Psychopharmacology (1983) 79:177–179

Psychopharmacology

Low Platelet MAO Activity in Chronic Schizophrenics: A Long-Term Effect of Neuroleptic Treatment?

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Abstract. Platelet MAO activity was determined, using ^{14}C-tryptamine and ^{14}C-β-phenylethylamine as substrates, in two groups of schizophrenic patients and a normal control population. The first patient group consisted of 75 schizophrenics who had been medication-free for 2 weeks and had not been exposed to neuroleptic drugs for at least 2 months before the off-drug period. The second patient group comprised 55 schizophrenics who were on treatment with haloperidol for at least 2 months.

The enzyme activity was found to be significantly decreased in both drug-free (using only tryptamine as substrate, $P < 0.05$) and haloperidol-treated ($P < 0.001$) chronic schizophrenics as compared with normal controls, and to be significantly lower ($P < 0.05$) in haloperidol-treated than in off-drug chronic schizophrenics. An in vitro study confirmed the lowering effect of haloperidol on MAO activity.

It is suggested that low platelet MAO values observed in chronic schizophrenics might be in part an effect of neuroleptic treatment.

Key words: Monoamine oxidase – Platelets – Schizophrenia – Neuroleptics

Since the first report by Murphy and Wyatt (1972) of significantly decreased mean platelet monoamine oxidase (MAO) activity in chronic schizophrenic patients as compared with normal control subjects, a number of investigators have been concerned with this putative "genetic marker" of vulnerability to schizophrenia. As recently reviewed by Wyatt et al. (1979), this original finding has been replicated in most (although not in all) studies carried out on chronic schizophrenics, whereas the evidence concerning acute schizophrenics appears to be much more controversial.

The biological significance of the reduction of platelet MAO activity in chronic schizophrenia is still open to debate. Although this activity has been proved to be, at least in part, under genetic control (Nies et al. 1973; Wyatt et al. 1973), an influence of drug treatment, institutionalization, diet or hormonal status cannot be ruled out.

As far as the effect of medication is concerned, early studies claimed that MAO activity is not affected (Murphy et al. 1974) or even increased (Brockington et al. 1976) by neuroleptics. In these last few years, however, a lowering effect of antipsychotic drug treatment on the enzyme activity has been reported in rat brain (Leelavathi and Smith 1980) as well as in human platelets (Jackman and Meltzer 1980; Chojnacki et al. 1981), and this finding has been supported by in vitro studies (DeLisi et al. 1981).

The aim of the present investigation is to verify these last data, determining platelet MAO activity in a large population of drug-free and haloperidol-treated schizophrenic patients, and testing in vitro the effect of different concentrations of haloperidol on the enzyme activity.

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Subjects and Methods

In Vivo Study. Two groups of patients and a normal control population were utilized.

The first patient group consisted of 75 schizophrenics (35 males and 40 females, age range 16–54 years, mean ± SD 28.4 ± 10.0), who had been medication-free for 2 weeks. They were diagnosed and subtyped into paranoid ($n = 55$) and hebephrenic ($n = 20$) according to ICD-9, and divided into acute ($n = 41$) and chronic ($n = 34$) on the basis of the criteria reported by Strahilevitz et al. (1975). Before the off-drug period they had all been exposed to neuroleptic drugs (including haloperidol, chlorpromazine, thioridazine and clotiapine) for at least 2 months. None of them had been ever treated with depot neuroleptics.

The second patient group comprised 55 schizophrenics (24 males and 31 females, age range 18–52 years, mean ± SD 29.0 ± 9.0), who were on treatment with haloperidol (at doses ranging from 6 to 25 mg/day) for at least 2 months, and had been never exposed to MAO inhibitors, tricyclic antidepressants or lithium. They were diagnosed, subtyped into paranoid ($n = 44$) and hebephrenic ($n = 11$) and divided into acute ($n = 30$) and chronic ($n = 25$) according to the above mentioned criteria.

The normal control population consisted of 67 subjects (31 males and 36 females, age range 17–57 years, mean ± SD 28.9 ± 8.5) without personal or family history of major psychoses. They had never been treated with neuroleptics, MAO inhibitors, tricyclic antidepressants or lithium.

Alcoholism, drug abuse and neurological and medical diseases excluded both patients and controls from entering the study.

Blood samples for MAO estimation were drawn by venepuncture at 9–10 a.m. Platelets were prepared by the method of Baezinger and Majerus (1974) as modified by Winter et al. (1978), and stored frozen at −40° C.

MAO activity was assayed by the method of Wurtman and Axelrod (1963) as modified by Winter et al. (1978), using

^{14}C-tryptamine and ^{14}C-β-phenylethylamine as substrates. Protein concentration in platelet lysates was determined according to Lowry et al. (1951).

Statistical analysis of data was performed by Student's t-test and Pearson correlation coefficient.

In Vitro Study. Platelet lysates from 21 normal controls were preincubated at 37° C for 20 min with haloperidol, at concentrations ranging from 10^{-7} to 10^{-5} M, according to DeLisi et al. (1981), and the remaining MAO activity was assayed by the above mentioned method, using ^{14}C-β-phenylethylamine as substrate.

Statistical analysis of data was performed by Student's paired t-test.

Results

In Vivo Study. Mean platelet MAO activity was significantly decreased in drug-free (using only tryptamine as substrate, $P < 0.05$) and haloperidol-treated ($P < 0.001$) chronic schizophrenics, in haloperidol-treated acute schizophrenics (using only β-phenylethylamine as substrate, $P < 0.05$) and in the group of haloperidol-treated schizophrenics as a whole ($P < 0.01$) as compared with the normal control population. Furthermore, the enzyme activity was found to be significantly lower ($P < 0.05$) in haloperidol-treated than in off-drug chronic schizophrenics (see Table 1).

Females had higher mean MAO values than males in both patient groups as well as in normal controls, but the difference was not significant. The enzyme activity did not correlate significantly with the age of subjects.

The Pearson correlation coefficient between MAO activities measured with tryptamine and β-phenylethylamine was 0.85 for drug-free schizophrenics, 0.82 for haloperidol-treated schizophrenics and 0.87 for normal controls ($P < 0.001$ in each case).

In Vitro Study. A significant decrease in MAO activity ($P < 0.001$) was observed after preincubation of platelet lysates with haloperidol at concentrations of 10^{-6} and 10^{-5} M (see Table 2).

Table 1. Platelet MAO activity in drug-free and haloperidol-treated schizophrenics and in normal controls

	No.	Platelet MAO activity (nmoles/mg protein/h)	
		tryptamine	β-phenylethylamine
Drug-free			
schizophrenics	75	4.93 ± 1.92	11.93 ± 3.21
acute	41	5.29 ± 1.95	12.38 ± 3.47
chronic	34	4.63 ± 1.62*	11.60 ± 2.80
Haloperidol-treated			
schizophrenics	55	4.35 ± 1.86**	10.69 ± 3.18**
acute	30	4.93 ± 2.03	11.31 ± 2.96*
chronic	25	3.69 ± 1.75***	10.10 ± 2.91***
Normal controls	67	5.38 ± 1.85	12.75 ± 3.58

All values expressed as mean ± SD

* Significantly lower than in normal controls, $P < 0.05$; ** $P < 0.01$; *** significantly lower than in normal controls, $P < 0.001$ and than in drug-free chronic schizophrenics, $P < 0.05$

Table 2. Platelet MAO activity after preincubation of platelet lysates from normal controls with haloperidol (substrate β-phenylethylamine)

	Platelet MAO activity (nmoles/mg protein/h)
Without haloperidol	12.30 ± 3.49
With haloperidol 10^{-7} M	12.15 ± 3.33
With haloperidol 10^{-6} M	10.97 ± 2.43*
With haloperidol 10^{-5} M	9.27 ± 2.89*

All values expressed as mean ± SD

* Significantly lower than without preincubation with haloperidol, $P < 0.001$

Discussion

The results of our investigation are consistent with previous reports of significantly reduced mean platelet MAO activity in chronic schizophrenics as compared with normal controls.

The decrease in the enzyme activity was significantly more prominent in haloperidol-treated than in drug-free patients, and in vitro experiments also displayed a lowering effect of haloperidol on MAO activity at concentrations that are likely to be reached in platelets under therapeutic conditions (DeLisi et al. 1981). These findings support the recent suggestion (Jackman and Meltzer 1980; Chojnacki et al. 1981; DeLisi et al. 1981) that low platelet MAO values observed in chronic schizophrenics might be at least in part an effect of neuroleptic treatment.

Nevertheless, MAO activity has also been found to be somewhat reduced in chronic schizophrenics after a 2-week wash-out period, that is, a time in which the entire population of platelets should be replaced (Harker and Finch 1969). It should therefore be concluded that MAO decline cannot be totally ascribed to antipsychotic drug treatment, or, alternatively, that the enzyme activity can be affected in some way by prior drug exposure, as suggested by a recent paper (Breier et al. 1981). In this study lower platelet MAO activities were observed after a 2-week off-drug period in chronic schizophrenics who had a prior history of neuroleptic treatment, as compared with patients who had never been exposed to psychoactive drugs.

This long-lasting effect of neuroleptics on platelet MAO activity might be mediated by an action on endogenous compounds or hormones (Robinson and Nies 1980), or by an influence on some aspects of the kinetics of platelet precursors or of the enzyme synthesis within marrow elements (Pisciotta et al. 1965). Moreover, it cannot be excluded that some neuroleptic metabolites may persist in blood even after a 2-week wash-out period, and exert a lowering effect on the enzyme activity.

To conclude, we suggest caution in rejecting the postulated role of low platelet MAO activity as a "genetic marker" of vulnerability to schizophrenia, also in account of data reported by some family studies (Wyatt et al. 1973; Berrettini et al. 1980) claiming a reduction of enzyme activity also in healthy relatives (never exposed to psychoactive drugs) of chronic schizophrenics. We think it should be recognized, however, that the amount of data supporting a lowering effect of neuroleptics on MAO activity is now considerable, and that the heterogeneity of patient population with regard to drug history might be a likely explanation of the discrepancy among findings reported in MAO studies.

References

Baezinger NL, Majerus PW (1974) Isolation of human platelets and platelet surface membranes. In: Methods in enzymology, vol 31, part A. Academic, New York San Francisco London, pp 149–155

Berrettini WH, Benfield TC, Schmidt AO, Ladman RK, Vogel WH (1980) Platelet monoamine oxidase in families of chronic schizophrenics. Schizophr Bull 8:235–244

Breier A, Hitzemann RJ, Hirschowitz J, Garver DL (1981) Kinetic analysis of platelet monoamine oxidase in chronic schizophrenia. Life Sci 28:1947–1951

Brockington I, Crow TJ, Johnstone EC, Owen F (1976) An investigation of platelet monoamine oxidase activity in schizophrenia and schizoaffective psychosis. In: Wolstenholme GEW, Knight J (eds) Monoamine oxidase and its inhibition. Elsevier, New York, pp 353–362

Chojnacki M, Kralik P, Allen RH, Ho BT, Schoolar JC, Smith RC (1981) Neuroleptic-induced decrease in platelet MAO activity of schizophrenic patients. Am J Psychiatry 138:838–840

DeLisi LE, Wise CD, Bridge TP, Rosenblatt JE, Wagner RL, Morihisa J, Karson C, Potkin SG, Wyatt RJ (1981) A probable neuroleptic effect on platelet monoamine oxidase in chronic schizophrenic patients. Psychiatr Res 4:95–107

Harker LA, Finch CA (1969) Thrombokinetics in man. J Clin Invest 48:963–974

Jackman HL, Meltzer HY (1980) Factors affecting determination of platelet monoamine oxidase activity. Schizophr Bull 6:259–265

Leelavathi DE, Smith RC (1980) Chronic neuroleptics and brain monoamine oxidase activity. Biol Psychiatry 15:479–484

Lowry OH, Rosenbrough NJ, Farr AL, Randall RJ (1951) Protein measurement with the Folin phenol reagent. J Biol Chem 193:265–275

Murphy DL, Belmaker R, Wyatt RJ (1974) Monoamine oxidase in schizophrenia and other behavioural disorders. J Psychiatr Res 11:221–247

Murphy DL, Wyatt RJ (1972) Reduced platelet monoamine oxidase activity in chronic schizophrenia. Nature 238:225–226

Nies A, Robinson DS, Lamborn K, Lampert RP (1973) Genetic control of platelet and plasma monoamine oxidase activity. Arch Gen Psychiatry 28:834–838

Pisciotta AV, Santos AS, Keller C, Hayes J (1965) Studies on agranulocytosis: The effect of clinical treatment with chloropromazine on nucleic acid synthesis of granulocyte precursors in normal persons. J Lab Clin Med 65:228–235

Robinson DS, Nies A (1980) Demographic, biologic, and other variables affecting monoamine oxidase activity. Schizophr Bull 6:298–307

Strahilevitz M, Narasimhachari N, Fischer GW, Meltzer HY, Himwich HE (1975) Indolethylamine-N-methyltransferase activity in psychiatric patients and controls. Biol Psychiatry 10:287–302

Winter H, Herschel M, Propping P, Friedl W, Vogel F (1978) A twin study on three enzymes (DBH, COMT, MAO) of catecholamine metabolism. Correlations with MMPI. Psychopharmacology 57:63–69

Wurtman RJ, Axelrod J (1963) A sensitive and specific assay for the examination of monoamine oxidase. Biochem Pharmacol 12:1439–1441

Wyatt RJ, Murphy DL, Belmaker R, Cohen S, Donnelly CH, Pollin W (1973) Reduced monoamine oxidase in platelets: A possible genetic marker of vulnerability to schizophrenia. Science 179:916–918

Wyatt RJ, Potkin SG, Murphy DL (1979) Platelet monoamine oxidase activity in schizophrenia. A review of the data. Arch Gen Psychiatry 136:377–385

Received May 21, 1982; Final version September 20, 1982