CATECHOLAMINE METABOLISM AND NEUROLOGIC DISEASE

THOMAS N. CHASE
Neurology Unit, National Institute of Mental Health, Bethesda, Maryland, U.S.A.

ALTERATIONS in central catecholamine metabolism have been found to attend a number of neurologic disorders. These changes have often been assumed to reflect altered nerve impulse activity in neural systems containing these amines. In some instances the metabolic abnormality appears directly attributable to the degeneration of a specific catecholaminergic pathway. In other disorders it is conceivable that altered catecholamine metabolism may be a functional response to a drug or disease induced change in the sensitivity of dopaminergic receptors or in the activity of some related neuronal system.

DOPAMINE METABOLISM

Early attempts to study catecholamine metabolism in the central nervous system of the living patient made extensive use of steady state levels of the principal metabolites of dopamine and norepinephrine in cerebrospinal fluid (CSF). The rationale for this approach derives from observations in the experimental animal as well as in man suggesting that CSF homovanillic acid (HVA), a major metabolite of dopamine, and 3-methoxy-4-hydroxyphenylglycol (MHPG), a major product of norepinephrine degradation, arises largely from central rather than peripheral metabolism and that CSF levels of these metabolites tend to follow those in the cerebral tissues (MOIR *et al.*, 1970; CHASE *et al.*, 1973). Substantial reductions in the CSF content of HVA have been found in patients with Parkinson's disease and related extrapyramidal disorders (Table 1). The validity of these observations in Parkinson's disease or Huntington's chorea has been confirmed by direct biochemical assay of brain tissues at autopsy (HORNYKIEWICZ, 1966, 1973). On the other hand, diminished HVA levels have also been found in disorders such as amyotrophic lateral sclerosis where lesions are not known to involve dopamine-containing neuronal systems. Such observations cast suspicion upon the presumed relationship between reduced HVA levels in lumbar CSF and functional alterations in cerebral dopaminergic systems.

More recent studies of central dopamine metabolism have employed the probenecid loading technique. Since the acute administration of probenecid inhibits HVA transport from the spinal fluid compartment, without substantially altering cerebral dopamine concentrations, the HVA rise in CSF should provide an index to the rate of metabolite formation and thus to the central turnover of the parent amine (WERDINIUS, 1967; KORF and VAN PRAAG, 1971; BOWERS, 1972). The probenecid-induced accumulation of HVA is substantially diminished in parkinsonian patients (Table 2). Less marked, yet statistically significant, reductions in HVA turnover have also been found in patients with Huntington's chorea and amyotrophic lateral sclerosis (Table 2). It remains to be determined, however, whether orally administered probenecid affects HVA transport to the same extent in patient and control groups.

TABLE 1. HOMOVANILLIC ACID (HVA) AND 3-METHOXY-4-HYDROXYPHENYLETHYLENE GLYCOL (MHPG) LEVELS IN LUMBAR SPINAL FLUID*

	HVA	MHPG
Controls	36 ± 4·0 (25)	15 ± 2·3 (11)
Parkinsonism	10 ± 1·2 (30)‡	15 ± 2·5 (13)
Huntington's chorea	16 ± 3·3 (14)‡	16 ± 0·7 (7)
Dystonia musculorum deformans	20 ± 3·6 (15)†	14 ± 2·1 (6)
Down's syndrome	56 ± 11 (9)	14 ± 3·5 (6)
Parkinsonism-dementia	9 ± 2·7 (16)‡	—
Progressive supranuclear palsy	8 ± 2·6 (3)‡	—
Jakob–Creutzfeldt disease	10 ± 3·7 (6)‡	—
Tardive dyskinesia	31 ± 4·4 (10)	—
Amyotrophic lateral sclerosis	13 ± 2·4 (21)‡	—
Spinocerebeller degenerations	25 ± 4·7 (10)	—

* Values are the means ± S.E.M. for the number of untreated patients given in parentheses, expressed in ng/ml. Spinal fluid collection and assay methods are as previously described (CHASE and NG, 1972).
† $P < 0{\cdot}01$.
‡ $P < 0{\cdot}001$.

NOREPINEPHRINE METABOLISM

Studies of central noradrenergic mechanisms based on CSF levels of MHPG have yet to yield much useful information. Steady state MHPG values are not significantly altered in any of the neurologic disorders studied (Table 1), including Parkinson's disease, where biochemical measurements at autopsy have shown a depression in brain norepinephrine (HORNYKIEWICZ, 1966). Moreover, estimates of central norepinephrine turnover based on the probenecid-induced accumulation of MHPG have not been possible, since the oral probenecid loading technique currently employed does not significantly influence lumbar CSF concentrations of either the free or conjugated form of this metabolite (CHASE *et al.*, 1973). Mechanisms in man subserving the transfer of MHPG from the central tissues to CSF or from CSF to blood would thus appear to differ from those mediating the efflux of HVA and 5-hydroxyindoleacetic acid (5-HIAA). This contention is supported by the lack of any difference between ventricular and lumbar CSF levels of free or conjugated MHPG in contrast to the steep concentration gradients for both HVA and 5-HIAA

TABLE 2. EFFECT OF PROBENECID ON HOMOVANILLIC ACID LEVELS IN LUMBARSPINAL FLUID*

	Number of patients	Baseline	Treatment	Difference
Controls	8	28 ± 6·8	194 ± 24	166 ± 24
Parkinsonism	20	12 ± 1·7	73 ± 12	62 ± 11‡
Huntington's chorea	12	14 ± 5·0	115 ± 14	100 ± 14†
Tardive dyskinesia	8	29 ± 5·0	146 ± 24	116 ± 22
Dystonia musculorum deformans	8	14 ± 4·9	168 ± 22	154 ± 19
Down's syndrome	6	48 ± 12	225 ± 35	178 ± 25
Amyotrophic lateral sclerosis	7	23 ± 7·7	128 ± 22	104 ± 16†

* Values are the means ± S.E.M., expressed in ng/ml, for untreated patients. Probenecid (2 g) was administered orally immediately after obtaining the baseline spinal fluid sample and again 3 and 6 hr later (CHASE and NG, 1972). The second lumbar puncture was performed 9 hr after the initial one.
† $P \leq 0{\cdot}05$.
‡ $P < 0{\cdot}001$.

(CHASE *et al.*, 1973). The absence of altered MHPG values in the lumbar CSF of patients with brain diseases such as parkinsonism might thus reflect the special nature of efflux mechanisms for MHPG or possibly be a consequence of rapid MHPG formation by noradrenergic terminals in the spinal cord.

NATURALLY-OCCURRING EXTRAPYRAMIDAL DISORDERS

Studies based on the probenecid loading technique suggest a close relationship between central dopaminergic mechanisms and overall parkinsonian severity (Fig. 1). Separate analysis of the 3 cardinal parkinsonian signs indicates, however, that this relationship holds for rigidity and akinesia but not for tremor (CHASE and NG, 1972). This observation as well as results from certain animal models of Parkinson's disease (BATTISTA *et al.*, 1969; GUMULKA *et al.*, 1970) support the contention that neurohumoral mechanisms subserving tremor may differ from those relating to rigidity or akinesia. It is probable that the amount of reduction in central dopamine turnover in untreated parkinsonian patients reflects the degree of degeneration of dopaminergic neurons originating in the substantia nigra.

Assays of post-mortem tissues (HORNYKIEWICZ, 1973) or lumbar CSF (CHASE, 1973a) suggest that a reduction in central dopamine metabolism also occurs in patients

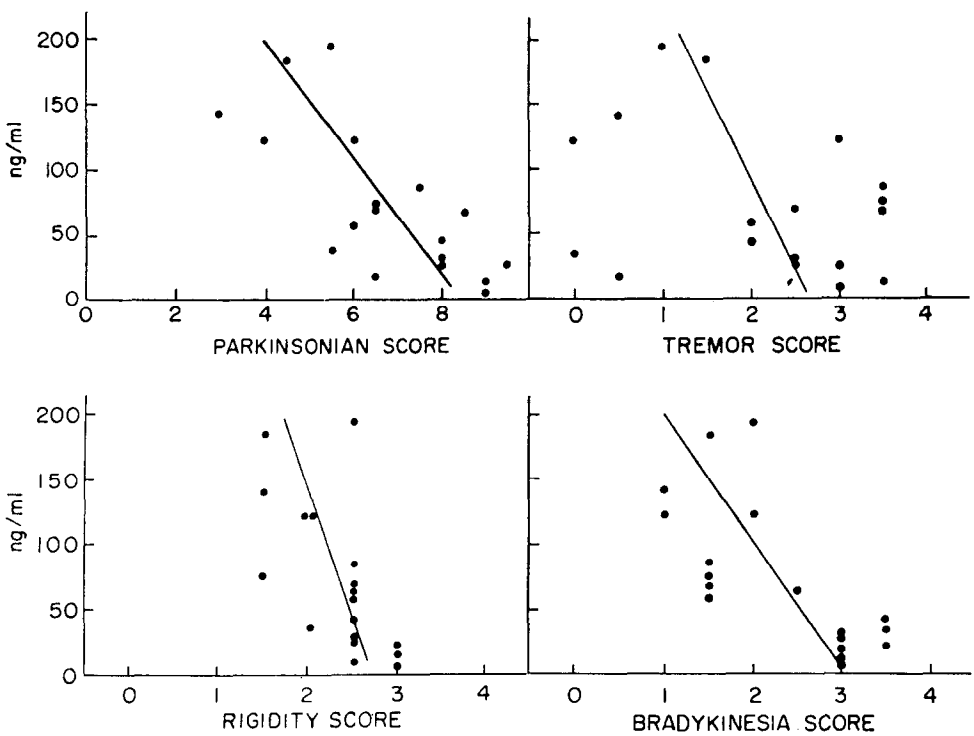

FIG. 1.—Effect of probenecid on homovanillic acid (HVA) levels in lumbar CSF of untreated parkinsonian patients. Rigidity, bradykinesia and tremor were each rated on a score of 0 (absent) to 4 (very severe) and combined to give an overall index of parkinsonian severity. Significant inverse correlations were found between the probenecid-induced accumulation of HVA and overall parkinsonian severity ($P < 0{\cdot}001$), rigidity ($P < 0{\cdot}01$) and bradykinesia ($P < 0{\cdot}01$), but not resting tremor ($P > 0{\cdot}05$).

with Huntington's disease. Although there is a tendency for an inverse correlation between choreatic severity and the probenecid-induced accumulation of HVA, this relationship is not statistically significant in the 11 patients studied to date ($r = 0{\cdot}590$; $P > 0{\cdot}05$). The characteristic histopathologic changes in Huntington's disease do not involve neurons known to contain dopamine. In further contrast to Parkinson's disease, drugs which elevate brain dopamine (for example, L-dopa) exacerbate choreatic movements in patients with Huntington's chorea, while those which presumably diminish dopaminergic function (for example, α-methylparatyrosine, tetrabenazine, or haloperidol) tend to ameliorate the extrapyramidal signs of this disorder (CHASE, 1973a). Altered dopamine metabolism in Huntington's chorea might thus be a secondary, functional response of neurons within the inhibitory nigrostriatal dopaminergic pathway to the degeneration of striatal neurons upon which they make synaptic contact.

Pharmacologic observations in the experimental animal suggest that a close relationship may exist detween the activity of postsynaptic dopaminergic receptors and dopamine turnover in the presynaptic neuron. Drugs which appear to block dopamine receptors such as the psychotropic phenothiazine and butyrophenone derivatives tend to increase dopamine turnover, while those which are believed to act mainly as dopamine receptor agonists exert the opposite metabolic effect (CORRODI *et al.*, 1967, 1972). Similar effects on central dopamine metabolism appear to attend the administration of these drugs to man (CHASE, 1973b). Treatment of 20 neurologic patients with haloperidol (a presumed dopamine receptor antagonist) at a maximum daily dose of 8–10 mg increased dopamine turnover, as determined by the probenecid technique, by $98 \pm 32\%$ ($P < 0{\cdot}01$). Conversely, the putative dopamine receptor agonist, 1-(2″-pyrimidyl)-4-piperonylpiperazine (ET 495), at an average daily dose of 230 mg, diminished the probenecid-induced accumulation of HVA in 10 neurologic patients by $51 \pm 15\%$ ($P < 0{\cdot}01$).

Alterations in dopamine metabolism in response to the administration of drugs which influence receptor mechanisms may provide useful information relative to the integrity of feedback systems affecting catecholamine synthesis as well as to the latent ability of the presynaptic neuron to synthesize dopamine. In preliminary studies ET 495 produced a substantially smaller decline in the probenecid-induced accumulation of HVA in 6 parkinsonian patients ($-23 \pm 13\%$; $P > 0{\cdot}05$) than in 4 individuals with various other central nervous system disorders ($-91 \pm 14\%$; $P < 0{\cdot}001$). Similarly, haloperidol (10 mg/day) had no significant effect on the rise in HVA with probenecid in 4 Parkinson's patients ($21 \pm 19\%$; $P > 0{\cdot}05$) but lead to a marked increase in the response to probenecid in 5 individuals with Huntington's chorea ($189 \pm 64\%$; $P < 0{\cdot}05$). These results are compatible with the hypothesis that the reductions in central dopamine metabolism in Parkinson's disease reflect the degeneration of dopaminergic neurons while diminished dopamine metabolism in Huntington's chorea may be due to compensatory functional changes which can be partially overcome by drugs which modify the activity of dopamine receptors.

DRUG-INDUCED EXTRAPYRAMIDAL DISORDERS

Studies of dopamine metabolism in patients with drug-induced parkinsonism or tardive dyskinesia suggest that the former state may in part be the clinical expression of diminished activity of nigrostriatal dopaminergic neurons while the latter condition may reflect hyperfunction of this neural system. Dopamine turnover, as estimated by

steady state HVA values in CSF, appears diminished in patients who develop parkinsonism while receiving α-methylparatyrosine, an inhibitor of catecholamine synthesis. In contrast to these results, as well as those in patients with the naturally-occurring disorder (Table 2), the probenecid-induced accumulation of HVA was normal or slightly increased in 10 patients who manifested parkinsonian signs during treatment with haloperidol (137 ± 21% of levels in 8 untreated control subjects). Inhibition of dopaminergic transmission due to receptor blockade rather than enhanced transsynaptic activity owing to increased amine synthesis would appear to have been the preponderant functional effect of haloperidol in these patients.

Preliminary results suggest that dopamine turnover may also be depressed in patients who manifest tardive dyskinesias long after neuroleptic withdrawal (Table 2). Such metabolic changes might reflect structural alterations in dopamine-containing neurons or be a functional response to a primary change in the sensitivity of dopaminergic receptors. The haloperidol-induced increase in dopamine turnover, as estimated by the probenecid test, appeared to be less in 6 patients with tardive dyskinesia (79 ± 18 ng/ml) than in 5 individuals with Huntington's chorea (185 ± 93 ng/ml). In view of evidence suggesting that morphologic changes occur in the substantia nigra and other brain stem areas of patients with tardive dyskinesias (CHRISTENSEN *et al.*, 1970) these biochemical findings support the view that some dopamine-containing neurons may be damaged in patients receiving long-term neuroleptic treatment. In such individuals dyskinesias might be the result of denervation supersensitivity of postsynaptic dopamine receptors.

CONCLUSIONS

Although methods for studying catecholamine metabolism in the central nervous system of man have advanced considerably during the past decade, they remain indirect and of uncertain validity. Moreover, the relation between the metabolic changes which these techniques attempt to measure and the state of neural transmission across synapses containing these amines has yet to be established. Furthermore, pathogenetic mechanisms in the human brain are undoubtedly more complex than suggested by the simplistic models currently advanced to explain available results. Neurohumoral mechanisms, nevertheless, appear to be sensitive indicators of central nervous dysfunction and of the effects of centrally active drugs. Efforts to improve our ability to examine catecholamines as well as other putative central neurotransmitters should prove eminently worthwhile.

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