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The Effect of Lithium on Platelet Monoamine Oxidase Activity in Bipolar and Schizoaffective Disorders

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Summary: Platelet monoamine oxidase (MAO) activity was studied in 33 in-patients with bipolar and schizoaffective disorder who were treated with lithium. Platelet MAO activity was found to increase following 10-41 days of lithium treatment compared to a prior drug free period, and the increase was positively correlated with the duration of lithium treatment. The increase in platelet MAO activity was not correlated with clinical improvement as measured by the Brief Psychiatric Rating Scale (BPRS) and the Global Assessment Scale (GAS). The number of platelets per unit of blood was also significantly correlated with the number of days of lithium treatment. However, the increase in the number of platelets in lithium-treated patients was not correlated with the increase in MAO activity and thus appears not to account for it. These results indicate that studies relating platelet MAO activity to psychiatric diagnosis should be interpreted cautiously if patients are receiving lithium carbonate.

Monoamine oxidase (MAO) is an enzyme which catalyzes the metabolism of biogenic amines such as dopamine, norepinephrine, and serotonin, and probably of trace amines such as octopamine, phenethylamine, and tyramine (Edwards, 1980). The synthesis, action, and/or disposition of these neurotransmitters has been hypothesized to be abnormal in affective disorders (e.g., Cowdry and Goodwin, 1978). Thus, individual differences in neurotransmitter-related enzymes such as MAO provide insight into abnormal neurotransmitter function which may be present in affective disorder. Since it is not usually possible to study brain MAO directly and because the platelet and brain share some properties with regard to serotonin metabolism, the platelet is frequently used as a model for brain MAO (Stahl, 1977). Platelet MAO is the Type B form of MAO which is also found in the brain (Edwards, 1980).

Lithium carbonate has been shown to have numerous effects on the synthesis, release, inactivation and interaction with receptors of neurotransmitters such as norepinephrine, serotonin and dopamine but none have been definitively related to the therapeutic actions of lithium. Since low platelet MAO activity has been associated with bipolar disorder in some studies (Landowski *et al*, 1975; Leckman *et al*, 1977; Sullivan *et al*, 1977), it would be useful to know whether lithium causes any direct or indirect changes in this regulatory enzyme, particularly in the direction of an increase or 'normalization' of activity.

There are several reports on the effect of lithium on platelet MAO activity that are based on studies in which a between subjects design was used. Patients receiving lithium therapy are compared with other patients not receiving lithium; often such comparisons are post hoc and based on small subsamples of patients who were subjects in a larger study of enzyme activity in relation to psychiatric diagnosis. Generally, no effect of lithium on MAO activity is found, and this result is used to justify the inclusion of lithium-treated patients in the diagnostic study. The conclusion that there is no drug effect may be misleading in this case because of the large variation in baseline enzyme activity among individuals. Determination of both baseline and drug platelet MAO in the same subject, i.e., a within subjects design, is necessary for a definitive study of the effect of lithium on platelet MAO activity.

Two studies of the effect of lithium on platelet MAO, in which a within subjects design was used, point to an increase in enzyme activity (Bockar *et al*, 1975; Mann, 1979). These investigators used ^{14}C-benzylamine as substrate and patients were diagnosed as having cyclothymic or bipolar disorder. On the other hand, Berrettini *et al* (1979) failed to find any change with lithium treatment in Km or Vmax using dopamine as substrate in six patients with bipolar disorder. Whether lithium has an effect on platelet MAO in patients with psychiatric disorder other than bipolar disorder such as schizoaffective disorder and

unipolar disorder (Mann, 1979) or in normal subjects (Pandey *et al*, 1975) is also unclear. The effect of lithium on platelet MAO activity in bipolar disorder and in schizoaffective disorder is the subject of this investigation.

Method

Patients were research unit inpatients at the Illinois State Psychiatric Institute who were treated with lithium. They gave written informed consent for this study. The main analysis included 15 manic, 7 bipolar depressed, 9 schizoaffective manic, and 2 schizoaffective depressed patients. They ranged in age from 19–61 years (mean age 29 ± 9 years), and 15 were female and 18 were male. Diagnoses were made according to the Research Diagnostic Criteria (Spitzer *et al*, 1978) by consensus of the research team using data from structured interviews at admission and throughout hospitalization. The 57 control subjects were research and hospital staff and paid volunteers. Five additional bipolar and schizoaffective patients were added for a subsequent analysis of the relationship between time on lithium treatment and change in platelet MAO activity.

Patients underwent a withdrawal period from all previous medication with the occasional exception of benzodiazepines and chloral hydrate. After the patients had been in the drug washout period for at least 7 days, between one and three blood samples were obtained for determination of baseline platelet MAO activity. Patients with other medication between the initial baseline and lithium treatment were included as long as there was a seven day (four weeks for fluphenazine decanoate) washout period from these other medications. Blood samples were obtained on 1, 2, or 3 occasions for determination of platelet MAO activity after the patients had been receiving lithium for 10 days or more. For subsequent analyses related to time on lithium treatment, data were included for days 5–9 of lithium treatment. Lithium levels were routinely checked while patients were on lithium for clinical reasons and if the lithium level fell below therapeutic level, i.e., below 0.5, on a day on or near the day a sample was drawn for determination of enzyme activity, the measurement was excluded from the analysis. However, lithium levels were not available for three patients. Blood samples were obtained from control subjects on two occasions separated by a 1–3 month time interval.

Blood was drawn in plastic syringes and immediately transferred to polypropylene tubes containing 1.5 ml acid-citrate-dextrose (ACD) anticoagulant for every 8.5 ml of blood. The blood samples were kept at 10°C for no more than two hours prior to the isolation of platelet-rich-plasma (PRP).

The method used to measure platelet MAO has been described previously (Jackman and Meltzer, 1980; Murphy *et al*, 1976). In brief, platelet-rich-plasma (PRP) was obtained by centrifugation of blood samples, mixed with ACD anticoagulant, at $600 \times g$ for 2.5 min at 4°C in a Sorvall RC-5 centrifuge using a fixed angle SS-34 rotor. An aliquot of the PRP was used to determine the platelet count with a Coulter Counter. PRP was then added to each reaction tube. Two tubes were used for each PRP sample, one containing pargyline (2.4×10^{-4}M) and one without pargyline. Platelet MAO activity is completely inhibited by pargyline while plasma amine oxidase (PAO) activity is not affected. The selective inhibition of the platelet enzyme permits measurement of combined MAO and PAO activities, and each component (Murphy *et al*, 1976). ^{14}C-benzylamine, at a concentration of 400 μM, was the substrate. Platelet MAO activity is reported as nmoles benzaldehyde/hr/10^8 platelets. The coefficient of variation using this procedure in our laboratory (all samples are run in duplicate) is less than 4.0 per cent.

The Global Assessment Scale (GAS) and the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) were administered during the first week following admission and again during the week of discharge from the hospital. Two clinical change measures were derived by taking the difference between the discharge and admission scores on these scales.

Results

Table I shows the means and standard deviations for platelet MAO activity separately for each sex, diagnostic group, and for patients in the manic and depressed state. An analysis of variance for repeated measures was calculated suing the following variables: sex × diagnosis × (pre/post lithium = repeated measures factor). The ANOVA revealed significantly greater platelet MAO activity in females compared to males ($P < .01$) and a significant increase in platelet MAO activity on lithium compared to baseline ($P < .04$). Changes in MAO activity during lithium treatment ranged from −29 per cent to +86 per cent with an average 14 per cent increase over all 33 patients. The percentage increase was higher in the bipolar group with nineteen of the 22 bipolar patients showing an increase, but only 5 of the 11 schizoaffective patients.

Evidence that these changes were not due to assay variance over time is provided by the normal control group. Platelet MAO activity was determined on two occasions at intervals of 1–3 months in 57 normal subjects, and, the difference in mean MAO activity between these two samples was negligible (Table I).

TABLE I

Lithium effect on mean platelet MAO activity (in Nmoles benzaldehyde/hr/10^8 platelets)

Group	Males N	Males Baseline	Males Lithium	Females N	Females Baseline	Females Lithium
Bipolar disorder:						
Depressed	4	9.6±2.1	12.3±3.4	3	11.7±4.0	13.3±7.1
Manic	8	9.0±2.5	11.4±3.6	7	12.1±5.5	14.3±5.4
Schizoaffective disorder:						
Depressed	1	4.1	7.2	1	15.4	13.9
Manic	5	11.6±2.5	10.3±1.9	4	14.6±2.9	15.6±3.6
Normal controls		Males and Females				
First determination	57	11.4±3.6				
Second determination	57	11.6±4.6				

Summary of repeated measures ANOVA

Source	df	Mean square	F	Probability
Diagnosis	1	0.16	0.01	0.94
Sex	1	189.13	6.87	0.01
Depressed/manic	1	19.56	0.71	0.41
Diagnosis × sex	1	45.34	1.65	0.21
Diagnosis × depressed/manic	1	20.37	0.74	0.40
Sex × depressed/manic	1	6.79	0.25	0.62
Diagnosis × sex × dep/man	1	24.29	0.88	0.36
Error	25	27.53		
Change MAO lithium	1	16.16	4.61	0.04
Change MAO × diagnosis	1	8.91	2.54	0.12
Change MAO × sex	1	1.94	0.55	0.46
Change MAO × dep/man	1	0.30	0.09	0.77
Change MAO × diag × sex	1	0.12	0.03	0.86
Change MAO × diag × dep/man	1	0.83	0.24	0.63
Change MAO × sex × dep/man	1	9.42	2.69	0.11
Change MAO × diag × sex × dep/manic	1	5.55	1.58	0.22
Error	25	3.51		

Reliability coefficients were high both for control subjects (r = 0.76) and for patients (baseline r = 0.79, lithium r = 0.74).

The correlation between change in MAO activity and baseline MAO activity was r = −.22 which was not significant. The correlation between change in platelet MAO and lithium level within the therapeutic range of lithium levels (i.e., 0.6 to 1.7) was also not significant (r = +.05).

Five additional patients who had measurements of platelet MAO activity between day 5 and day 9 of lithium treatment were added to the original sample of 33 in a study of the time course of the increase in platelet MAO activity on lithium. The results indicated that the increase in MAO activity was greater the longer the patients received lithium (r = +.41, P .001, 38 patients, n = 72). Most patients had more than one measurement of MAO activity at different time points on lithium treatment, and therefore these patients were included more than once in the above analysis. However, the correlation was also significant when only the first determination of enzyme activity for each patient was used (r = +.63, P .001, 38 patients, n = 30). Fig 1 shows the time course for change in platelet MAO activity with lithium treatment.

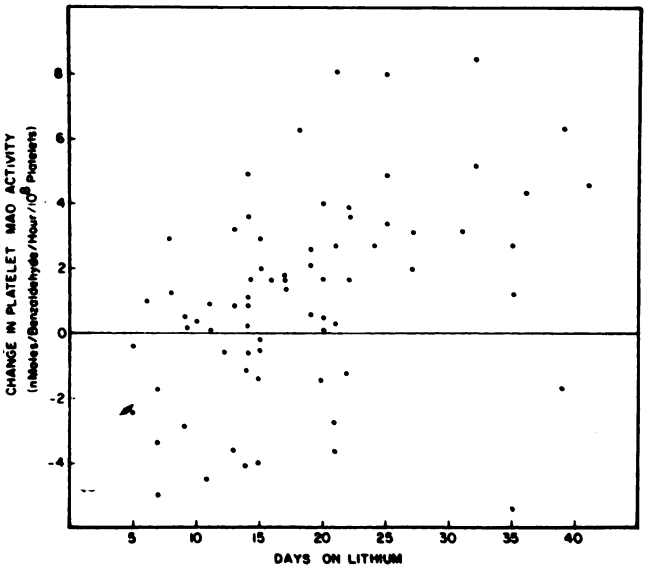

FIG 1.—Scattergram showing the time course for the difference between platelet MAO activity on lithium and platelet MAO activity at baseline. Data points above the zero difference line represent increases in MAO activity during lithium treatment and data points below indicate decreases. Data from 38 patients are represented but most patients had two, and occasionally three, measurements of platelet MAO at different time points during their lithium treatment resulting in 72 data points.

Platelet count was examined for 18 of the 33 patients included in the main study. Change in platelet count was positively correlated with the number of days the patient received lithium as shown in Fig 2a (r = +.59, P .001, 18 patients, n = 32). For comparison, the change in MAO activity on lithium for these same patients is shown in Fig 2b (r = +.63, P .001, 18 patients, n = 32). The time course of change in enzyme activity and the time course of change in platelet count are similar. However, the correlation between change in platelet count and change in MAO activity was not significant either with days on lithium partialled out (r = −.12) or without days on lithium partialled out (r = +.30). It can also be seen from Fig 2 that the increase in platelet MAO occurs slightly earlier than the increase in platelet count: with the change in platelet count tending to be negative up to about day 15 of lithium treatment.

Nearly all of the patients improved with lithium treatment. There was, however, no relationship between change in enzyme activity on lithium and change in the BPRS or GAS scores. Similarly, there was no relationship between change in platelet count and clinical response in the subsample of 18 patients.

Discussion

The increase in platelet MAO with lithium treatment in bipolar disorder found in the present study is in agreement with the studies of Bockar *et al* (1975) and Mann (1979) both of whom also used benzylamine C^{14} as the substrate. The average increase of 22 per cent in the bipolar group was not as high as the 50–65 per cent change reported by these investigators. This discrepancy could be explained by the fact that patients in their studies were on lithium longer. Similarly, the decrease in platelet MAO found by Pandey *et al* (1975) in normal subjects given lithium may have been due to the fact that platelet MAO determinations were made after only 5 days of lithium administration.

It is also possible that differences in magnitude of the increase in platelet MAO on lithium between the present study and previous studies is due to the fact that subgroups of bipolar disorder exist and our patient sample was representative of a different subgroup. Our bipolar patients as a group, in fact, did not have lower than normal baseline platelet MAO activity as has sometimes been reported (Eckert *et al*, 1980; Fieve *et al*, 1980; Landowski *et al*, 1975; Leckman *et al*, 1977; Murphy and Weiss, 1972; Sullivan *et*

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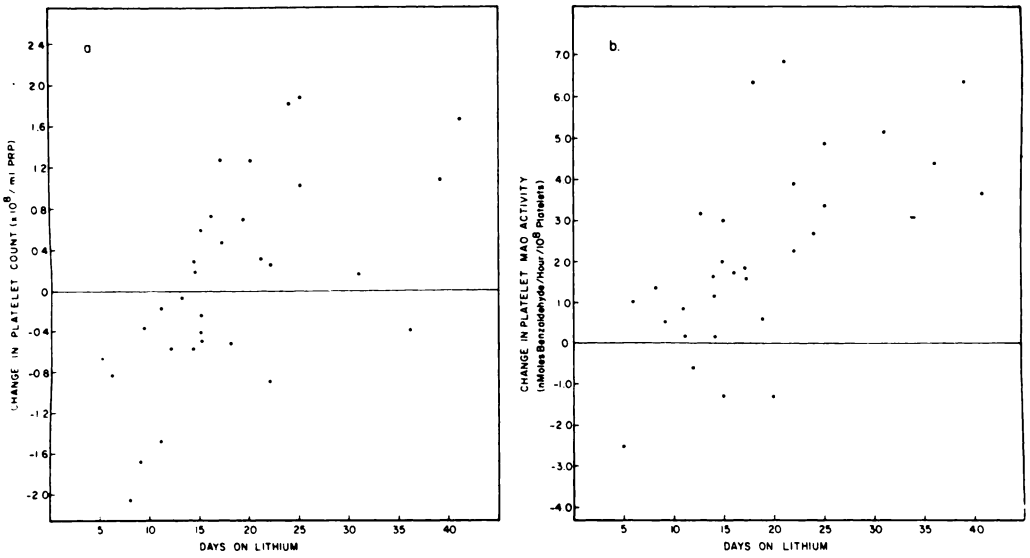

FIG 2.—Scattergrams showing the time course for the difference between lithium and baseline measurements of (a) platelet count, and (b) platelet MAO activity. Data points above the zero difference line represent increases in the variable during lithium treatment and points below the line indicate decreases. Data are from 18 patients, a subsample of the 38 patients whose data are presented in Fig 1. Most of the 18 patients had more than one measurement of these variables during their lithium treatment resulting in 32 data points.

al, 1977). In regard to the issue of diagnostic specificity of the effect, it should be mentioned that significant increases in platelet MAO on lithium have not been found in unipolar patients (Mann, 1979) or in normals (Pandey *et al*, 1975). There was also a tendency for the increase to be less pronounced in schizoaffective patients than in bipolar patients in the present study.

It is difficult to infer processes underlying these lithium associated enzyme activity changes. Animal studies of lithium-induced changes in monoamine neurotransmitter functioning suggest that lithium may act in several ways. It is unlikely that the increase in platelet MAO is due to a direct effect of lithium on platelet MAO. Lithium increases MAO *in vitro* only at higher than usual clinical level concentrations (Mann, unpublished observations as cited in Mann, 1979). The long delay before the increase in platelet MAO activity on lithium treatment is observed would also tend to argue against the increase being a direct effect of lithium on the enzyme. One interesting lead in regard to underlying process is that the increase in platelet MAO activity on lithium is correlated with an increase in 5-HIAA (Heninger *et al*, 1974).

Platelet count was analyzed in the present study because an increase in platelet count with lithium treatment count could reflect a change in the population of platelets (Jackman and Meltzer, 1980). A larger proportion of younger platelets, richer in MAO, could explain the observed lithium related increase in platelet MAO activity. The positive relationship between change in platelet count and time on lithium found in the present study corresponds to earlier reports of an increase in platelet count on lithium (Billie *et al*, 1975; Medina *et al*, 1980).

Although failure in the present study to find a significant correlation between change in platelet MAO activity and change in platelet count does not rule out the possibility that an increase in platelet count is responsible for the increase in MAO activity, it would appear from these results that lithium is acting on the two systems independently.

Results of studies of the relationship of baseline platelet MAO to diagnosis in affective disorders have been inconsistent. As mentioned above, low platelet MAO in bipolar disorder and cycloid psychosis has been the most frequent finding. One study (Leckman *et al*, 1977) also reported low platelet MAO activity in relatives of bipolar patients. However, there have also been reports of an elevation in platelet MAO activity

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or of no difference in platelet MAO between bipolar patients and controls (Belmaker *et al*, 1976; Edwards *et al*, 1978; Nies *et al*, 1974; Reveley *et al*, 1981). Studies on platelet MAO activity in schizoaffective disorder are also inconclusive (Brockington *et al*, 1976; Orsulak *et al*, 1978). Some of the contradictions among these studies can be attributed to methodological issues, e.g., differences in the substrate used to determine enzyme activity, differences in diagnostic procedures, or differences in the patient population sampled. In addition, the significance of the fact that patients were ill at the time MAO activity was determined in some studies and in the euthymic state in other studies has not been sufficiently explored.

A major consideration, however, is that patients in some of the studies were on medication at the time that MAO activity was measured. In fact, two studies reporting higher platelet MAO activity in bipolar patients compared to control subjects involved lithium-treated patients (Belmaker *et al*, 1976; Reveley *et al*, 1981). The increase in platelet MAO activity found in the present study makes it imperative that future studies relating diagnosis to enzyme activity in the affective disorders avoid being confounded by medication. Sub-analyses in diagnostic studies which purport to prove the null hypothesis; i.e., no drug effect, are often methodologically flawed (cross-subject comparisons of platelet MAO activity) and based on small subject samples. The use of an adequate washout period for medications before enzyme activity is measured is the minimum requirement for future well-controlled diagnostic studies.

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