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Correspondence

PILOT STUDY OF AMINO ACIDS IN SENILE DEMENTIA

DEAR SIR,

Lehmann (1979) suggested that a proportion of patients in senescence did not absorb amino acids normally, and as a result developed a secondary dementia. He estimated uptake of tryptophan in most instances by plotting concentrations in plasma against time after giving 100 mg tryptophan per kg body weight by mouth, with 400 mg l-dopa added as a putative competitor at the amino acid uptake sites in the gut. Amounts of indican in the urine in patients with low plasma levels of tryptophan were increased, showing that they had a reduced uptake, not enhanced utilization or degradation of the amino acid. He found that the 'low absorbers' improved in both intestinal and mental function following a high protein diet.

The aims of the present investigation were to assess:

(i) Amino acid levels in plasma in fasting patients with senile dementia, an elderly and also a younger control group.

(ii) Tryptophan absorption in both patients with senile dementia and elderly controls.

(iii) The clinical effects of amino acid supplements in senile dementia.

(iv) Relationships between positive findings in (i), (ii) and (iii) above.

Individuals with significant physical abnormalities were excluded. None of the patients had affective illness or multi-infarct dementia, but they had errors in all three parts of the Hare (1978) scale, sufficient to classify them as having advanced senile dementia.

Venous blood samples were drawn after overnight fasting at 08.30–09.30 hr for assay of total (Denckla and Dewey, 1967) and non-protein bound (Riley and Shaw, 1981) tryptophan, and the total spectrum of amino acids (Dr D. M. Bradley, Department of Medicine, W.N.S.M.) from patients, elderly and younger controls (expt. (i)).

A proportion of this group, 32 patients and 67 elderly controls, after giving the zero-time venous blood sample, took 60 mg/kg body weight l-tryptophan (Scientific Hospital Supplies; Berk Pharmaceuticals Ltd) in ice cream (J. Thayer and Sons, 1.43 g/kg body weight), and blood was collected at 1, 2, 3, 4, and 6 hours afterwards. The areas under the graphs of tryptophan concentrations in plasma plotted against time (6 hours) were measured (expt. (ii)).

Twenty-nine of the 32 patients with senile dementia (23 F, 6 M) went on to take part in a double blind, randomized crossover trial of supplements of a balanced mixture of amino acids (Scientific Hospital Supplies) in a vehicle, against the vehicle alone without amino acids, but with the same calorific value as the active mixture (expt. (iii)). In this trial the amino acid supplements (1.43 g mixture [0.43 g amino acids] per kg body weight) were taken in 4 aliquots throughout the day, and 24 mg l-tryptophan/kg body weight suspended in 20 g chocolate flavoured 'Angel Whirl' (commercial formula, General Foods Ltd) was given at 21.00 hours. Placebo was 'Angel Whirl' without tryptophan. This was in addition to their normal diet. Patients were monitored before, at crossover and at the end of the trial by means of a global rating (by E. A. Sweeney).

Expt. i. Patients with senile dementia had significantly lower fasting levels of total and free tryptophan, and reduced ratios of both free and bound tryptophan to the sum of phenylalanine, tyrosine, leucine, isoleucine and valine as compared to those of the 2 control groups (Table I). Other abnormalities in fasting levels of amino acids present in the dementia group as compared to the elderly controls included increased levels of ornithine ($P < 0.001$) and a low ratio of tyrosine to the sum of tryptophan, leucine, phenylalanine, valine and isoleucine. The total amino acid content of plasma of the three groups was similar.

Expt. ii. The areas under the 0–6 hr curves of plasma tryptophan plotted against time (means and SEM) were 1964 ± 64 μM 6 hr in patients with dementia and 1934 ± 45 in elderly controls. The range of values was wide in both groups (880–2970, $n = 32$; and 1200–2700, $n = 67$).

Expt. iii. Of the 29 patients included in the trial of amino acid supplements, 6 on active treatment showed unequivocal improvement in blind global assessment. None of the patients on placebo had a similar rating, one was assessed as having doubtful improvement.

Expt. iv. Clinical improvement following the dietary supplements was not related to fasting tryptophan concentrations (free or total) nor to the plasma levels with time after a tryptophan load; nor to the

TABLE

Fasting plasma tryptophan concentration and other values (means ± SEM)

	Tryptophan in plasma μmol/l^{-1}				Ratio of tryptophan to sum of phenylalanine, tyrosine, leucine, isoleucine and valine				Ornithine μmol/l^{-1}		Ratio of tyrosine to sum of tryptophan (total) phenylalanine, tyrosine, leucine, isoleucine and valine	
	Total	N	Non-bound	N	Total	N	Non-bound	N		N		N
Senile dementia	53.6±1.8	32	12.4±0.5	31	0.10±0.004	29	0.023±0.001	27	98.2±3.6	29	0.12±0.003	29
Elderly controls	61.2±1.2	70	13.6±0.3	70	0.12±0.004	35	0.027±0.001	33	77.6±3.3	35	0.14±0.003	35
Younger controls	65.7±1.5	46	13.8±0.5	31	0.14±0.006	12	0.029±0.002	12	82.2±5.6	12	0.11±0.005	12
Senile dementia v. Elderly controls	P<0.001		<0.05		P <0.001		P <0.02		P<0.001		P <0.001	
Elderly v. Younger controls	P<0.02		NS		P <0.002		NS		NS		P <0.001	
Senile dementia v. Younger controls	P<0.001		<0.05		P <0.001		P <0.01		P <0.02		NS	

Two way Anova. Because of the sex differences in tryptophan concentrations the group means were adjusted for unequal numbers of males and females (Snedecor and Cochran, 1967).

The mean ages of the dementia and elderly control group were 77.1 (n = 32) and 70.1 (n = 70). These were significantly different, but none of the values correlated with age in the combined elderly and younger controls (sexes analysed separately).

The mean age of the younger controls was 42.2.

ratio of free or total tryptophan concentrations to the six amino acids.

In summary, ability of the elderly to absorb tryptophan showed a wide range of values, which merits further study. The results confirm Lehmann's findings that a small group of patients with senile dementia may be marginally but noticeably improved by amino acid or protein feeding. No relationship to the parameters studied here distinguished this group. However, our technique differed from that of Lehmann in several ways (amounts of amino acid given in the loading test, and absence of l-dopa as a competitor for absorption).

Entry of tryptophan to the brain is in part dependent on its concentration (free and bound) and on the ratio of its concentration to those of other amino acids (mostly phenylalanine, tyrosine, leucine, isoleucine and valine), which compete for the same transport mechanism (Fernstrom, Madras, Munro *et al*, 1974). These factors are themselves affected by the plasma concentration of albumin and non-esterified fatty acids (Curzon, Friedel and Knott, 1973) and insulin (Dickerson and Pao, 1975) as well as a number of drugs. Thus the reasons for the results could be many. They may be primary or secondary, or even something as simple as the effects of the timing and

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type of meals. Whatever the causes of the observed decreases in plasma concentrations of tryptophan and in the amino acid ratio in senile dementia, they could put the supply of tryptophan to the brain at risk.

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D. M. SHAW
S. F. TIDMARSH
B. M. KARAJGI
E. A. SWEENEY
S. WILLIAMS
M. ELAMEER
C. TWINING

Department of Psychological Medicine, Whitchurch and Royal Hamadryad Hospital, Welsh National School of Medicine, Cardiff

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