, characteristics of the patient and efficacy of the depletion. A recent discussion noted that some participants in ATD studies experienced relatively modest depletions of plasma tryptophan levels. A reanalysis of these data suggested that a minimum 60% depletion was necessary, though not sufficient, to elicit the reappearance of depressive symptoms (Van der Does, 2001).

Treatment modality is the best-studied variable related to whether ATD reverses antidepressant efficacy. A transient reversal of clinical efficacy has been seen in patients being treated with SSRIs (6/7 published reports: Delgado et al., 1990; Delgado et al., 1991; Delgado et al., 1999; Bremner et al., 1997; Åberg-Wistedt et al., 1998; Smith et al., 1999, but not Moore et al., 1998), MAOIs (2/2: Delgado et al., 1990; Smith et al., 1999) and phototherapy (2/2: Lam et al., 1996; Neumeister et al., 1998a). In comparison, ATD does not appear to reverse the clinical efficacy of tricyclics (3/3: Delgado et al., 1990, 1991, 1999), lithium (3/3: Benkelfat et al., 1995; Cassidy et al., 1998; Hughes et al., 2001), ECT (1/1: Cassidy et al., 1997) or sleep deprivation (1/1: Neumeister et al., 1998b). One interpretation is that the mechanism of some antidepressant treatments might be more dependent than others on uninterrupted serotonin neurotransmission (Delgado et al., 1999). This is not a sufficient explanation, though, and only 50–60% of patients being treated with an SSRI, MAOI or phototherapy experience a reappearance of depressive symptoms following ATD. An alternative — though not incompatible — explanation is that susceptibility to ATD-related depressive symptom induction varies during treatment and might be highest during the first few weeks of reduced symptomatology (Moore et al., 1998). A recent study indicates that administration of an SSRI per se is not sufficient to elicit vulnerability to ATD mood lowering. In six healthy subjects (four men and two women), fluoxetine administration (20 mg/day for 6 weeks) did not increase their affective response to ATD (Barr et al., 1997).

As in remitted patients off medication, there is evidence that characteristics of the subject may also predict whether ATD will lead to a reversal of antidepressant efficacy. Some post hoc analyses suggest that ATD is more likely to lead to a mood-lowering effect in women than in men (Moreno et al., 2001). Additional factors not yet assessed include family history, risk for self-injury and genotype.

2.2. Tryptophan supplementation

The acute effect of tryptophan in normal subjects, like that of ATD, results in a mood change, in this case euphoria, in a minority of subjects when tryptophan is given at doses 0.5–7 g (Leathwood and Pollet, 1983; Charney et al., 1982; Greenwood et al., 1975; Smith and Prockop, 1962). However, there is no understanding of the factors that lead to mood changes in some subjects and not in others. Similarly, the antidepressant effect of tryptophan seems to vary depending on how and to whom it is given. There seems to be a consensus that tryptophan is not as effective as standard antidepressants in severely depressed inpatients (Cole et al., 1980; Baldessarini, 1984; Young, 1986). However, the largest and longest study of tryptophan as an antidepressant looked at its effect relative to placebo, amitriptyline and the combination of tryptophan and amitriptyline in mild to moderately depressed outpatients over 12 weeks (Thomson et al., 1982). Tryptophan was better than placebo and equivalent to amitriptyline in efficacy and

had fewer side effects than amitriptyline. The combination of tryptophan and amitriptyline was not better than either drug alone.

Four placebo-controlled studies have demonstrated the ability of tryptophan, given at dose of L-tryptophan from 3.5 to 18 g/day, to potentiate the antidepressant action of monoamine oxidase inhibitors (Pare, 1963; Coppen et al., 1963; Glassman and Platman, 1969; Ayuso Guttierrez and Lopez-Ibor Alino, 1971). However, tryptophan also potentiated the side effects of the monoamine oxidase inhibitors. Unlike the combination of tryptophan with MAOIs, the addition of tryptophan to tricyclic antidepressants has only occasionally shown any potentiation of clinical effect. Negative results came from several studies, which looked at the combination of tryptophan with clomipramine or desipramine (Shaw et al., 1975), imipramine (Chouinard et al., 1979) and zimelidine (Wålinder et al., 1981). In a study comparing tryptophan and placebo in patients treated with amitriptyline, there was a trend for the combination to give better results, but this effect was not statistically significant (Lopez-Ibor Alino et al., 1973). However, the combination of clomipramine with DL-tryptophan was significantly better than clomipramine alone (Wålinder et al., 1976). As mentioned above, the largest and longest study of the effect of the addition of tryptophan to other antidepressants found no significant difference between the three active treatment groups, and all were significantly better than placebo (Thomson et al., 1982). However, the Hamilton Depression Scale item ''depressed mood'' showed significantly better improvement for the combination than for either active treatment alone. A single preliminary study on specific serotonin reuptake inhibitors reported that patients treated with fluoxetine plus tryptophan responded significantly faster than those treated with fluoxetine and placebo (Levitan et al., 2000).

As with tryptophan depletion studies, the clinical use of tryptophan provides clear evidence that altered tryptophan levels can result in an alteration of mood in some circumstances. This is seen most clearly in patients with mild to moderate depression.

3. Interpersonal interaction

3.1. Tryptophan depletion

The most studied aspect of interpersonal interaction is aggression. A wealth of animal data supports the idea that there is an inverse relationship between serotonin and aggression and in particular impulsive aggression (Eichelman, 1993; Higley and Linnoila, 1997). Correlational data in humans (e.g., between levels of the serotonin metabolite 5-hydroxyindoleacetic acid in the cerebrospinal fluid and aggressive behavior) support the idea that low serotonin also predisposes humans to impulsive aggressive behavior (Virkkunen and Linnoila, 1993; Mann, 1995). ATD has been used in conjunction with laboratory measures to investigate a causal link between low serotonin and aggression in humans. The tests used include behavioral measures of ''aggression'' and paper-and-pencil tests that look at related phenomena such as irritability. Spontaneous acts of aggression are usually too infrequent to study during the short time of an ATD study, which is why laboratory measures of aggression, which obviously suffer from a certain artificiality, and feelings such as irritability, are usually studied.

One measure of aggressive responding that has been used in conjunction with ATD is the Taylor Competitive Reaction Time task (Taylor, 1967, 1983). Subjects are told that they are competing in a reaction time trial with an opponent in another room, although the opponent is in fact fictitious. The response of the opponent is programmed into a computer. Before each trial, the subject adjusts a switch or presses one of several buttons to set the level of a sound or an electric shock (below the previously determined painful threshold) to be delivered to their opponent, should the subject win the trial. Should the subject lose the trial, s/he receives a stimulus within the same intensity range. The measure of aggression is the level of the stimulus administered to the opponent. This can be studied when the subject's opponent delivers both low-intensity stimuli or provokes the subject by administering a high-intensity stimulus. Using this measure with healthy male subjects, Smith et al. (1986) found no effect of ATD. However, subsequently, the same group used a slightly different design with higher levels of provocation and found that aggression varied inversely with tryptophan levels (Pihl et al., 1995). Alcohol also increased aggressive responding. The effects of altered tryptophan and alcohol were additive, suggesting that some subjects become aggressive when they drink because of low serotonin levels. Cleare and Bond (1995) studied subjects with low or high trait aggression as measured by the Buss–Durkee Hostility Inventory (Buss and Durkee, 1957). ATD had no effect on subjects with low trait aggression, but subjects with high aggression showed greater aggressive responding on the Taylor task and also became more angry, aggressive, annoyed, hostile and quarrelsome on subjective measures.

Another measure that has been used is the Point-Subtraction Aggression Paradigm. In this test, subjects can press one of two buttons. The first uses a fixed ratio to add points, each with a monetary value, to the subject's total displayed on a monitor. The second uses a lower fixed ratio to subtract points from a fictitious opponent and is used as the measure of aggression. The response to point (monetary) loss, due to the actions of the opponent, is an important component of this task.

Using the Point-Subtraction test, ATD increased aggressive responding in unselected male volunteers (Moeller et al., 1996; Bjork et al., 1999), and the effect was greatest in those with high trait hostility (Dougherty et al., 1999). In a recent study, two groups of men with or without a history of aggression were studied. In the aggressive men, ATD

increased aggressive responding, whereas the opposite occurred in the nonaggressive men (Bjork et al., 2000). Another study using a questionnaire supported the idea that trait hostility enhances the response to ATD. The relationship between changes in plasma tryptophan and changes in hostility was stronger in healthy male subjects with preexisting hostile traits than in those with low hostility (Finn et al., 1998). Two studies in patients also reported increases in hostile or irritable mood after ATD. The first was on patients with premenstrual syndrome, who had a susceptibility to irritability (Weltzin et al., 1995). The second was on patients with bulimia, who showed an increase in irritability but no change in depressed mood (Weltzin et al., 1995). While bulimic patients are not necessarily susceptible to irritability, they may have lowered serotonin function (Brewerton, 1995).

Not all studies of susceptible subjects have shown an increase in irritability or aggression after ATD. In patients with Intermittent Explosive Disorder, ATD did not increase irritability or events as measured by the Overt Aggression Scale (Salomon et al., 1994). A second study looked at sons of male alcoholics in their early 20s, who were themselves not alcoholic but would have a high probability of developing alcoholism. In these subjects, ATD did not change responses on the Taylor Aggression task, although there was an increase in commission errors on a Go/No Go task (LeMarquand et al., 1999). This latter finding suggests an increase in impulsivity due to lowered serotonin, and an increase in impulsivity in real life situations could lead to enhanced aggression. However, ATD did not increase Go/No Go commission errors in adolescent males who had been aggressive throughout their childhood (LeMarquand et al., 1998).

While the results on ATD and irritability/aggression do not present as consistent a picture as those with mood, studies using both behavioral measures of aggressive responding and self report measures of irritability indicate that lowered serotonin can enhance both aggressive feelings and behavior in some circumstances. Surprisingly, the most aggressive subjects showed no change. This observation may be analogous to the finding that ATD does not exacerbate symptoms in currently ill patients with major depressive disorder. More work will be needed to determine if this is due to ceiling effects or if more disturbed patients are less susceptible to the effects of lowered serotonin. In patients with currently expressed disorders, an aggravation of symptoms may occur only after alterations of other neuronal systems.

3.2. Tryptophan supplementation

As with ATD, tryptophan supplementation has been studied more in relation to mood than to irritability/aggression. However, both acute studies and clinical trials have been reported in the literature. ATD studies using both the Taylor task (Pihl et al., 1995) and the Point-Subtraction test (Bjork et al., 2000) have also included a tryptophan supplemented group. In this situation, supplementation refers to levels above that present in the normal control treatment, which is an amino acid mixture containing the amount of tryptophan in a good protein source. In both these studies, there was a gradation of effect, with the tryptophan-depleted groups showing the greatest aggressive response and the tryptophan-supplemented group showing the least response.

Two studies have investigated the possible effect of tryptophan in pathologically aggressive patients. The first was performed on aggressive schizophrenics whose behavior was not controlled by neuroleptics (Morand et al., 1983). Some were on neuroleptics during the study, but none were taking neuroleptics with significant binding to serotonin receptors. Tryptophan caused a significant reduction in uncontrolled behaviors relative to placebo. In the second study, on aggressive psychiatric inpatients, tryptophan did not decrease aggressive acts, relative to placebo. However, the patients required significantly less neuroleptic medication to control their aggression when they were on tryptophan (Volavka et al., 1990).

A recent study has looked at the effect of tryptophan on two aspects of social behavior in healthy subjects (Moskowitz et al., 2001). The event sampling methodology used for assessing behavior in this study came from the social science literature on social interaction. While details vary, typically, interpersonal behaviors are organized in a circle defined by two major axes (e.g., Carson, 1969; Foa, 1961; Kiesler, 1983; Leary, 1957; Wiggins, 1995; Wiggins and Broughton, 1985). One axis encompasses dominant and submissive behaviors. The second axis encompasses agreeable and quarrelsome behaviors. These behaviors are studied using an event sampling method in which subjects fill in a brief questionnaire about their behavior after each important social interaction throughout the day. While behavior along each axis varies greatly from one interaction to another, after about 70 interactions (six per day for 12 days), mean values settle down to a value that is a characteristic of the individual. The event sampling method has several advantages. First, it investigates behavior in everyday life and avoids the artificiality of laboratory studies. Second, it minimizes the extent of retrospective reporting that often occurs with self-report questionnaires and therefore reduces biases and distortions that alter the memory of past events. Third, as applied to dominant/submissive and quarrelsome/agreeable behaviors, it reduces subjective biases by asking about the behavior of the individual in the interaction, not the individual's feelings about what occurred.

The two axes of human social behavior are similar to two aspects of social behavior in monkeys often referred to in the primate literature as dominant/submissive and agonistic/affiliative. Altered serotonin affects behavior on both these axes. Treatments that lower serotonergic function in monkeys tend to increase aggression, while treatments that increase serotonin function not only decrease

aggression but also increase affiliative behaviors such as grooming (Chamberlain et al., 1987; Raleigh et al., 1980, 1991; Raleigh and McGuire, 1991). Furthermore, serotonin has also been related to dominant and submissive behaviors in monkeys. In monkeys, there is a two-way interaction between dominance and serotonin (Higley et al., 1996a; Raleigh and McGuire, 1991; Raleigh et al., 1984, 1983). In vervet monkey troops, the alpha male has high platelet and brain serotonin, and these levels fall when dominance is lost. Conversely, raising brain serotonin function promotes acquisition of dominance in males (Raleigh and McGuire, 1991).

In a recent study, tryptophan and placebo were each given for 12 days to 98 healthy human subjects in a crossover design (Moskowitz et al., 2001). Behavior was measured by the event sampling technique described above. Relative to placebo, tryptophan caused a significant decrease in quarrelsome behaviors, no change in agreeableness, a significant increase in dominant behavior and no change in submissive behavior. This suggests that serotonin can influence behaviors along the continuum from verbal quarrelsomeness to outright physical aggression. Furthermore, it raises the possibility that serotonin is a factor-regulating dominant behavior in humans.

4. Conclusion

Studies with altered tryptophan levels show conclusively that such alterations can change both mood and feelings and/or behavior related to irritability and aggression. The most plausible explanation for this is that serotonin does have a direct effect on mood, irritability and aggression. The relationship works in two different directions, with lowered serotonin resulting in more negative mood and/or behavior while increased serotonin levels have the opposite effect. The effects on mood and aggression seem to be independent, but this issue has not been studied directly and this conclusion must remain tentative.

One pervasive theme in most of the studies discussed above is the susceptibility of some subjects to the effect of altered tryptophan availability, while other subjects remain unaffected. This is not surprising. Aspects of mood and behavior are not under the control of a single neurotransmitter. Effects are seen, presumably, only when the alteration in serotonin function is large enough to overcome the homeostatic effects of other neurotransmitter systems. One pertinent question is whether subjects who show an effect of ATD already have low serotonin, and ATD pushes it below a critical level. Alternatively, they may have normal serotonin, but alterations in other neurotransmitter systems that reduce the homeostatic effect that normally operates to control mood or aggression. This could be tested by studying whether subjects with demonstrated preexisting low serotonin levels are particularly responsive to ATD, but such a study has not yet been done.

Far more studies have been carried out on the effects of altered tryptophan levels on mood than on aggression. This presumably reflects in part the fact that simple measures are available to measure mood changes over both the short and long term. Measures of aggressive behavior over the short term suffer from a certain artificiality, while clinical studies on aggressive subjects are difficult to carry out. Furthermore, while the relationship between irritability, aggression and quarrelsomeness seems intuitively obvious, exactly how they are related is not clear. For example, irritability would be more likely to lead to verbal or physical aggression in subjects who were impulsive, but not all subjects who are quarrelsome are necessarily impulsive. Nonetheless, the fact that alterations of tryptophan levels give consistent results independent of whether the measure is irritability, a behavioral measure of aggression, or a self-assessment measure of quarrelsome behavior during social interactions, suggests that these measures are all tapping into a similar construct that is partially under the control of serotonin.

The recent demonstration that tryptophan administration can alter dominant behavior introduces an additional level of complexity into the study of the role of serotonin in the control of human mood and behavior. The increase in dominance occurred at the same time as a decrease in quarrelsomeness, raising the possibility that higher serotonin levels may be associated with more constructive social interactions. In monkeys, low levels of the serotonin metabolite 5-hydroxyindoleacetic acid in the cerebrospinal fluid are associated with low social status and inappropriate aggression (Higley et al., 1996a,b). While it would be interesting to know if lowered serotonin leads to more submissive, albeit more aggressive, behaviors in humans, there is no suitable method to look at behavior along the dominant/submissive axis in humans over the short time period of an ATD study.

The results discussed above suggest that low serotonin is involved in the etiology of depression and pathological aggression in some patients. How a possible role of serotonin as a modulator of dominant/submissive behavior fits in with this is not known. A decline in feelings of submissiveness, if this were to occur in patients treated with SSRIs, could possibly help to attenuate feelings of depression or aggression, but this needs to be studied. It remains to be seen to what extent mood, aggression and dominance are independent in humans and how alterations in one may, over the long term, alter the other two.

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