CSF studies on the relationship between dopamine and 5-hydroxytryptamine in Parkinsonism and other movement disorders

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SUMMARY In Parkinson's disease, the concentration of homovanillic acid (HVA) was reduced in lumbar CSF from patients with idiopathic Parkinsonism ($n=54$, $P<0.05$) and post-encephalitic Parkinsonism ($n=19$, $P<0.01$). The reduction in the concentrations of 5-hydroxyindolylacetic acid (5-HIAA) was not significant, and there was no alteration in the levels of 4-hydroxy-3-methoxyphenylethylene glycol (MHPG). Treatment with L-dopa increased the concentration of HVA in the CSF ($P<0.05$) but had no effect on the levels of 5-HIAA and MHPG. Carbidopa given in combination with L-dopa produced similar CSF concentrations of dopa as did L-dopa alone but caused less than half the rise in HVA. Fourteen patients who became functionally independent on treatment with L-dopa had higher 5-HIAA levels than 23 patients who showed no such improvement ($P<0.001$), suggesting that intact 5-hydroxytryptamine neurones may be important in the therapeutic response to L-dopa. In a variety of movement disorders, the levels of HVA, 5-HIAA, and MHPG were not significantly different from age-matched controls. Treatment with tetrabenazine did not significantly alter the metabolite levels in patients in whom it produced either improvement, or side effects.

Numerous studies have shown that the concentration of homovanillic acid (HVA), the major metabolite of dopamine in the brain, is decreased in CSF in Parkinsonism (Johansson and Roos, 1965, 1974; Pullar *et al.*, 1970; Chase and Ng, 1972; Rinne *et al.*, 1973). However, the concentration of 5-hydroxyindolylacetic acid (5-HIAA), the major metabolite of 5-hydroxytryptamine (5-HT), has been more variably reported to be normal (Pullar *et al.*, 1970; Parkes *et al.*, 1971) or decreased (Gumpert *et al.*, 1973). The relationship between the CSF concentrations of HVA and 5-HIAA and the subsequent clinical response to L-dopa could indicate the importance of dopamine and 5-HT in Parkinsonism. This relationship has been examined in the present study. The role of noradrena-

line in Parkinsonism is uncertain. The concentration of the major noradrenaline metabolite in brain, 4-hydroxy-3-methoxyphenylethylene glycol (MHPG) has, therefore, been measured in CSF from Parkinsonism patients before and after treatment with L-dopa and L-dopa in combination with the peripheral decarboxylase inhibitor, carbidopa.

The levels of the monoamine metabolites in CSF of patients with various involuntary movement disorders are reported. We have also studied the effect of tetrabenazine in these patients.

Patients and methods

LUMBAR PUNCTURE PROCEDURE AND BIOCHEMICAL ESTIMATIONS

All lumbar punctures (LPs) were performed at midday in patients who had been recumbent and fasting for at least 12 hours. Patients who were receiving phenothiazines, antihypertensive drugs, salicylates, antidepressants, and barbiturates were excluded. The first 5 ml of CSF was taken, as described by Davidson *et al.* (1977), into glass

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Accepted 9 August 1977

test tubes for metabolite analysis and was immediately frozen and stored at -20°C until the estimations were carried out.

HVA, 5-HIAA, and dopa were estimated fluorimetrically (Guldberg and Yates, 1968; Davidson *et al.*, 1977). 'Total' 4-hydroxy-3-methoxyphenylethylene glycol (MHPG) was measured by gas-liquid chromatography after incubation with a sulphatase preparation to hydrolyse MHPG sulphate (Davidson *et al.*, 1977).

CONTROLS

Fifteen patients with migraine, tension headache, diabetic neuropathy, ocular myopathy, or lumbar disc disease who were having LPs as part of their routine clinical investigation, as well as three healthy physicians, served as control subjects. None of the patients with lumbar disc disease showed evidence of restricted CSF flow to the lumbar sac. Of these 18 controls, five, with a mean age of 61 ± 8 years, were used as controls for the Parkinsonism patients who had a mean age of 62 ± 8 years. The 18 controls were divided into three age groups which corresponded to the ages of (1) the senile chorea patients, (2) the Huntington's chorea and spasmodic torticollis patients, and (3) the congenital choreoathetosis, dystonia musculorum deformans, and Wilson's disease patients, respectively.

PATIENTS

Parkinsonism Fifty-six patients suffering from the idiopathic form of the disease and 20 patients with postencephalitic Parkinsonism were studied. Samples of lumbar CSF were taken from these

patients before treatment with L-dopa, or L-dopa plus carbidopa. Fifteen patients who were receiving anticholinergic drugs were maintained on these drugs throughout the whole investigation. Clinical evaluations were made by a neurologist who was unaware of the CSF results. The severity of hypokinesia, rigidity, and tremor were respectively graded as none, mild, moderate, severe. To 73 of the Parkinsonism patients L-dopa, 0.5 g daily, was introduced and increased gradually over at least two weeks. When an optimal dose was reached the LP was repeated in 37 patients. The response to L-dopa was assessed as intolerant—that is, unacceptable side effects; unresponsive—no observable improvement; grade 1—observable but functionally insignificant improvement; grade 2—functional improvement but remaining dependent; grade 3—good response, functionally independent. Nine patients were given L-dopa 625 mg daily, in combination with carbidopa, 62.5 mg daily, for two to four weeks before a further LP was performed.

Involuntary movement disorders Lumbar punctures were performed on 32 patients with various movement disorders (Table 1). Eleven patients had a repeat LP three weeks later when established on tetrabenazine in the optimal dose for reducing involuntary movements without unacceptable side effects.

Results

The concentrations of HVA, 5-HIAA, and MHPG in lumbar CSF in Parkinsonism are shown in Tables 2 and 3 and the results for involuntary

Table 1 Concentrations of HVA, 5-HIAA, and MHPG in lumbar CSF from patients with various involuntary movement disorders, and the effect of tetrabenazine

		Mean $\pm$ SD (n)		
		Age (yr)	ng/ml	
			HVA	5-HIAA
				MHPG
Disorder				
Control		66 $\pm$ 4(4)	40 $\pm$ 19(3)	18 $\pm$ 3(3)
Senile chorea		70 $\pm$ 5(7)	67 $\pm$ 27(7)	26 $\pm$ 10(7)
Control		47 $\pm$ 5(6)	31 $\pm$ 13(5)	21 $\pm$ 10(7)
Huntington's chorea		49 $\pm$ 13(13)	31 $\pm$ 17(13)	20 $\pm$ 13(13)
Spasmodic torticollis		50 $\pm$ 7(4)	48 $\pm$ 12(4)	12 $\pm$ 8(4)
Control		31 $\pm$ 5(8)	23 $\pm$ 7(8)	17 $\pm$ 7(8)
Congenital choreoathetosis		28 $\pm$ 7(4)	25 $\pm$ 6(3)	9 $\pm$ 3(3)
Dystonia musculorum deformans		25 $\pm$ 1(2)	17 $\pm$ 18(2)	15 $\pm$ 12(2)
Wilson's disease		16 $\pm$ 22(2)	21 $\pm$ 35(2)	4 $\pm$ 11(2)
Effect of tetrabenazine				
Less than 100mg/day	Pretreatment		41 $\pm$ 18(5)	16 $\pm$ 4(5)
	Treatment		42 $\pm$ 16(5)	19 $\pm$ 6(5)
More than 100mg/day	Pretreatment		41 $\pm$ 18(6)	14 $\pm$ 7(4)
	Treatment		26 $\pm$ 22(6)	9 $\pm$ 4(4)

— indicates no estimate

Table 2 Concentrations of HVA, 5-HIAA, and MHPG in lumbar CSF in idiopathic and postencephalitic Parkinsonism before and after treatment with L-dopa alone or in combination with carbidopa

Group	Mean $\pm$ SD (n)	ng/ml			
		HVA	5-HIAA	MHPG	DOPA
	Age (yr)				
Control	61 $\pm$ 8(5)	38 $\pm$ 19(5)	20 $\pm$ 12(5)	7 $\pm$ 3(3)	
Parkinson's disease					
Before L-dopa treatment					
Idiopathic	63 $\pm$ 8(56)	22 $\pm$ 14*(54)	14 $\pm$ 9(55)	9 $\pm$ 5(18)	
Post-encephalitic	58 $\pm$ 5(20)	15 $\pm$ 10†(19)	13 $\pm$ 7(19)	7 $\pm$ 3(7)	
All	62 $\pm$ 8(76)	20 $\pm$ 30(73)	14 $\pm$ 8(74)	8 $\pm$ 5(25)	
After L-dopa treatment					
L-dopa alone		198 $\pm$ 169*(37)	13 $\pm$ 10(37)	10 $\pm$ 5(7)	112 $\pm$ 57(7)
L-dopa + carbidopa		62 $\pm$ 65(9)	10 $\pm$ 8(9)	9 $\pm$ 5(4)	95 $\pm$ 20(8)

* $P < 0.05$ } compared with controls.† $P < 0.01$ }Other values not significantly different ($P > 0.05$) from controls.

Table 3 Concentrations of HVA and 5-HIAA in lumbar CSF from patients with Parkinsonism in relation to their subsequent response to L-dopa therapy

Response to treatment with L-dopa		Mean $\pm$ SD (n)	
		ng/ml	
		HVA	5-HIAA
Intolerant		19 $\pm$ 11(11)	19 $\pm$ 4(11)
No response		28 $\pm$ 14(4)	13 $\pm$ 6(4)
Least response	—grade 1 improvement (mean daily dose 3.0 g)	19 $\pm$ 11(22)	11 $\pm$ 6†(23)
Intermediate response	—grade 2 improvement (mean daily dose 2.6 g)	23 $\pm$ 17(22)	14 $\pm$ 7*(23)
Best response	—grade 3 improvement (mean daily dose 2.7 g)	14 $\pm$ 11(14)	20 $\pm$ 8(14)

Description of grade 1, 2, and 3 responses is given in Methods.

* $P < 0.05$ versus grade 3† $P < 0.001$ versus grade 3

movement disorders in Table 1. All statistical comparisons were made using Student's *t* test and *P* values of ≤ 0.05 were taken to indicate a significant difference.

PARKINSONISM

The HVA concentrations were lower in patients with idiopathic Parkinson's disease than in controls ($P < 0.05$), and were lower still in patients suffering from postencephalitic Parkinsonism ($P < 0.01$). The concentrations of 5-HIAA and MHPG in both forms of Parkinsonism were not significantly different from control values (Table 2). There was no correlation of duration of Parkinsonism, severity of hypokinesia, rigidity, or tremor with HVA, 5-HIAA, or MHPG concentrations. The concentrations of metabolites in CSF from patients receiving anticholinergic drugs did not differ from the concentrations in patients not given anticholinergics. There was no difference between the proportion of patients receiving anticholinergics in the patient groups shown in Table 2.

Treatment with L-dopa produced an increase ($P < 0.05$) in HVA which was greater than the increase, which did not reach significance, in HVA produced by treatment with L-dopa in combination with carbidopa. The concentrations of dopa in the CSF were similar after both treatments. Administration of L-dopa by itself or with carbidopa had no effect on the concentrations of 5-HIAA or MHPG in the CSF (Table 2). In patients given L-dopa alone, the increase in the concentration of HA in the CSF correlated with the dose of L-dopa ($r = 0.54$, $P < 0.05$) but not with the therapeutic response.

Patients who showed the best (grade 3) response to treatment with L-dopa had higher pretreatment 5-HIAA concentrations than patients with an intermediate (grade 2) response and patients showing the least (grade 1) response (Table 3). The concentration of 5-HIAA in patients showing no response was markedly less than in patients with the best response, but this difference did not reach significance probably because of the small number

of patients in the former group. The pretreatment concentrations of HVA, on the other hand, tended to be lower in patients with the best response to L-dopa than in patients with an intermediate response, patients with the least response, and patients showing no response. Within each response group, there was no difference between the concentrations of HVA and 5-HIAA in CSF from patients not receiving anticholinergics and from patients on anticholinergics. The number in some of these groups was, however, only two or three.

INVOLUNTARY MOVEMENT DISORDERS

There were marked differences in HVA and 5-HIAA concentrations in different groups of disorders, but no group was significantly different from age-matched controls (Table 1). Tetrabenazine did not significantly alter the concentrations of HVA, 5-HIAA, and MHPG in the entire group, although there was some reduction in patients receiving doses of 100 mg or more per day.

Discussion

CONTROLS

Selection of an appropriate control group is difficult since abnormalities of monoamine metabolites have been reported in a variety of neurological disorders. In our study the controls comprised three healthy physicians and a miscellaneous group of patients without major disorders of the CNS who had migraine, tension headaches, neuropathies, and lumbar disc disease. The heterogeneity of this group may contribute to the wide variation in results. Age-matched controls were used for the patients groups since we found, in common with others (Gottfries *et al.*, 1971; Bowers, 1972), that the concentrations of HVA and 5-HIAA increased with age. Exercise increases HVA and 5-HIAA concentrations in the CSF (Post *et al.*, 1973), and failure to enforce recumbency before lumbar puncture results in higher HVA levels (Davidson *et al.*, 1977). Patients were, therefore, kept recumbent for 12 hours before puncture. Withdrawal of a standard CSF volume of 5 ml should avoid variations in metabolite levels related to the volume of CSF removed (Jakupčević *et al.*, 1977).

INVOLUNTARY MOVEMENT DISORDERS

The concentrations of the amine metabolites in different movement disorders were not significantly different from age-matched controls. The observation that tetrabenazine, a synthetic benzoquinolizine derivative which depletes central monoamines, did not significantly alter HVA and

5-HIAA concentrations in CSF, despite clear clinical effects suggests that these estimations are of limited use in the study of involuntary movement disorders.

PARKINSONISM

Concentrations of HVA Our findings confirm numerous previous reports that HVA concentrations in lumbar CSF are low in Parkinsonism (Johansson and Roos, 1965; Pullar *et al.*, 1970; Rinne *et al.*, 1973), and are lower in postencephalitic disease (Table 2). As the concentrations of HVA overlap with the normal range such estimations are of little value in the diagnosis of Parkinsonism. There was no correlation between the concentrations of HVA in CSF and the severity of hypokinesia, although in postmortem studies the reduction in HVA and dopamine in the caudate nucleus has been shown to be related to the degree of hypokinesia (Bernheimer *et al.*, 1973). The present study confirms others (Parkes *et al.*, 1971; Gumpert *et al.*, 1973) in that there was no correlation between the concentrations of HVA and 5-HIAA and the severity of the clinical features of hypokinesia, rigidity, or tremor.

The HVA concentrations in CSF of patients with the best response to L-dopa were slightly but not significantly lower than in CSF from patients with a minimal response (Table 3). A negative correlation of pretreatment HVA concentration with response to L-dopa has been found by Lakke *et al.* (1971) using probenecid, and by Jéquier and Dufresne (1972). However, Chase and Ng (1971), Weiner and Klawans (1973), and Granerus *et al.* (1974), did not find CSF HVA a useful predictor of response to L-dopa. The small group of four Parkinsonism patients who had normal pretreatment HVA concentrations (Table 3), and who showed no clinical improvement and no side effects after large doses of L-dopa is a small, interesting group who may be metabolically different from other patients suffering from Parkinsonism. Our findings of a marked increase in HVA after L-dopa therapy (Table 2), confirms well-established observations (Godwin-Austen *et al.*, 1971). The increase correlated with the dose of L-dopa but not with the therapeutic response. A smaller increase in the HVA concentration, unaccompanied by a change in the CSF dopa concentration, was found when L-dopa was given in combination with carbidopa. A possible explanation for this observation is that carbidopa, which inhibits peripheral dopa decarboxylase, may inhibit dopa decarboxylase in the cerebral blood vessels.

Concentrations of MHPG The concentration of MHPG in the CSF of idiopathic and postencepha-

litic Parkinsonism patients did not differ from controls, despite the decreased noradrenaline concentration found in postmortem samples of caudate nucleus and hypothalamus taken from postencephalitic Parkinsonism patients (Ehringer and Hornykiewicz, 1960). Although L-dopa is a potential precursor of MHPG, loading with the amino acid did not alter the concentration of MHPG in the CSF. Similar results have been reported by Chase *et al.* (1973) and Wilk (1976). It is uncertain whether this arises from the constancy of brain noradrenaline turnover or the inadequacy of CSF estimation of MHPG as an index of noradrenaline turnover. The rapid diffusion of MHPG from CSF to blood (Wolfson and Escriva, 1976) supports the latter explanation.

Concentrations of 5-HIAA In agreement with the results of Pullar *et al.* (1970) and Parkes *et al.* (1971), but not those of Rinne *et al.* (1973) and Gumpert *et al.* (1973), we did not find significantly reduced concentrations of 5-HIAA in CSF despite the decreased 5-HT concentration found in the basal ganglia of patients suffering from Parkinsonism (Bernheimer *et al.*, 1961). Chase and Ng (1971, 1972), on the basis of probenecid loading of Parkinsonism patients, have suggested that the turnover rates of both dopamine and 5-HT are reduced in Parkinsonism. Chase (1974) suggested that the reduced turnover of 5-HT reflected a diminished function of 5-HT neurones which was secondary to a primary reduction in dopaminergic activity. If this were so, L-dopa treatment, which should increase the activity of dopaminergic neurones, might be expected to increase CSF 5-HIAA. However, under these conditions we found no change in 5-HIAA; Van Woert and Bowers (1970) found a significant reduction in 5-HIAA after the administration of L-dopa.

The pretreatment 5-HIAA concentrations are of particular interest when related to the therapeutic response to L-dopa (Table 3). Good responders had significantly higher concentrations of 5-HIAA than patients with an intermediate or poor response. The small group of patients showing no response to L-dopa also had lower 5-HIAA concentrations than the good responders, although the difference because of the small number did not reach statistical significance. There has been much discussion on the possibility that L-dopa treatment might modify 5-HT metabolism and that this change may be involved in the long-term effects of L-dopa therapy, but there has been little evidence that pretreatment 5-HT turnover might be an important determinant of therapeutic response to L-dopa. Investigations into the use of amine metabolite levels in the CSF as predictors of re-

sponse to L-dopa have concentrated on HVA (Chase and Ng, 1971; Lakke *et al.*, 1971; Jéquier and Dufresne, 1972; Weiner and Klawans, 1973; Granerus *et al.*, 1974). Gumpert *et al.* (1973), however, found a tendency for patients responding well to L-dopa to have high 5-HIAA concentrations. Our results suggest that the presence of intact 5-HT neurones may be important in the therapeutic response to L-dopa. Dopa may be decarboxylated in 5-HT neurones in man, as suggested by the accumulation of dopamine which occurs in 5-HT neurones in the rat after administration of dopa and a decarboxylase inhibitor (Butcher *et al.*, 1970). An alternative explanation is that the reduced 5-HT turnover in Parkinsonism (Chase and Ng, 1971, 1972) is related to an impairment of 5-HT neurones, possibly the raphe-caudate fibres (Cools and Janssen, 1974), which is not secondary to a reduction in dopaminergic activity. Patients with very low CSF 5-HIAA concentrations, who did not respond well to L-dopa, might represent a group in whom loss of 5-HT function is more important than loss of dopaminergic function. These particular patients might respond to treatment with 5-hydroxytryptophan despite evidence that this drug worsens Parkinsonism (Chase, 1970).

We are most grateful to Dr G. W. Ashcroft and Dr T. B. B. Crawford for discussion and advice, and to Mrs Nancy Kinloch and Miss Eileen Walker for careful technical assistance.

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