Phosphatidylserine Inhibition of Monoamine Oxidase in Platelets of Schizophrenics

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Phosphatidylserine (PS) has recently been reported to be a specific inhibitor of B-type monoamine oxidase (MAO-B). The effect of added PS liposomes on platelet MAO-B activity was examined in two schizophrenic groups (paranoid and a mixture of residual/undifferentiated) and in normal controls. PS was a potent partial–mixed–uncompetitive inhibitor of the platelet enzyme, whereas other phospholipids tested were without effect. The PS concentration required for 50% inhibition was significantly higher for the paranoid relative to the residual/undifferentiated group and controls. This correlated with a lower mean basal MAO-B activity in this group. Hill plots, as a measure of the concentration dependence of PS sensitivity, however, revealed a similarity between the two schizophrenic groups in regard to inhibitor binding properties. Mean Hill coefficients for both groups were significantly different from the controls. The results were consistent with an in vivo role for PS as an allosteric regulator of platelet MAO-B.

Introduction

As the principal enzyme in the degradation of biogenic amine neurotransmitters in the central nervous system, the role of monoamine oxidase (MAO) in various behavioral disorders has been of interest. This membrane-bound mitochondrial enzyme is found in most mammalian tissues and, when isolated from different sources, is of essentially identical physical properties except for the functional distinction between the multiple forms (designated A and B). There is much speculation that the MAO in human blood platelets may serve as a biochemical marker in the diagnosis of various mental disorders. Particular emphasis in these studies has been placed on the relationship of platelet MAO to schizophrenia. Although findings remain controversial, the majority of laboratories investigating the problem have found significantly lower mean levels of MAO in the platelets of schizophrenics (for recent reviews see Wyatt et al. 1980; Rodnight 1983), and a number of these studies have suggested this to be most pronounced in paranoid schizophrenics (Murphy and Wyatt 1972; Schildkraudt et al. 1980; Rawat et al. 1981).

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This latter association, although also controversial (Baron et al. 1980), is consistent with our recent reported findings (Tachiki et al. 1982, 1984a,b). Our reported differences cannot be explained in terms of medication effects on the activity of MAO (DeLisi et al. 1981; Meltzer et al. 1982; Giller et al. 1984). Inhibition of MAO-B by neuroleptics was at most 20% whereas mean differences between our paranoid and residual/undifferentiated groups were greater than 50%. Moreover, in our study, the patient groups received essentially the same medication and dosage levels (Tachiki et al. 1984a,b). Thus, even though the effects of neuroleptics on platelet MAO-B activity may be real, our earlier reported findings (Tachiki et al. 1984a,b) and the above indicate that these drug effects cannot explain the reported differences in blood enzyme activities between the various subtypes of schizophrenic patients.

Buckman et al. (1983a,b) reported a potential natural inhibitor of MAO in a variety of tissues that could provide a possible molecular basis for the regulation of MAO activity, as well as the lower MAO levels in platelets of schizophrenics. They found the lipid phosphatidylserine (PS) to be a highly specific inhibitor of the liver mitochondrial enzyme MAO-B (which is the same enzyme form found in platelets), yet it had no effect on the A-form of the enzyme. Their evidence (Buckman et al. 1983b) suggested that PS must be incorporated into the native mitochondrial outer membrane environment of MAO to be effective as an inhibitor and that the mechanism involved a direct lipid–enzyme interaction. Based on these findings, the lower apparent MAO-B levels in platelets of certain schizophrenics could be explained in terms of PS–MAO interactions. Thus, the decreased platelet MAO-B activity might be the result of an inhibitory regulation by PS rather than altered rates of MAO-B metabolism or an enzyme structural defect. Such a proposal is made more cogent by recent reports of higher PS levels in platelet and red blood cell membranes of schizophrenic patients (Stevens 1972; Henn 1981; Sengupta et al. 1981), although the evidence for an elevation of PS levels in the red cell membranes is controversial (Lautin et al. 1982; Henn, personal communication).

We report the effect of exogenous PS on platelet MAO preparations from two groups of schizophrenic patients and from normal controls. If, according to our hypothesis, the platelet MAO activity of the schizophrenics, particularly in the paranoid group, is lower due to PS inhibition in the in situ membrane environment, then the enzyme for this group should show altered sensitivity to exogenous inhibitor.

Methods

Materials

Lipids, including phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylcholine (PC), a fully hydrogenated derivative (HPS) of PS, and lyso-phosphatidylserine (lyso-PS) from bovine brain and phosphatidylinositol (PI) from soybean, were of the highest purity commercially available (95%) from Sigma Chemical Co., St. Louis, MO. All gave a single spot in two standard thin-layer chromatography systems for phospholipid separation. Radiolabeled (^{14}C) benzylamine was from New England Nuclear Corp., Boston, MA. Pargyline was a gift of Abbott Laboratories.

Subjects

Thirty-two male subjects were used in this study. Eleven were normal controls with a mean age of 37.4 ± 12.7 years (mean ± SD), 10 were schizophrenics who were diag-

nosed as either residual or undifferentiated (R/U), mean age 39.8 ± 9.5 years, and 11 were schizophrenics, paranoid type, mean age 33.6 ± 8 years. All schizophrenic patients were voluntary inpatients at Sepulveda VAMC, carried a diagnosis of schizophrenia for 3–25 years, and had a history of multiple admissions. Although all had been on various neuroleptics during the course of their illness, we compared the medication regimen between our paranoid and nonparanoid groups and, as observed previously (Tachiki et al. 1984b), could not find any differences in MAO-B activity that could be related to differences in type or dosage of their drugs. Diagnostic classification for each subject was arrived at by consensus opinion of two staff psychiatrists using DSM-III criteria (Endicott and Spitzer 1978) following a Schedule for Affective Disorders and Schizophrenia (SADS) interview (i.e., a review of the patient's past history and an analysis of the current mental status). Schizophrenic subjects who were classified as paranoid exhibited a preponderance of one of the following symptoms: persecutory, grandiose, or jealous delusions and/or hallucinations. These symptoms were overt during excerbation of the illness or were continuous for those who did not remit. This was in contrast to those subjects whom we classified as undifferentiated, in whom such delusions or hallucinations were not the predominant feature of their illness or in whom the nature of the psychotic symptoms varied over time such that the patients fit the criteria for two or more schizophrenic subtypes. Those patients classified as residual displayed the typical social withdrawal, had blunted affect and paucity of thought, and had a history of many years of continuous hospitalization. Patients with a history of chronic alcoholism, central nervous system (CNS) disease, or concurrent medical illness were excluded from the study. Each subject was entered into the study after informed consent was obtained.

All patients were housed on one of two units but with the same environment and diet. Control subjects were laboratory and hospital personnel. Thus, although the patient groups all consumed a similar diet, the diet of the controls was not monitored.

Biochemical Procedures

PS, as well as other phospholipids for addition to platelet preparations, were in the form of aqueous liposome vesicle dispersions prepared by sonication (15 min at full power at 50°C) and Laboratory Systems high-power bath sonicator in an inert atmosphere. Details of this procedure have been described previously elsewhere (Buckman et al. 1983a).

For mechanism studies, human blood platelets were isolated from platelet-rich plasma (PRP) obtained from the university hospital blood bank by centrifugation at 600 × *g*. The isolated platelets were stored frozen as a suspension (10 mg platelet protein/ml) until used. After thawing, the platelet suspension was disrupted by sonication (Kontes minisonicator, Kontes, Vineland, NJ, power 3.5, 30 sec). Prior to assay for MAO activity, the disrupted platelets were incubated with liposomes in 0.1 M sodium borate, pH 7.4, at 37°C for 30 min. For the experiments, phenylethylamine (PEA) served as substrate for the enzyme. Enzymatic activity was determined using the coupled colorimetric method of Kochli and Von Wartburg (1978) to obtain accurate initial rates.

For the clinical studies, the PRP was prepared by the fractional centrifugational procedure previously described by Corash (1980), starting with 20 ml of venous blood drawn between 8 and 10 AM. The isolated PRP was sonicated (Bronstad probe sonicator, 80% power for 10 sec, twice) and preincubated at 37°C for 30 min with PS liposomes at concentrations of 0.001–0.1 mg PS/mg PRP protein in 0.2 M sodium borate buffer (pH 9.1). The MAO activity was assayed utilizing the radioisotopic procedure previously

described by Tachiki et al. (1982, 1984b), with ^{14}C-benzylamine as substrate. Pargyline inhibition of the platelet mitochondrial enzyme was used to determine the contribution to total activity of the soluble plasma amine oxidase (Murphy et al. 1976), which is not sensitive to pargyline inhibition.

Parameters reflecting differences between schizophrenic and control populations were calculated from the percent inhibition of MAO as a function of PS concentration and from Hill plots of the data. Results were analyzed by linear regression and one-way analysis of variance. Clinical evaluations and biochemical analyses were performed employing a double-blind technique.

Results

PS added as liposome suspensions to sonicated PRP or platelets isolated from normal subjects acted as a potent inhibitor of MAO-B, with detectable inhibition at concentrations as low as 0.001 mg PS/mg protein (Figure 1). In contrast, other lipids tested in PRP preparations, including PC, PE, and PI, were completely without inhibitory effect at a 1000-fold higher concentration under the same conditions. With PS at this higher concentration, inhibition was greater than 90%. Structural requirements for inhibition were further delineated by the experiment shown in Figure 2. Liposomes of two structural analogs of PS (lyso-PS and HPS), when incubated with isolated platelets, were much less effective inhibitors of MAO-B activity over a range of lipid to protein ratios (weight:weight) from 0.002:1 to 0.05:1.

Lineweaver-Burk plots of inhibition of platelet MAO-B by PS with PEA as a substrate show a decrease in both K_m and V_{max} with increasing concentration of PS (Figure 3). Quantitatively, the decrease in V_{max} was greater than the degree of decrease in appar-

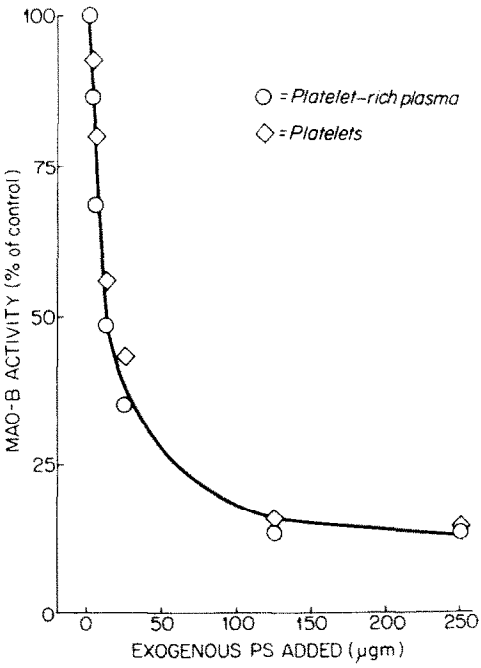

Figure 1. Inhibition of platelet MAO-B by exogenously added PS liposomes. Platelets or platelet-rich plasma were isolated from whole blood by fractional centrifugation techniques, and MAO-B assayed using [^{14}C]benzylamine as substrate. Maximum activity for the platelets was 24.8 U and 0.67 U for the platelet-rich plasma sample. One unit of enzyme activity is defined as 1 nmol product formed/mg protein/hr.

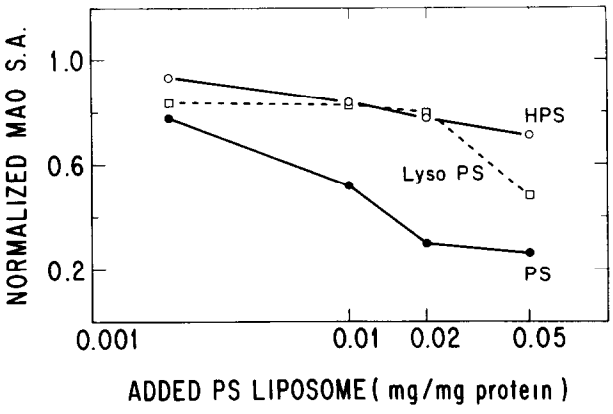

Figure 2. Comparison of inhibition of platelet MAO-B by PS (●), lyso-PS (□), and HPS (○). Platelets obtained from a university blood bank were assayed following a preincubation with liposomes by the colorimetric assay method using 50 μM PEA as substrate.

ent K_m, which is consistent with a partial–mixed–uncompetitive inhibition mechanism (Segal 1975).

Representations of these kinetic data using the Hill formulation (Hoftsee 1959) revealed an additional complexity to the effect of PS on MAO substrate binding. This representation of the data provides information about cooperativity effects in ligand binding and/or differences in the number of binding sites. The observed decrease in slope of the Hill plots with added PS reflects negative cooperativity. Also, a Hill coefficient is calculated from the Hill formulation, which is a characteristic of the enzyme and is defined as the slope of the Hill plot at 50% MAO-B inhibition (i.e., when log $[V_{PS}/(V_c - V_{PS})] = 0$, where V_{PS} is the enzyme activity in the presence of added PS, and V_c is the enzyme activity in the absence of added PS).

The dependence of platelet MAO-B inhibition on PS liposome concentration with PRP preparations from our clinical subject groups showed the anticipated relationship between sensitivity to added PS and basal MAO-B activity (Table 1). Based on one-way analysis of variance, the means of our groups in Table 1 for basal MAO-B, for PS-50 (i.e., concentration of PS giving 50% MAO-B inhibition), and for the Hill coefficients differ

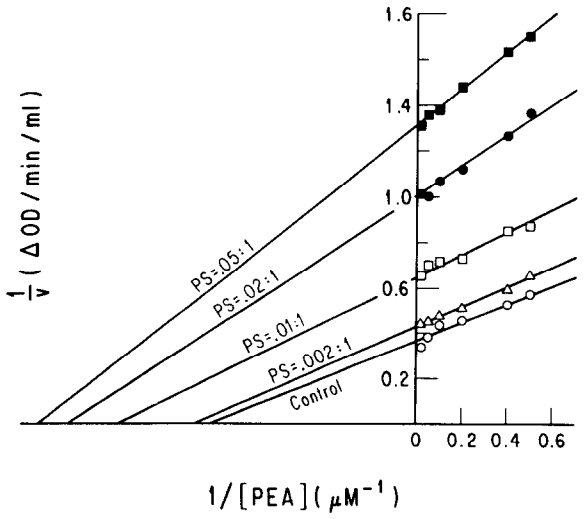

Figure 3. Lineweaver-Burk plot of substrate concentration dependence in the presence of various amounts of PS (PS to protein ratio: control, ○; 0.002:1, △; 0.01:1, □; 0.02:1, ●; and 0.05:1, ■). MAO-B activity was assayed by the colorimetric method, with PEA as substrate and platelets from a university blood bank.

Table 1. Basal Levels of Platelet Monoamine Oxidase Activity, the Concentration of Phosphatidylserine Giving 50% Inhibition, and the Hill Coefficients of Phosphatidylserine Inhibition in Normal Control Subjects and Subgroups of Schizophrenics

Subject groups	Basal MAO-B (nmol produced/hr/g protein)	PS_{50}[a] (ng/mg PRP protein)	Hill coefficient
Normal controls (n = 11)	402.4 ± 49.9	4.17 ± 0.69	−0.66 ± 0.04
Paranoid schizophrenics (n = 11)	258.1 ± 39.9[b]	7.04 ± 1.12[b]	−0.55 ± 0.04[b]
Residential/undifferentiated schizophrenics (n = 10)	402.7 ± 40.8[b]	3.76 ± 0.67[c]	−0.49 ± 0.02[c]

Values are means ± SEM.

[a]Concentration of exogenously added phosphatidylserine inhibiting 50% of the total platelet MAO-B activity. The PS_{50} and Hill coefficient values were calculated from results based on 13 different concentrations of exogenously added PS, ranging from 0.13 to 1200 μg PS/mg protein.

[b]$p < 0.05$.

[c]$p < 0.01$; the differences between the groups were analyzed by one-way analysis of variance and by Tukey's method of testing all possible pairs of treatment means (Li 1964).

significantly among themselves (i.e., the difference between groups was of a greater variation than could be attributed to random sampling from populations with a common population mean). The F-statistic values for the three biochemical measures were significant at better than the 5% level (i.e., $p < 0.05$).

The mean basal MAO-B activity given in Table 1 for the paranoid schizophrenic group was significantly lower than that for either our control population ($p < 0.05$) or the R/U group ($p < 0.05$). On the other hand, the means for the R/U and control groups were essentially identical. As previously noted, the mean ages of all groups and the medication history for the paranoid and the R/U groups showed no significant differences. The paranoids, with a lower mean basal activity, also showed a lower mean sensitivity to exogenous inhibitor, as reflected by the higher concentration of added PS necessary for 50% inhibition (paranoid versus controls, $p < 0.05$; paranoid versus R/U group, $p < 0.01$).

To explore further the nature of the interaction between the inhibitor and the enzyme, Hill coefficients as a measure of the dependence of MAO-B activity on ligand concentration were determined from Hill plots with respect to added PS concentrations. The Hill coefficient means for the three subject populations given in Table 1 showed differences between the normal controls and the paranoids ($p < 0.05$) and for the R/U group relative to controls ($p < 0.01$).

Discussion

Our results are in agreement with previous studies that have found lowered mean levels of platelet MAO-B activity in schizophrenic populations and provide further evidence that the paranoids are the major subgroup responsible for this effect. We have also found that PS is a potent specific inhibitor of MAO-B activity in human platelets and differentially affects the enzyme in normal versus schizophrenic subjects. The results with respect to sensitivity of the enzyme to exogenous PS are consistent with the expectations of our hypothesis: namely, that the paranoids who have an apparent lower basal enzyme activity also have a lower sensitivity to the added PS. This difference in sensitivity to the exogenous inhibitor may perhaps be the result of an altered PS–MAO regulatory interaction. In a subsequent study with a high degree of overlap with subjects used in the present report,

preliminary data of phospholipid analyses showed a higher percentage of PS in platelet membranes of paranoid schizophrenics relative to normal control subjects ($p < 0.02$). These preliminary findings are in agreement with an earlier study (Sengupta et al. 1981) in which higher PS levels were also found in platelet membranes from schizophrenics. Literature reports of PS levels in membranes from red cells are controversial, with findings of elevated PS levels (Stevens 1972; Henn 1981; Sengupta et al. 1981) as well as no differences (Lautin et al. 1982; Henn, personal communication) in schizophrenics relative to control subjects. An absence of the MAO enzyme in red cell membranes may be related to the equivocal findings reported from an analysis of red cell membranes.

An elevated level of PS in platelet membranes could provide a basis for our findings of reduced activity of platelet MAO-B in the paranoid schizophrenic patients. If PS is involved in platelet MAO-B regulation, fluctuations in membrane lipid metabolism and/or composition could account for some of the temporal and individual variability in the MAO-B activity observed, and thus, may contribute to the controversy as to whether or not schizophrenics have lower mean platelet MAO-B activity. In our study, both patient groups were maintained on similar diets. Thus, it is unlikely that dietary factors in themselves would be sufficient to explain the differences obtained in the PS inhibition of MAO-B activity between patient groups.

The complete lack of inhibition of MAO-B by the other phospholipids tested (PC, PE, and PI) and the lower sensitivity to the PS analogs HPS and lyso-PS are indicative of a specific enzyme–inhibitor interaction. These results with platelets are consistent with the findings of Buckman et al. (1983b) for other tissues. The effect of PS on Hill plots with respect to amine substrate concentration in the laboratory platelet studies (Figure 4) and the lower Hill coefficients calculated with respect to PS in the clinical material (Table 1) suggest an allosteric character to the PS–MAO inhibition. Furthermore, the lower mean Hill coefficients (Table 1) for both schizophrenic subgroups relative to normal controls

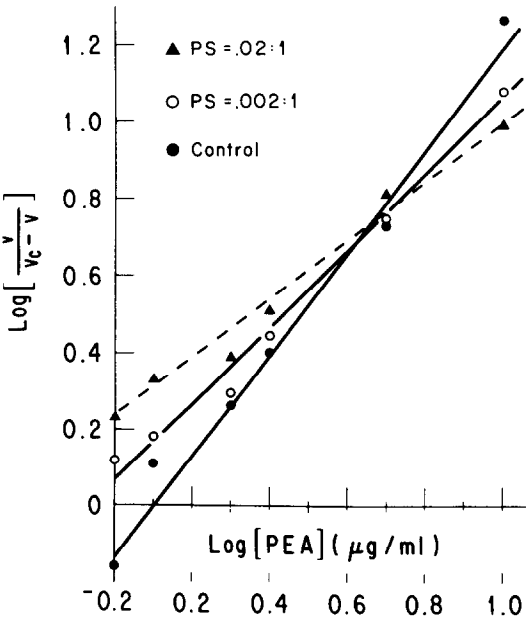

Figure 4. Hill plots of MAO-B activity with varying concentrations of PEA as substrate: PS to protein ratios of 0 (●), 0.002 (○), and 0.02 (▲). Conditions are same as in Figure 3. The slopes of the three curves are as follows: control, slope = −0.992 (correlation = 0.992); PS ratio 0.002, slope = −0.974 (correlation = 0.994); and PS ratio 0.02, slope = −0.773 (correlation = 0.989). V is the activity in the presence of added PS liposome, and V_c is the activity of MAO-B in the absence of added PS.

suggest the differences in response to added PS between the groups in this study to be more complex than just variations in endogenous inhibitor levels in platelet membranes. However, the theoretical considerations on which this interpretation is based were derived for a soluble enzyme in equilibrium with free and bound ligand. As previous studies (Buckman et al. 1983b) indicate that only membrane-bound PS is effective as an inhibitor, a true equilibrium of this type does not exist, and the usual interpretations of the Hill plot may not be strictly applicable. Nevertheless, the differences in Hill coefficient should still qualitatively reflect differences in enzyme properties. This distinction applies to both groups of schizophrenics, despite different sensitivities to inhibition by added exogenous PS revealed in the data of Table 1.

Several laboratories have proposed that MAO activity may be a genetic marker for vulnerability to the schizophrenic disorder (Breakfield and Edenstein 1980; Wyatt et al. 1980). In view of the data presented here, it is suggested that the local lipid environment of MAO may be the focus of this vulnerability. Observations from the present study that are relevant to this problem can be summarized as follows: (1) PS may serve as an in vivo regulator of MAO, resulting in differences in apparent activity levels between individuals and clinical populations; and (2) structural differences in the enzyme between normal and schizophrenic populations may determine, or at least modulate, the nature of the interaction between MAO-B and PS.

The minimum requirement for an in situ PS–MAO interaction is satisfied by reports that PS is a natural, minor constituent of the mitochondrial outer membrane (Parsons et al. 1967; Stoffel and Schiefer 1968) (consistent with unpublished findings in our own laboratory). PS has also been shown in vitro to influence strongly the activity of other proteins important in neurotransmission and membrane transport; e.g., tyrosine hydroxylase (Lloyd and Kaufman 1974), dopamine receptor systems (Levery and Lehotoy 1976), Na^+–K^+ ATPase (Tanaka 1969), and in vivo injections have produced a number of dramatic pharmacological effects in the CNS (Canonice et al. 1981).

A continuation of this study is presently in progress using a larger clinical population and including analyses of other potentially relevant platelet biochemical parameters to explore further the nature of the PS–MAO interaction and its relation to in vivo regulation of MAO-B activity. Lipid analysis on platelet samples from our various subject groups should provide a mechanistic basis to explain our observations of altered sensitivities to exogenous PS between these groups. Difference in mean concentrations of added exogenous PS required for MAO inhibition between the groups is nevertheless a phenomenon that stands alone, whatever the ultimate interpretation at a molecular level.

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