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Monoamine Mechanisms in Chronic Schizophrenia: Post-Mortem Neurochemical Findings

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SUMMARY Dopamine and its metabolites homovanillic acid and dihydroxyphenylacetic acid, noradrenaline, serotonin and its metabolite 5-hydroxyindoleacetic acid, and tryptophan and its metabolite kynurenine have been assayed in 9 schizophrenic and 10 control brains, together with the monoamine-related enzymes tyrosine hydroxylase monoamine oxidase, dopamine-β-hydroxylase, and catechol-o-methyl-transferase. In schizophrenic brains dopamine, noradrenaline and serotonin were significantly increased in some areas of corpus striatum, but there were no significant changes in enzyme activity or monoamine metabolite concentrations in any of the brain areas examined. The findings are not consistent with theories that serotonin or noradrenaline stores are grossly depleted or noradrenaline neurones have degenerated, or that monoamine oxidase activity is abnormal, in schizophrenia, and provide no direct support for the hypothesis that dopamine neurones are overactive.

Introduction

Interest in possible disturbances of monoamine metabolism in schizophrenia has been stimulated by observations that the clinical features of the amphetamine psychosis (Connell, 1958) closely resemble those of acute paranoid schizophrenia. Amphetamines facilitate the release of both dopamine and noradrenaline from their stores in nerve terminals and the symptoms of the amphetamine psychosis are attenuated by drugs which are effective in schizophrenia (Gunne *et al*, 1972; Angrist *et al*, 1974). Since such drugs are all effective dopamine antagonists (Miller *et al*, 1974; Clement-Cormier *et al*, 1974) and this action is well correlated with anti-psychotic potency, it has been suggested (Randrup and Munkvad, 1972; Matthysse, 1973; Snyder, 1973; Stevens, 1973) that there may be a primary disturbance of dopaminergic transmission in schizophrenia.

Besides dopamine, there have been other monoamine theories of the neuro-humoral defect. Gaddum (1954) and Woolley and Shaw (1954) suggested that there might be a deficiency of serotonin and more recently Stein and Wise (1971) attributed the 'anhedonia' or loss of affective response to degeneration of the central noradrenergic pathways (e.g. the coerulo-cortical system) which may function as components of the central mechanisms mediating the response to rewarding stimulation (Crow *et al*, 1972). On the basis of an observation (Murphy and Wyatt, 1972), still the subject of dispute (Owen *et al*, 1976), that platelet monoamine oxidase (MAO) may be reduced in schizophrenia, it has been held that a deficiency of one or more of the different forms of MAO (Johnston, 1968) located within central monoamine neurones may be the chemical basis of the psychological disturbance.

In this investigation, we attempted to assess these possibilities by applying chemical techniques for assaying monoamines and their enzymes and metabolites to post-mortem brain

tissue, collected at autopsy from patients who had suffered from long-standing schizophrenic illnesses.

Methods

(a) *Clinical material*

Patients with schizophrenia: Brains from patients with a hospital diagnosis of schizophrenia were received from a number of psychiatric hospitals. The case notes were studied and the brain was included in the sample only if the following operational criteria for schizophrenia were both satisfied: the symptoms could be included within the 'nuclear syndrome' of schizophrenic symptoms on the syndrome checklist of Wing *et al* (1974), and the disease could be described as 'definite' or 'probable' schizophrenia according to the criteria of Feighner *et al* (1972). Brains were excluded if there was a prior or family history of organic brain disease or serological evidence of luetic infection. Five patients were known to be receiving neuroleptics shortly before their deaths.

Controls: Control brains were obtained from autopsies carried out in the Pathology Department of a district general hospital. Samples were matched for age and sex with the patient population and cases in which there was evidence of cns disease were excluded. The range of causes of death, including myocardial infarction, chronic heart disease, carcinomatosis and the complications of acute poisoning, was similar in the schizophrenic sample and controls.

The mean age, sex ratio, time between death and storage at 4°C, time at 4°C before post-mortem and duration of storage at −40°C or lower were similar in the two groups (Table I).

Storage and dissection: Brains were deep frozen (at −40°C), as soon as possible after removal from the cranium, in a polystyrene mould designed to retain normal brain shape. Cases in which the delay between death and refrigeration at 0–4°C was greater than six hours, or between death and autopsy was greater than 96 hours, were eliminated.

For dissection, brains were removed from storage and allowed to reach −10°C to 0°C before they were cut into coronal sections at 1–2 cm intervals, using a meat slicer (Krups type 370). Slices were placed on a foil covered cold plate and the areas were dissected according to the atlas of De Armond *et al* (1974). Tissue from each area was diced, mixed and stored at −40°C (or in liquid nitrogen in the case of later specimens) in screw-cap plastic vials.

The nucleus accumbens is of particular interest in schizophrenia, but is not easily identified in the human brain. A region was dissected out which corresponded as closely as possible to the nucleus accumbens septi, as described by De Armond *et al* (1974). In practice, this was taken as that infero-medial portion of the corpus striatum which is rostral and ventral to the anterior commissure. The region dissected was limited to those three sections of brain rostral to the anterior commissure.

TABLE I

Mean age at death and sex of the two groups of subjects and storage times for the brains. Time at room temperature is the time before removal of the body to the mortuary refrigerator, time at 4°C is the remaining time before post-mortem was carried out

	Schizophrenics (n = 9)	Controls (n = 10)
Age (years)	73.4 ± 6.6 (SD)	76.4 ± 6.9
Sex	4M, 5F	5M, 5F
Time at room temperature (h)	2.8 ± 1.6	2.5 ± 0.6
Time at 4°C (h)	55 ± 31	48 ± 22
Duration of storage (days)	297 ± 163	258 ± 100

(b) *Chemical techniques*

Dopamine and its metabolites: Homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC) were assayed by the gas chromatographic technique of Watson *et al* (1974). Dopamine and noradrenaline were assayed radiochemically according to Coyle and Henry (1973).

Dopamine-β-hydroxylase (DBH), the enzyme which catalyses the final step in the synthesis of

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noradrenaline, was assayed by the single step radiometric method of Wise (1976), using tyramine as substrate.

Catechol-o-methyl transferase (*COMT*) activity was assayed by the radiometric method described by McCaman (1965).

Serotonin (*5-HT*), *tryptophan and their metabolites:* following homogenization in acid-butanol, tryptophan, 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) were assayed using a modification (Joseph and Baker, 1976) of a previously described procedure (Curzon *et al*, 1972). Kynurenine was assayed in an aliquot of the dilute acid phase from this procedure by gas liquid chromatography (Joseph *et al*, 1978).

Tyrosine hydroxylase (TOH) activity, was assayed by a tritium release method (Cicero *et al*, 1972) as modified by Lerner *et al* (1977) using $DMPH_4$ as cofactor.

Monoamine oxidase (*MAO*) *activity* was assayed using serotonin (5-HT), benzylamine, tyramine and dopamine as substrates by the radiometric technique of Robinson *et al* (1968). All assays were carried out with saturating concentrations of substrate.

Differences between schizophrenics and controls samples were tested for significance in individual areas with 2-tailed 't' tests.

Results

Dopamine and its metabolites homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC) were assayed separately in caudate nucleus, putamen and in nucleus accumbens (Table II). Dopamine concentrations were modestly increased in schizophrenic patients and this reached significance ($P < 0.05$) in the caudate nucleus and putamen. There were no significant changes in HVA or DOPAC in any area. Noradrenaline concentrations, also measured in these regions of the basal ganglia, were low (37–185 ng/g), but were significantly

TABLE II

Monoamines in basal ganglia and relaed areas

	Caudate		Putamen		Nucleus Accumbens		Amygdala	
	schiz.	controls	schiz.	controls	schiz.	controls	schiz.	controls
DA ug/g	2.4±0.6*	1.2±0.1	2.1±0.3*	1.2±0.2	0.6±0.2	0.5±0.2	—	—
HVA ug/g	4.0±0.9	5.3±0.5	5.8±0.9	4.1±0.7	4.7±0.6	4.3±0.7	—	—
DOPAC ug/g	0.7±0.3	1.1±0.3	0.6±0.5	0.6±0.1	1.5±0.1	1.9±0.2	—	—
NA ng/g	104±12	75±15	119±20**	65±10	131±20	132±30	—	—
COMT nmol/ mg protein/h	10.1±0.7	11.1±0.9	8.2±0.8	8.3±0.9	9.6±0.7	10.2±0.9	5.1±0.2	5.2±0.3
tryp ug/g	—	—	17.7±1.3	15.0±1.4	—	—	—	—
kyn ng/g	—	—	738±157	615±141	—	—	—	—
5-HT ng/g	—	—	268±22*	208±14	—	—	—	—
5-HIAA ug/g	—	—	1060±151	922±94	—	—	—	—
MAO (nmol/mg protein/h)								
5HT	47±2	47±2	43±2	44±1	74±2	68±2	72±3	71±4
benzylamine	92±3	86±5	75±4	85±4	145±10	130±8	71±3	76±3
tyramine	145±5	145±9	133±7	137±11	195±11	189±7	183±8	196±7
dopamine	28±2	30±1	20±2	17±2	51±3	51±2	21±1	19±1
TOH (n mol/g tissue/h)	33.6±2.9	37.2±1.8	40.0±3.0	39.5±2.7	28.3±3.8	28.5±2.7	—	—

values ± 1 SEM * $p < 0.05$ ** $p < 0.001$

(DA—dopamine; HVA—homovanillic acid; DOPAC—dihydroxyphenylacetic acid; NA—noradrenaline; COMT—catechol-o-methyl transferase; tryp—tryptophan; kyn—kynurenine; 5-HT—5-hydroxytryptamine; 5-HIAA—5-hydroxyindoleacetic acid; MAO—monoamine oxidase; TOH—tyrosine hydroxylase. (Assays were carried out only in those brain areas where values are given).

increased ($P < 0.001$) in putamen in schizophrenics.

Dopamine-β-hydroxylase (the marker enzyme for noradrenergic neurones) was assayed in four areas of neocortex and hippocampus (Table III) and was found to be closely similar in all these areas in patients and controls.

Serotonin (5-HT) concentrations were increased by about 25 per cent in putamen (Table II) ($P < 0.05$), but not significantly in temporal cortex (Table III). The concentrations of the serotonin metabolite (5-HIAA) were also increased in schizophrenic brain, but this did not reach statistical significance. The

TABLE III

Monoamines in neo- and palaeo-cortex

	Cortex								Hippocampus	
	Temporal		Parietal		Frontal		Occipital			
	schiz.	control	schiz.	control	schiz.	control	schiz.	control	schiz.	control
DBH (nmol/g tissue/h	26±3	25±2	18±2	25±2	25±3	24±3	27±3	24±2	23±3	21±2
COMT (nmol/mg protein/h)	3.5±0.3	3 9±0 5	4.1±0.5	4.1±0.8	5.0±0.5	6.5±1.0	5.1±0.7	6.3±1.0	9.7±0.7	10.2±1.2
tryp μg/g	13±1	12±2	—	—	—	—	—	—	—	—
kyn ng/g	584±112	460±118	—	—	—	—	—	—	—	—
5-HT ng/g	83±9	73±7	—	—	—	—	—	—	—	—
5-HIAA ng/g	250±27	231±38	—	—	—	—	—	—	—	—
MAO (nmol/mg protein/h)										
Substrates										
5-HT	41±3	36±2	41±2	37±2	45±1	44±2	49±3	56±5	75±4	69±4
benzylamine	40±2	43±2	31±3	30±2	42±2	41±2	40±3	46±4	89±4	82±5
tyramine	94±6	100±7	89±4	97±5	112±4	121±9	91±4	98±8	142±5	134±6
dopamine	14±1	15±1	21±2	18±2	25±1	28±2	26±1	30±3	28±1	32±2

Values ± 1 SEM

(Assays were carried out only in those brain areas where values are given)

TABLE IV

Monoamines in diencephalon and brainstem

	Hypothalamus		Thalamus		S. Nigra		Cerebellum	
	schiz.	control	schiz.	control	schiz.	control	schiz.	control
DBH (nmol/g tissue/h)	147±17	121±12	—	—	—	—	—	—
COMT (nmol/mg protein/h)	14.0±1.8	12.7±1.1	5.8±0.4	5.8±0.4	5.9±0.5	6.3±0.7	6.2±0.2	6.0±0.6
MAO (nmol/mg protein/h)								
Substrates								
5-HT	70±4	82±7	48±3	51±1	59±5	56±2	31±2	25±3
benzylamine	117±6	131±10	60±3	59±4	63±3	58±4	14±2	16±2
tyramine	183±11	214±14	113±4	112±5	133±9	113±6	35±2	38±2
dopamine	32±3	34±3	27±1	28±2	15±1	14±1	4±0.3	4±0.3

Values ± 1 SEM

(Assays were carried out only in those brain areas where values are given)

concentrations of tryptophan, the precursor of 5-HT, and of kynurenine, a tryptophan metabolite also found in brain (Joseph *et al*, 1978), were not significantly different in these two areas in patients and controls.

Monoamine oxidase activity (Tables II to IV) was closely similar in patients and controls, using four substrates (5-HT, benzylamine, tyramine and dopamine) in fourteen different brain areas.

Tyrosine hydroxylase (TOH) activity was similar in patients and controls in caudate nucleus, putamen and nucleus accumbens (Table II). Catechol-o-methyl transferase (COMT) activity did not differ in patients and controls in fourteen different brain areas (Tables II to IV).

Discussion

These findings fail to provide support for a number of current hypotheses of the neurochemical defect in schizophrenia—for example that dopamine release is in excess (Randrup and Munkvad, 1972; Matthyse, 1973; Snyder, 1973; Stevens, 1973), that serotonin (Gaddum, 1954; Woolley and Shaw, 1954) or noradrenaline (Stein and Wise, 1971) are depleted or that monoamine oxidase activity is decreased (Murphy and Wyatt, 1972). Of these theories, the dopamine hypothesis has been the most favoured, since there is now compelling evidence that the antipsychotic effect of neuroleptic drugs is related to their ability to block dopamine receptors (Crow and Johnstone, 1977; Johnstone *et al*, 1978a). There was a modest increase in dopamine concentrations ($P < 0.05$) in the caudate nucleus and putamen, but the levels of the dopamine metabolite homovanillic acid (HVA), which may perhaps be taken as an index of turnover, were not increased. This is surprising in view of the fact that many of these patients had been on neuroleptic drugs, which themselves increase dopamine turnover at least on acute administration. The finding conflicts with the dopamine neurone overactivity hypothesis of schizophrenia. CSF studies (Bowers, 1974; Post *et al* 1975) of unmedicated patients have also failed to reveal evidence of increased dopamine turnover. The modest increase in dopamine concentrations in corpus striatum may be secondary to drug administration, since such changes have sometimes been observed after chronic neuroleptic administration in animal experiments (O'Keefe *et al*, 1970). An increase in dopamine in nucleus accumbens, rather than in striatum, as in the present study, in schizophrenia has recently been reported by Bird *et al* (1977). In the present study, noradrenaline (assayed along with dopamine) was also increased in the basal ganglia (Table II) and serotonin was increased in that area (putamen) in which it was assayed. However, there were no significant differences in the concentrations of the serotonin precursor tryptophan or the metabolites 5-HIAA and kynurenine and thus no evidence of a gross change in turnover of serotonin. Thus, we have evidence of an increase in dopamine and serotonin in at least some areas of schizophrenic brain, without any evidence of a change in turnover of either amine. The explanation of the increased concentrations of monoamines found in some areas is obscure, but it seems possible that these changes may be secondary to the neuroleptic medication that many of these patients were receiving at the time of their death.

The view (Stein and Wise, 1971) that in schizophrenia there is a degeneration of a central noradrenergic reward pathway (which might account for 'anhedonia') has already been challenged by an earlier study (Wyatt *et al*, 1975) of DBH (a marker for noradrenaline neurones) in post-mortem brains. It has been argued (Wise and Stein, 1975) that DBH deficits are to be expected in chronic non-paranoid patients. However, of the present sample, all but one of the schizophrenics would be classified as chronic non-paranoid. Thus, a deficit of DBH is unlikely to be a general finding in schizophrenia.

There has been considerable interest in the suggestion that low platelet MAO activity might be a genetic marker for vulnerability to schizophrenia (Wyatt *et al*, 1973). However, whilst several groups have confirmed the initial finding of Murphy and Wyatt, 1972 (Meltzer and Stahl, 1974; Zeller *et al*, 1975; Schildkraut *et al*, 1976; Domino and Khanna, 1976; Sullivan

et al, 1977) others have found platelet MAO activity to be no different in schizophrenics from controls. (Friedman *et al*, 1974; Shaskan and Becker, 1975; Carpenter *et al*, 1975; White *et al*, 1976; Belmaker *et al*, 1976; Owen *et al*, 1976). The most interesting implication of those studies with a positive finding is that the reported low activity of platelet MAO in schizophrenia might reflect similar deficits in brain. Apart from a minor regional difference reported by Utena *et al* (1968), however, there is little support for this view in the literature (Vogel *et al*, 1969; Domino *et al*, 1973; Schwartz *et al*, 1974; Wise *et al*, 1974) or from the present findings. There may be two types of enzyme in brain, each with a different substrate specificity—type A for which serotonin is a substrate and type B for which benzylamine is a substrate (Johnston, 1968), tyramine being a substrate for both types. It has also been suggested that there is a specific monoamine oxidase for dopamine (Youdim, 1974). However, with none of these substrates was there evidence for a deficiency of enzyme activity in any of fourteen brain areas.

The present findings fail to support any of the monoamine hypotheses of schizophrenia recently proposed and perhaps increase the interest of recent reports (Owen *et al*, 1978; Lee and Seeman, personal communication) that there may be abnormalities at the postsynaptic receptor rather than in the presynaptic monoamine neurone. However, the possibility cannot be excluded that there are sub-groups of patients, defined by particular clinical characteristics, who may show specific neurochemical changes in one of the parameters we have assessed. For example, patients with acute schizophrenia differ substantially from those with the defect state and none of the former have been included in the present study. It may be possible to subdivide chronic schizophrenic illnesses into those with and without paranoid changes (Winokur *et al*, 1974) and those with and without evidence of cognitive impairment (Crow and Mitchell, 1975; Johnstone *et al*, 1976; Johnstone *et al*, 1978b). To study such variables, it will be necessary to have larger tissue collections and detailed assessment of pre-mortem clinical state.

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