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Lack of Effect of Tyrosine Depletion on Mood in Recovered Depressed Women

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The role of dopamine (DA) pathways in the pathophysiology of depressive disorder is poorly understood. However, because DA plays a key role in motivational behavior, it is important to study in a disorder characterized by anhedonia, lack of energy and psychomotor retardation. A recently developed dietary manipulation ('tyrosine (TYR) depletion') offers a novel method to assess the role of DA in major depression. We studied 15 euthymic women with a past history of recurrent depression, who received a 74 g amino-acid drink lacking TYR and phenylalanine (PHE) (TYR-free) and a balanced (BAL) amino acid drink on two separate occasions in a double-blind, random-order, crossover design. Plasma prolactin levels rose following the TYR-free drink relative to the balanced mixture, while performance on a spatial recognition memory task was impaired. However, relative to the BAL drink, the TYR-free drink did not lower objective or subjective measures of mood. We conclude that as in healthy volunteers, TYR depletion in euthymic subjects, with a past history of major depression, attenuated DA function, as reflected in increased plasma prolactin levels and decreased spatial memory performance. However ratings of depression were unaffected, suggesting that disruption of dopaminergic function by this manipulation does not induce a lowering of mood in individuals vulnerable to depression.
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INTRODUCTION

Dopamine (DA) has been implicated in the pathophysiology of mood disorders, both mania and depression (Wilner, 1995; Anand *et al*, 2000). Levels of the DA metabolite homovanillic acid (HVA) in cerebrospinal fluid are consistently decreased in depressed patients and some but not all brain-imaging studies demonstrate increases in post-synaptic DA receptor binding (see Verhoeff, 1999). These changes are proposed to result from a decrease in presynaptic DA release. Consistent with this, a post-mortem study of suicide victims has indicated decreased DA metabolism in basal ganglia (Bowden *et al*, 1997).

Recent studies in animals have shown that repeated administration of different kinds of antidepressant increases DA-mediated behaviors and D_2 receptor binding in the nucleus accumbens (Ainsworth *et al*, 1998a, b). Chronic administration of antidepressant drugs is also reported to increase expression of the D_3 receptor in the nucleus accumbens (Lammers *et al*, 2000). Thus, localized DA deficiency could account for the loss of motivation and anhedonia commonly seen in depressed patients, while an increase in DA function in the mesolimbic system could play a key role in the antidepressant actions of medication (Wilner, 1995).

It is possible that the changes in DA biochemistry seen in major depression are a consequence of the depressed state (for example, due to the accompanying motor retardation) rather than causal to it. One way of looking at this question is to assess the psychological consequences of acutely lowering DA function in people known to be at risk of major depression but who are currently well. DA function can be acutely lowered by using a dietary technique called tyrosine (TYR) depletion. TYR is a naturally occurring amino acid from which DA, and also noradrenaline, are synthesized. Administration of an amino-acid mixture free of TYR, and of the TYR precursor, PHE, lowers plasma TYR and prevents TYR brain entry by competition at the blood–brain barrier (Biggio *et al*, 1976; Moja *et al*, 1996; Sheehan *et al*, 1996). The result is a marked lowering in the plasma ratio of TYR and PHE to neutral amino acids, which leads to a reduction in the availability of TYR for brain catecholamine synthesis (Fernstrom and Fernstrom, 1995; McTavish *et al*, 1999).

TYR-free amino-acid mixtures have been demonstrated to interfere selectively with central DA neurotransmission

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in animal models and also in healthy volunteers where TYR depletion consistently increases plasma prolactin (Harmer *et al*, 2001; McTavish *et al*, 2001), presumably by decreasing the inhibitory effect of DA on prolactin release. More recently, a study using positron emission tomography (PET) demonstrated increased striatal binding of the D_2 receptor ligand, raclopride, after TYR depletion consistent with lowered presynaptic release of DA (Montgomery *et al*, 2003). Functionally, TYR depletion appears to disrupt basal DA function sufficiently to reduce performance on tasks of spatial recognition memory and spatial working memory (Harmer *et al*, 2001), which are sensitive to DA manipulation (Elliott *et al*, 1997; Mehta *et al*, 1999). In some but not all studies in healthy volunteers, TYR depletion has been associated with changes in self-rating scales consistent with mildly lowered mood (Leyton *et al*, 2000; Harmer *et al*, 2001; McTavish *et al*, 2001); however, clinical depressive symptomatology has not been described.

Similar dietary manipulations involving tryptophan (TRP) depletion have been used to study the effects of lowered brain serotonin activity in both healthy subjects and subjects vulnerable to depression (Booij *et al*, 2003). TRP depletion does not produce a reliable change in mood in nonvulnerable healthy volunteers, yet it causes clinical depressive symptoms in euthymic subjects with a past history of depression (Booij *et al*, 2003). This finding is frequently cited as evidence for an involvement of serotonin in depression.

The present study examined the effects TYR depletion on mood and cognition in subjects with a past history of depression to test the hypothesis that subjects vulnerable to depression would respond to TYR depletion by experiencing clinically significant relapses in depressive symptoms

SUBJECTS AND METHODS

Subjects and Design

A total of 15 female volunteers with a past history of major depression, currently well, between the ages of 21 and 57 years (mean age of 41.3 years) participated in this study. All subjects were assessed with the structured clinical interview for DSM-IV (SCID), which gives current and lifetime psychiatric diagnoses according to the criteria of the Diagnostic and Statistical manual for Mental Disorders (DSM-IV). All the women had had at least two episodes of major depression as defined by DSM criteria with at least one episode meeting criteria for the melancholic subtype. Subjects with bipolar disorder were excluded. All subjects were clinically recovered at the time of assessment (Frank *et al*, 1991) and had been well and off antidepressant medication for at least 6 months. The mean duration of remission was 41 months (range 6–156 months). Only two subjects had ever been hospitalized for depression. All subjects gave written informed consent to the study, which was approved by the local ethics committee. As part of the informed consent procedure, volunteers were told explicitly that participation in the study could lead to a return of depressive symptoms.

The study was conducted in a double-blind crossover fashion. Volunteers were tested on two occasions, at least 1 week apart and received, on one occasion, an amino-acid mixture balanced with TYR/PHE ('BAL') and, on the other, an amino-acid mixture free of TYR and PHE ('TYR-free') in randomized order. Six subjects received the TYR-free drink first, and nine subjects received the BAL drink first. Volunteers were all tested within the follicular phase of their menstrual cycle.

Amino-Acid Mixtures

The composition of the TYR-free mixture was isoleucine 12 g, leucine 18 g, lysine 14 g, methionine 4 g, valine 14 g, threonine 8 g, and TRP 4 g. The BAL mixture contained additionally TYR 10 g and PHE 10 g. The amino acids were suspended in tap water, which was flavored with blackcurrant in order to disguise the unpalatable taste of the mixture.

Procedure and Mood Ratings

Subjects came to the laboratory at 0830 hours on the morning of each test having followed a low-protein diet (total protein content less than 20 g) for the preceding 24 h and fasted from midnight. Following arrival, baseline blood samples were taken for amino-acid and prolactin estimation. Ratings of depressive symptoms were carried out by an observer who was unaware of the mixture allocation with a modified version of the Hamilton rating scale for depression (HAM-D) both before the amino-acid mixture was taken and 6 h after its administration. This version of the HAM-D has been shown to be sensitive to short-term changes in mood changes induced by TRP depletion (Smith *et al*, 1997). Subjects were also asked to complete the Befindlichkeits-Scale (BFS) (von Zerssen *et al*, 1974) completing BFS 1 before and BFS 2 six hours after amino-acid administration. In this scale, higher scores indicate a lowering of mood and well being. In addition, subjects completed baseline 100-mm visual analog scales (VAS) for the following items: 'happy', 'tired', 'depressed', 'anxious', and 'sociable'. The VAS ratings were repeated at 30 min, 60 min and then at 60 min intervals thereafter for 6 h. On each test day, volunteers were given the cognitive tests described below between 300 and 360 min following the amino-acid drink. Further blood tests for amino acids and prolactin were taken at the end of the study (approximately +360 min).

Cognitive Tests

On both occasions, subjects were given the same cognitive tests in the same order. On the first session, the tests were preceded with a motor screening task designed to familiarize subjects with the computer and procedures. For the pattern/spatial recognition tasks, parallel versions were given in sessions 1 and 2. Subjects were not practiced on the tests prior to the first session. All tests were administered using a datalux 486 microcomputer fitted with a touch-sensitive screen for responses where appropriate.

Pattern and spatial recognition tests assess visual and visuo-spatial short-term recognition memory (Owen *et al*, 1995). In the pattern recognition memory, volunteers were presented with a series of 12 abstract patterns. In the second stage, the patterns were displayed in the reverse order, each

paired with a novel distracter, and subjects were required to pick out the pattern that they had seen before (forced choice discrimination). This test was then repeated with 12 novel patterns. In the spatial recognition memory task, subjects were shown a set of five squares one by one in different locations on the computer screen. Recognition memory for location was tested using a forced choice discrimination between target and distracter squares. This test was repeated with three further sets of five squares giving a total of 20 locations. Percentage of correct choices and the mean reaction time for these correct choices were measured in both tasks.

The spatial working memory test is a self-ordered search task that required subjects to search through a spatial array of colored boxes for tokens without returning to a box that had already contained a token. After two practice trials with three boxes, there were four test trials with each of four, six, and eight boxes. The number of errors and an overall strategy score were recorded. A low strategy score is associated with better performance.

Biochemical Analysis

Plasma was separated by means of centrifugation and stored at −30°C. Prolactin levels were measured using a standard immunoradiometric assay with inter and intra-assay coefficients of variation of 4.8 and 2.4%, respectively. The plasma total amino-acid concentrations (lysine, leucine, isoleucine, methionine, threonine, PHE, valine, TYR) were measured using an automated high-performance liquid chromatography (HPLC) system with fluorescence end-point detection and precolumn sample derivatization adapted from the method of Furst *et al* (1990). Norvaline was used as an internal standard. The limit of detection was 1.3 pg/ml and inter- and intra-assay coefficients of variation were 13 and 8%, respectively. Total TRP levels were determined using a separate isocratic HPLC method of analysis, removing plasma proteins by precipitation with 3% trichloroacetic acid and centrifugation at 10 000*g*, again with fluorescence end-point detection.

Statistical Analysis

Data were analyzed using a two-way repeated measures analysis of variance (ANOVA) with amino-acid mixture ('drink') and time of assessment ('time) as the within-subject factors. The Huynh–Feldt correction was used where the assumption of sphericity was violated. Uncorrected degrees of freedom are shown for clarity. *Post hoc* tests were carried out using paired *t*-tests. Performance in the spatial working memory was also analysed using paired *t*-tests.

RESULTS

The amino-acid mixtures were generally well tolerated but eight of the 15 subjects reported nausea which started shortly after mixture ingestion and reached a peak at about 3 h. Nausea occurred to a similar extent after both mixtures.

Biochemical Changes

Following the TYR-free mixture, there was a reduction in plasma levels of both TYR (TYR) and PHE (PHE) leading to a marked lowering of the plasma ratio of TYR + PHE to other neutral amino acids (NAA). A more modest lowering was seen after the BAL mixture (Table 1). Both the TYR-free and BAL mixtures produced a lesser but significant lowering of the plasma ratio of TRP : NAA (Table 1). Following the TRY-free mixture, plasma prolactin levels increased at the time of the 6 h sampling point, while prolactin levels after the BAL mixture declined (Table 1).

Mood Ratings

ANOVA of the HAM-D ratings showed no main effect of drink ($F = 0.17$; $df = 1,14$; $p = 0.68$) but a main effect of time ($F = 5.76$; $df = 7,98$; $p = 0.001$). The drink by time interaction was not significant ($F = 0.54$; $df = 7,98$; $p = 0.80$). On both test occasions, HAM-D ratings were slightly but significantly greater at the time of the second rating (Figure 1). Rather similar findings were seen with the BFS scores where the ANOVA showed no main effect of drink ($F = 2.98$; $df = 1.14$; $p = 0.11$) or drink by time interaction ($F = 0.55$; $df = 1,14$; $p = 0.47$) but a borderline effect of time ($F = 4.35$; $df = 1,14$; $p = 0.056$) where BFS scores were modestly higher at the + 360 min (data not shown).

VAS ratings of 'sociable' ($F = 2.98$; $df = 7, 98$; $p = 0.028$), 'depressed' ($F = 4.03$; $df = 7,98$; $p = 0.005$), 'tired' ($F = 5.76$; $df = 7,98$; $p = 0.001$), and 'anxious' ($F = 3.40$; $df = 7,98$; $p = 0.041$) all showed significant effects of time but there were no significant main effects of drink, or drink by time interactions (all *p*-values > 0.1). Overall, the changes in

Table 1 Effect of Amino-Acid Mixtures on Plasma Ratios of Tyrosine (TYR)+Phenylalanine (PHE) and Tryptophan (TRP) to Neutral Amino Acids (NAA) and on Plasma Prolactin before ('0' mins) and 360 mins Post Mixture Ingestion

	Balanced mixture		Tyrosine-free mixture	
Time	**0 mins**	**+360 mins**	**0 mins**	**+360 mins**
TYR+PHE : NAA[a]	0.248 ± 0.012	0.116 ± 0.010	0.254 ± 0.013	0.006 ± 0.001***
TRP : NAA[b]	0.128 ± 0.015	0.026 ± 0.002	0.123 ± 0.016	0.029 ± 0.004
Prolactin (miU/l)[c]	284 ± 51	240 ± 55	316 ± 47	414 ± 90**

[a]Drink × time interaction ($F = 85.3$; $df = 1,14$; $p = 0.001$).
[b]Main effect of time ($F = 57.0$; $df = 1,14$; $p = 0.001$).
[c]Drink by time interaction ($F = 5.77$; $df = 1,14$; $p = 0.031$).
Different from +360 min balanced mixture, ***$p = 0.001$; **$p = 0.002$ (paired *t*-test).

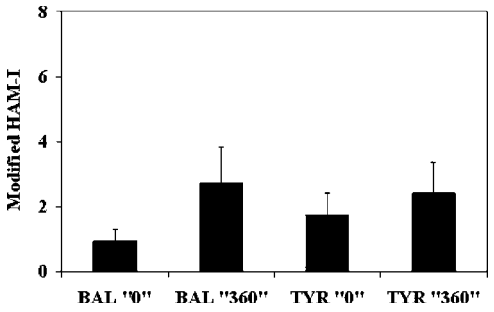

Figure 1 Modified (mean ± SEM) HAM-D rating of 15 depressed subjects before ('0') and 6 h after ('360') ingestion of balanced amino-acid mixture (BAL), or the same mixture lacking TYR and PHE (TYR-free). Main effect of time on HAM-D scores, F = 5.76; df = 7,98; $p = 0.001$ (ANOVA).

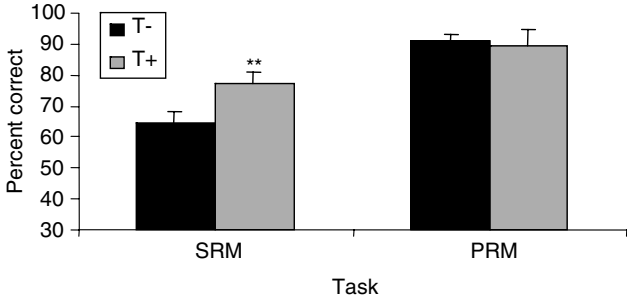

Figure 2 Percentage correct in the spatial (left) and pattern (right) recognition memory tasks taken from the CANTAB. Dark bars following the TYR (TYR)-free drink; light bars following the balanced (BAL) amino-acid drink. Data are presented as mean ± SEM. Statistical comparisons in text. $^{**}p < 0.01$.

ratings over time from baseline to end point were similar after both drinks and consistent with lowered mood (increases in ratings of 'tired' and 'depressed' and a decrease in 'sociable'); however, ratings of 'anxiety' fell.

Cognitive Tasks

Mean accuracy levels on the pattern and spatial recognition tasks are shown in Figure 2. The repeated measures ANOVA revealed a significant interaction between task (spatial/pattern recognition) and amino-acid drink (F = 6.1; df = 1,14; $p = 0.03$). Overall, accuracy on the spatial recognition task was significantly worse after the TYR-free compared to the BAL drink ($t = 3.0$, df 14, $p = 0.009$). Performance on pattern recognition memory was unaffected by drink ($t = 0.4$, df = 14; $p = 0.7$). Speed to identify correctly the target item in both tasks was unaffected (drink × task: F = 0.7; df = 1,14; $p = 0.4$). Performance on the spatial memory working task was also unaffected by TYR depletion (strategy score $t = 1.5$; df = 14; $p = 0.15$; errors $t = 1.9$; df = 14; $p = 0.08$).

DISCUSSION

The main finding from this study is that despite producing endocrine and neuropsychological effects consistent with lowered brain DA function, TYR depletion did not provoke clinical depressive symptomatology in any of the recovered depressed subjects studied. Furthermore, ratings designed to capture more subtle changes in subjective state revealed no effect of this dietary manipulation relative to the control mixture on self-ratings of mood and energy level.

Although administration of the BAL mixture increases plasma levels of PHE and TYR, (Sheehan *et al*, 1996) overall, as found in the present study, it produces some lowering in the plasma ratio of TYR + PHE : BCAA (Harmer *et al*, 2001; Montgomery *et al*, 2003). For reasons that are not clear, the extent of this reduction varies somewhat between studies but it is always substantially less than that produced by the TYR-free mixture. The BAL mixture therefore acts as a 'conservative' control in the sense that it may limit DA function to some extent and thereby make it harder to show differences between active and control depletions. Use of an inert placebo in addition to the two amino-acid mixtures might therefore improve the sensitivity of the methodology.

We have previously presented data indicating that relative to the BAL mixture, the TYR-free mixture used in the present study appears to decrease DA activity in the human brain and similar effects were noted here. In particular, TYR depletion increased plasma prolactin and diminished performance on the spatial recognition memory both of which are consistent with lowered DA neurotransmission (Mehta *et al*, 1999; Harmer *et al*, 2001). We have previously noted both these effects in healthy male and female volunteers (Harmer *et al*, 2001) and similar effects were apparent in the present group of recovered depressed subjects.

If TYR depletion lowers brain DA function, it is presumably due to decreased availability of the catcholamine precursors TYR and PHE for brain DA synthesis (Biggio *et al*, 1976; Moja *et al*, 1996). Indeed in a recent PET imaging of TYR depletion, we found that the increase in D_2 receptor binding as measured by [^{11}C]raclopride correlated significantly with the fall in the plasma ratio of TYR and PHE to large neutral amino acids (Montgomery *et al*, 2003). A similar finding was reported by Leyton *et al* (2004) who found that the ability of TYR depletion to attenuate the decrease in [^{11}C]raclopride binding produced by d-amphetamine correlated linearly with reduction in plasma TYR levels.

In a previous study, Berman *et al* (1999) found that over two-thirds of a group of unmedicated depressed patients experienced a return of clinical depressive symptomatology when treated with the catecholamine-depleting agent, alpha-methyl-para-tyrosine (AMPT). Clearly our findings differ from this observation and there are a number of explanations for this discrepancy. First, it possible that the patients in the current study were less vulnerable to depressive relapse than those studied by Berman *et al* (1999). Against this we have demonstrated that the related procedure of TRP depletion, administered in an identical placebo-controlled crossover design, causes significant depressive relapse in a similar group of recovered depressed subjects (Smith *et al*, 1997). Indeed a recent review of the effects of TRP depletion in recovered depressed patients suggested that female subjects with a history of multiple episodes were particularly at risk of clinical depressive relapse (Booij *et al*, 2002).

The possibility that recovered depressed women would be more vulnerable than men to the mood lowering effects of

TYR depletion was the reason why the present study was conducted in women. However, TYR depletion could produce mood lowering in recovered depressed men if men were more vulnerable than women to reductions in DA function. The women in the present study had mostly been recovered for long periods of time and it is possible that long duration of remission may make subjects less vulnerable to the mood lowering effects of monoamine depletion. However, the literature on TRP depletion does not support this possibility (Booij *et al*, 2002). All our subjects had at some time point met criteria for the melancholic subtype of depression because we predicted that subjects who had experienced anhedonia might be more vulnerable to lowered DA function. However, none suffered from bipolar illness, which might also theoretically be a risk factor for psychological vulnerability to TYR depletion.

AMPT treatment is, of course, a different pharmacological procedure to that of TYR depletion. For example, unlike TYR depletion, AMPT can produce extrapyramidal movement disorders (Booij *et al*, 2003) and, consistent with this, PET imaging studies of [^{11}C]raclopride displacement suggest that AMPT produces a substantially greater impairment in DA release than does TYR depletion (Laruelle *et al*, 1997; Montgomery *et al*, 2003). It is possible therefore that relative to AMPT, the impairment in DA function produced by TYR depletion is too modest to provoke clinical depressive symptomatology in vulnerable individuals.

TYR is a precursor for both DA and noradrenaline, and AMPT lowers both brain DA and noradrenaline function in humans (Booij *et al*, 2003). However, TYR depletion appears to have minimal effects on noradrenaline release in animal experimental studies. For example, using *in vivo* microdialysis, McTavish *et al* (1999) found in rodents that while TYR depletion attenuated the release of DA produced by amphetamine, noradrenaline release was unaffected. Similarly in humans, AMPT lowered the night-time release of melatonin, a sensitive marker of noradrenaline release, but TYR depletion did not (Zimmermann *et al*, 1994; Sheehan *et al*, 1996). Therefore, while TYR depletion predominantly lowers DA activity, AMPT attenuates both DA and noradrenaline function. Hence, the ability of AMPT to produce relapse in recovered depressed patients might be attributable to attenuation of noradrenaline activity either alone or in combination with lowered DA function.

In healthy subjects, TYR depletion produces fairly modest and inconsistent effects on mood (Booij *et al*, 2003). We did detect some minor but significant mood changes over the course of the study whereby both TRY-free and BAL mixtures appeared to decrease both objective and subjective ratings of mood to a small extent. This could reflect the rather tedious nature of the experimental procedure coupled with experience of mild to moderate degrees of nausea in about half the subjects. Another possibility is that both amino-acid mixtures lowered the ratio of TRP : NAA, which may have compromised brain serotonin function to some extent (Booij *et al*, 2003). This might explain a lowering of mood in vulnerable subjects. Indeed we have previously noted that ingestion of the amino acid valine is sufficient to produce minor mood lowering on VAS ratings in recovered subjects treated with selective serotonin reuptake inhibitors (Williamson *et al*, 1995). The present findings are consistent with this earlier investigation and indicate that our study had sufficient power to detect the kind of changes in HAM-D score typically seen in depletion studies.

This finding raises the possibility that an effect of TYR depletion to produce depressive symptomatology may have been 'masked' by the psychological effects of concomitant TRP depletion. This is perhaps unlikely because full monoamine depletion typically produces greater changes in mean HAM-D scores than were seen in the present study (Booij *et al*, 2003). However, if the effects of TYR depletion on mood are fairly subtle, they may have been obscured by the present design. The decrease in TRP availability after TYR depletion must be considered a limitation of the current methodology (McTavish *et al*, 2004). It might be possible to remedy this situation by adding a larger amount of TRP to the amino-acid mixtures; however, this could lead to problems in tolerability.

In conclusion, the findings of our study are consistent with previous observations indicating that TYR depletion impairs DA function and suggest that it produces qualitatively similar effects in this respect in recovered depressed patients and healthy controls. However, the relatively modest attenuation of brain DA activity produced by TYR depletion appears insufficient to produce clinical depressive symptomatology in recovered depressed subjects.

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