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Clinical and Biochemical Responses to Therapy in Alzheimer's Disease and Multi-Infarct Dementia

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Summary. Memory performance, central monoaminergic function and sympathetic nerve activity were studied in patients with dementia of the Alzheimer type (DAT) or with multi-infarct dementia before and after 4 weeks with single or combined drug therapy (choline-piracetam). Analysis of the levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), 3-methoxy-4-hydroxyphenylacetic acid (HVA) and 5-hydroxyindolacetic acid in the cerebrospinal fluid (CSF) and also in urine (plus 3-methoxy-4-hydroxy mandelic acid) showed that the basal values of HVA in the CSF and urine were lower in the more severely demented compared with the mildly demented subjects in both groups. The combined drug treatment resulted in a statistically significant increase in the MHPG level in the CSF of mildly demented subjects of the DAT group, while it seemed not to influence the other monoamine metabolites. The sympathetic nerve activity was similar in both patient groups and was unchanged after therapy. These findings suggest a dopaminergic deficit in advanced stages of the disease and a possible enhancement of the central noradrenergic output with therapy. No effects of therapy on memory performance or correlations between monoamine levels and memory test scores were noted.

Key words: Alzheimer's disease – Multi-infarct dementia – Monoamines – Sympathetic nerve activity – Treatment response

Introduction

Precursor therapy with choline or lecithin in dementia of the Alzheimer type (DAT) has failed to demonstrate a consistent pattern of clinically significant effects (Ferris et al. 1979; Pomara et al. 1981; Bartus et al. 1982; Brinkman et al. 1982a, b; Etienne et al. 1981). Similarly, treatment with a "metabolic enhancer" such as piracetam alone seemed not to improve the cognitive symptoms of DAT (Reisberg et al. 1981).

Studies in rats have shown (Giurgea et al. 1986) that piracetam significantly increased levels of 3–4 dihydroxyphenylacetic acid, of homovanillic acid (HVA) and of 3-methoxy-4-hydroxyphenylglycol (MHPG) in some brain areas. These changes were attributed more to an accelerated turnover of brain catecholamines by release of the transmitter than to a receptor blockade.

Furthermore, combined treatment with piracetam plus choline seemed to improve learning tasks in aged rats (Bartus et al. 1981) and in mice (Platel et al. 1984) more than treatment with either agent alone, while another study (Ennaceur and Delacour 1987) reported no beneficial effects of combined administration in rats.

These responses in animals raise the possibility that drugs which enhance brain metabolism might potentiate the effects of cholinergic precursors and have a synergistic effect on memory retention. Thus some clinicians (Friedman et al. 1981; Ferris et al. 1982; Smith et al. 1984; Kazdova et al. 1984) administered the acetylcholine precursors in combination with piracetam in DAT, and some of these investigators claimed that the combination had a positive effect.

Few studies have dealt with the influence of drugs on the activities of the central monoaminergic systems (see review by Gottfries 1987); these are considered abnormal (Gottfries et al. 1985; Arai et al. 1984; Gottfries 1983; Rossor and Iversen 1986; Palmer et al. 1984; Bareggi et al. 1982; Tyrrell et al. 1987).

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Stirling Meyer et al. (1977) indicated some increase of HVA and 5-hydroxy-indolacetic acid (5-HIAA) levels in the cerebrospinal fluid (CSF) after administration of a preparation consisting of tyrosine, 5-hydroxytryptophan and carbidopa to patients with Alzheimer's or multi-infarct dementia (MID). Adolfsson et al. (1978) observed an increase in HVA levels, a trend towards lower 5-HIAA concentrations and slightly higher MHPG concentrations in comparison to baseline values in the CSF of DAT patients treated with levodopa.

Argentiero and Tavolato (1980) noted that treatment with phospholipids produced a significant increase in HVA and 5-HIAA CSF levels in patients with presenile Alzheimer dementia.

Other authors have analysed the course of MHPG, HVA and 5-HIAA in DAT after treatment with ergoloid mesylate (Seeldrayers et al. 1985) or with zimelidine (Cutler et al. 1985).

On the basis of the improvement reported with drug combinations and considering the possible presence of multiple neurotransmitter dysfunction in DAT, we studied the influence of cytidinediphosphate phosphatidylcholine, a cholinergic precursor, and piracetam, a metabolic enhancer, on memory and on the activity of the monoaminergic systems in a group of subjects affected by DAT or MID. The two drugs were administered singly or in combination.

The choice of patient groups with two rather different conditions, DAT and MID, made it possible to compare responses in subjects whose loss of cognitive functions was underlain by different mechanisms and who may have suffered different types of damage to the different neurotransmitter systems, as has been suggested by recent studies (see Wester et al. 1988).

We analysed:

1. Memory functions, by tests that specifically explored: (a) primary memory, (b) acquisition into secondary memory and (c) forgetting from secondary memory

2. The central monoamine metabolism, measuring the neurotransmitter metabolites MHPG, HVA and 5-HIAA in the CSF (Raskind et al. 1984; Redmond et al. 1986)

3. The overall monoamine metabolism, analysing the excretion of the same three metabolites and also 3-methoxy-4-hydroxymandelic acid (VMA) in 24-h urine (Vandel et al. 1985; Kopin 1985; Siever et al. 1986)

4. The sympathetic nerve activity, by checking the changes of plasma noradrenaline (NA) level, as well as blood pressure (BP) and pulse rate (PR) in response to orthostatic challenge (Lake et al. 1976).

Comparison of these parameters was made before and after treatment, between the DAT and MID patient groups, and also within the two groups between subgroups of subjects classified on the basis of clinical severity.

Some preliminary data have been previously published (Corona et al. 1983).

Subjects and Methods

Subjects. Twenty-six female inpatients with DAT and 26 female inpatients with MID were initially included in this study.

Clinical diagnosis of MID or DAT was established by DSM III criteria and Hachinski et al.'s (1975) ischaemic score. Discordant cases (comparing DSM III and Hachinski's score) and patients with an ischaemic score = 6 were considered "mixed" and excluded from the present investigation.

Patients and/or their relatives were informed about the aim and the nature of the study, and verbal consent was obtained before admission to the study.

All subjects were hospitalized in the Neurological Department in Pavia. All fulfilled DSM III criteria for dementia, had a score of at least 0.5 on Hughes et al. (1982) CDR scale and had a deterioration score of at least 20% on the Wechsler-Bellevue scale. Patients with a history of schizophrenia or who had been treated for long periods with neuroleptic or antidepressive drugs were excluded.

Patients in whom dementia was part of another neurological disorder, such as Parkinson's disease, or with evidence of dementia of endocrine, metabolic or toxic origin were not included. Clinical severity was established by means of the CDR scale. Owing to the relatively limited number of subjects only two stages (I = CDR 0.5 and 1; II = CDR 2 and 3) were considered. After 4 weeks of therapy, only 21 subjects with DAT (65.9 ± 8.7 years, mean $\pm$ SD; range 45–77) and 16 with MID (69.1 ± 4.8 years, mean $\pm$ SD; range 53–85) completed all tests and were consequently evaluated in this study. There was no statistically significant difference between the mean ages of the mildly demented – CDR I (DAT $n = 13$: 68.6 ± 7.3 years; MID $n = 12$: 67.6 ± 5.2 years) – and the severely demented groups – CDR II (DAT $n = 8$: 61.5 ± 9.3 years; MID $n = 4$: 71.0 ± 1.3 years).

The subjects were randomly allocated to single or combined drug treatment.

Methods. All subjects were given a standardized hospital diet with restriction of food and beverages known to affect catecholamine metabolism for at least 24 h before sample collection. After a wash-out period of at least 7 days the patients received CDP-choline (1 g/3/die i.m.) and piracetam (3 g/2/die i.v.) alone or combined for 30 days.

Before the beginning of the treatment (day-2) 24-h urine was collected. A volume of 0.8001 and a creatinine value of 15 mg/kg per 24 h were regarded as minimum values for the acceptability of urine collection. Blood samples for NA determination were taken the next day (day-1) at 8.00 a.m. after overnight fasting, following the indications of Lake et al. (1976). Concurrent blood pressure and pulse rate at rest and after orthostatic challenge were determined by mercury sphyg-

momanometer and by radial palpation respectively. Lumbar puncture was performed at day 0 between 8.00 a.m. and 9.00 a.m. after overnight fasting and while patients were still in bed. Ten millilitres of CSF were withdrawn and the last 2 ml of the sample was frozen and stored at −20°C until assay.

Plasma NA was determined by a fluorimetric method (Corona et al. 1977) while CSF and urine monoamine metabolites were assayed by using high-performance liquid chromatography with electrochemical detection (Anderson et al. 1979; Frattini et al. 1982, 1983; Santagostino et al. 1982). All determinations were repeated at the end of drug treatment.

Memory tests. Before and after drug administration the patients were subjected to the following memory tests:

I. Primary memory (De Renzi 1977): (a) digit span; (b) sequential visual memory; (c) Corsi blocks

II. Acquisition into secondary memory (De Renzi 1977): (a) Corsi supra span; (b) words association; (c) story repetition

III. Forgetting from secondary memory (Baldi 1979) recall test: (a) verbal material; (b) visual material; (c) auditory material

The sums of the scores of the three items in each section were considered for data analysis.

Statistical analysis was performed using Student's *t*-test, Pearson's product moment correlation, and ANOVA for repeated measures when appropriate.

Table 1. Basal monoamine metabolite concentrations (mean ± SD) in CSF and in urine of patients

	DAT patients ($n = 21$)	MID patients ($n = 16$)
CSF (ng/ml)		
MHPG	6.6 ± 2.4	8.6 ± 2.7*
HVA	42.5 ± 21.9	46.7 ± 18.5
5-HIAA	21.5 ± 9.6	29.8 ± 14.5
Urine (μg/mg creatinine)		
MHPG	1.81 ± 0.46	2.11 ± 1.13
VMA	6.02 ± 1.72	7.52 ± 3.20
HVA	5.57 ± 3.19	5.63 ± 2.39
5-HIAA	5.23 ± 6.52	5.12 ± 3.00

* $P < 0.05$ versus DAT patients group values
DAT = Dementia of Alzheimer type; MID = multi-infarct dementia; CSF = cerebrospinal fluid; MPHG = 3-methoxy-4-hydroxyphenylglycol; HVA = homovanillic acid; 5-HIAA = 5-hydroxyindolacetic acid

Results

Memory Data and Monoamine Metabolite Levels

Basal values

Memory Tests. No differences were observed between MID and DAT patients in memory test basal scores. In both the diagnostic subgroups basal scores were almost identical in patients who were assigned to monotherapy or combined therapy, whereas the scores of patients in the mildly demented (CDR group I) were significantly lower than those of group II; an exception to this was the primary memory and acquisition into secondary memory in MID patients, which showed no significant difference.

Biochemical Values. Baseline monoamine metabolite levels in the CSF and urine in the DAT and MID groups are given in Table 1.

We noted that HVA and 5-HIAA levels in CSF and in urine and VMA concentration in urine were not significantly different. Basal MHPG levels in the CSF were higher in the MID group in comparison with the DAT group; the difference was significant ($t = 2.26$; $P < 0.05$).

Table 2. CSF monoamine metabolite levels (ng/ml; mean ± SD) before (1) and after (2) single or combined drug treatment

Severity stage	Therapy	*n*	MHPG		5-HIAA		HVA	
			1	2	1	2	1	2
			DAT patients					
I	C, P	7	5.6 ± 1.5	6.6 ± 1.8	24.6 ± 11.7	18.9 ± 5.5	48.5 ± 22.1	46.7 ± 21.3
	C+P	6	7.8 ± 3.4	12.5 ± 5.9*	23.3 ± 10.0	25.5 ± 8.5	50.2 ± 27.6	56.5 ± 32.5
II	C, P	6	5.6 ± 1.3	7.1 ± 1.6	20.2 ± 5.6	19.0 ± 5.6	30.7 ± 14.1	29.1 ± 10.7
	C+P	2	8.0 ± 1.4	11.0 ± 1.4	10.0 ± 2.8	10.5 ± 4.9	31.0 ± 8.4	23.0 ± 5.6
			MID patients					
I	C, P	7	9.8 ± 2.4	11.4 ± 5.3	27.2 ± 12.9	20.2 ± 8.7	49.6 ± 10.9	40.0 ± 14.5
	C+P	5	7.0 ± 2.8	9.6 ± 3.9	28.9 ± 13.8	29.6 ± 12.1	48.1 ± 27.0	62.2 ± 18.6
II	C, P	3	10.0 ± 2.8	9.0 ± 4.2	23.0 ± 4.2	24.5 ± 0.7	33.0 ± 15.6	37.5 ± 2.1
	C+P	1	7.7	11.2	60.6	80.0	48.3	53.0

C = CDP-choline; P = piracetam; *n* = number of patients
* $P < 0.05$ versus corresponding pre-treatment value

Table 3. Urinary monoamine metabolite levels (μg/mg of creatinine; mean ± SD) before (1) and after (2) single or combined therapy

Severity stage	Therapy	*n*	MHPG		VMA		HVA		5-HIAA	
			1	2	1	2	1	2	1	2
					DAT patients					
I	C, P	7	1.94 ± 0.61	1.96 ± 0.67	5.84 ± 1.41	5.52 ± 1.79	4.31 ± 1.51	3.25 ± 1.12	5.47 ± 4.89	2.91 ± 1.31
	C+P	6	1.68 ± 0.45	1.80 ± 0.64	5.21 ± 1.54	6.11 ± 2.48	6.20 ± 4.09	8.65 ± 3.28	3.65 ± 1.63	4.26 ± 2.12
II	C, P	6	1.81 ± 0.39	1.56 ± 0.18	6.31 ± 1.68	5.02 ± 1.41	4.33 ± 2.58	4.25 ± 2.86	6.96 ±11.46	3.21 ± 1.56
	C+P	2	1.76 ± 0.30	2.38 ± 1.02	8.20 ± 2.72	9.38 ± 1.91	5.80 ± 3.21	6.86 ± 0.46	3.95 ± 0.49	4.42 ± 3.08
					MID patients					
I	C, P	7	2.14 ± 1.40	2.30 ± 1.65	7.39 ± 4.20	6.34 ± 2.94	4.92 ± 1.47	4.82 ± 1.85	4.66 ± 2.20	4.54 ± 1.75
	C+P	5	1.73 ± 0.64	1.58 ± 0.69	7.10 ± 1.24	7.03 ± 4.08	7.26 ± 3.49	5.73 ± 1.29	6.78 ± 4.83	8.53 ± 6.00
II	C, P	3	3.14 ± 0.30	2.55 ± 0.48	9.02 ± 3.31	8.41 ± 2.15	5.47 ± 2.76	5.94 ± 5.59	5.10 ± 1.29	4.81 ± 3.13
	C+P	1	0.74	1.53	5.59	11.07	4.58	8.64	1.76	5.22

C = CDP-choline; P = piracetam; *n* = number of patients

Table 4. ANOVA of memory test scores with test-retest differences. Two between-subjects factors (severity: 2 levels; and group of therapy: 2 levels) as well as one within-subject factor (retest: 2 levels) have been considered

	Primary memory			Acquisition into secondary memory			Forgetting from secondary memory		
Source of variation	SS	*df*	*F*	SS	*df*	*F*	SS	*df*	*F*
				DAT patients					
Within cells	103.28	17		71.90	17		1326.95	17	
RET	2.82	1	0.46	10.94	1	2.59	79.53	1	1.02
SEV × RET	25.93	1	4.26	1.68	1	0.40	47.67	1	0.61
THE × RET	0.59	1	0.10	0.33	1	0.08	125.88	1	1.61
SEV × THE × RET	16.61	1	2.73	10.01	1	2.37	107.26	1	1.37
				MID patients					
Within cells	56.65	12		219.57	12		77.90	12	
RET	3.11	1	0.66	45.61	1	2.49	0.29	1	0.04
SEV × RET	1.08	1	0.23	7.77	1	0.42	6.80	1	1.05
THE × RET	3.11	1	0.66	16.25	1	0.89	12.18	1	1.88
SEV × THE × RET	0.69	1	0.15	9.12	1	0.50	0.34	1	0.05

All *F* values were not significant
SEV = severity (CDR I, II); THE = group of therapy (mono, combined); RET = retest (basal, retest)

When the patients were divided according to the severity criterion, the concentrations of HVA and 5-HIAA in the CSF and urine were found to differ in both groups; this, however, was not statistically significant (Tables 2, 3).

No correlations were found between these parameters and patient age in either patient group. No correlations were found between memory test scores and biochemical parameters in basal conditions.

Effects of drug treatment

Memory Tests. There was no overall modification of memory test scores in either patient group. Analysis of variance for repeated measures showed no effects relating either to severity or treatment group in test-retest differences in either patient group (see Table 4).

Biochemical Values. In comparison with basal values, the administration of CDP-choline plus piracetam caused a significant increase in CSF MHPG concentrations only in the mildly demented DAT patients subgroup ($t = 3.26$, $P < 0.05$) (Table 2). The same drug treatment seemed to induce a slight, though not significant, increase in VMA urinary excretion values in the subjects of the same subgroup (Table 3). In patients grouped according to the criteria described

Table 5. Plasma noradrenaline (NA) levels and cardiovascular measurements (mean ± SD) in supine (S) and upright (U) positions before therapy

		NA (ng/ml)	Blood pressure (mm Hg)	Pulse rate (bpm)
DAT patients ($n = 21$)	S	0.15 ± 0.06	153 ± 19/ 88 ± 13	71 ± 10
	U	0.25 ± 0.15*	156 ± 24/ 88 ± 14	79 ± 16*
MID patients ($n = 16$)	S	0.19 ± 0.13	163 ± 16/ 96 ± 13	76 ± 12
	U	0.28 ± 0.12*	166 ± 15/100 ± 15	84 ± 14*

Significance: * $P < 0.01$ versus corresponding value in supine position

above, no correlations were found between the modifications of the biochemical parameters and the memory test scores.

Sympathetic Nerve Activity

Basal Values

The analysis of NA plasma concentrations and of the cardiovascular parameters at rest and after orthostatic challenge showed that sympathetic activity was not significantly different in the DAT and MID groups (Table 5).

Indeed the absolute values of NA and PR measured with the subjects in an upright position were significantly different as compared with those obtained in a supine position. In the DAT group NA was $t = 4.13$, $P < 0.001$ and PR $t = 3.24$, $P < 0.001$, whereas in the MID group NA was $t = 2.99$, $P < 0.01$ and PR $t = 4.87$, $P < 0.001$.

No correlations between biochemical or cardiovascular parameters and patient age were found in either group.

We did, however, note a significant correlation of the supine NA plasma level with diastolic BP in both the DAT and MID groups (DAT: $r = 0.53$, $P < 0.05$; MID: $r = 0.73$, $P < 0.005$) and with systolic BP in the DAT group only ($r = 0.47$, $P < 0.05$). Grouping the patients on the basis of severity, we observed that in the MID group the significant correlation noted between NA plasma concentration and diastolic BP in supine position was found only in the mildly demented subjects ($r = 0.77$, $n = 12$, $P < 0.05$), whereas there was a significant difference between mildly and severely demented subjects in the baseline levels of NA in an upright position ($t = 2.84$, 14 df, $P < 0.05$).

Effects of Drug Treatment

The single or combined drug therapy did not significantly modify NA plasma levels or cardiovascular values in either the DAT or MID groups or in the mildly and severely demented subgroups.

Discussion

One of the fundamental symptoms necessary for the diagnosis of dementia according to the DSM III criteria is impairment of memory, a CNS function which can be quite easily quantified.

Our clinical trial, in agreement with most previous studies (Ferris et al. 1979; Pomara et al. 1981; Bartus et al. 1982; Brinkman et al. 1982a, b; Etienne et al. 1981) failed to reveal any significant effect of pharmacological treatment in dementia of degenerative or vascular origin on the various memory functions which we explored.

Furthermore no other significant effect of therapy could be observed, either in relation to the severity of the dementia or to the type of drug therapy.

There may be a number of reasons for the negative clinical results we report. Firstly, the treatment, as monotherapy or as a combination, may not be clinically effective, or it may have such a small effect that it could only be detected with a greater number of patients. Alternatively the drug treatment may be effective on other CNS functions which we did not explore. Secondly, our results may be negative because the observation period was too short to show clinical effects, although it was long enough to show biochemical modifications; these might precede clinical change.

The NA metabolism seemed not to be affected in DAT since the basal CSF-MHPG values were in the range reported previously (Raskind et al. 1984; Wood et al. 1982; Soininen et al. 1981). The same seems true for the MID patients, in whom similar values were found. In this last group, however, the significantly higher level of MHPG observed in comparison to the DAT group may suggest a more active NA metabolism (Table 1).

We also observed that the basal 5-HIAA and HVA CSF levels in our DAT group were higher than those reported by Wester et al. (1988). However, when we considered the more severely demented patients our concentrations approached those reported by these workers.

The basal CSF values in our severely demented subjects with DAT were also higher than the HVA levels reported by Kaye et al. (1988) for patients with extrapyramidal features, and the 5-HIAA and HVA concentrations noted by Koyama et al. (1988).

We did not find the low levels of HVA that Wester et al. (1988) presumed were characteristic of patients affected by MID. On the basis of the reported differences we believe that the analysis of these variables should be performed not only by taking into account the type of dementia, but also by dividing mildly from severely demented subjects, as we did.

The combined treatment was responsible for changes in the concentration of some neurotransmitter metabolites. In particular the combined administration of cytidine-diphosphate-choline and piracetam seemed mainly to influence the noradrenergic output.

This impression derived from the significant increase in CSF MHPG level and the slight increment (about 17%) of urinary VMA concentration in mildly demented subjects from the DAT group (Tables 2, 3) treated with the two combined drugs. The increase (about 37%) of CSF MHPG concentrations which was also observed in the MID group (Table 2) could be an additional indication of this.

This possible enhancement of the noradrenergic output could be attributed to a higher activity of those NA neurons outside the locus coeruleus, where some workers (Bondareff et al. 1982; Mann et al. 1982) noted a loss of NA neurons in Alzheimer disease and/or to a compensatory activity of the remaining locus ceruleus NA neurons. The higher MHPG levels could be also explained by an increased activity of the COMT, according to Volicer et al. (1985), and/or of other enzymes involved in the biotransformation of NA to MHPG. However, in this case the biotransformation of a greater number of neurotransmitter molecules should in the end require an increased NA turnover. We were not able to establish whether the treatment significantly influenced dopamine or serotonin metabolism because the irregular course of the levels of HVA and 5-HIAA in the CSF and urine prevented us from drawing any clear conclusions.

In summary, the present results suggest that:

1. There were no improvements of memory performance in demented subjects in either group, even with the adoption of a treatment protocol based on acetylcholine replacement in combination with a "metabolic enhancer".

2. The maintenance of similar plasma NA levels and cardiovascular responses to orthostatic challenge in both patient groups, and in both slightly and severely demented subjects, suggests that the impulse flow in the peripheral noradrenergic system was quite regular in both forms of neurological illness.

3. The central noradrenergic output might be influenced by treatment with drugs that improve the cholinergic system activity, although further clinical and biochemical studies are needed to confirm the increment of MHPG and VMA levels induced by therapy in patients affected by DAT and to elucidate if it is associated with some functional improvement.

4. The lower modification of monoamine metabolite levels with therapy in the more severely demented subjects of the DAT group, compared with the mildly demented subjects, may suggest that in the advanced stages of the disease impairment of the central monoaminergic activity cannot be surmounted by drugs like those used in the present study.

Finally we believe that longitudinal psychometric and biochemical evaluations could reveal the possible influence of the progressive severity of the illness on psychological functions and monoaminergic system activities and whether prolonged therapy might preserve these functions. Such a study is still in progress.

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