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THE EFFECTS OF PSYCHOPHARMACOLOGICAL AGENTS ON CENTRAL NERVOUS SYSTEM AMINE METABOLISM IN MAN

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INTRODUCTION AND CAVEATS

In assessing the effects of psychopharmacological agents on the disposition and turnover of biogenic amines in the central nervous system (CNS) of man, investigators are ethically limited to the use of indirect experimental approaches. Most investigators have focused on changes in concentrations of amine metabolites in cerebrospinal fluid (CSF) that are associated with drug administration, and the greatest attention has been paid to 3-methoxy-4-hydroxyphenethyleneglycol (MHPG), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) as these are the principal metabolites of norepinephrine (NE), dopamine (DA), and serotonin (5-HT), respectively, in the CNS. To a lesser extent, changes in the concentration of urinary MHPG in relationship to drug administration have also been studied in an attempt to understand the effects of psychotropic agents upon CNS NE metabolism. Each of these approaches has certain advantages and inherent limitations, which are briefly reviewed below. It is thought that such comments will help to place in better perspective the data obtained by using these techniques with human subjects.

There is a gradient between ventricular CSF HVA and lumbar CSF HVA of approximately 10:1 (1). Obstructions to flow between the cistern and lumbar spaces are associated with a marked reduction in the concentration of CSF HVA (2–4). DA is found in the spinal cord in very low concentrations (5, 6) and there is a barrier to the movement of HVA from blood into CSF (7, 8). As a group, these studies suggest that HVA in lumber CSF originates principally in structures within brain. The degree to which various structures in brain contribute to lumber CSF HVA is

unknown but it is likely that a significant proportion of the HVA originates in structure that are close to the ventricles, e.g. the caudate nucleii (4, 9). Following the administration of probenecid (which blocks the efflux of HVA from brain), there is a lag time of approximately four hours before lumbar CSF HVA levels begin to increase (10). While this supports the conclusion that most of the lumbar CSF HVA originates in brain it also suggests that relatively transient changes in the functional activity of DA neurons in brain may not be readily detected by examination of concentrations of HVA in lumbar CSF.

There is a barrier to the movement of 5-HIAA from blood to CSF (11, 12) and there is a ventriculolumbar gradient for 5-HIAA of approximately 5:1 (1). Although it has been found that there is a lag between probenecid administration and the increase in CSF 5-HIAA (10), there is a controversy as to the brain versus spinal cord origins of lumbar CSF 5-HIAA. Some investigators have found that with a complete block of the subarachnoid space at the thoracic level lumbar CSF 5-HIAA levels were normal (3, 4), whereas in another study it was found that the concentration of 5-HIAA was significantly reduced below complete blocks (2). A variety of other experimental techniques have been utilized to resolve the question of the brain versus cord origins of 5-HIAA, but because of apparent differences in methodology and perhaps species differences the issue remains unsettled. On balance it would appear that lumbar CSF 5-HIAA is partially derived from brain and partially from cord, but the relative contributions of each is uncertain. [For a review of the data dealing with this problem, see (13).]

There is no ventriculolumbar gradient for MHPG (14). Spinal cord transection in humans is associated with the lowering of lumbar CSF MHPG whereas a block of CSF flow between higher and lower centers is associated with no decrement in lumbar CSF MHPG (3). It has also been noted that CSF MHPG is continually lost through capillaries within the spinal cord and that the degree of this loss differs as a function of the depth of the region within the spinal cord; that is, the deeper the site of production of the metabolite the smaller the proportion that would be expected to reach CSF. For these reasons it seems unlikely that lumbar CSF MHPG will provide an index of NE metabolism in brain. The degree to which lumbar CSF MHPG will reflect NE metabolism in cord has also been questioned (15).

Depending upon the particular technique used as well as the species of animal, estimates of the quantity of urinary MHPG which is derived from the CNS varies. In the rat it has been estimated that between 10 and 30% of urinary MHPG comes from CNS NE (16–18), whereas in the dog and monkey the estimates are in the range of 25–65% (19, 20). In man exact figures are not available but it has been suggested that the amount of urinary MHPG originating in CNS NE metabolism may be quite large (21, 22). All of the methods used are indirect and require certian assumptions and inference. Until more definitive data are available, a reasonably exact idea of the fraction of urinary MHPG originating in brain versus periphery must remain an open question.

Probenecid has been found to block the efflux of weak organic acids from brain and as such it has been reasoned that increases in concentrations of HVA or 5-HIAA which are associated with probenecid may give some measure of the

turnover of the amine under investigation. [Changes in human CSF MHPG following probenecid are either absent or modest and the probenecid technique has not been used extensively in studies of this metabolite (23, 24).] In evaluating data obtained with the probenecid technique the following points should be noted. The administration of probenecid is frequently a stressful experience for the patient in that it is often associated with nausea and vomiting. In at least one case, it has been demonstrated that a psychopharmacological agent alters CSF levels of probenecid (25) and hence the interaction between the effectiveness of the probenecid block and the preceding drug treatment is a question which is of importance but not often studied. The kinetics of the changes in CSF HVA and 5-HIAA produced by probenecid are complicated and the relationship of baseline to postprobenecid concentrations of metabolites may be of importance. However, because of the practical and clinical problems raised by repeating the lumbar puncture, in practice, CSF samples are often obtained only after probenecid administration. In summary, while probenecid is of use in studying the actions of drugs on DA and 5-HT metabolism the data obtained may be semiquantitative.

Despite the problems associated with each of the above approaches, important data have been obtained with these techniques. It should be noted that these data as to the effects of psychopharmacological agents on amine metabolism in patients are of special value in that in contrast to many animal studies they have frequently been obtained from subjects receiving therapeutic doses of drugs for the period of time usually required to obtain therapeutic effects. In addition, these drugs, by definition, have been given to patients having specific psychiatric illnesses rather than normal experimental animals.

This review is limited to effects associated with the use of antipsychotic drugs and agents used in the treatment of affective disorders (mania and/or depression) or other psychotic states, e. g. schizophrenia. Finally, wherever possible the implications of the data for an increase in our understanding of the biological bases of psychopathology is noted.

ANTIPSYCHOTIC DRUGS AND HUMAN CNS AMINE METABOLISM

In 1963 Carlsson & Lindqvist concluded from a series of animal studies that while the antipsychotic drugs chlorpromazine or haloperidol did not alter endogenous brain stores of NE or DA they did produce increases in the metabolites of these amines. Furthermore, these changes were not produced by a phenothiazine, promethazine, which does not possess antipsychotic properties. Although there is still debate as to the mechanisms by which this increase in turnover is produced, results from a number of animal studies are consistent with the original observations by Carlsson & Lindqvist (26). Given these observations that emerged from acute experiments with animals, interest was aroused as to the effects of a number of different antipsychotic drugs upon DA and 5-HT metabolism in patients suffering from a variety of psychotic disorders. In these studies, which are summarized below, the focus has been primarily upon the metabolites of DA and 5-HT in CSF.

In 1968 Persson & Roos (27) reported that two schizophrenic patients who previously had been treated with neuroleptics without effect and who were unmedicated at the time of the study were accidentally given 20 and 40 mg of haloperidol respectively. It was noted that the patient who had received the 40 mg of haloperidol had a twofold increase in CSF HVA, whereas in the other patient CSF HVA did not change. In a subsequent and more systematic study they examined the effects on CSF HVA and 5-HIAA of antipsychotic drugs of the phenothiazine type in 40 chronic schizophrenic patients (28). The patients were divided into groups according to whether they had received high, medium, or low doses of the drugs. All patients were then taken off medication for four days and samples of CSF were obtained. It was found that those patients who had been receiving high or medium doses of drugs had significantly greater levels of CSF HVA than did those patients who had received the low doses of the drugs. There were no differences noted in CSF 5-HIAA.

Bowers et al (29) examined the effects of phenothiazine treatment (equivalent to 600 mg per day of chlorpromazine) on CSF 5-HIAA and HVA levels. They found no significant differences between the predrug and treatment values. It should be noted, however, that all of the schizophrenic patients in this study had received some phenothiazines prior to admission and that the drug treatment CSF specimens were obtained one to four months after the patients had been started on a phenothiazine drug. This last issue is important because of the development of "biochemical" tolerance, as is discussed later in this review. The authors further note that the values for CSF HVA both before and during drug treatment were high and make the comment that this is consistent with data from animal studies that indicate that these drugs produce an increased turnover of brain DA. It is thus possible that the lack of a difference in the quantities of CSF in HVA between the pretreatment and treatment periods was due to the treatment of the schizophrenic patients with antipsychotic drugs prior to entry into the study and/or the development of tolerance. No differences in CSF 5-HIAA were noted between the pretreatment and treatment periods.

Fyrö et al (30) examined the effects of chlorpromazine on CSF HVA levels of schizophrenic patients using a more sensitive and specific method, i. e. mass fragmentography. Further, the patients in this study had an extended washout period of two months and were given a single drug, chlorpromazine, in the range of 200 to 600 mg per day for 12 days. They found that women had significantly higher HVA levels than did men, but that for both sexes treatment with chlorpromazine produced a twofold or greater increase in CSF HVA. Interestingly enough, they also found a negative correlation between the dose of chlorpromazine and the increase in CSF HVA; that is, the lower the dose of chlorpromazine the greater the increase in HVA during treatment.

Chase et al (31) examined the effects of antipsychotic drugs on CSF HVA and 5-HIAA in a chronic schizophrenic patient group with particular emphasis upon the relationship of amine metabolites to drug-induced extrapyramidal disorders. Three patients groups were chosen. Group one was composed of chronic schizophrenic patients who had received no drug treatment for at least two weeks. Groups

two and three were patients who had been on a variety of phenothiazine drugs for periods of greater than one year with patients in Group two being those who had no extrapyramidal signs and those in Group three being patients with extrapyramidal disorders. It was found that there were differences between Groups one and two in terms of CSF HVA and 5-HIAA; that is, these metabolites were increased in the group of patients receiving drugs. In contrast, many of those patients who had extrapyramidal side effects had metabolite levels similar to those in Group one. The authors speculated that compensatory increases in amine metabolism may be impaired in subjects having extrapyramidal disorders. If one excludes the issue of motoric dysfunctions as induced by the drugs, the data from this study are generally supportive of the concept that phenothiazine drugs in man produce an increased turnover of DA and perhaps 5-HT.

Beginning in 1972 a series of studies appeared in which the problem of DA and 5-HT metabolism as influenced by the antipsychotic drugs was again evaluted but with the use of probenecid. Sjöstrom & Roos (32) examined the effects of probenecid versus probenecid plus methylperidol (a neuroleptic). They found that the probenecid plus the methylperidol produced a further increase in 5-HIAA which was significant, whereas there was only a trend toward a further increment in HVA. In another study they determined CSF HVA and 5-HIAA during a baseline period, following probenecid, and finally following probenecid plus methylperidol. The results of this second study were similar to those obtained in the first one. In addition, Sjöstrom & Roos used as their control subjects patients who had a variety of neurological diseases; they noted that many of these comparison subjects had been taking neuroleptics of the phenothiazine or butyrophenone type for some time and that there was no differences in CSF HVA or 5-HIAA between those subjects who did, and those who did not, take neuroleptics.

Using the probenecid technique, Bowers (33) examined the effect on CSF 5-HIAA and HVA in patients treated with phenothiazines, haloperidol, and in some cases benztropine. Twenty-five acutely psychotic patients made up the study group and patients were maintained off drugs for at least two weeks prior to obtaining the baseline CSF specimens. Following the institution of antipsychotic drug treatment, CSF specimens were again obtained after a two to six month period. It was found that HVA but not 5-HIAA was significantly increased by drug treatment. There was, however, no correlation between the increase in HVA and the dosage of medication used, nor did the use of the anticholinergic agent, benztropine, appear to have a relationship to changes in HVA. Parenthetically, it should be noted that Guldberg et al found that ventricular quantities of CSF HVA or 5-HIAA were not changed by some commonly used anticholinergic drugs (34).

Bowers noted that in several of the studies that examined the relationship between antipsychotic drugs and changes in CSF metabolites, there was a significant incidence of extrapyramidal side effects that occurred in conjunction with the use of these drugs, and as such, the question arose as to whether or not the noted changes of HVA in CSF occurred as a function of the extrapyramidal side effects or as a function of the antipsychotic properties of the drugs. He approached this problem via the use of thioridazine which has a low incidence of extrapyramidal disorders

associated with its usage. In this study, fourteen patients diagnosed as being within the schizophrenic spectrum were maintained drug free for two weeks and a CSF specimen following probenecid was obtained. Thioridazine treatment was then started, and another CSF specimen following probenecid was obtained 18 to 44 days after the beginning of treatment. It was noted that significant extrapyramidal side effects were found in only one patient but that there was a significant increase in CSF HVA induced by thioridazine. Bowers also found that treatment with thioridazine resulted in a significant reduction of 5-HIAA in CSF; however, he also found that the drug produced a decrease in CSF probenecid levels and concluded that the effects of 5-HIAA were probably artifactual (25). The finding that this particular drug can influence CSF levels of probenecid should serve as a note of warning to future investigators that it cannot be assumed that antipsychotic drugs have no effect upon probenecid levels in the CSF.

Gerlach et al (35) examined the relationship between extrapyramidal reactions and amine metabolites in CSF during haloperidol and clozapine treatment of schizophrenic patients. This study was particularly well designed in that it was done in a double-blind fashion with drug crossovers, and CSF specimens were obtained at 0, 4, and 21 days for both drugs. Furthermore, there was a washout period of three weeks prior to the beginning of the first and second drugs. It was found that with haloperidol treatment the HVA levels were increased over baseline at four days and there was a tendency to return toward baseline by 21 days. Clozapine induced a fall in HVA of 34%, which was statistically significant, but after 21 days of treatment the CSF HVA levels were not significantly different from baseline. The concentration of 5-HIAA was not affected by treatment with haloperidol but was significantly decreased after four days of treatment with clozapine, although after 21 days of treatment the levels of 5-HIAA were not significantly different from baseline. CSF probenecid levels were not assayed in this study.

Post & Goodwin (36) focused specifically upon the temporal effects of antipsychotic drug administration in relationship to changes in CSF HVA levels. Their patients were not followed longitudally and the number of patients treated for the short period of time was relatively small; however, their data are generally consistent with that of other investigations; that is, after 15–19 days of treatment with phenothiazines there was an increase in CSF HVA, but there was no significant difference after treatment for 25 to 77 days. These investigators also examined five patients who were treated with pimozide and found that in three of these patients the initial elevation in HVA that occurred between days five and twelve of treatment were not seen after 16 to 26 days of treatment.

Rüther et al (38) studied the temporal relationships between changes in CSF HVA and 5-HIAA and shifts in psychopathological states (paranoid-hallucinatory syndrome) associated with treatment with haloperidol. They found significant differences in CSF HVA (but not 5-HIAA) five days after drug treatment although the change in psychotic symptoms was slight. After 15 days of treatment significant antipsychotic effects were observed, but there was only a trend toward a significant difference in CSF HVA. In another study from the same group, Schilkrut et al (37) examined the relationships between changes in psychopathological symptoms, ex-

trapyramidal side effects, and CSF HVA and 5-HIAA during treatment with haloperidol. They found at 15 days that there were significant antipsychotic effects, that parkinsonism scores had increased slightly, and that CSF HVA, but not 5-HIAA, was significantly increased.

In summary, the following statements may be made regarding the effects of the antipsychotic drugs on central nervous system amine metabolism in man.

1. Although there are exceptions, most investigators have found increases in human lumbar CSF HVA following the administration of structurally dissimilar drugs which have in common, however, antipsychotic properties. This increase in CSF HVA is probably due to an increased turnover of DA. This finding is consistent with data that have been obtained by more direct approaches in experimental animals.

2. The study by Gerlach et al (35) is particularly important in that these investigators have found that clozapine, an antipsychotic drug, produced a decrement rather than an increment in CSF HVA and 5-HIAA when given acutely. Since clozapine possesses antipsychotic properties the decrement (rather than an increment) in CSF HVA poses problems for a DA theory of schizophrenia.

3. The situation with 5-HIAA is less clear than with HVA. Several investigators have not found changes in CSF 5-HIAA, with or without probenecid, following the administration of antipsychotic drugs but there are some important exceptions. In general, where changes in 5-HIAA have been found, they appear to be less dramatic than those that occur with HVA.

4. Increases in CSF HVA following the administration of antipsychotic drugs occur even though extrapyramidal symptoms are not present.

5. Inspection of the data presented in several reports indicates that with chronic adminstration of the antipsychotic drugs there is a tendency for amine metabolite concentrations to return toward predrug levels. This development of "tolerance" is also compatible with data obtained from experiments with animals.

6. A relationship between drug-induced changes in CSF amine metabolites and alterations in clinical state has not been established. This issue of CSF amine metabolite concentration and therapeutic change has not, however, been intensively studied.

ANTIDEPRESSANT DRUGS AND HUMAN CNS AMINE METABOLISM

In an initial report, Bowers et al (29) noted that patients who were being treated with amitriptyline had significant reductions in CSF 5-HIAA relative to a baseline period. In contrast, no significant differences in homovanillic acid concentration during the two periods were seen. In a subsequent study Bowers (39) used the probenecid technique to further examine the effects of amitriptyline upon the accumulation of 5-HIAA and HVA in lumbar CSF. In this study the patient group consisted of 11 subjects who were diagnosed as having unipolar depressions with the dose range of amitriptyline being 150–300 mg per day. Baseline and repeat CSF specimens (after probenecid) were taken after six to eight weeks of drug treatment.

It was found that during the period of drug treatment there was a significant decrease in CSF 5-HIAA and a trend toward a decrease in HVA. In another study Bowers further found that levels of L-tryptophan in the CSF before and during treatment with amitriptyline were the same, suggesting that the differences in CSF 5-HIAA during drug treatment were not secondary to precursor availability (40).

Papeschi & McClure (41) also noted similar significant decreases in CSF 5-HIAA but not homovanillic acid following two weeks of imipramine treatment. Post & Goodwin (42) noted that the treatment of patients with amitriptyline or imipramine was associated with a decreased accumulation of 5-HIAA in CSF, but they found no differences for HVA. Sjöstrom & Roos (32) compared the effects of antidepressant tricyclic drugs (not further specified) versus some other "adequate medication" for depressed subjects but found no differences for the two groups between CSF 5-HIAA and HVA. Mendels et al (43) noted that there was a small increase in CSF 5-HIAA after treatment of manic-depressive, depressed patients and a slight drop in 5-HIAA after treatment of the manic patients. In constrast, it was noted that in a small number of subjects there was an increase in CSF HVA after the treatment. Although it can be assumed that some specific form of antimanic or antidepressant treatment was given, the type of drugs used was not indicated and hence the data are difficult to evaluate.

Jori et al (44) examined the effects of ECT and imipramine treatment on the concentrations of CSF 5-HIAA and HVA of depressed patients. Lumbar punctures were performed both before and after probenecid administration prior to and after antidepressant treatment. The pretreatment lumbar punctures were performed five to seven days apart and the third and fourth lumbar punctures were performed seven days after the ECT or the last dose of imipramine and the fourth and final lumbar punctures (with probenecid) five to seven days later. It was found that ECT treatment was associated with an increase in the absolute (preprobenecid) values of CSF HVA and 5-HIAA whereas imipramine treatment was not. When the accumulation of the two acids as a function of probenecid administration was examined it was found that there were no significant differences between the pretreatment and treatment periods for either ECT or imipramine. It should be noted, however, that the fourth lumbar puncture in this study was performed two weeks following the cessation of drug treatment and this artifactual washout period may account for the discrepancy between the results found by this group of investigators and those of others.

Asberg et al (45) examined the effects of nortriptyline administration on CSF 5-HIAA and IAA. In this study the metabolites were assayed using the method of mass fragmentography and all patients had been on medication for three weeks prior to the performance of the second lumbar puncture. It was found that during treatment the concentrations of 5-HIAA and IAA decreased significantly, but the decrements were not correlated with plasma levels of nortriptyline. Bertilsson et al (46) determined CSF MHPG and 5-HIAA levels in CSF both before and during the treatment of depressed patients with chlorimipramine or nortriptyline. The second CSF specimen (during treatment with one of the noted antidepressant drugs) was obtained three weeks after the beginning of treatment. It was found that MHPG

levels in CSF decreased significantly with treatment with either chlorimipramine or nortriptyline. Nortriptyline treatment was also associated with a decrement in CSF MHPG, but in contrast to the earlier study of Asberg et al (45) there was no change in CSF 5-HIAA during the treatment with nortriptyline.

Three separate groups of investigators (47–49) have demonstrated that treatment of patients with imipramine results in marked decrements in the urinary excretion of vanilylmandelic acid (VMA) and an increment in urinary normetanephrine (NM) (which did not, however, equal the decrement in VMA). The experimental approaches in these investigations did not allow for a definitive interpretation as to the mechanisms that might be involved, although it appeared that a decrement in overall synthesis of catecholamines was being produced by imipramine. If therapeutic outcome is ignored (see later), imipramine treatment is not associated with a significant change in urinary MHPG.

In addition to the above-noted general pharmacological effects on amine metabolism of a variety of tricyclic antidepressant drugs, there are preliminary data that suggest that the changes in amine metabolism and/or dispostion that occur with treatment with the tricyclic drugs may vary with the repsonse of the patient to a particular drug and conversely that pretreatment amine metabolite levels may be associated with response, or a failure of response, to a particular drug.

As an example, Maas et al (49) reported that patients who responded well to imipramine or desmethylimipramine had low pretreatment 24-hr urinary MHPG values and that when MHPG was assayed during the fourth week of treatment with these drugs, the level of MHPG in the urine for the responder group showed modest increments or no change. In marked contrast were those patients who had normal or high pretreatment MHPG concentrations; that is, these patients tended not to respond to imipramine or desmethylimipramine, and during the fourth week of treatment there was a marked decrement in urinary MHPG. While pretreatment urinary NM was not associated with a response to imipramine or desmethylimipramine those patients who responded particularly well to imipramine or desmethylimipramine had marked increases in NM during the fourth week of treatment relative to baseline periods. There was a significan
whether or not the patients responded to treatment. Schildkraut et al (50) found in a preliminary study that high or normal baseline urinary MHPG was associated with a favorable response to amitriptyline. Beckmann & Goodwin (51) also found that low pretreatment urinary MHPG concentrations were associated with a good response to imipramine and a failure to respond to amitriptyline. They also noted that normal or greater than normal amounts of MHPG in urine were associated with a favorable response to amitriptyline and failure of response to imipramine. However, in contrast to the findings of Maas et al (49), imipramine treatment was associated with a decrease in urinary MHPG in the responder group.

Asberg et al (45) made the observation that while as a group nortriptyline produced a decrement in 5-HIAA and IAA in CSF, if one looked at the patients in terms of those having low versus high CSF 5-HIAA levels, a different pattern emerged. In seven of the patients who had pretreatment 5-HIAA levels below 15 ng/ml of CSF, the 5-HIAA concentration increased in five patients and decreased

in two. In contrast, in the 13 patients with an initial 5-HIAA concentration higher than 15 ng/ml the 5-HIAA levels decreased in all.

Van Praag & Korf (52) have published preliminary data indicating that the therapeutic response of patients to 5-hydroxytryptophan may be associated with the pretreatment rate at which patients accumulate 5-HIAA in CSF following probenecid; that is, those depressed patients having the smallest increments in 5-HIAA accumulation after probenecid do best when given 5-hydroxytryptophan. Goodwin & Post (53) observed that tricyclic drug treatment was associated with a slight increase in CSF MHPG among those patients who were classified as responders but that there was a significant decrease in MHPG among the nonresponders. They note that the responder/nonresponder difference in the tricyclic effect on MHPG was highly significant ($P<0.001$). They also note that patients who subsequently responded to treatment with the tricyclic drugs had higher pretreatment accumulations of 5-HIAA and HVA following probenecid as compared with those who did not respond (the types of tricyclic drugs used in these studies were not specified).

The above studies are of interest because they indicate that some types of biochemical responses that one obtains with treatment with a particular drug may vary as a function of the therapeutic outcome. In addition, these reports support the concept that depression is a biochemically heterogeneous illness and have led to the suggestion that there are biochemical and pharmacological criteria by which two types of depression may be separated (54).

In summary the following CNS amine metabolite changes have been found with antidepressant drug treatment.

1. Most investigators have found that amitriptyline or imipramine administration to depressed patients for three weeks or longer is not associated with changes in CSF HVA accumulation following probenecid. This finding is in agreement with animal studies which indicate that at doses similar to those that are used therapeutically the tricyclic antidepressants have little effect upon brain DA systems.

2. Although there are discrepant findings, it would appear that treatment of depressed patients with amitriptyline or imipramine for three weeks or longer is associated with a decrement in the accumulation of CSF 5-HIAA after probenecid administration. This finding is consistent with data from animal studies that indicate that these two drugs produce a decrease in brain 5-HT turnover.

3. Changes in MHPG associated with tricyclic antidepressant drug treatment have been less well studied than those of 5-HIAA and HVA. There is some suggestive evidence, however, which indicates that this metabolite may change as a function of the therapeutic response of the patient, i.e. patients who respond well to treatment may have modest increments in MHPG whereas nonresponders have marked decrements. Further, there is agreement among different groups of investigators that pretreatment levels of urinary MHPG are predictive of a response, or failure of response, to amitriptyline versus imipramine. It thus appears that there may be interactions between pretreatment amine metabolism, the type of tricyclic drug used, therapeutic response, and the type of biochemical change associated with the drug being used.

LITHIUM TREATMENT AND CNS AMINE METABOLISM

In 1971 Mendels reported that two manic patients who had been treated with lithium for 85 and 57 days had a marked increment in CSF 5-HIAA during the treatment period as compared to the prelithium period (55). Wilk et al noted that there was a sharp increase in CSF 5-HIAA with a moderate increase in HVA in two manic patients who were treated with lithium carbonate. The time of treatment in this study was not specified (56). In contrast to these preliminary findings neither Bowers (29) nor Sjöstrom & Roos (32) found any effects on 5-HIAA or HVA in CSF as a consequence of lithium treatment. It should be noted, however, that in the Bowers et al study the time on lithium was not specified. In addition, in the Sjöstrom & Roos study 57 manic patients were studied but one third of these had been on lithium before inclusion in the research and some of the manic patients received antipsychotic drugs during the time of treatment. Some of these design and pharmacological problems may have confounded the results.

Fyro et al (57) studied a group of 13 acutely manic or hypomanic patients. None of the patients had received any drugs for at least one month prior to study. CSF specimens were obtained both prior to beginning lithium and 12 days after the start of lithium treatment. Plasma levels were maintained within the therapeutic range of 0.7 and 1.4 meq/liter. It was found that the quantities of CSF 5-HIAA as well as HVA increased significantly during the treatment period.

Goodwin & Post (58) in contrast to the other studies examined the effects on CSF metabolites of lithium carbonate in depressed rather than manic patients. They found that during the treatment period depressed patients had probenecid-induced accumulations of 5-HIAA which were low in comparison to the prelithium period. HVA was not significantly altered between the treatment and nontreatment periods. It is of interest that the changes in 5-HIAA induced by or accompanying lithium treatment in depressed patients were in the opposite direction of those found with manic subjects.

Wilk et al (56) found that treatment with lithium carbonate of two manic patients produced a marked decrease in CSF MHPG. Both patients had good clinical responses to lithium. Schildkraut (59) noted that there was a sharp increase in urinary MHPG which occurred coincident with the beginning of lithium treatment and lasted for approximately seven to ten days. Even though the patient was continued on lithium, however, the urinary MHPGs then returned toward baseline levels and remained there for the next 35 days. Beckmann et al (60) treated ten depressed patients (eight bipolar and two unipolar) with lithium carbonate and looked at both the therapeutic responses of the patients and the changes in urinary MHPG that occurred during the lithium treatment. In their group they found that there were four patients who were unequivocal responders and six patients who were nonresponders to lithium treatment. They noted that during the first week there was no consistent change in urinary MHPG but looking at the third to fourth week of treatment all of the responders had increases in urinary MHPG values and all nonresponders had a decrement in urinary MHPG or no change in this NE metabolite.

In summary there are relatively few studies of the effects of lithium upon CNS amine metabolism in man but taking into account a variety of methodological issues it appears that lithium treatment of manic patients is associated with an increase in CSF 5-HIAA and HVA. This finding is consistent with the report that lithium induces an increased turnover of brain amines in animals. However, the finding by Goodwin et al (58) that depressed patients in contrast to manic patients have a *decrement* in CSF 5-HIAA accumulation during treatment with lithium indicates that the pharmacological response of patients may vary as a function of the type or phase of the illness. The report (60) which indicates that depressed patients who respond to lithium have changes in MHPG that differ from those of nonresponders again raises this issue.

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