Short report

Anticonvulsant drugs alter plasma tryptophan concentrations in epileptic patients: implications for antiepileptic action and mental function

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SUMMARY In epileptic patients carbamazepine and diphenylhydantoin have opposite effects on whole and free plasma tryptophan concentrations, the former elevating and the latter depressing them. It is unlikely that these observations relate to the similar anti-epileptic properties of these two drugs but they may relate to their different effects on mental function and mood.

In animals several anticonvulsant drugs increase serotonin (5HT) concentrations due to a decrease in 5HT turnover.¹ There has been much interest in whether this observation relates to the therapeutic or toxic effects of the drugs.^{1,2} However, studies of the effects of anticonvulsants on the concentration of 5-hydroxyindoleacetic acid (5HIAA), a product of 5HT metabolism, in cerebrospinal fluid from epileptic patients have produced conflicting results.^{2,3} Since free plasma tryptophan concentrations may influence brain 5HT turnover⁴ we have investigated the influence of anticonvulsants, in particular carbamazepine and diphenylhydantoin on whole, bound and free plasma tryptophan concentrations in chronic epileptic patients and in newly diagnosed epileptic patients before and after the introduction of single drug therapy.

Patients and methods

The epileptic patients were attending the neurological out-patient department of King's College Hospital, London. They included (1) 24 untreated new referrals (median age 25 years, range 12 to 61), 14 of whom had tonic-clonic seizures, four partial and six mixed tonic-clonic and partial seizures; (2) 56 chronic patients (median age 25 years, range 17 to 75), 30 of whom had tonic-clonic seizures, 17 partial and nine mixed tonic-clonic and partial seizures

treated with a single anticonvulsant drug (carbamazepine for 14 patients; diphenylhydantoin for 35, and phenobarbitone for seven patients). A control group consisted of 33 normal volunteers from the staff of King's College Hospital (median age 26 years, range 16 to 62). In 10 new referrals tryptophan concentrations were re-examined between 2 weeks and 23 months after the introduction of carbamazepine (400–800 mg daily) in seven and diphenylhydantoin (200–300 mg daily) in three.

At each out-patient clinic attendance 20 ml of venous blood was taken for analysis. No dietary or fluid restrictions were imposed on the subjects. Whole and free plasma tryptophan were measured by the method of Eccleston;⁵ bound plasma tryptophan was estimated by subtraction of free from whole plasma tryptophan. Plasma concentrations of carbamazepine were measured by the gas chromatographic technique of Toseland *et al.*,⁶ diphenylhydantoin and phenobarbitone by the technique of Kupferburg.⁷

Results

Table 1 summarises the plasma tryptophan concentrations in epileptic patients on different drugs, in untreated epileptics and in normal controls. Untreated epileptic patients had slightly lower whole and bound plasma tryptophan levels than normal volunteers. In patients on drug therapy a striking finding is that carbamazepine is associated with a significant elevation of whole, bound and free plasma tryptophan in comparison with all the other groups. The bound-to-free plasma tryptophan ratio also fell significantly with carbamazepine in comparison with all other groups. By contrast diphenylhydantoin is associated with a significant fall in whole, bound and free plasma tryptophan and

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Table 1 Plasma tryptophan concentrations (95% confidence limits) in epileptic patients sub-divided by drug therapy, untreated epileptics and normal volunteers

Group	Clinic visits (patients)	Whole plasma tryptophan (µg/ml)	Bound plasma tryptophan (µg/ml)	Free plasma tryptophan (µg/ml)	Bound/free tryptophan ratio
<i>Epileptics</i>					
Carbamazepine	28 (20)	12.65* (11.83, 13.52)	9.86* (9.20, 10.57)	2.70* (2.38, 3.05)	3.65* (3.22, 4.13)
Diphenylhydantoin	53 (38)	8.60§ (8.20, 9.03)	7.41§ (7.05, 7.79)	1.15† (1.05, 1.26)	6.44 (5.89, 7.05)
Phenobarbitone	8 (7)	8.86 (7.82, 10.04)	7.82 (6.87, 8.90)	1.01† (0.80, 1.27)	7.76 (6.15, 9.79)
Untreated	16 (15)	9.17 (8.40, 10.01)	7.67‡ (7.00, 8.41)	1.32 (1.12, 1.55)	5.83 (4.95, 6.88)
<i>Normal volunteers</i>					
	34 (33)	10.12 (9.52, 10.75)	8.76 (8.23, 9.33)	1.33 (1.19, 1.49)	6.59 (5.89, 7.38)

Plasma tryptophan concentrations and bound/free tryptophan ratio were transformed logarithmically and analysed using a nested three-factor analysis of variance (clinic visit within patients within "drug" groups). Comparisons between means were made using the least significant difference (based on the mean square between patients within "drug" groups; $df = 108$). Figures are antilog (mean) (and antilog (95% confidence limits)) of transformed data. *All comparisons with carbamazepine group are significant ($p < 0.001$) except with bound plasma tryptophan for phenobarbitone group ($p < 0.005$) and normal volunteers ($p < 0.025$); other comparisons with normal volunteers † $p < 0.05$; ‡ $p < 0.025$; § $p < 0.001$.

phenobarbitone associated with a significant fall in free plasma tryptophan, in comparison with normal volunteers. For diphenylhydantoin and phenobarbitone similar trends were seen in comparison with untreated epileptic patients.

Table 2 relates plasma tryptophan concentrations to plasma concentrations of carbamazepine in patients treated with this drug. For carbamazepine whole, bound and free plasma tryptophan concentrations rise with increasing drug concentration. For diphenylhydantoin there is little change in tryptophan concentrations (except for a slight decline in free tryptophan) with increasing drug concentration (data not shown).

These results are supported by separate regression analyses of plasma tryptophan concentrations on drug plasma concentrations in patients treated with carbamazepine and diphenylhydantoin (data not shown). Total and free plasma concentrations increase with drug concentrations for carbamazepine; they show little change (regression coefficients negative but not significant at $p = 0.05$) for diphenylhydantoin.

Further support was obtained by an analysis of tryptophan concentrations in the 10 untreated epileptics who were subsequently re-examined on

drug therapy. Total plasma tryptophan concentrations increased in all seven patients after the introduction of carbamazepine (paired t test: $t = 3.35$, $df = 6$, $p < 0.05$) and decreased (though not significantly) in all three patients after the introduction of diphenylhydantoin; the difference between the changes in the two drug groups was highly significant ($F = 11.9$, $df = 1, 8$, $p < 0.001$). Both free and bound plasma tryptophan also increased in the patients given carbamazepine and decreased in those given diphenylhydantoin though these changes were not statistically significant at $p = 0.05$.

Discussion

We have found that carbamazepine and diphenylhydantoin have opposite effects on whole and free plasma tryptophan concentrations, the former elevating and the latter depressing them. In a small sample the effect of phenobarbitone was similar to that of diphenylhydantoin. The mechanisms by which carbamazepine and diphenylhydantoin produce different alterations in plasma tryptophan concentrations are unknown. Carbamazepine is structurally related to the tricyclic anti-depressants and it has been shown recently that the latter inhibit

Table 2 Plasma tryptophan concentrations (95% confidence limits) in epileptic patients treated with carbamazepine sub-divided by plasma drug concentration

Plasma drug concentration	Clinic visits (patients)	Whole plasma tryptophan (µg/ml)	Bound plasma tryptophan (µg/ml)	Free plasma tryptophan (µg/ml)	Bound/free tryptophan ratio
Subtherapeutic (<5 µg/ml)	9 (9)	11.93† (10.52, 13.52)	9.39 (8.25, 10.69)	2.48† (2.01, 3.07)	3.78 (3.09, 4.63)
Therapeutic (5–10 µg/ml)	15 (12)	12.40* (11.25, 13.66)	9.69 (8.76, 10.71)	2.61† (2.21, 3.07)	3.72 (3.18, 4.34)
Toxic (>10 µg/ml)	4 (4)	15.54 (12.88, 18.76)	11.75 (9.68, 14.27)	3.74 (2.71, 5.14)	3.15 (2.33, 4.26)

Plasma tryptophan concentrations and bound/free tryptophan ratio were transformed logarithmically and analysed using a crossed two-factor analysis of variance (drug (carbamazepine/diphenylhydantoin) and drug concentration (subtherapeutic/therapeutic/toxic)). There is a significant ($p < 0.05$) interaction between the two factors for whole and free plasma tryptophan. Comparisons between means were made using the least significant difference ($df = 75$). Figures are antilog (mean) (and antilog (95% confidence limits)) of transformed data. Significance of comparisons with toxic drug concentration group: * $p < 0.05$; † $p < 0.025$.

liver tryptophan pyrrolase probably as a result of the prevention of conjugation of the apoenzyme with its cofactor haem.⁸ The possibility that carbamazepine has a similar effect requires investigation. The decrease in bound plasma tryptophan associated with diphenylhydantoin might reflect the high degree of protein binding of this drug causing displacement of the amino acid from its albumin binding site.⁹ Indeed, diphenylhydantoin and phenobarbitone competitively inhibit the binding of L-tryptophan onto human serum albumin *in vitro*.¹⁰ Another possibility is that both diphenylhydantoin and phenobarbitone enhance the activity of tryptophan pyrrolase by enzyme induction.⁹ However, carbamazepine is also a potent enzyme inducer, but has the reverse effects on plasma tryptophan concentrations.

Clinical studies suggest that there is little difference in the anti-epileptic efficacy of carbamazepine and diphenylhydantoin.¹¹ It is therefore unlikely that the opposite effects of these two drugs on plasma tryptophan concentrations can be related to the anticonvulsant action of either drug. However, there is considerable evidence that the two drugs have different chronic effects on mental function. An encephalopathy has been reported with diphenylhydantoin (and phenobarbitone) but not with carbamazepine.^{12,13} In comparative studies of the two drugs in normal volunteers,¹⁴ chronic epileptic patients¹⁵ and new referrals with epilepsy,¹⁶ tests of psychomotor performance, attention, memory and mood have consistently favoured carbamazepine. Indeed, it has been claimed that carbamazepine has positive psychotropic effects with a beneficial influence on both mania and depression.¹⁷ In view of the evidence of a relationship between central serotonergic function and mood¹⁸ we suggest that the different effects of carbamazepine and diphenylhydantoin on tryptophan concentrations which we have observed may be related to the different influence of the two drugs on mental function.

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