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Substrate-Typic Changes of Platelet Monoamine Oxidase Activity in Sub-Types of Schizophrenia

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Summary. Monoamine oxidase (MAO) activity has been measured in the platelets of controls ($n = 42$) and schizophrenic patients ($n = 49$) of three sub-types, using β-phenylethylamine, p-tyramine, and tryptamine as substrates. Characteristic differences of MAO activity were observed between platelets of patients and controls; the differences were substrate-typic: decreased enzyme activity was found with all three substrates in platelets of the parnaoid sub-type. With tryptamine, MAO activity was decreased in the platelets of all three sub-types of schizophrenia. With p-tyramine, MAO was low in patients with affective psychoses and paranoid schizophrenia.

The value of MAO activity measurements as a means for distinguishing sub-types of schizophrenic disorders is improved by using two substrates; tryptamine and p-tyramine. Possible mechanisms of the substrate-typic changes of platelet MAO activity in schizophrenia are discussed.

Key words: Monoamine oxidase – Blood platelets – Schizophrenia – Sub-types.

Introduction

Murphy and Wyatt (1972) reported decreased platelet monoamine oxidase (MAO) activities in 33 chronic schizophrenic patients. Since then the possible role of platelet MAO as marker of vulnerability to schizophrenia has attracted considerable attention. Platelet MAO activities of patients with schizophrenic disorders have often been measured (Wyatt et al., 1973, 1975; Nies et al., 1974; Meltzer and Stahl, 1974; Owen et al., 1974; Friedman et al., 1974; Shaskan and

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Becker, 1975; Carpenter et al., 1975; Domino and Khanna, 1976; Schildkraut et al., 1976), but reduced enzyme activities have not been found in all schizophrenic subjects. It has been suggested that reduced platelet MAO activities are more frequent in chronic than in acute schizophrenic disorders (Wyatt and Murphy, 1975). However, recent findings of Schildkraut et al. (1976), and Meltzer (private communication) indicated lower enzyme levels only in a subgroup of schizophrenic patients, characterized by the presence of auditory hallucinations and paranoid delusion.

Platelet MAO is considered a uniform enzyme of type B (Collins and Sandler, 1971; Murphy and Donelly, 1974; Zeller et al., 1976). With few exceptions, therefore, tryptamine was used as substrate. However, the most significant differences in platelet MAO activities between schizophrenic patients and controls were observed with tyramine (Meltzer and Stahl, 1974). It seemed to be of interest to compare MAO activities in sub-types of schizophrenia, using different substrates.

Subjects

A total of 49 chizophrenic patients, 8 patients with affective psychoses, and 42 controls were studied for platelet MAO activity.

The control subjects (21 males and 21 females) aged from 20 to 62 years were 'drug free' and carefully examined, especially to exclude any hormonal disturbances. This control group consisted of members of the clinical staff. It is not identical with that of our previous work (Demisch et al., 1976).

The schizophrenic patients were grouped into paranoid type ($n = 12$; 6 males, 6 females; 42 ± 16 years), schizophrenic defect ($n = 22$; 14 males, 8 females; 40 ± 11 years), and schizo-affective sub-type ($n = 15$; 13 males, 2 females; 39 ± 12 years) according to the criteria suggested by the ICD (Degwitz et al., 1975). The medical records of the patients and controls were reviewed in detail by two independent psychiatrists. The subjects identities and diagnoses were unknown to the investigators performing the enzyme determinations.

The paranoid type schizophrenics were characterized mainly by the presence of delusions of persecution or grandeur. This group includes patients with auditory and kinesthetic hallucinations and cognitive disorders. The group with schizophrenic personality defects was characterized by reduction of ambition, initiative, available energy, and emotional responsiveness. The schizo-affective subgroup contained patients with a strong mixture of either depressive or euphoric affects with otherwise definite schizophrenic symptomatology. In the diagnosis of these patients the schizophrenic symptomatology took precedence over the affective symptoms. The group of affective psychosis was a mixed group of patients mainly with bipolar affective disorders. All schizophrenic patients have had schizophrenic episodes for at least 2 years. They have been hospitalized for different durations. At the time of the study, 32 patients of the total group of schizophrenics were inpatients (Philipps Hospital, Goddelau, Federal Republic of Germany) and 17 patients were outpatients (Zentrum der Psychiatrie, J. W. Goethe University, Frankfurt/M., Federal Republic of Germany).

All schizophrenic patients were treated with neuroleptic drugs for at least 1 year prior to study. The patients with affective disorders were outpatients. Three out of the eight depressive patients were treated with Clomipramin (Anafranil®) at the time of blood sampling. There was no correlation between drug intake and MAO activity.

Isolation of Blood Platelets, Determination of Platelet MAO Activity and Protein Determination

Blood samples (5—10 ml) were drawn by venipuncture of non-fasted subjects at about 10 a. m. Isolation of platelets and assay of MAO activity and protein were carried out as has been

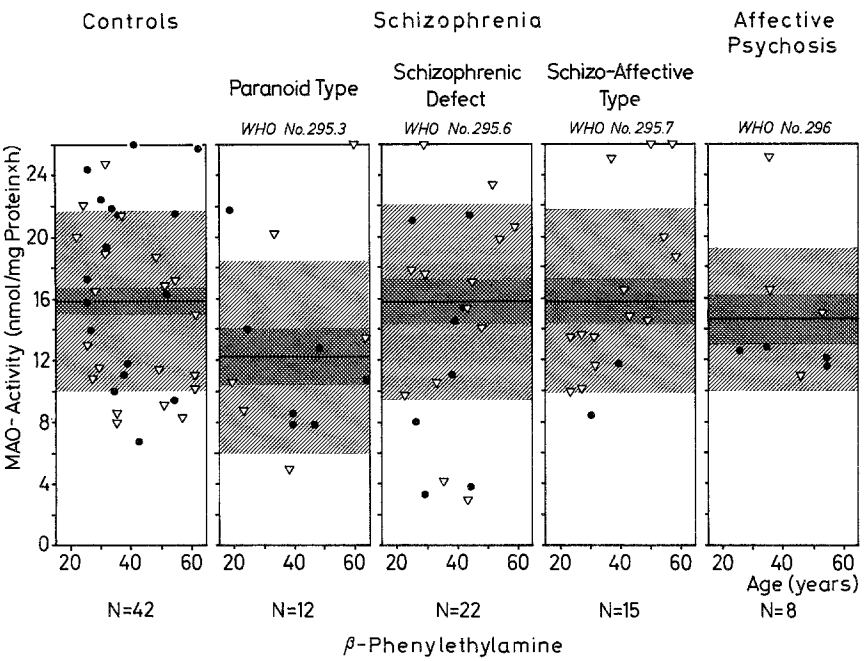

Fig. 1. Monoamine oxidase activity of human blood platelets as measured with β-phenylethylamine hydrochloride as substrate (Substrate conc. 5.7×10^{-5} M; 66 mM phosphate buffer pH 7.2; 30 min incubation at 38°C). Triangles: males; dots: females. Mean values of the age and sex matched groups are indicated in the figures. Shaded areas represent standard deviation (SD) and standard error of the mean (SEM), respectively. n = number of subjects considered for the statistical evaluations. WHO numbers are from Degwitz et al., 1975

previously described (Demisch et al., 1976), with the following modifications: substrate concentrations were 57 µM for β-phenylethylamine hydrochloride (1-amino-2-phenyl [1-^{14}C] ethane hydrochloride, sp. radioactivity 51 Ci/mol (Km = 1.0 µM) (Christ et al., 1976); 52 µM for p-tyramine hydrochloride (1-amino-2-(4-hydroxyphenyl) [1-^{14}C] ethane hydrochloride, sp. radioactivity 50.2 Ci/mol (Km = 50–59 µM) (Christ et al., 1976; Murphy and Donelly, 1974); and tryptamine bisuccinate (1-amino-2-indolyl [2-^{14}C] ethane bisuccinate, sp. radioactivity 48.5 Ci/mol (Km = 7.4 µM) (Christ et al., 1976).

All radiochemicals were from New England Nuclear Corp., Boston, Mass., USA.

Incubations were carried out at 38° C for 30 min. Enzyme activity (reaction velocity) was expressed in nmol of neutral and anionic reaction products formed per hour and per mg of platelet protein.

Results

The results are summarized in Figures 1—3. In these figures the mean values of platelet MAO activities of all subjects of each group are indicated, together with the standard deviation (SD) and the standard error of the mean (SEM). In the calculations, we did not distinguish between age or sex, however male and female subjects are indicated in the figures by triangles and dots respectively. The figures also show the age distributions within each group.

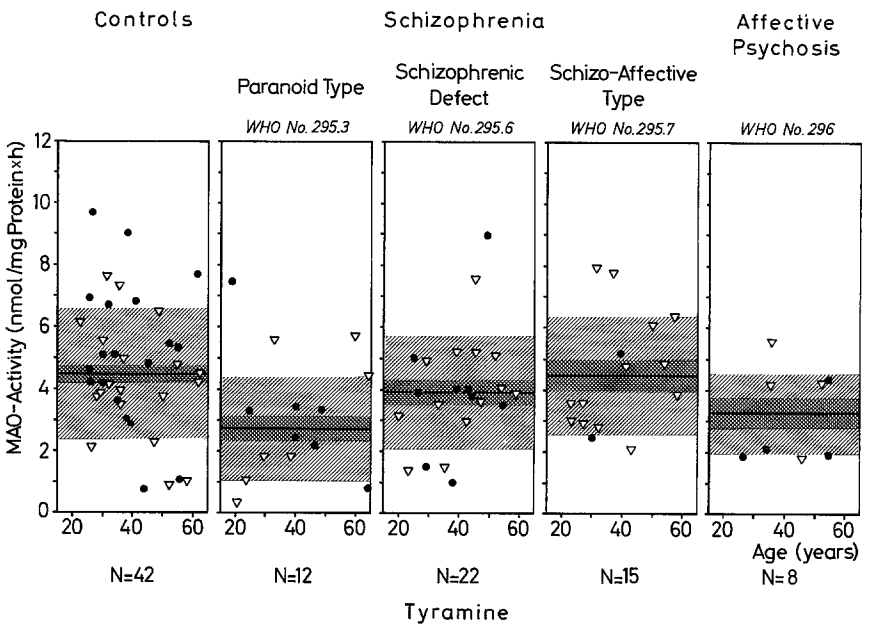

Fig. 2. Monoamine oxidase activity of human blood platelets as measured with p-tyramine hydrochloride as substrate (Substrate conc. 5.2×10^{-5} M; for other details see legend to Fig. 1)

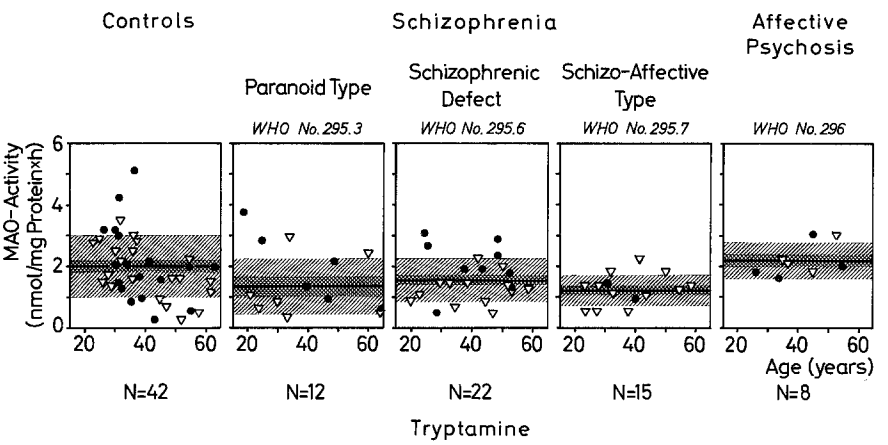

Fig. 3. Monoamine oxidase activity of human blood platelets as measured with tryptamine bi-succinate as substrate (Substrate conc. 5.2×10^{-5} M; for other details see legend to Fig. 1)

With β-phenylethylamine as substrate, reduced platelet MAO activity was only found in the paranoid-type schizophrenics, however, this difference was not statistically significant (Fig. 1). With p-tyramine as substrate, a similar pattern of MAO activity as with β-phenylethylamine was observed (Fig. 2). Again, the paranoid patients showed reduced enzyme activity in comparison with the controls. The difference between these groups was statistically significant ($P < 0.05$;

Student's t-test). Patients with other schizophrenic disorders showed no significant reduction of MAO activity. Only the small group with affective psychosis seems to have lower platelet MAO activity than the control group. The small number of subjects in this non-homogenous group, however, does not allow the drawing of conclusions. The pattern with tryptamine is in obvious contrast to the MAO pattern obtained using β-phenylethylamine and p-tyramine as substrates (Fig. 3).

Reduction of platelet MAO activity with tryptamine is not only typical for the paranoid-type, but for other schizophrenic disorders as well. The mean value ($\pm$ SD) of MAO activities of all schizophrenic patients (1.44 ± 0.7 nmol/mg protein $\times$ h; $n = 49$) is statistically significant compared with the control group (2.0 ± 1 nmol/mg protein $\times$ h; $n = 42$; $P = 0.01$). It is interesting to note that the group with affective psychoses shows no reduction of platelet MAO activity with tryptamine (2.1 ± 0.6 nmol/mg $\times$ h). A significant reduction of MAO activity is observed in the schizo-affective group (1.1 ± 0.5 nmol/mg protein $\times$ h; $P < 0.05$).

In order to elucidate the changes of platelet MAO activity in schizophrenia with respect to the different substrates, ratios of reaction velocities (v) of oxidative deamination of the different substrates were calculated (Table 1). The ratios $v_{\text{p-tyramine}}/v_{\beta\text{-phenylethylamine}}$ and $v_{\text{tryptamine}}/v_{\beta\text{-phenylethylamine}}$ were not significantly different between the different groups of patients and the controls. In contrast, the $v_{\text{tryptamine}}/v_{\text{p-tyramine}}$ ratios showed highly significant differences for the schizo-affective type schizophrenia and the affective psychosis. These ratios are also significantly different from the respective values of the paranoid type schizophrenia and the schizophrenic defects.

Discussion

In most published papers on platelet MAO activity in schizophrenia chronic and acute cases were compared. We did not follow this categorization in our work, since many of the old prognostic patterns have changed (Hawk et al., 1975). Patients were grouped according to the WHO criteria (Degkwitz et al., 1975), however, with more emphasis on the longitudinal course of the illness, than on the symptom picture. Symptom picture and course of illness are considered as representative of separate 'systems' with their own determinants (Strauss and

Table 1. Reaction velocity ratios of the individual platelet MAO activities, with respect to tryptamine and p-tyramine as substrates ($v_{\text{tryptamine}}/v_{\text{p-tyramine}}$)

	Controls	Schizophrenia			Affective psychosis
		paranoid type	Schizophrenic defect	Schizo-affective type	
Mean $\pm$ SD	0.44 ± 0.1	0.54 ± 0.2	0.49 ± 0.4	0.31 ± 0.2	0.81 ± 0.2
Statistical difference		NS	NS	$P < 0.01$	$P < 0.001$

Carpenter, 1975). Phasic courses with complete remission of symptoms, analogous to affective psychoses, seem to be characteristics of the schizo-affective psychoses, while personality deteriorations are more frequently observed in other schizophrenic disorders.

Zeller et al. (1976) recently showed a slight increase of platelet MAO activity above the age of 50 years. This increase, however, is much less than that observed by Robinson et al. (1971), and is also in contrast with our findings (Demisch et al., 1976). Both in males and females a small decrease of enzyme activity was observed at an age > 50 years. The control group of the present work shows the same tendency to decreased MAO activity with increased age. In confirmation of our previous work (Demisch et al., 1976) and other papers (Robinson et al., 1971; Meltzer and Stahl, 1974; Zeller et al.,1976; Murphy et al., 1976) we find platelet MAO activity in females to be somewhat higher than in males. We did not, however, consider this difference to be great enough to distinguish between males and females in the statistical evaluation of our results. (In the graphs platelet MAO activity of males and females was, nevertheless, distinguished).

Within the groups of our patient population the paranoid sub-type showed the greatest decrease of platelet MAO activity with p-tyramine as substrate. This difference was statistically significant at the 0.05 level of confidence.

Presumably, our group of paranoid schizophrenics is comparable with those patients having auditory hallucinations described by Schildkraut et al. (1976). The patients in this latter study also showed marked reduction of platelet MAO activity.

β-phenylethylamine is one of the most typical substrates of B type MAO. In fact, the highest reaction velocities in our study were observed with this substrate. It is, therefore, interesting to note that the least significant differences in platelet MAO activity were observed with this amine. Nies et al. (1974) reported comparable results using benzylamine, another typical substrate of the B type MAO. However, the general tendency of decreased enzyme activity with β-phenylethylamine in the paranoid sub-type and the normal values in the other schizophrenic disorders is quite similar to what we observe with the much more polar p-tyramine.

Tryptamine was used by many authors in platelet MAO works (Murphy and Wyatt, 1972, 1974; Friedman et al., 1974; Meltzer and Stahl, 1974; Nies et al., 1974;

Table 2. Comparison of platelet MAO activity of in- and outpatients with schizophrenic defect (WHO No. 295.6). (Mean values ± SD; statistical significance of the difference between patients and controls (unpaired Student's *t*-test) in brackets)

Subjects	Subject No.	Substrate		
		β-phenylethylamine (nmol/mg protein × h)	p-tyramine	tryptamine
Total patient group	22	15.9 ± 6 (NS)	3.9 ± 2 (NS)	1.6 ± 0.3 (NS)
Outpatients	13	14.5 ± 6 (NS)	3.9 ± 2 (NS)	1.9 ± 0.8 (NS)
Inpatients	9	17.7 ± 6 (NS)	4.0 ± 1 (NS)	1.2 ± 0.4 ($P < 0.05$)
Controls	42	15.7 ± 6	4.4 ± 3	2.0 ± 1

Carpenter et al., 1975; Wyatt et al., 1975; Domino and Khanna, 1976; Schildkraut et al., 1976). In contrast to β-phenylethylamine and p-tyramine, we find reduced MAO activities with tryptamine in all three types of schizophrenia as compared to controls and patients with affective psychoses. The overall decrease in platelet MAO activity with tryptamine as substrate was significant ($P < 0.01$). It was of interest to compare inpatients and outpatients. Since only the group of patients with schizophrenic defects contained comparable numbers of the two groups, it was sub-grouped and evaluated separately. Table 2 shows the results. Only the group of inpatients with schizophrenic defect showed a statistically significant decrease of platelet MAO activity with tryptamine as substrate. Analogous differences were not observed with p-tyramine or β-phenylethylamine as enzyme substrates.

From the different patterns of enzyme activity we find with the three substrates, it appears that the total amount of MAO is not changed with the possible exception of the platelets of the paranoid-type schizophrenia. In this latter case the mean changes in enzyme activities are approximately the same for all three substrates.

The most convincing differences are observed with p-tyramine as substrate, in accordance with the results of Meltzer and Stahl (1974). Different forms of MAO in platelets have not been observed (Collins and Sandler, 1971; Murphy and Donelly, 1974; Zeller et al., 1976). Therefore, there is presently no experimental evidence for a hypothesis (Meltzer and Stahl, 1974) of an altered isoenzyme pattern in the platelets of certain schizophrenic disorders.

As Murphy (1973) has pointed out, platelets have a number of characteristics in common with nerve ending preparations of brain, including similarities in amine transport mechanism, amine storage, vesicle functions, receptor response, and the possession of other enzymes involved in amine degradation besides MAO. Therefore, regulation of platelet MAO should resemble regulation in brain cells.

Genetic contributions to human platelet MAO activity have been suggested (Nies et al., 1973, 1974; Wyatt et al., 1973). Moreover, hormonal actions on the regulation of MAO synthesis and degradation in mammals (Wurtmann and Axelrod, 1963; Collins et al., 1970; Bhagat et al., 1973; Goridis and Neff, 1973; Parvez and Parvez, 1973; Gandhi and Kanungo, 1974; Petrovic and Janic, 1974; Youdim et al., 1974; Grosso and Gawienowski, 1975; Philipson and Sandler, 1975; Redmond et al., 1975), stress and other environmental factors (Eleftheriou and Boehlke, 1967; Maura et al., 1974, 1975), and direct hormone actions on human platelet MAO (Belmaker et al., 1974; Gentil et al., 1975; Demisch and Demisch, 1977) have been published. At present, it is not possible to relate the observed reduction of platelet MAO activity in the paranoid type schizophrenia to one of these modifying influences. The relatively small direct and indirect hormonal effects on platelet MAO activity, as shown by Belmaker et al. (1974) for the menstrual cycle-related hormones and by Zeller et al. (1976) for the gonadotropins, should not be interpreted as indicating a prevalent genetic determinant of reduced platelet MAO activity in schizophrenia.

Phenothiazines seem to have little influence on platelet MAO (Meltzer and Stahl, 1974; Murphy and Wyatt, 1974). Tricyclic antidepressive agents inhibit in vitro human platelet MAO (Edwards and Burns, 1974). Long term treatment with

amitryptiline and other antidepressants had, however, no effect on MAO (Honecker and Hill, 1977). A number of factors secondary to the course of the illness, nutritional influences (Belmaker et al., 1974), physical activity, and psychological stress (Murphy and Wyatt, 1975) seem also to have little influence on human platelet MAO activity. Nevertheless, one cannot exclude that MAO may be influenced, or even regulated by normal or abnormal products of intermediary metabolism, or by unknown intrinsic factors. It should be emphasized in this connection that modifications of catalytic properties of MAO are easily affected by a number of experimental conditions (e.g., hypervitaminosis D_2, radiation injury, parenteral administration of oxidized oleic acid) that influence thiol groups in vitro or in vivo (Gorkin, 1973, 1976; Gorkin and Tatyanenko, 1967; Gorkin and Akopyan, 1971).

It is well documented that changes in the phospholipid pattern or in the immediate lipid environment of mitochondrial MAO and other membrane bound enzymes have profound effects on the enzyme properties (Houslay and Tipton, 1976; Youdim and Woods, 1975). It has been suggested (Tipton et al., 1976), that certain changes of the properties of the enzyme in diseased states are a result of altered membrane environment, rather than alterations in the enzyme protein itself. Phospholipid patterns of platelet mitochondria of normal and diseased humans have, however, not been studied.

Our data confirm that measurement of platelet MAO activity is without any significance for the diagnosis of schizophrenia. However, such measurements could be of value in characterization of sub-types. Exact characterization of subtypes is of enormous importance for the development of criteria for homogenous patient populations in research. Even more important are the clinical aspects. Although there are differing views about the prognosis with different sub-types of schizophrenia (Tsuang and Winokur, 1974, Hawk et al., 1975), there is agreement that schizophrenia is not a single process but a composite of several partially-independent processes, best conceptualized as open-linked systems (Tsuang and Winokur, 1974; Strauss and Carpenter, 1974, 1975). Knowledge of factors that predict prognosis are essential for evaluating treatment effectiveness. In this respect, measurement of platelet MAO activity with p-tyramine as substrate might be useful for the characterization of the paranoid type. Since there is a considerable overlap of the values of patients and controls, platelet MAO determination is of low diagnostic value in the assessment of the individual.

The $v_{tryptamine}/v_{p\text{-}tyramine}$ ratios of enzyme activities in platelets of patients with schizo-affective schizophrenia and the affective disorders were found to be significantly different from the control values and different from each other, as well. We can assume, therefore, that platelet MAO measurements using both tryptamine and p-tyramine as substrate could be of greater importance for the biochemical differentiation of these disorders and for the sub-typing of schizophrenia than measurements with only a single substrate. Although the data available on patients with affective disorders are not yet sufficient to be definitive, the results suggest the value of a thorough study of the clinical relevance of these measurements.

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