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ORIGINAL INVESTIGATION

C.J. Harmer · S.F.B. McTavish · L. Clark
G.M. Goodwin · P.J. Cowen

Tyrosine depletion attenuates dopamine function in healthy volunteers

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Abstract *Rationale*: Tyrosine depletion has been shown to reduce dopamine over activity in animal and human investigations. However, the effects on basal dopamine function have not been explored. Such information could establish tyrosine depletion as an effective probe of dopamine function in healthy volunteers and would also have relevance for future therapeutic applications of this manipulation. *Objective*: The present study investigated the effect of acute tyrosine depletion on dopamine function in healthy volunteers using a combination of neuroendocrine, neuropsychological and subjective measures. *Methods*: On one occasion, volunteers received an amino acid drink selectively lacking tyrosine and phenylalanine (TYR-free), whilst on the other they received a balanced (BAL) amino acid drink. Plasma prolactin, amino acid levels and subjective state were monitored over 6 h following the two drinks, and volunteers also completed a battery of tests from the CANTAB, including measures of spatial memory previously found to be sensitive to changes in dopamine function. *Results*: Plasma prolactin levels rose following the TYR-free drink relative to the balanced mixture, indicative of decreased dopamine neurotransmission within the hypothalamus. Following the TYR-free drink, volunteers were impaired at spatial recognition memory and spatial working memory. Volunteers also tended to report that they felt less good following the TYR-free than the BAL mixture. *Conclusion*: Tyrosine depletion in healthy volunteers affected baseline dopamine function on the different measures employed in this study. Tyrosine depletion would thereby seem valuable as a probe of dopamine function in human volunteers. Ratings of depression and other aspects of cognitive function were unaffected, suggesting that this manipulation may be free of significant side effects when used as a treatment for conditions characterised by dopamine over activity, such as acute mania and schizophrenia.

Keywords Dopamine · Noradrenaline · Tyrosine depletion · Spatial memory

C.J. Harmer (✉) · S.F.B. McTavish · L. Clark · G.M. Goodwin
P.J. Cowen
University Department of Psychiatry, Warneford Hospital,
Oxford OX3 7JX, UK
e-mail: catherine.harmer@psych.ox.ac.uk
Tel.: +44-1865-22649, Fax: +44-1865-251076

Introduction

The synthesis of dopamine and noradrenaline in the brain are dependent on the availability of their precursor amino acid, tyrosine, from plasma. Acute administration of an amino acid mixture that selectively lacks both tyrosine and its precursor phenylalanine has been shown to be effective in decreasing availability of tyrosine to the brain through processes of increased protein synthesis (lowering plasma tyrosine levels) and increased competition for transport across the blood–brain barrier (Oldendorf and Szabo 1976; Pardridge 1977). In animals, administration of this tyrosine-free (TYR-free) mixture decreased brain tyrosine and catecholamine synthesis, suggesting a potential action on dopamine function (McTavish et al. 1999b). Consistent with this, rats administered the TYR-free mixture, as opposed to a balanced (BAL) combination of amino acids, showed reduced dopaminergic (McTavish et al. 1999b) and locomotor (McTavish et al., unpublished observations) responses to the psychostimulant drug *d*-amphetamine. By contrast, the noradrenergic response to amphetamine or idazoxan (McTavish, et al. 1999a) was not affected, suggesting that dopamine is preferentially affected by acute tyrosine depletion.

Preliminary evidence suggests that tyrosine depletion attenuates pathological increases in dopamine activity in man as it does in animal models. First, volunteers showed reduced psychostimulant and subjective effects of amphetamine following tyrosine depletion relative to the BAL amino acid mixture (McTavish et al. 1999c and unpublished observations). Consistent with results from the animal studies, these effects appeared to largely

affect dopamine-mediated functions (such as ratings of mind-race/buzz and reaction time on a measure of sustained attention) as opposed to the largely noradrenergic effects (ratings of hunger, blood pressure and response sensitivity on the sustained attention task). Acute mania has also been related to dopamine over activity and, in line with predictions, tyrosine depletion was found to reduce symptom severity in acutely manic inpatients (McTavish et al. unpublished observations). These findings suggest that tyrosine depletion could have therapeutic applications to conditions in which over activity of dopamine is believed to play a role, such as in acute mania (Jacobs and Silverstone 1986) schizophrenia (Laruelle and Abi-Dargham 1999) and, potentially, psychostimulant drug-associated craving (Pilla et al. 1999).

Given the effects of tyrosine depletion on states of dopamine over activity, it is of interest to determine whether this manipulation has significant action on dopamine function under basal conditions. Dietary manipulations of tryptophan have previously been found to impair serotonergic functioning in healthy volunteers. This method has been highly valuable in elucidating the role of serotonin in verbal memory consolidation (Riedel et al. 1999), paired associate learning (Park et al. 1994) and decision making (Rogers et al. 1999). In contrast, dopamine has been implicated in memory for spatial information. Spatial, but not pattern, recognition memory is impaired in patients with Parkinson's disease (Owen et al. 1993a; Postle et al. 1997) as well as in healthy volunteers administered the D2 receptor antagonist sulpiride (Mehta et al. 1999). Deficits in spatial *working* memory have also been shown following administration of a dopamine receptor antagonist (Luciana and Collins 1997), while administration of the dopamine receptor agonists bromocriptime (Luciana et al. 1998) and methylphenidate (Elliott et al. 1997) facilitate performance. Hence, assessment of spatial memory following tyrosine depletion may provide an indication of its dopaminergic effects.

Dopamine activity can also be assessed through neuroendocrine analysis of plasma prolactin levels. Since dopamine exerts an inhibitory action on prolactin release in the hypothalamus, increased prolactin levels would be indicative of a decrease in dopamine function, as shown following neuroleptic administration (Checkley 1980). The present study therefore used a combination of these two techniques to assess the effects of tyrosine depletion on dopamine activity in healthy volunteers. Volunteers received the TYR-free drink or the BAL mixture in a cross-over design, and plasma prolactin levels were monitored over 6 h. Volunteers were assessed on a battery of cognitive tests from the CANTAB, designed to be sensitive to changes in central dopamine function, including measures of spatial recognition memory and spatial working memory. Control tasks, which were predicted to be unaffected by dopamine depletion, were also used to assess the non-specific actions of the TYR-free mixture.

Methods

Subjects and design

Twelve volunteers (seven male, five female) between the ages of 23 years and 34 years participated in this study (with a mean age of 26.6 years). Subjects with any history of psychiatric or significant physical illness were excluded. All subjects gave written informed consent, and the protocol was approved by the local ethics committee.

The study was conducted in a double-blind cross-over fashion. Volunteers were tested on two occasions, at least 1 week apart and received, on one occasion, an amino acid mixture balanced with tyrosine/phenylalanine and, on the other, an amino acid mixture deficient in tyrosine and phenylalanine (randomised order). Five subjects received the TYR-free drink first (three males, mean age: 27.2 years), whereas the other seven subjects received the BAL drink first (four males, mean age: 26.2 years). Female volunteers were all tested within the follicular phase of their menstrual cycle.

Amino acid mixtures

The composition of the TYR-free mixture for male subjects was isoleucine 15 g, leucine 22.5 g, lysine 17.5 g, methionine 5 g, valine 17.5 g, threonine 10 g and tryptophan 2.5 g. The BAL mixture for males contained additionally tyrosine 12.5 g and phenylalanine 12.5 g. Female subjects received 20% less by weight of each amino acid than their male counterparts. The amino acids were suspended in tap water which was flavoured with blackcurrant in order to disguise the unpalatable taste of the mixture.

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 familiarise subjects with the computer and procedures. For the pattern/spatial recognition and paired associate learning task, parallel versions were given in sessions 1 and 2. Subjects were not practised 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

Pattern and spatial recognition tests assess visual and visuo-spatial short-term recognition memory (Sahakian et al. 1988; 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.

Paired associate learning

Paired associate learning (PAL) is a test of visual pattern and visuospatial memory and learning, which contains aspects of a delayed response procedure and a conditional learning task (Owen et al. 1995). Initially, subjects were required to remember the location of six stimuli over a short delay within a maximum of ten trials.

The task was then repeated with eight stimuli. The number of errors made and trials required to reach criterion were recorded.

Rapid Visual Information Processing

Rapid visual information processing (RVIP) is a measure of sustained attention (Sahakian et al. 1989). Initially in the 2-min training phase, subjects were presented with a white box in the centre of the screen in which digits between 2 and 9 appear, one at time, in a pseudo-random order at a rate of 200 per min. Subjects were asked to monitor the digits for a three-digit sequence (3–5–7) and press a response button when they detected it. In the training phase, the target sequence digits were coloured and both prompting and feedback from the computer were given. In the testing phase, subjects were asked to monitor the digits for any one of three specified digit sequences (2–4–6, 3–5–7 or 4–6–8) for a period of 7 min in the absence of colour or prompting cues. There were three principal performance measures in this task: number of targets correctly detected (hits), number of responses made in the absence of targets (false alarms) and reaction time for correct detections.

Spatial working memory

The spatial working memory test is a self-ordered search task which required subjects to search through a spatial array of coloured boxes for tokens without returning to a box that had already contained a token (Owen et al. 1990). 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.

Procedure

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, an indwelling venous cannula (non-dominant arm) was inserted and baseline blood samples were taken for amino acid and prolactin estimation. Subjects completed baseline 100-mm visual analogue scales (VAS) for the following items: hungry, feeling good, tense, depressed, sleepy, mind-racing and buzz. The VAS ratings were repeated at 30-min intervals together with the venous blood samples for a further 6 h. On each test day, volunteers were given the RVIP prior to drink administration and 255 min following the amino acid drink. The other psychological measures were given between 300 min and 360 min post-drink.

Chemical 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, phenylalanine, valine, tryptophan and tyrosine) were measured using an automated high-performance liquid chromatography (HPLC) system with fluorescence end-point detection and pre-column sample derivatisation 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.

Statistical analysis

Plasma prolactin levels were compared using two-way repeated-measures analysis of variance (ANOVA) with drink and time (13 points) as factors and completed using simple main effect analyses. VAS values were only analysed up until time 300 min because cognitive task performance may interfere with mood ratings. For each VAS, the mean change from baseline score (from time 30 min to 300 min inclusive) was compared using paired *t*-tests. If appropriate, cognitive test data were analysed using two-way repeated ANOVAs between drink and task (spatial/pattern recognition) or session (RVIP pre- versus post-drink) and completed using simple main effect analyses. Performance in the spatial working memory and PAL were analysed using paired *t*-tests.

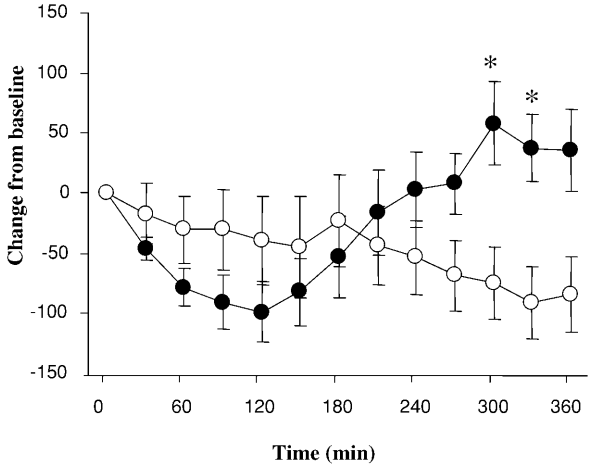

Fig. 1 Plasma prolactin levels following the tyrosine (TYR)-free drink relative to the balanced (BAL) amino acid drink. *Dark symbols* following the TYR-free drink; *light symbols* following the BAL drink. Data are presented as mean±1 SEM. Statistical comparisons are shown above, **P*<0.05

Results

Amino acid levels

Following the TYR-free mixture, there was a marked lowering in plasma TYR relative to the BAL drink (percentage of basal levels being 13% relative to 392% at 240 min following administration). The ratio of TYR and PHE to other large neutral amino acids, a measure of tyrosine availability to the brain, was also significantly lower. The ratio of TYR/PHE to large neutral amino acids (LNAA) fell from a mean of 0.11 to 0.001 relative to a fall from 0.11 to 0.093 for the BAL drink (time × drink $F_{1,10}$=74.8, P<0.001).

Plasma prolactin

Basal levels of plasma prolactin were similar on the two test days. However, prolactin levels were significantly increased following the TYR-free, relative to the BAL drink (mixture × time interaction $F_{12,60}$=6.1, P<0.001, Fig. 1), specifically at 300 min ($F_{1,11}$=2.4, P<0.05) and 330 min ($F_{1,11}$=2.6, P<0.05) following drink administration. This increase is indicative of diminished release of dopamine at the hypothalmic level.

Cognitive function

Amino acid drink order (first or second session) or gender did not interact significantly with drink action in

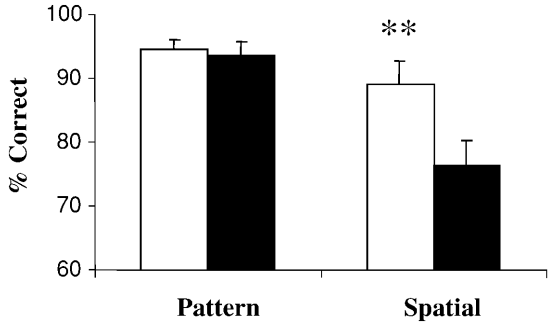

Fig. 2 Percentage correct in the pattern (*left*) and spatial (*right*) recognition memory tasks taken from the CANTAB. *Dark bars* following the tyrosine (TYR)-free drink; *light bars* following the balanced (BAL) amino acid drink. Data are presented as mean±1 SEM. Statistical comparisons are shown above, $^{**}P<0.01$

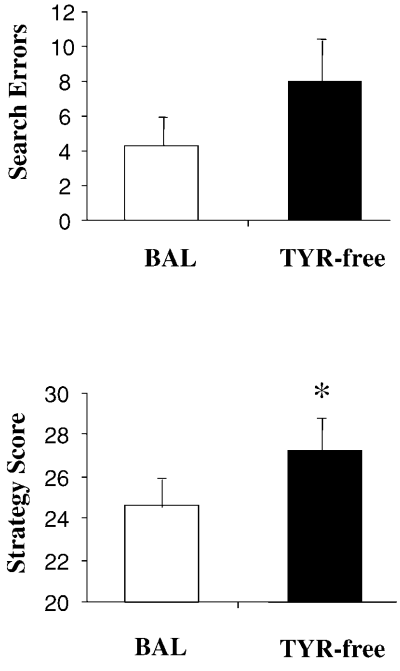

Fig. 3 Search errors (*top*) and strategy scores (*bottom*) in the spatial working memory task following ingestion of tyrosine (TYR)-free and balanced (BAL) amino acid mixtures. *Error bars* represent standard errors of the mean. *Dark bars* following the TYR-free drink; *light bars* following the BAL drink. Data are presented as mean±1 SEM. Statistical comparisons are shown above, $^{*}P<0.05$

any of the tasks used here. Therefore, cognitive task data were collapsed across these factors in the analyses reported.

Spatial and pattern recognition memory

Mean accuracy levels in these tasks are shown in Fig. 2. The 2×2 ANOVA conducted on these data revealed a significant interaction between task and amino acid drink ($F_{1,11}$=7.9, P=0.017). Following tyrosine depletion, volunteers made more errors in the spatial recognition memory task than when they received the BAL drink ($F_{1,11}$=11.2, P=0.007), in the absence of impairment in pattern recognition memory ($F_{1,11}$=0.2, NS). Speed to correctly identify the target item in both tasks was unaffected. Mean response latency in the spatial recognition task was 2080.3 ms (SEM: 152.6) and 1966.0 ms (SEM: 122.1) for the TYR-free drink and BAL mixture, respectively, and in the pattern recognition memory task mean speed was 1898.7 ms (SEM: 155.2) versus 1783.2 ms (SEM: 135.3) for the two drinks respectively (drink × task: $F_{1,11}$=0.0, NS; drink: $F_{1,11}$=1.4, NS).

Spatial working memory task

One subject's performance on this task was highly anomalous, scoring 9 standard deviations below group mean (49 errors scored against a group mean of 4.3) following the BAL drink (second testing session). Performance on the first occasion was also 3 standard deviations below the group mean (scoring 24 relative to a group mean of 8). When this subject's data were excluded from the analysis, there was a significant effect of tyrosine depletion on strategy score ($t_{1,10}$=3.1, P=0.01), with volunteers using less efficient strategies on the occasion they received the TYR-free drink (Fig. 3). Error rates in this task were not statistically different (Fig. 3; $T_{1,10}$=1.4, P=0.19) and did not correlate significantly with strategy score in either group (r=0.3, P=0.3 and r=0.2, P=0.5 following the TYR-free mixture and BAL drink, respectively).

RVIP and PAL

In line with predictions, performance on the RVIP (Table 1) and PAL (trials to criterion: $t_{1,11}$=–1.3, P=0.2 and errors: $t_{1,11}$=–1.2, P=0.2) tasks was unaffected by tyrosine depletion, arguing against an account in terms of sedation. These results thereby indicate a specific action of tyrosine depletion on spatial memory in the absence of changes in other aspects of memory, learning, speed and sustained attention.

Subjective effects

Table 2 shows the mean change from baseline score for each of the visual analogue rating scales. Subjects generally reported feeling less good following the TYR-free mixture than after the BAL drink ($t_{1,11}$=–2.6, P<0.05). By contrast, the VAS rating of tension, depression, sleepiness, mind-race, buzz and hunger were not significantly different on the two test days (Table 2).

Table 1 Mean performance levels (±SD) following the tyrosine (TYR)-free drink relative to the balanced (BAL) mixture on the rapid visual information processing (RVIP) task taken from the CANTAB

Measure	TYR-free mixture		BAL mixture		Significance
	Baseline	Post-drink	Baseline	Post-drink	
Latency (ms)	502.8±109.0	460.9±71.0	471.7±58.4	456.8±65.7	Test × drink: $F_{1,11}$=1.3, P=0.3
Number of hits	37.8±15.4	42.2±14.0	37.5±11.6	42.0±13.5	Test × drink: $F_{1,11}$=0.0, P=0.98
Number of false alarms	3.2±2.5	2.2±2.1	3.1±2.6	2.5±1.8	Test × drink: $F_{1,11}$=0.13, P=0.7

Table 2 Effect of the two amino acid mixtures on subjective state using visual analogue scale ratings. For each subject, change from baseline scores have been averaged from 30 min to 300 min post-drink. Values represent mean±SD

	Tyrosine-free	Balanced	Significance
Feel good	–10.05±10.56	–4.28±9.42	t=–2.6, P=0.03
Tense	–5.29±16.77	–9.46±11.20	t=0.7, P=0.5
Depressed	2.03±4.98	–4.20±15.23	t=1.2, P=0.2
Sleepy	13.04±26.59	3.34±16.25	t=1.3, P=0.2
Hungry	–5.87±23.02	–6.29±25.42	t=0.1, P=0.9
Mind race	–1.21±10.76	–4.56±18.52	t=0.6, P=0.6
Buzz	0.70±3.69	–3.51±9.19	t=1.4, P=0.2

Discussion

Using a combination of approaches, this study assessed the effect of a TYR-free amino acid drink on dopamine function in healthy young volunteers. Results from these different approaches consistently indicated that tyrosine depletion significantly decreased dopaminergic function. First, plasma prolactin levels were increased following the TYR-free drink relative to the BAL mixture, which is indicative of decreased dopaminergic activity within the hypothalamus. Second, administration of the TYR-free drink impaired spatial recognition memory and spatial working memory performance, a profile also reported following administration of the D2 antagonist sulpiride (Mehta et al. 1999). Finally, volunteers tended to report that they felt less good following the TYR-free drink than the BAL drink.

While administration of the BAL drink increased plasma tyrosine levels (by 392%), it is unlikely that this would have increased central dopamine levels. This is because the critical determinant of tyrosine brain entry is the ratio of tyrosine to other LNAAs which compete for transport across the blood–brain barrier (Oldendorf and Szabo 1976). This ratio was significantly decreased following the TYR-free drink and, to a lesser extent, by the BAL mixture. Therefore, instead of increasing central dopamine levels, the BAL drink would seem to have acted as a conservative control. The interpretation of the present results in terms of decreased dopamine function following the TYR-free drink is also supported by data from the cognitive test battery. Accuracy in the spatial recognition memory task following the BAL drink was similar to levels previously reported in young healthy volunteers following placebo treatment (e.g. Mehta et al. 1999 reported levels of approximately 88% correct in the spatial recognition memory test relative to the mean level here of 89%), whereas performance following the TYR-free mixture was decreased relative to these values (mean value of 76%).

Plasma prolactin was significantly increased 5–6 h following the TYR-free drink relative to the BAL mixture, which is consistent with decreased central dopamine function. However, there was also a non-significant trend for initial levels of prolactin to be decreased in this condition (between 1–2 h). The speed of this trend suggests that it cannot represent effects on central neurotransmitter function, but must rather occur via some peripheral action, such as a direct effect on the pituitary. Administration of neutral amino acids has been reported to directly stimulate prolactin levels via this site (Villalobos et al. 1997) and it therefore remains a possibility that the greater overall level of amino acids in the BAL drink has a slightly greater action on the pituitary. However, the finding that these two drinks produced very different effects after 4–6 h administration suggests that the effects of central dopamine changes were able to reverse this non-specific trend.

The selective pattern of impairment reported here in the cognitive tasks also cannot be explained in terms of non-specific effects such as task difficulty or sensitivity to the effects of sedation. The RVIP, PAL and pattern recognition tasks were not affected by tyrosine depletion, and previous studies suggest that these tasks can also be selectively affected by different manipulations. For example, Owen et al. (1995) has shown that patients with temporal lobe excisions show impaired pattern recognition, but not spatial recognition, forming a double dissociation with the results from patients with frontal lobe lesions. Second, diazepam impaired performance on the RVIP and PAL tasks, which were unaffected in the present study (Coull et al. 1995). Third, the present results form a double dissociation with those from tryptophan depletion which has been reported to impair PAL in the absence of effect on spatial memory (Park et al. 1994). Hence, the effect of the TYR-free mixture would appear to be qualitatively different from the tryptophan-free drink, providing further evidence for the selectivity of these amino acid depletion paradigms and the different roles of serotonin and dopamine in cognitive performance.

The present profile of impairment is similar to that reported following sulpiride administration of moderate

doses (200–400 mg) in healthy volunteers (Mehta et al. 1999). In this study, volunteers showed no change in performance on the RVIP and PAL tasks from the CANTAB, but were similarly impaired on the spatial recognition and spatial working memory tasks. Patients with Parkinson's disease also show impaired performance on spatial memory tasks, in the absence of changes in pattern recognition (Owen et al. 1993a; Postle et al. 1997). Conversely, a facilitatory effect of the dopamine receptor agonists methylphenidate (Elliott et al. 1997) and bromocriptine (Luciana et al. 1998) on spatial working memory has also been reported. The observation that it is possible to impair spatial memory using an amino acid depletion paradigm in young healthy volunteers highlights the potential use of tyrosine depletion as a tool to further investigate dopamine function. Further, these data support the role of dopamine in spatial working memory.

Both spatial recognition memory and spatial working memory are sensitive to fronto-striatal dysfunction (Owen et al. 1995; Robbins 1996). The effect of tyrosine depletion on these tasks is in line with a growing body of evidence indicating the importance of dopamine in executive function. Thus, performance in the tower of London task and attentional set-shifting have also been reported to be affected by sulpride (Mehta et al. 1999) and are also impaired in patients with Parkinson's disease (Owen et al. 1992, 1993b). The impairment in strategy formation found here following tyrosine depletion is particularly consistent with this role of dopamine and suggests that the site of action may involve neural networks within, or intimately connected with, the prefrontal cortex. Investigations of the effect of tyrosine depletion on measures of planning and set-shifting are currently in progress to examine this hypothesis further.

Following the tyrosine depletion mixture, volunteers tended to indicate that they felt less good than after the BAL drink. A similar effect on mood has been reported following neuroleptic administration (Browne et al. 1998) and may be the subjective experience accompanying decreased dopamine. Dopamine is well known to play a fundamental role in various reward processes (Robbins and Everitt 1996; Koob and Nestler 1997) and has been implicated in acute mania and depression (Willner 1983; Jacobs and Silverstone 1986). A recent investigation also found an effect of acute tyrosine depletion on the elation–depression scale of the profile of mood states, although this was only apparent following the induction of stress with public speaking and mental arithmetic tasks (Leyton et al. 2000). The present decrease in mood was evident prior to the battery of tests suggesting that subtle effects on subjective experience can be produced by dopamine depletion. Although some other subjective ratings also appeared to be different following tyrosine depletion (such as sleepiness), these did not approach statistical significance because of the large variance in scores. Hence, the present data suggest that this mixture may be relatively free of subjective side effects when given alone, although a larger sample is needed to confirm that further changes are not apparent.

In contrast to the selective effects of tyrosine depletion when given under basal conditions, this manipulation has been found to produce more widespread effects under conditions of pathologically increased dopamine function in humans. Thus, administration of the TYR-free mixture attenuated the effect of amphetamine on ratings of mind-race and buzz and on response latency in the RVIP task (McTavish et al. 1999c and unpublished observations). Furthermore, patients with acute mania, which has been related to dopamine over activity, showed, on average, a 35% reduction in symptom severity following the TYR-free drink, but no change following the BAL mixture (McTavish et al., unpublished observations). Since tyrosine depletion results in a reduction in dopamine synthesis, rather than post-synaptic blockade, it may be well suited as a therapeutic intervention for conditions that are believed to involve dopamine over activity, such as acute mania (Jacobs and Silverstone 1986), schizophrenia (Laruelle and Abi-Dargham 1999) and drug-induced craving (Pilla et al. 1999). Such an effect would be predicted to target areas of over activity, whilst leaving normal function relatively intact.

Evidence suggests that tyrosine depletion decreases dopamine activity while apparently sparing noradrenergic function. Results from animal models indicate that, in contrast to its inhibitory effect on stimulated dopamine release, tyrosine depletion does not modify amphetamine- or idazoxan-induced increase in extracellular noradrenaline (McTavish et al. 1999a, 1999b). In man, tyrosine depletion also failed to attenuate the noradrenergic effects of methamphetamine, including decreased hunger, increased blood pressure and enhanced response sensitivity in the RVIP task, in contrast to the largely dopaminergic functions reviewed above (McTavish et al., unpublished observations). Third, in another investigation, tyrosine depletion did not effect the evening rise in melatonin relative to the BAL drink; this is indicative of a failure to reduce noradrenergic activity in the pineal gland (Sheehan et al. 1996). Consistent with these findings, the present measures of baseline noradrenaline function (RVIP response sensitivity and ratings of hunger) were unchanged.

In conclusion, results from a combination of approaches consistently indicate that tyrosine depletion attenuated dopamine function in healthy volunteers in the absence of changes in tasks previously reported to be affected by noradrenaline or serotonin. These results suggest that tyrosine depletion can be used as an effective probe of global dopamine function in man. Although volunteers reported feeling less good following the TYR-free mixture, this was not sufficient to increase ratings of depression or tension. Taken together with the results from previous studies indicating significant effects on symptoms of acute mania and methamphetamine administration, the relative selective changes found here suggest that this intervention may particularly target currently active (or overactive) systems.

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