Interactions between central monoaminergic systems: dopamine–serotonin

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SUMMARY Concentration of dopamine and serotonin metabolites (HVA and 5-HIAA) in the CSF was evaluated before and after pharmacological treatment in 19 patients with different neuropsychiatric diseases. In every case a reciprocal modification of the two metabolites occurred after treatment. The result supports the hypothesis of a functional balance between the monoaminergic systems in the central nervous system.

Interactions between systems involving different neurotransmitters in the CNS have been indicated by pharmacoclinical, histochemical, and neurophysiological techniques (Garattini *et al.*, 1978 for review).

A close relationship has been established, for example, between the dopaminergic and the cholinergic system, and their reciprocal connections, both anatomical and functional, explain how an impairment of one system can enhance the activity of the other (Landinsky *et al.*, 1978). This phenomenon has a relevant clinical application in the treatment of extrapyramidal disorders. Both dopaminergic stimulants and anticholinergic drugs are widely used in Parkinson's disease, whereas in Huntington's chorea, which is commonly regarded as the biochemical counterpart of Parkinsonism, dopamine blocking agents are often successfully employed as well as acetylcholinesterase inhibitors (Barbeau, 1973).

On the other hand, evidence for interaction between the dopaminergic and the serotonergic systems is unsatisfactory. The two systems display a functional antagonism on common effectors (Hornykiewicz, 1976; Martin *et al.*, 1977), and some neuropharmacological treatments can affect both systems (Pradhan and Bose, 1978). However, the available evidence only suggests that the functional activity of each system may somehow be modified by the other (Green *et al.*, 1976; Heal *et al.*, 1976; Erickson, 1978; Pradhan and Bose, 1978).

Our aim in this study was to investigate the interaction between the dopaminergic and the serotonergic system, by evaluating the CSF concentration of the main monoamine metabolites before and after a pharmacological treatment.

Patients and methods

The study was performed on 19 patients (11 men and eight women), aged between 18 and 65 years, with a mean age of 42.7 years. In each case the diagnosis was based on the patient's family and personal history, as well as on neurological examination and psychiatric interview. According to the classification of mental disorders suggested by the American Psychiatric Association (Stengel, 1960), the patients were affected by the following diseases: Huntington's chorea (APA item 19.1), nine cases; manic-depressive reaction, depressed type (item 21.1), eight cases (hereafter referred to as endogenous depression); acute schizophrenic reaction, undifferentiated type (item 22.4), one case; (mild) chronic schizophrenic reaction, paranoid type (item 22.3) associated with tardive dyskinesia, one case (Table 1). All reported cases were inpatients at the Neurological Clinic of the University of Genoa, and gave their informed consent to the procedures.

On admission any pharmacological treatment was discontinued (patients were given only 30 mg flurazepam and 2.5 mg lorazepam as evening medication) and at least 15 days "wash-out" period was observed in every case, until clinical conditions became stable. The first CSF sample (before treatment) was drawn at the end of the

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wash-out period, by lumbar puncture performed at the L2–L3 intervertebral space, with the patient lying on his right side, after he had been resting in bed for at least 10 hours and had not been given any drugs for 12 hours. The puncture was performed at about 9 am. A pharmacological treatment was then started and the drugs and doses for every patient are given in detail in Table 1. As soon as some improvement from the baseline condition was noted a second CSF sample (after treatment) was drawn using the same procedures as before.

Concentrations of HVA and 5-HIAA were evaluated in the first 4 ml of each sample, according to the technique of Korf *et al.* (1971a, b).

Results

Levels of HVA and 5-HIAA in the CSF before and after treatment are shown in detail in Table 1. The results obtained from 17 of the 19 patients (those with Huntington's chorea and depression, since cases 2 and 3 were excluded from the computations, being single cases) were evaluated by unweighted means analysis of variance with nested factors (treatment-diagnosis) and repeated measures. A summary of the statistical analysis is given in Table 2. The general impression, that the changes of each metabolite show no unequivocal behaviour in the whole group of patients, was confirmed. However, there was a significant interaction between different treatments (nested within diagnoses) and changes of either metabolite (HVA: F (df 2,13)=19.59, $P<0.001$; 5-HIAA: F (df 2,13)

=12.06, $P<0.005$). Such an outcome allows individual comparisons between "before" and "after" concentrations within single treatment-diagnosis combinations (Table 2).

The most remarkable result, however, was a tendency to reciprocal modifications of HVA and 5-HIAA—that is, a rise of HVA corresponded to a drop of 5-HIAA and vice versa. This is confirmed by the significance of the correlation coefficient between the changes in concentration of the two monoamine metabolites ($r=-0.67$; $P<0.005$).

Discussion

The determination of the CSF concentration of a single monoamine metabolite can provide only indirect and unreliable information on the functional state of the system under investigation (Gessa and Gessa, 1975). It is conceivable, however, that a rise in HVA indicates an increase of dopamine turnover, probably deriving from a higher discharge rate of dopamine producing neurones, and that a decrease of dopamine turnover may be revealed by a drop of HVA in the CSF (Gessa and Gessa, 1975). Similar arguments can reasonably fit the behaviour of 5-HIAA as an index of serotonin metabolism.

A reason for the different behaviour associated with single treatments may be sought in the probable mechanism of action of each drug. Chlorimipramine blocks the re-uptake of serotonin, whereas it displays no direct influence on the dopaminergic system. A remarkable serotonergic

Table 1 Summary of results

Case	Age (yr)	Sex	Diagnosis	Treatment	HVA (ng/ml)		5-HIAA (ng/ml)	
					Before	After	Before	After
1	48	M	Endogenous depression	Chlorimipramine (50 mg/day iv)	11	31	21	11
2	35	F	Acute schizophrenia	Haloperidol (4 mg/day orally)	14	19	18	8
3	52	F	Chronic schizophrenia with tardive dyskinesia	Trazodone (400 mg/day iv)	17	15	15	16
4	38	F	Endogenous depression	Trazodone (400 mg/day iv)	123	54	54	60
5	27	M	Endogenous depression	Chlorimipramine (50 mg/day iv)	10	35	33	26
6	51	F	Endogenous depression	Chlorimipramine (50 mg/day iv)	14	41	9	6
7	34	M	Endogenous depression	Trazodone (400 mg/day iv)	23	14	13	15
8	18	F	Endogenous depression	Imipramine (100 mg/day orally)	14	27	28	25
				Amitriptyline (100 mg/day orally)				
9	34	M	Endogenous depression	Trazodone (400 mg/day orally)	100	21	20	60
10	29	M	Endogenous depression	Imipramine (100 mg/day orally)	54	105	30	13
				Amitriptyline (100 mg/day orally)				
11	60	M	Huntington's chorea	Fluphenazine (100 mg/day orally)	12	43	16	4
12	62	M	Huntington's chorea	Baclofen (100 mg/day orally)	86	34	21	62
13	24	M	Huntington's chorea	Baclofen (100 mg/day orally)	166	69	3	5
14	48	F	Huntington's chorea	Baclofen (100 mg/day orally)	97	75	4	10
15	47	M	Huntington's chorea	Fluphenazine (100 mg/day orally)	54	130	57	15
16	65	M	Huntington's chorea	Baclofen (100 mg/day orally)	93	54	30	80
17	53	F	Huntington's chorea	Baclofen (100 mg/day orally)	70	57	13	18
18	49	F	Huntington's chorea	Fluphenazine (100 mg/day orally)	10	30	100	20
19	38	M	Huntington's chorea	Fluphenazine (100 mg/day orally)	10	50	60	10

Table 2 Analysis of variance of monoamine metabolite CSF concentrations before and after pharmacological treatment

Source of variation	df	HVA		5-HIAA	
		SS	F	SS	F
Between subjects	16	38219.64		9445.16	
Diagnosis (A)	1	2140.38	0.98	14.28	0.02
Treatment (B) under (A)	2	7693.22	1.76	1609.47	1.34
Error between	13	28386.04		7821.41	
Within subjects	17	19315.50		8595.00	
Change before-after (C)	1	398.07	1.11	150.42	0.71
Interaction A × C	1	252.41	0.71	560.46	2.64
Interaction B(A) × C	2	14014.93	19.59†	5123.63	12.06†
Error within	13	4650.09		2760.48	
Total	33	57535.14		18040.16	

A=diagnosis (A1: Huntington's chorea; A2: Endogenous depression)
B=treatment (B1: Phenothiazines; B2: Baclofen; B3: Tricyclic antidepressants; B4: Trazodone)
C=change before-after (C1: Before treatment; C2: after treatment)

	HVA		5-HIAA	
	Change	F	Change	F
Phenothiazines (Huntington's chorea)	+41.75	9.91*	-46.0	20.27†
Baclofen (Huntington's chorea)	-44.6	11.31*	+20.8	4.14
Tricyclic antidepressants (Endogenous depression)	+27.2	4.21	- 8.0	0.61
Trazodone (Endogenous depression)	-52.33	15.57†	+16.0	2.45

* = $P < 0.01$

† = $P < 0.005$

‡ = $P < 0.001$

action is shared also by amitriptyline and imipramine, which probably have no effect at all on the dopaminergic system (Goodwin *et al.*, 1978). The drop of CSF 5-HIAA after treatment with tricyclic antidepressants substantiates the hypothesis of their serotonergic action (Goodwin and Post, 1975).

The effect of trazodone on the central monoaminergic systems is at present rather uncertain. Dopamine stimulating properties were previously demonstrated by Garattini (1974) and Hontela and Nair (1975), but at very high doses the drug has been reported to have a blocking action on serotonin re-uptake quite similar to that of chlorimipramine (for reference see Silvestrini, 1978). The drop of HVA in our cases is consistent with the dopamine stimulating properties (Roos, 1969; Corrodi *et al.*, 1972; Garattini *et al.*, 1972), and we were not able to confirm the serotonin re-uptake blocking properties since a rise in 5-HIAA occurred.

Fluphenazine, like other phenothiazines, reveals its effect of blocking dopaminergic receptors by increasing CSF HVA concentration (Goodwin and Post, 1975).

Baclofen, which is reported to decrease the rate of discharge of dopamine producing neurones

(Carlsson *et al.*, 1977), actually causes a drop in HVA, as described in a previous report (Roccatali *et al.*, 1978).

In every patient in this study, reciprocal changes of HVA and 5-HIAA occurred after pharmacological treatment, indicating that an increase of dopamine turnover is associated with a decrease of serotonin turnover and vice versa.

In view of these data, the observation that response to treatment was never limited to a single monoaminergic system but always involved both, makes it conceivable that a drug-induced "primary" change in either system causes a new functional adjustment of the other, as a result of a real interaction.

These data are consistent with some previous reports (Erickson, 1978; Pradhan and Bose, 1978). Although they need further confirmation (since, for instance, we did not use the probenecid technique), they disclose new prospects for study. Some current opinions on the pathogenesis of extrapyramidal disorders and psychoses, inferred mainly from the response to different drugs, ascribe these diseases to the impairment of a single monoaminergic system. They should be revised after consideration of the kind of balance shown by our studies.

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