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ORIGINAL INVESTIGATION

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A dose-finding study on the effects of branch chain amino acids on surrogate markers of brain dopamine function

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Abstract *Rationale*: We have previously shown in healthy volunteers that an amino acid mixture lacking tyrosine and phenylalanine reduces tyrosine availability to the brain and produces cognitive and neuroendocrine effects consistent with reduced dopamine function. This could provide a potential nutritional approach to disorders such as mania and schizophrenia, which are characterised by overactivity of dopamine pathways. The amino acid mixture we tested previously is unpalatable, whereas mixtures containing only branch chain amino acids can be made more palatable. However, the effects of such mixtures on dopamine function in humans have not been studied. *Objective*: To assess the tolerability of different doses of branch chain amino acids and to measure their effects on neuroendocrine and cognitive measures sensitive to changes in dopamine function. *Methods*: We used a randomised, double-blind, crossover design in 12 healthy volunteers to assess the effect of single oral doses of 10 g, 30 g and 60 g branch chain amino acids on plasma prolactin and a test of spatial recognition memory *Results*: The branch chain amino acids were well tolerated. The availability of tyrosine for brain catecholamine synthesis decreased in a dose-related manner. As hypothesised, the drink increased both the plasma prolactin and the latency to respond on the spatial recognition memory task. *Conclusions*: A drink containing branch chain amino acids is well tolerated in healthy volunteers and produces effects consistent with lowered dopamine function.

Keywords Dopamine · Branch chain amino acid · Tyrosine depletion

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Introduction

Overactivity of brain dopaminergic pathways has been implicated in the pathophysiology of a number of psychiatric disorders including mania and schizophrenia (Silverstone 1985; Laruelle et al. 1996). Treatment with post-synaptic dopamine (DA) D_2 receptor antagonists is the mainstay of therapy for these disorders but often results in unpleasant side effects, notably extrapyramidal movement disorders. Accordingly, a means of normalising pre-synaptic DA overactivity without blocking DA receptors could prove a useful and better tolerated therapeutic approach.

The synthesis of a monoamine neurotransmitter such as DA is dependent on the availability of its precursor amino acids tyrosine (TYR) and phenylalanine (PHE) from plasma (Milner et al. 1987). Acute administration of an amino acid mixture that lacks TYR and PHE (TYR-free) decreases the availability of TYR to the brain. This happens through increased protein synthesis (which lowers plasma TYR) and by increased competition for transport across the blood–brain barrier (Oldendorf et al. 1976; Pardridge 1977). In rodents, administration of a TYR-free mixture decreased brain TYR and catecholamine synthesis in DA-rich brain regions, suggesting a potential inhibitory action on pre-synaptic DA function (McTavish et al. 1999). Consistent with this, in microdialysis studies the TYR-free mixture also lowered the increase in DA but not the increase in noradrenaline produced by amphetamine in rodents (McTavish et al. 2000).

In humans, an oral TYR-free mixture also produced changes suggestive of lowered DA neurotransmission. For example, relative to a nutritionally balanced control mixture, the TYR-free mixture increased plasma prolactin (PRL) and impaired spatial recognition memory, the effects of which are consistent with impaired DA function (Harmer et al. 2001). These findings support the hypothesis that restricting the availability of TYR to the brain may provide a novel means of lowering brain DA function. Indeed, preliminary evidence suggests that

administration of the TYR-depleting mixture reduced symptom severity in acute mania (McTavish et al. 2001). Unfortunately, the TYR-free mixture is rather unpalatable and would be unsuitable for repeated administration required in the management of pathological conditions. The purpose of the present study was to investigate whether similar effects on markers of DA neurotransmission could be obtained using a simpler amino acid mixture consisting of the three branch chain amino acids (BCAAs) only (valine, leucine and isoleucine). This preparation is quite palatable and is known to be well tolerated during longer-term administration (Harper et al. 1984; Berry et al. 1990; Richardson et al. 1999). In line with previously reported effects of TYR depletion, we hypothesised that the BCAA drink would increase plasma levels of PRL and decrease spatial recognition memory in a dose-dependent manner.

Materials and methods

Subjects

We studied 12 healthy subjects, 7 men and 5 women (age range 21–55 years). On the basis of a full medical and psychiatric examination, including the Structured Clinical Interview from the Diagnostic and Statistical Manual of Mental Disorders, 4th edn. (DSM-IV), they were determined to be free of current medical and psychiatric disorders. Subjects had no past history of mood disorder and had been drug free for the last month. All subjects gave written informed consent to the study, which was approved by the local ethics committee.

Amino acid mixtures

The study had a double-blind, randomised crossover design in which each subject was tested on three occasions 1 week apart. On each test day, the subject was given a drink containing either 10, 30, or 60 g of BCAA, each consisting of valine, isoleucine and leucine in the ratio 3:3:4. The drinks contained, respectively: valine 3 g, isoleucine 3 g and leucine 4 g; valine 9 g, isoleucine 9 g and leucine 12 g; and valine 18 g, isoleucine 18 g and leucine 24 g. A water placebo would have been easily distinguished and the 10 g BCAA was therefore used as a placebo control.

The drinks were made more palatable by adding 0.05 g sodium saccharin, 0.1 g ascesulfane K, 0.6 g citric acid and 0.25 g orange liquid flavouring containing 0.24 g carbohydrate (Givaudan Roure Ltd, Milton Keynes, UK). To improve solubility and taste, 53 g calogen (Alembic Products Limited, Chester, UK), containing 26.5 g peanut oil, consisting of non-esterified fatty acids, was added. Finally, cooled mineral water was added to give a volume of 300 ml. All drinks were prepared and administered by a research nurse not involved in the further execution of the study. The drinks were required to be consumed within a few minutes.

Biochemical measures

Venous blood samples were taken in heparinised tubes before ingestion of the amino acid drink and then subsequently every 30 min for the following 6 h. Plasma was separated by centrifugation and stored at –30°C until assay. The plasma total amino acid concentrations of leucine, isoleucine, valine, PHE, TYR and tryptophan were measured using an automated high-performance liquid chromatography system that used fluorescent end-point detection and pre-column sample derivatisation (Furst et al. 1990). PRL levels were determined using a standard immunoradiometric assay (Netria, London).

Neuropsychological tests

Computerised neuropsychological tests were given from the Cambridge Neuropsychological Test Automated Battery (Cantab; Robbins et al. 1994). This is a language-free, touch-screen method of cognitive assessment. All tests apart from the rapid visual information processing (RVIP) were only performed at 300 min. All tests were briefly explained to the participants at 270 min on the first occasion (with a short illustration of each) to avoid learning effects, which make these tests less sensitive to processing changes.

Pattern recognition memory

Pattern recognition memory (PRM) is a test of visual recognition memory in a two-choice, forced-discrimination paradigm. Participants were presented with two different series of 12 coloured, abstract patterns. Five seconds after the end of each series, participants were required to choose, from a series of 12 random sets of two patterns, the one that was presented previously. Accuracy (percentage correct) and latency were recorded.

Spatial recognition memory

Spatial recognition memory (SRM) is a test of spatial recognition memory in a two-choice, forced-discrimination paradigm. A sequence of open white squares was presented at five different locations on the computer screen. After the end of each of four sequences, participants were required to choose which location had been presented previously from the target and a square in a distracter location. Accuracy (percentage correct) and response latency were recorded.

Paired associates learning

This paired associates learning (PAL) task assesses new learning and memory for both ‘stimulus’ and ‘stimulus location’. The participant was presented with six and eight boxes on one screen, which opened up one by one to reveal an abstract pattern. The patterns were then displayed individually in the centre of the screen, and the participant was required to indicate the box in which the pattern was initially presented. The results are recorded in terms of number of stimuli identified correctly on the first trial for both presentations of six and eight stimuli (memory), the total number of trials required to reach criterion and total number of errors made overall (learning).

Rapid visual information processing

The RVIP is a fast version of a test of visual sustained attention with a small working memory component. Participants were required to detect 3-digit sequences (3-5-7, 2-4-6 and 4-6-8) in a continuous stream of digits presented in the centre of the screen, at a rate of 150 digits per minute. The test lasted for 280 s, during which 63 target sequences were presented. The test measures accuracy (how many targets are correctly detected), response bias (how many false alarms are made by the participant) and latency (response time in milliseconds). In order to omit any practice effects from the results, responses to the first 40 s of presentations were discarded. This test was performed at 0 min and 300 min and was always preceded by a brief training session at 0 min. In the training phase, the target sequence (3-5-7) digits were coloured, and both prompting and feedback from the computer were given.

Table 1 Average plasma levels of aromatic and branch chain amino acids and their ratios at 0 min and 300 min after 10 g, 30 g, and 60 g branch chain amino acids. *TYR* tyrosine, *PHE* phenylalanine, *TRP* tryptophan

Dose (g)	10		30		60	
Time (min)	0	300	0	300	0	300
TYR	63.0±18.8	23.5±12.5	63.9±20.4	12.3±9.25	59.5±18.8	9.08±4.94
PHE	58.7±23.4	30.8±16.5	55.9±16.8	14.9±9.14	54.2±16.8	13.2±9.19
TRP	50.4±8.84	27.6±6.20	52.3±6.09	24.5±5.02	51.6±8.23	20.7±3.65
Leucine	157±70.2	226±96.8	173±87.4	695±362	138±58.4	2009±836
Isoleucine	70.4±21.7	114±34.7	73.4±19.9	399±166	65.1±14.8	1323±543
Valine	247±89.3	412±124	234±76.3	1006±295	227±42.9	2337±672
Ratio TRP/BCAA	0.12±0.035	0.038±0.011	0.12±0.036	0.013±0.0054	0.12±0.030	0.0042±0.0018
Ratio TYR+PHE/BCAA	0.27±0.055	0.075±0.034	0.26±0.054	0.014±0.0080	0.27±0.067	0.0041±0.0019

Questionnaires

Visual analogue scales

Participants were asked to rate themselves for feelings of 'nausea', 'good', 'sleepy', 'depressed' and 'tense' at 0, 30, 90, 150, 210, 270, and 330 min. Participants were asked to place a mark on a 100-mm line, marked 'not at all' at one end and 'extremely' at the other end. The scales were measured in terms of position of each mark on the scale.

Profile of mood states questionnaire

The profile of mood states questionnaire (POMS) is a 24-item questionnaire, which is highly sensitive to non-clinical changes in mood (McNair et al. 1971). It measures six dimensions: anxiety, depression, anger, fatigue, confusion and vigour. Participants are requested to rate each item on a scale of 0–4, where 0='not at all', 1='a little', 2='moderately', 3='quite a bit' and 4='extremely'. For an overall score, the totals for the first five categories were added, from which the score on 'vigour' was subtracted. The POMS was administered at 0, 270 and 330 min, the latter immediately following the neuropsychological tests.

Statistical analysis

For plasma PRL analysis, the area under the curve was calculated using the trapezoidal rule with subtraction of baseline secretion extrapolated from time 0. Plasma amino acids were analysed at two time points, baseline and at 300 min just before the neuropsychological tests. Normally distributed data were analysed using repeated-measures analysis of variance (ANOVA). Any significant interaction was examined further using post-hoc paired comparisons. The two-tailed Wilcoxon signed ranks test was used for non-parametric data. Neuropsychological data were analysed with repeated-measures ANOVA for dose and occasion. VAS and POMS were analysed using repeated-measures ANOVA for dose by time and for occasion by time. For significant findings we performed post-hoc pairwise comparisons.

Results

Tolerability

The drinks were well tolerated, and no adverse effects were reported by any of the volunteers whilst in our unit. One female participant experienced mild stomach discomfort from 12 h to 36 h after the 30-g drink, probably unrelated to the drink.

Amino acids

Baseline values for all amino acids were comparable. As expected, plasma levels of BCAA rose in a dose-related manner after administration (Table 1). In addition, plasma TYR plus PHE levels fell more after the 30-g and 60-g drinks than after the 10-g drink, suggesting increased utilisation of these two amino acids (main effect of drink at time 300 min: $F_{2,22}$=26.5, P<0.001). Simple main effects showed a significant difference between the 10-g and 30-g drinks ($t_{1,11}$=7.0, P<0.001), between the 10-g and 60-g drinks ($t_{1,11}$=5.1, P<0.001) but not between the 30-g and 60-g drinks ($t_{1,11}$=1.4, P=0.2).These effects resulted in a significant dose-related decrease in the ratio of TYR plus PHE: BCAA at time 300 min (main effect of drink $F_{2,22}$=56.1, P<0.001; 10 g vs 30 g $t_{1,11}$=7.7, P<0.001; 10 g vs 60 g $t_{1,11}$=7.5, P<0.001; 30 g vs 60 g $t_{1,11}$=4.6, P<0.001). Indeed after the 60-g drink, the reduction was more than 60-fold. Plasma tryptophan levels also fell, but mainly with the 60-g mixture (main effect of drink $F_{2,22}$=7.4, P<0.01; 10 g vs 30 g $t_{1,11}$=1.7, P=0.1; 10 g vs 60 g $t_{1,11}$=3.6, P<0.01; 30 g vs 60 g $t_{1,11}$=2.3, P<0.05). The ratio of tryptophan:BCAA was also decreased at time 300 min (main effect of $F_{2,22}$=115.5, P<0.001; 10 g vs 30 g $t_{1,11}$=9.7, P<0.001; 10 g vs 60 g $t_{1,11}$=12.0, P<0.001; 30 g vs 60 g $t_{1,11}$=7.5, P<0.001).

Prolactin

PRL levels increased, particularly after the 60-g drink (Fig. 1). A Wilcoxon signed ranks test showed a significant increase of the area under the plasma concentration–time curve (AUC) after 60 g relative to 10 g ($Z_{1,11}$= –2.4, P<0.05) and after 60 g relative to 30 g ($Z_{1,11}$=2.1, P<0.05).

Neuropsychological data

Overall mean scores for accuracy and reaction times for each of the neuropsychological tests are summarised in Table 2. Performance on the RVIP and PAL tests were not affected by BCAA dose (Table 2).

Table 2 Average scores (±SD) on CANTAB tests after 10 g, 30 g and 60 g branch chain amino acids. Statistical significance values represent the interaction of dose × time of test for the rapid visual information processing task and the main effect of dose for all other tests

Neuropsychological tests	Drink dose			Statistical significance
	10 g	30 g	60 g	
Rapid visual information processing				
Accuracy – time 0 (%)	59±13	63±13	59±17	
Accuracy – time 300 (%)	65±14	64±14	59±16	$F_{2,22}$=0.6, P=0.6
False hits – time 0	3.5±5.5	6.3±8.8	5.8±9.0	
False hits – time 300	4.4±6.3	4.3±7.1	4.8±9.5	$F_{2,22}$=2.3, P=0.1
Latency – time 0 (ms)	466±60	474±81	469±75	
Latency – time 300 (ms)	451±43	476±67	462±67	$F_{2,22}$=0.7, P=0.5
Pattern recognition memory				
Accuracy (%)	91±7	93±6	93±6	$F_{2,22}$=1.2, P=0.3
Latency (ms)	1813±507	1826±540	1964±661	$F_{2,22}$=1.3, P=0.3
Spatial recognition memory				
Accuracy (%)	80±10	84±10	82±12	$F_{2,22}$=0.4, P=0.7
Latency (ms)	1685±506	1945±595	1994±653	$F_{2,22}$=3.2, P=0.06
Paired associates learning				
Accuracy (/6)	5±1	5±1	5±2	$F_{2,22}$=0.1, P=0.9
Accuracy (/8)	4±3	5±3	5±2	$F_{2,22}$=0.6, P=0.5
Trials to criterion	5±3	5±2	5±2	$F_{2,22}$=0.2, P=0.8
Errors	10±12	8±9	8±7	$F_{2,22}$=0.4, P=0.7

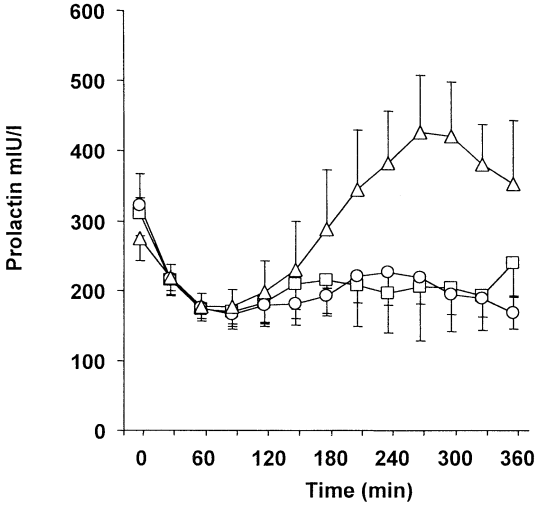

Fig. 1 Plasma prolactin (mU/l) following the different doses of branch chain amino acid mixture. *Squares* 10 g; *circles* 30 g; *triangles* 60 g

For the SRM task, latency tended to increase with increasing dose ($F_{2,22}$=3.2, P=0.06). Exploratory post-hoc pairwise comparison resulted in increased latency after 60 g relative to 10 g ($t_{1,11}$=2.5, P<0.05), after 30 g relative to 10 g ($t_{1,11}$=2.2, P=0.05), but no difference between 30 g and 60 g ($t_{1,11}$=0.3, P=0.8). To control for a possible trade-off between speed and accuracy, these measures were combined to yield an efficiency score ([accuracy/reaction time]; Christie and Klein 1995). This analysis revealed a significant effect of drink ($F_{2,22}$=3.4, P=0.05), although only the 60-g and 10-g drinks ($t_{1,11}$=2.3, P<0.05) were significantly different in the post-hoc analyses. Pearson correlation coefficients between spatial recognition efficiency and PRL AUC were not significant (P values >0.8), though correlations between spatial recognition efficiency and TYR plus PHE/BCAA ratio approached statistical significance (10 g r=0.5, P=0.1; 30 g r=0.3, P=0.4; 60 g r=0.5, P=0.1).

By contrast, no effects were found for the PRM test on accuracy rates ($F_{2,22}$=1.2, P=0.3), speed ($F_{2,22}$=1.3, P=0.3) or efficiency score ($F_{2,22}$=0.6, P=0.5).

Subjective ratings

BCAA dose did not affect subjective state assessed through VAS ratings (P>0.2) or the POMS (P>0.4).

Discussion

Administration of the three doses of BCAA to healthy volunteers was well tolerated and led to dose-dependent increases in plasma concentrations of BCAA and PRL. BCAA treatment also decreased performance on a neuropsychological task sensitive to impaired DA function.

The present study did not use a placebo control, instead a low-dose (10 g) BCAA drink was used as a comparison. The reason for this is that a plain water drink without amino acids would have prevented the study from being blind because of the significant difference in taste and texture. A ‘balanced’ drink with additional TYR and PHE would have suffered the same disadvantage. We cannot be sure that the 10-g mixture is, in fact, devoid of effects on DA function; it is possible that rela-

tive differences between the higher dose BCAA drinks and a true placebo drink may be greater than our present design suggests.

As expected, the ingestion of BCAA increased plasma BCAA levels substantially, which resulted in a significant fall in the ratio of TYR plus PHE:BCAA; this would be expected to lower the brain entry of TYR. However, our data suggest that administration of BCAA also diminishes plasma concentrations of TYR and PHE. The most likely mechanism of this effect is stimulation of protein synthesis and utilisation of endogenous stores of PHE and TYR. This reduction in plasma concentrations of TYR and PHE would have contributed to any decrease in brain entry of TYR produced by the BCAA drink. In addition, the BCAA drink lowered plasma tryptophan concentration and produced an overall substantial decrease in the ratio of tryptophan:BCAA. This would be expected to lower the brain entry of tryptophan and might impair brain 5-HT function. Prevention of this effect would require a BCAA drink supplemented with a balanced amount of tryptophan.

However, the pattern of results found in the neuroendocrine and neuropsychological assessments are suggestive of impaired dopaminergic function.

Prolactin

We found that decreasing the availability of TYR to the brain increased plasma PRL levels. This is consistent with our previous work (Harmer et al. 2001). DA plays an inhibitory role in the release of PRL and our findings therefore suggest that a 60-g BCAA drink significantly lowers the release of DA in the hypothalamus. 5-HT pathways stimulate PRL release and so the reduction in tryptophan availability is unlikely to have caused this effect (Attenburrow et al. 2001). Some studies have suggested that amino acids by themselves can increase plasma PRL by a direct effect on the pituitary. However, in our previous study, we found that an amino acid mixture balanced with TYR and PHE did not produce this effect (Harmer et al. 2001).

Neuropsychological tests

We hypothesised that the drink would selectively reduce performance on the SRM in a dose-related way in the absence of effect on the other tests. The SRM reaction times were the only parameter to show an effect of increasing dose; pair-wise comparison showed that subjects were significantly slower to make correct responses in this task following the 60-g and 30-g drinks relative to the control 10-g mixture. Impairments in this task would be expected if DA neurotransmission were decreased. SRM but not PRM is impaired in patients with Parkinson's disease (Owen et al. 1997; Postle et al. 1997). In addition, impairments are seen in healthy volunteers when administered the D_2 receptor antagonist sulpiride (Mehta et al. 1999) or the mixture of neutral amino acids lacking TYR (Harmer et al. 2001). Whilst accuracy was impaired in our last study with TYR depletion, speed was affected by sulpiride. Hence, it is likely that both measures of performance are sensitive to dopaminergic changes, and subjects can make a trade-off between speed and accuracy to try and maintain performance. When speed and accuracy values were combined in a measure of efficiency, performance was still impaired following the 60-g mixture.

While the effects of the mixture on SRM are suggestive of decreased DA function, the absence of an effect on the PAL task implies no effect on serotonin function. Tryptophan depletion has been found to decrease PAL performance as well as other measures of learning and visual memory (Park et al. 1994; Schmitt et al. 2000). However, we cannot completely exclude the possibility that dose effects on PAL and RVIP were obscured by the reported learning effects. Subjects may find strategies easy to adopt for these tests and they may be most useful in a parallel design. It would be helpful to assess the sensitivity of these measures to serotoninergic (versus dopaminergic) changes within the same study by the inclusion of a classic tryptophan depleting condition.

Subjective effects

We did not find any dose effects on the POMS. Recently, another group found a lowering of mood on the POMS after neuropsychological testing during TYR depletion (Leyton et al. 2000). However, this was for a bipolar version of the POMS, which may be more sensitive to change.

Comparison with a balanced drink without TYR

We have not compared the effect of this BCAA drink directly with the original balanced drink without TYR, as used in previous work by our group. The difference in palatability, although not directly assessed in this study, is, in our experience, so large that blinding of such a study would have been impossible. However, the effects of the BCAA drink on PRL and SRM efficiency are similar in magnitude to those of the balanced drink without TYR.

In conclusion, the BCAA drink employed here produced effects consistent with lowered DA neurotransmission. This mixture may have potential as a treatment for acute manic or psychotic states (McTavish et al. 2001). In particular, the 60-g dose is well tolerated and has a relatively long-lasting effect, which should make it possible to administer just once a day. Future studies should address the possible effects on the serotonergic system.

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