Treatment of Parkinson's Disease with Sodium Valproate: Clinical, Pharmacological, and Biochemical Observations

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SUMMARY: *Because there is biochemical evidence of decreased GABAergic function in Parkinson's disease, sodium valproate, an inhibitor of GABA catabolism, was administered to eight Parkinsonian patients. Valproate treatment did not significantly alter any Parkinsonian feature, but tended to increase the dyskinesia in the "on-off" patients. The increased dyskinesias were not a result of altered peripheral metabolism of L-dopa. Despite obtaining high plasma levels of valproate, no consistent alteration of CSF GABA levels could be demonstrated. Thus, in these patients, an effect of valproate on GABA metabolism is unproven, and in turn, the role of GABA in Parkinsonism and dyskinesia uncertain.*

RÉSUMÉ: *Traitement de la maladie de Parkinson par le Valproate Sodique: Observations cliniques, pharmacologiques et biochimiques.*

Parce qu'il existe des évidences biochemiques en faveur d'une réduction des fonctions GABA ergiques dans la maladie de Parkinson, nous avons administré le valproate sodique, un inhibiteur du catabolisme du GABA, à 8 patients parkinsoniens. Le traitement du valproate n'a modifié significativement aucun aspect du parkinson, mais tendait à augmenter les dyskinésies chez les patients ayant le phénomène "on-off". Cette augmentation des dyskinésies n'était pas le résultat de modifications du métabolisme périphérique de la L-DOPA. Malgré l'obtention de hauts taux plasmatiques de valproate, nous ne pûmes démontrer aucun changement constant des taux de GABA du LCR. Donc. chez ces patients, nous n'avons pu prouver un effet du valproate sur le métabolisme du GABA et, secondairement, le rôle du GABA dans le Parkinson et les dyskinésies reste incertain.

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INTRODUCTION

The extrapyramidal system contains high concentrations of the putative neurotransmitter, gamma-aminobutyric acid (GABA), and its synthesizing enzyme, glutamic acid decarboxylase (G.A.D.), [Fahn, 1976; Perry et al., 1971; Okada et al., 1971]. GABA may serve as the neurotransmitter for some striatal interneurons [McGeer and McGeer, 1975]. for neurons projecting from the striatum to the substantia nigra (striato-nigral tract) [Okada, 1976; Fonnum et al., 1974] and possibly for striatal neurons projecting to the pallidum [Fonnum et al., 1974; Toshida et al., 1972] and pallidal neurons projecting to the substantia nigra [McGeer et al., 1974]. Electrophysiological and pharmacological studies have suggested that the GABAergic striatonigral tract is an inhibitory feedback loop to the dopaminergic neurons of the substantia nigra (Gale and Guidotti, 1976; Precht and Yoshida, 1971; Racagni et al., 1977].

Parkinson's disease is associated with a decrease of G.A.D. in the substantia nigra, striatum, and globus pallidum, although the concentration of GABA in the same regions is not concomitantly reduced (Hornykiewicz et al., 1976; Laaksonen et al., 1976; Lloyd et al., 1975]. GABA receptors are also reduced in the substantia nigra of Parkinsonian brains, possibly reflecting loss of receptors on the dopaminergic neurons which degenerate in Parkinsonism, [Rinne et al., 1978; Lloyd et al., 1976]. Treatment with L-dopa increases the activity of basal ganglia G.A.D. [Hornykiewicz et al., 1976; Laaksonsn et al., 1976; Lloyd, 1975].

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The clinical importance of these observations is uncertain, but several hypotheses are tenable. First, the decreased GABAergic function may contribute to the rigidity or tremor of Parkinson's disease as suggested by Hornykiewicz et al., 1976. Alternatively, if GABA participates in a negative feedback loop to the dopaminergic neurons of the substantia nigra, the activity of GABAergic systems may be decreased in the basal ganglia as a compensation for decreased dopaminergic function. Finally, since striatal GABA is also decreased in the hyperkinetic disorder of Huntington's disease [McGeer et al., 1973; Stahl and Swanson, 1974; Bird and Iverson, 1974] it may be speculated that a deficiency of GABAergic activity in the presence of normal dopaminergic function is responsible for the choreiform movements seen in Huntington's disease and some L-dopa treated Parkinsonian patients.

To explore the role of GABAergic systems in Parkinsonism we have treated 8 patients with sodium valproate, an agent which reputedly raises brain GABA levels by inhibition of the GABA degradative enzymes, GABA transaminase and succinic semialdehyde dehydrogenase [Godin et al., 1969; Simler et al., 1973; Harvey et al., 1975].

METHODS

Patients:

Eight patients with idiopathic Parkinsonism participated in the study after giving informed consent. Five exhibited dyskinesias and marked fluctuation of motor performance not related to time of drug administration ("on-off" phenomenon). The clinical characteristics of the patients and their concurrent medications are presented in Table 1. Patients were hospitalized for the duration of the study.

Design

The study was conducted as a double-blind comparison of valproate and placebo. A placebo phase preceded and followed valproate therapy. Sodium valproate or identical appearing placebo was administered four times daily. Valproate dosages are expressed as milligrams of valproic acid. The drug was initiated at 400 mg per day and increased by 200 mg every second to eighth day to a maximum of 2800 mg/day or until toxicity appeared. Sodium valproate was withdrawn abruptly by substitution of placebo. Parkinsonism features were assessed two to three times per week by a "blind" observer using a 0 (absent) to 4 (severe) scoring system for tremor, rigidity, speech, facial expression, rising from chair, balance, posture, and gait. The number of times a patient could successively oppose the thumb to the four fingers in 20 seconds was counted for each hand. Fluctuations in response were recorded by the patient and the nurses each hour while the patient was awake using an analog scale with 0 equal to normal and 100 equal to severe dyskinesia, and a second analog scale with 0 equal to

TABLE I

Clinical Features of Patients

PATIENTS	AGE/SEX	DURATION OF DISEASE (years)	CLINICAL FEATURES	CONCURRENT MEDICATIONS mg/day	
1.	65/M	19	Marked on-off	L-dopa	1050
2.	76/M	22	Moderate response to L-dopa Severe Parkinsonism	L-dopa Carbidopa Benztropine	1500 150 2.5
3.	63/M	3	Mild Parkinsonism	L-dopa Carbidopa Bromocriptine	200 20 20
4.	57/M	17	Bilateral thalamotomies Unresponsive to L-dopa	Procyclidine	15
5.	56/F	20	Severe on-off L thalamotomy	L-dopa Bromocriptine Trihexdyl	1000 125 8
6.	55/F	10	Moderate on-off	L-dopa Carbidopa	1050 105
7.	59/F	19	Marked on-off L thalamotomy Mild dementia	L-dopa Carbidopa Ethopropazine	2475 247 30
8.	48/F	19	Moderate on-off L thalamotomy	L-dopa Carbidopa Benztropine	550 40 2

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normal and 100 equal to severe bradykinesia.

Plasma L-dopa Concentration:

Plasma L-dopa concentrations were measured in five patients both on and off valproate following a standard dose of L-dopa/carbidopa. The patients were kept at bed rest for the 9 hours preceding the test. At 8:00 a.m., they received their morning dose of valproate or placebo and were served a light breakfast of coffee, toast, and fruit juice. At 9:00 a.m., L-dopa/carbodopa was administered and blood samples were collected over the succeeding three hours. Blood was immediately cooled following collection and at the termination of the test, the plasma was separated and stored at -20°C until assayed. L-dopa was measured fluorometrically [Tyce et al., 1970]. Patient 9 who participated in this part of the study was not Parkinsonian, but was on valproate as part of another clinical trial.

Plasma Valproate Concentrations:

Plasma for valproate levels was collected in the morning before the first daily dose of valproate (10 hours after last dose). Vaproate was assayed by gas-liquid chromatography [Kupferberg, 1978].

CSF GABA Concentrations:

Six patients had spinal taps during the placebo and high dose valproate phases. Lumbar punctures were performed at 9:00 a.m., after the patient had been at bed rest and fasting for 9 hours. CSF was stored at -20°C. GABA was measured by the radio-receptor assay [Enna, 1977] in an aliquot from the sixth to twelfth cc of CSF removed. All samples were analyzed in the same assay.

Statistical Analysis:

Both paired t tests and Wilcoxon signed rank tests were used to test for significance between placebo and high dose valproate treatment. Placebo scores are the average of all evaluations except the first rating obtained during the placebo phases (3 to 7 evaluations). The treatment score is the average of the three final evaluations obtained during the maximum valproate doses.

RESULTS

The patients achieved relatively high oral dosages of valproate and had correspondingly high plasma concentrations of the drug (Table 2). Mild to moderate personality and intellectual changes were evident in the majority of patients on high doses of the drug. A mild thrombocytopenia occurred in five patients, but was not associated with any bleeding problems and platelets returned to normal after withdrawal of the drug.

Valproate treatment had no statistically significant effect on any Parkinsonian feature, although there

TABLE 2

Durations of Therapy, Maximum Doses, Maximum Plasma Concentrations and Side Effects of Valproate

PATIENT	DURATION OF VALPROATE TREATMENT (days)	VALPROATE MAXIMUM DOSE mg/kg	MAXIMUM PLASMA CONCENTRATION μg/ml	SIDE EFFECTS
1.	33	49	110	Sleepiness Confusion
2.	22	38	128	Sleepiness Confusion Sialorrhea Thrombocytopenia
3.	30	30	112	Personality Change Thrombocytopenia
4.	33	50	109	Sleepiness Confusion Asterixis Thrombocytopenia
5.	41	62	120	Lethargy Confusion Asterixis Thrombocytopenia
6.	18	29	116	Rash Thrombocytopenia
7.	18	27	93	Confusion Asterixis
8.	30	41	123	Personality Change

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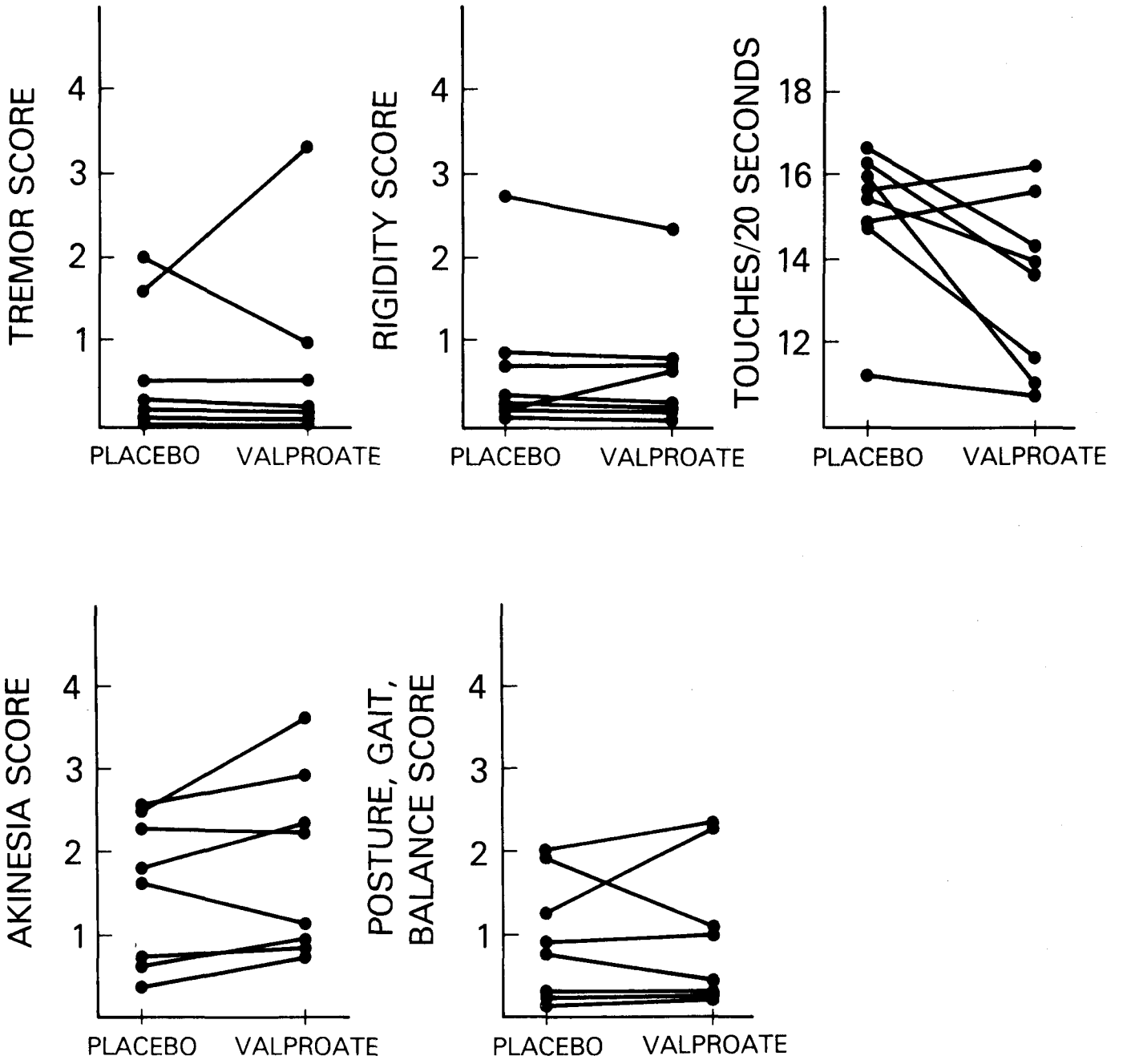

Figure 1 — Effects of valproate on Parkinsonian features. The akinesia score is the total of the disability scores for speech, facial expression, and rising from a chair.

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was a tendency for akinesia scores to increase and performance of the timed finger touching task to deteriorate (Fig. 1). There also was no evidence of improvement of Parkinsonian scores at lower valproate dosages (not shown). These results are slightly confounded by the fact that during the trial, several of the "on-off" patients became more consistently dyskinetic and L-dopa/carbidopa was reduced 67%, 17%, and 18% in patients 1, 6, and 8 respectively. Following the drug study, these patients' L-dopa requirements increased to pre-study levels. This apparent enhancement of the action of L-dopa was not observed in the patients without the "on-off" phenomenon. The fluctuations in the five patients with the "on-off" phenomenon were not improved, even when L-dopa/carbidopa was decreased, as judged by clinical impression, and by patients and nurses scoring of severity of fluctuations or percentage of time over and under dosed.

Because of the potentiation of L-dopa effects in the "on-off" patients, plasma L-dopa concentrations were measured in 5 patients during the valproate and placebo phases. As seen on Figure 2, the maximum plasma L-dopa level and the half life of plasma L-dopa were not increased by valproate.

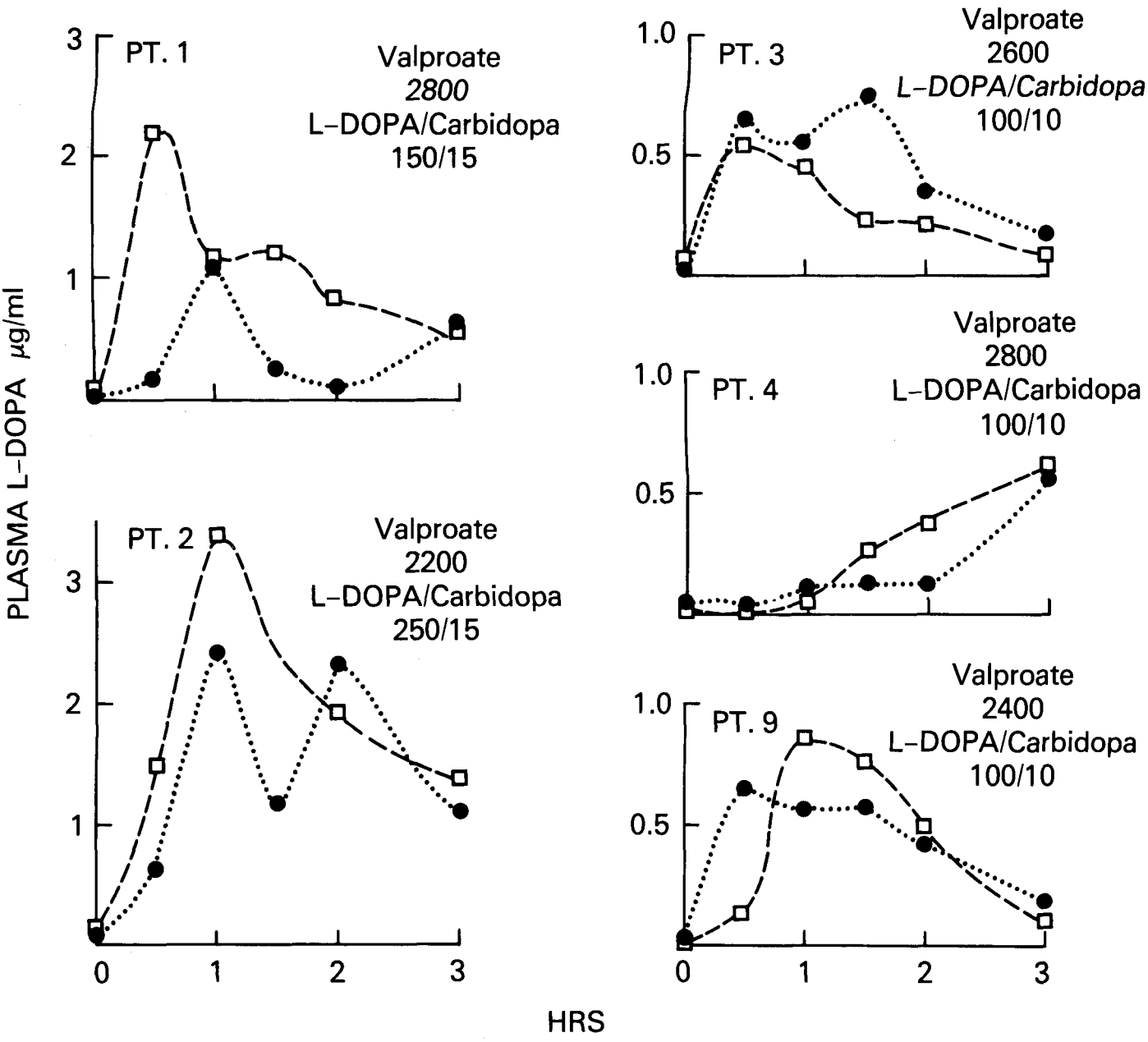

Figure 2 — Effect of valproate on plasma L-dopa concentration. The lines are the plasma L-dopa concentrations after a single oral dose of L-dopa while the patient was receiving valproate (dotted line) and while receiving placebo (dashed line).

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The concentration of GABA in the CSF was not consistently affected by valproate treatment (Fig. 3).

DISCUSSION

Sodium valproate did not significantly alter any feature of Parkinson's disease. However, it exacerbated the dyskinesia in 4 of the patients with the "on-off" phenomenon, necessitating a reduction of L-dopa in 3. Even following the reduction in L-dopa dosage, there was no improvement of the fluctuations compared to placebo phases. The apparent enhancement of L-dopa's effects in the dyskinetic patients was not evident in the patients who did not have fluctuations. Price et al., (1978) also found that valproate did not produce any objective changes in Parkinsonian signs. However, there was a subjective improvement of dyskinesia in 6 of 9 patients, although this improvement was not evident on the "blind" assessments. The difference between the response of dyskinesia to valproate in the study of Price et al. (1978) and the current investigation is probably attributable to the different dosages employed. Price et al. (1978) used 1200 mg of sodium valproate daily as opposed to an average maximum daily dosage of 2800 mg of sodium valproate in this study. It also suggests that the subjective improvement of dyskinesia in their study was not a threshold effect which would become objectively quantifiable with larger doses of valproate.

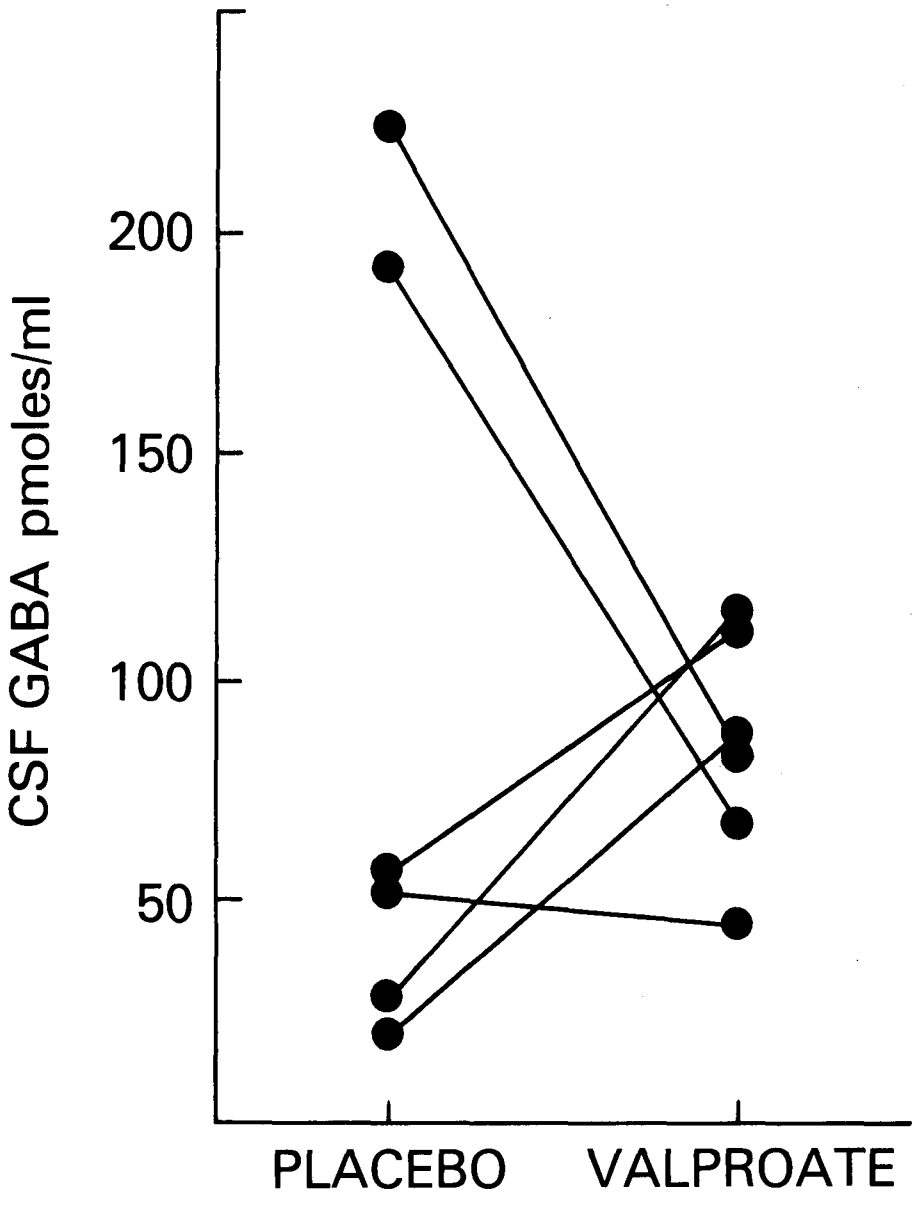

Figure 3 — Effect of valproate on CSF GABA levels.

The failure of sodium valproate to benefit Parkinsonism or the "on-off" phenomenon was not due to inadequate doses of valproate. Therapeutic plasma levels of valproate in the treatment of seizures are believed to be 50 μg/ml or greater [Pinder et al., 1977]; levels which all of the patients exceeded. It might be questioned if valproate toxicity obscured any beneficial effects, but there was no evidence of improvement of the Parkinsonism or "on-off" phenomena at lower doses of valproate when there were no signs of toxicity.

The exacerbation of the dyskinesias by valproate could most simply be explained by an alteration of L-dopa absorption or metabolism. However, peak plasma concentrations and plasma half life of L-dopa were not influenced by valproate. As the exacerbation of "on-off" phenomenon tended to occur when the patients were exhibiting mild encephalopathic signs, it may represent some nonspecific interaction of valproate and dopaminergic agents.

The final question is whether valproate, as administered in this study, facilitated central GABAergic transmission. The absence of changes in CSF GABA in valproate treated patients would indicate that it did not have any consistent action on GABAergic mechanisms. Measurement of CSF GABA is difficult and these results should be viewed with caution, especially since these values are lower than other published values for CSF GABA in Parkinson's disease [Enna et al., 1977; Huizinga et al., 1978]. However, Neophytides et al. (1978), using a high pressure liquid chromotography assay, also found no change in CSF GABA in patients treated with valproate. Furthermore, animal studies suggest that elevation of brain GABA occurs only after very

large doses of valproate [Sawaya et al., 1975; Anzelzark et al., 1976]. Of course, it remains unproven that lumbar CSF GABA concentration reflects spinal or supraspinal GABAergic neurotransmission.

In conclusion, valproate, in doses effective in epilepsy, is of no benefit in the treatment of Parkinson's disease or the "on-off" phenomenon. However, as enhancement of central GABAergic neurotransmission by valproate is unproven in man, no inferences can be made of the role GABAergic systems may have in the symptomatology of Parkinson's disease or L-dopa induced dyskinesias.

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