MHPG Excretion in Depressive Disorders: Relation to Clinical Subtypes and Desynchronized Sleep

Abstract. *The urinary excretion of 3-methoxy-4-hydroxyphenylglycol (MHPG) was significantly lower in patients with manic-depressive depressions than in patients with chronic characterological depressions. There was an inverse relationship between MHPG excretion and the amount of time spent in desynchronized sleep, particularly in the manic-depressive disorders. Excretion of MHPG was not related to the degree of retardation, agitation, or anxiety in these patients.*

The changes in norepinephrine metabolism produced by drugs used in the treatment of affective disorders (depressions and manias) have served to stimulate the investigation of norepinephrine metabolism in depressive and manic disorders (*1*). Considerable study is currently focused on the urinary excretion of 3-methoxy-4-hydroxyphenylglycol (MHPG), a metabolite of norepinephrine which may provide some index of the synthesis and metabolism of norepinephrine in the brain (*2–4*). Although all findings do not support this (*5*), and although the peripheral sympathetic nervous system as well as the brain is a source of urinary MHPG, recent studies in nonhuman primates suggest that an appreciable fraction of urinary MHPG may derive from norepinephrine originating in the brain; however, the exact amount remains problematic (*6*).

Several longitudinal studies of patients with naturally occurring or amphetamine-induced manic-depressive episodes have shown that the amount of MHPG excreted in urine was relatively lower during depressions and higher during manic or hypomanic episodes than after clinical remissions (*7–9*), but all findings do not agree (*10*). Other studies have indicated that not all depressed patients excrete comparably low levels of MHPG, and that MHPG excretion may provide a biological criterion for classifying the depressive disorders and for predicting the responses to specific forms of antidepressant pharmacotherapy (*11*). Differences in physical activity or stress could conceivably account for the differences in MHPG excretion observed in patients with affective disorders (*12*). Moreover, the relationship between urinary MHPG excretion and central noradrenergic activity remains an unresolved issue, and it has even been questioned whether MHPG (or any biogenic amine metabolite) measured in urine can provide meaningful information about the activity of the central nervous system in patients with affective disorders (*13*).

In order to explore these problems, we compared the urinary excretion of MHPG in a small group of patients with various clinically defined subtypes of depressive disorders, and attempted to relate MHPG excretion to clinical measures of motor activity and anxiety as well as to electroencephalographic measures of central nervous system activity. We report here that MHPG excretion is significantly lower in depressed patients with manic-depressive disorders (in which there is a history of hypomania or mania) than in patients with chronic characterological depressions (dysphoric depressive syndromes with no history of hypomania or mania). Excretion of MHPG did not appear to be related to the degree of retardation, agitation, or anxiety in these patients, but was inversely related to the time spent in desynchronized—that is, rapid eye movement (REM)—sleep, particularly in patients with manic-depressive disorders (*14*).

Twelve patients (six men and six women, ages 18 to 66 years) hospitalized for treatment of depressive disorders were studied before initiation of antidepressant drug or electroconvulsive treatment. The depressive disorders were classified according to our clinical diagnostic criteria (*1*). There were five manic-depressive depressions, five chronic characterological depressions, one schizoaffective depression, and one recurrent endogenous depression (*15*). Three to ten separate 24-hour urine samples were obtained from each patient during drug-free periods (patients received no psychoactive drugs for at least 1 week before the first collection). Samples were assayed for MHPG [measured by an electron-capture gas-liquid chromatographic method (*16*)] and for creatinine (*17*). Individual values were averaged to obtain an overall value for each patient, which was then used for subsequent intersubject data analysis.

As shown in Table 1, MHPG excretion (expressed as micrograms per 24 hours or per gram of creatinine) was significantly lower in patients with manic-depressive depressions than in patients with chronic characterological depressions (*18*). In the patient with a schizoaffective depression, MHPG excretion was lower than the mean for the manic-depressive depressions; in the patient with a recurrent endogenous depression, MHPG excretion fell between the means for the manic-depressive and chronic characterological depressions.

These differences in MHPG excretion in different subtypes of depressive disorders, which suggest different underlying pathophysiological processes (*19*), may be related to the observation that platelet monoamine oxidase activity is markedly reduced in patients with schizophrenic disorders, decreased to a lesser extent in patients with manic-depressive disorders, but is relatively elevated in patients with other types of depressive disorders (*20*). While it is not known whether platelet monoamine oxidase activity provides an index of monoamine oxidase activity in other tissues (particularly the brain), it is possible that the relatively decreased levels of MHPG in patients with manic-depressive or schizoaffective depressions may, in part, reflect a relative reduction in the intraneuronal deamination of norepinephrine and a consequently lower rate of norepineph-

Table 1. Excretion of MHPG in depressive disorders. Creatinine and MHPG were determined in three to ten separate 24-hour urine samples obtained from each patient, and MHPG excretion was expressed as micrograms per 24 hours and per gram of creatinine. The average value for each patient was used to compute means and standard errors of the mean for the manic-depressive and chronic characterological depressions.

Clinical subtype of depression	*N*	MHPG	
		Micrograms per 24 hours	Micrograms per gram of creatinine
Schizoaffective	1	870	510
Manic-depressive	5	1240 ± 160*	970 ± 190†
Recurrent endogenous	1	1550	1210
Chronic characterological	5	1800 ± 90*	1950 ± 310†

* $P < .02$ for difference between manic-depressive and chronic characterological depressions. † $P < .05$ for difference between manic-depressive and chronic characterological depressions.

rine biosynthesis [due to intraneuronal feedback inhibition of the rate-limiting enzyme, tyrosine hydroxylase (*21*)]. In contrast, the higher levels of MHPG in patients with chronic characterological depressions may reflect an increase in the deamination of norepinephrine by monoamine oxidase.

A correlation of borderline statistical significance between MHPG excretion and age was observed in the total group of 12 depressed patients ($r = .55$). However, this may be related to the fact that the manic-depressive patients in this study tended to be younger than the patients with chronic characterological depressions (*22*); no correlation was found between MHPG excretion and age in a large series of control subjects (*23*).

It has been suggested that the relative decrease in MHPG excretion in some patients with depressive disorders may be secondary to decreased motor activity or stress (*12*). However, in a longitudinal study of manic-depressive patients we observed a relative reduction in MHPG excretion during depressions, despite the fact that these depressed patients were agitated (*7*).

In the total group of 12 depressed patients studied here, we found no significant relationships (as determined by Pearson product-moment correlations) between MHPG excretion and the scores for retardation ($r = .24$), agitation ($r = -.19$), psychic anxiety ($r = -.19$), or somatic anxiety ($r = .11$) obtained on a modified Hamilton depression rating scale (*24*). Moreover, no significant differences were found between the manic-depressive and chronic characterological depressions on these or any other items on the Hamilton scale except for items related to sleep disturbances (*25*); nor were there significant differences in total Hamilton scale scores. Thus, our results provide no support for the suggestion that differences in MHPG excretion in patients with affective disorders reflect only differences in activity or stress (*26*). Similarly, Post *et al.* (*27*), who reported a decreased concentration of MHPG in the cerebrospinal fluid of depressed patients, found no significant correlations between MHPG values and clinical ratings of depression, retardation, agitation, or anxiety.

We also attempted to relate MHPG excretion to certain aspects of central nervous system activity as reflected by all-night electroencephalographic sleep recordings. These were obtained regularly during hospitalization and scored by conventional criteria (*28*). It was of particular interest to examine the relationship between MHPG excretion and time spent in desynchronized—that is, REM—sleep (D time), since pharmacological studies in animals and man suggest that central catecholaminergic activity and D time may be inversely related (*29*), although this has not been confirmed in all studies (*30*). If D time is inversely related to central catecholaminergic activity and if urinary MHPG provides an index of central noradrenergic activity, there should be an inverse relationship between MHPG excretion and D time.

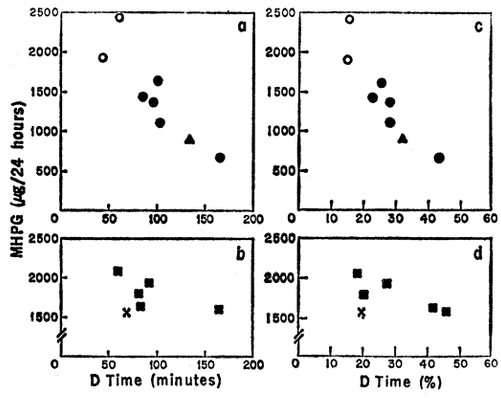

Fig. 1. Relation between MHPG excretion and time spent in desynchronized sleep (D time) in affective disorders. The overall average values for MHPG and D time (expressed in minutes or as a percentage of total sleep time) were plotted for each patient. The data for patients with hypomanias (○), manic-depressive depressions (●), or schizoaffective depressions (▲) are shown in (a) and (c); data for patients with chronic characterological depressions (■) or recurrent endogenous depressions (X) are shown in (b) and (d).

We did observe a statistically significant inverse correlation between MHPG excretion and D time in the total group of 12 depressed patients ($r = -.66$; $P < .02$). To confirm that this correlation reflected a true linear relationship and not simply the existence of two groups, one with relatively low MHPG excretion and high D time and another with relatively high MHPG excretion and low D time, correlations were examined separately in depressed patients with relatively low MHPG excretion (that is, manic-depressive and schizoaffective depressions) and in those with relatively higher MHPG excretion (that is, chronic characterological and recurrent endogenous depressions). The inverse relation between MHPG excretion and D time was evident in the former group (Fig. 1a) but was less apparent in the latter group (Fig. 1b) (*31*).

While other possibilities must also be considered, these results are compatible with the hypothesis that a relatively smaller fraction of urinary MHPG derives from the intraneuronal deamination of norepinephrine in manic-depressive than in chronic characterological depressions, since intraneuronal deamination does not necessarily involve the interaction of norepinephrine with receptors, and MHPG derived from this pathway, therefore, does not necessarily reflect noradrenergic activity. In the brain, MHPG can also derive from norepinephrine that is discharged extraneuronally onto receptors and then *O*-methylated to form normetanephrine (*3, 4*); it is this fraction of the total urinary MHPG that may reflect central noradrenergic activity.

Data for two patients studied during hypomanic episodes (one of whom had been studied when depressed) are also shown in Fig. 1a. Excretion of MHPG was higher and D time was lower during these hypomanic episodes than during depressive episodes, consistent with other studies of patients with manic-depressive disorders (*7, 8, 32*). A high and significant inverse correlation between MHPG excretion and D time was found for all data in Fig. 1a ($r = -.87$; $P < .01$).

No statistically significant correlations were observed between MHPG excretion and total sleep time or slow wave (stages 3 and 4) sleep time in the entire group of patients or in any of the subgroups. However, to ascertain further that the inverse relationship between MHPG excretion and D time was not a function of differences in total sleep time among these patients, the time spent in desynchronized sleep was also expressed as a percentage of the total sleep time (Fig. 1, c and d).

It is conceivable that the inverse correlation between MHPG and D time could be related to age, because in the total patient group there was a positive correlation between MHPG excretion and age and a negative correlation between D time and age. However, we do not think that the inverse relationship between MHPG excretion and D time is simply a function of age, because this inverse relationship was maintained when the subgroup of pa-

tients with manic-depressive and schizoaffective depressions was examined separately (Fig. 1a), although neither MHPG nor D time appeared to be related to age in this subgroup.

In conclusion, MHPG excretion was lower in patients with manic-depressive depressions than in patients with chronic characterological depressions. We also observed a significant inverse correlation between MHPG excretion and D time which was most pronounced in the manic-depressive disorders. Taken in conjunction with pharmacological studies that have suggested an inverse relationship between D time and central catecholaminergic activity, our results support the view that MHPG excretion reflects central noradrenergic activity, particularly in patients with manic-depressive disorders. Further studies in a larger series of patients are needed to confirm and extend these observations.

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25. Patients with chronic characterological depressions tended to score higher on hypochondriasis (and related items) than did manic-depressive patients; however, this difference was not statistically significant ($.20 > P > .10$).
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Equipotentiality Quantified: The Anatomical Distribution of the Engram

Abstract. *Sensory events and the representation of past experience cause distinctive changes in the electrical activity of widespread regions of the brain. These regions have similar roles in the engram in the sense that they all seem to participate in responses to external events and in subsequent representations of these events. However, the relative contribution of these processes to the activity of different brain regions is quantitatively different, in that some regions are much more strongly affected than others. These results may constitute the basis for reconciliation of localizationist and antilocalizationist views of brain function.*

Almost half a century ago, Lashley formulated his well-known law of mass action (*1*), a quantitative assessment of the effects on learned behaviors observed after brain lesions in rats, asserting that the amount of functional loss was roughly proportional to the volume of tissue excised, independent of locus. Implicit in these findings was the law of equipotentiality, that is, a variety of brain regions had the potentiality to perform the functions normally mediated by some specific region in the intact brain. More recent studies of brain damage in man have provided some support for these ideas, in that