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Platelet Monoamine Oxidase in Healthy Subjects: The "Biochemical High-Risk Paradigm" Revisited

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Summary. Activity of platelet monoamine oxidase (MAO) has repeatedly been reported to be associated with various forms of psychopathology. This investigation was designed to reexamine the "biochemical high-risk paradigm" developed by Buchsbaum et al. (1976). In 383 healthy students (193 males, 190 females) platelet MAO activity was measured. The 35 students with the lowest and 37 with the highest enzyme activities were then examined with three personality tests (16 PF of Cattell, Freiburger Persönlichkeitsinventar, Eysenck Personality Questionnaire). Furthermore, biographic data with respect to psychosocial problems were explored. There were no consistent differences between subjects with low or high platelet MAO. Therefore, we could not confirm any correlation between psychopathology and platelet MAO in this study.

Key words: Platelet MAO – Psychiatric vulnerability – Behaviour genetics

Zusammenfassung. Es bestehen Hinweise auf einen Zusammenhang zwischen Thrombocyten-Monoaminoxidase (MAO) und verschiedenen psychopathologischen Symptomen. In dieser Studie wurden die von Buchsbaum et al. (1976) erstmals publizierten Befunde an einer deutschen Population nachuntersucht. Bei 383 gesunden Studenten (190 Frauen und 193 Männer) war die MAO-Aktivität in den Thrombocyten bestimmt worden. 35 derjenigen Probanden mit der niedrigsten und 37 derjenigen mit der höchsten Enzymaktivität wurden dann mit drei Persönlichkeitsfragebögen (16 PF von Cattell, Freiburger Persönlichkeitsinventar, Eysenck-Persönlichkeitsfragebogen) untersucht. Überdies wurden biographische Daten im Hinblick auf psychosoziale Auffälligkeiten erfaßt. Insgesamt fanden sich keine konsistenten signifikanten Unterschiede zwischen Probanden mit hoher und niedriger MAO-Aktivität. Wir können daher eine Korrelation zwischen psychopathologischen Sympto-

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men und der Höhe der MAO-Aktivität in dieser Untersuchung nicht bestätigen.

Schlüsselwörter: Thrombocyten-MAO-Aktivität – Psychiatrische Vulnerabilität – Verhaltensgenetik

Introduction

The "biochemical high-risk method" (Buchsbaum et al. 1976; Coursey et al. 1979) offers an ingenious strategy to avoid the problems of etiologic heterogeneity and unreliability of psychiatric diagnoses often encountered in usual research designs. As reported in numerous publications (for review: Buchsbaum et al. 1980) these investigators measured platelet monoamine oxidase (MAO) activity in a large population of healthy probands and compared various psychological and psychopathological traits in the decile of subjects with the lowest versus the decile with the highest values of platelet MAO activity.

Estimation of this particular enzyme had been chosen for the following reasons:

1. Platelet MAO (monoamine: oxygen oxidoreductase, deaminating, EC 1.4.3.4, form B) has been reported to be lower in patients with chronic schizophrenia (for review: Wyatt et al. 1979) and bipolar affective disorder (Murphy and Weiss 1972).

2. MAO activity shows remarkable intraindividual stability but also interindividual variation that is mainly genetic in origin (cf. Friedl et al. 1981).

3. An alteration of MAO levels would be consistent with leading hypotheses on biochemical abnormalities in the major psychoses. Buchsbaum and his associates (1976, 1977) found that individuals with low MAO activities reported more frequent psychiatric or psychological counseling, conflicts with the law and suicide attempts in comparison with those with high MAO activities. Similar tendencies were detected in the relatives of these probands. Further investigations revealed a correlation between low MAO values with high scores on the Sensation Seeking Scale (Murphy et al. 1977; Schooler et al. 1978), increased social interaction (Coursey et al. 1979), use of stimulating drugs and social approval seeking and more "other-directed social concern" as evidenced by MMPI scores (Donnelly et al. 1979). Puchall et al. (1980) examined the parents of subjects with either low or high MAO activities. Among the parents of low MAO probands they found a higher incidence of "low MAO related disorders" (schizophrenia, bipolar affective disorder, alcoholism, antisocial personality), whereas among the parents of the high MAO probands "high MAO related disorders" (major or minor depression, depressive personality) prevailed.

Shaughnessy et al. (1980) applied the Clinical Analysis Questionnaire, which includes the 16 PF test of Cattell, to 65 normal females. Women having low MAO activity had lower super-ego strength and more anxious depression, they were less likely to accept group standards and were more frivolous, self-indulgent and undependable; in addition they were more tense, easily upset, irritable, and lacking in self-confidence, and they had less insight and more difficulty in handling abstract problems than women with high MAO activity.

The purpose of this study was to reexamine these findings independently in a comparable population, because most of the investigations referred to were performed in subjects drawn from the sample established by Buchsbaum et al. (1976).

Methods

Subjects. Students of the University of Heidelberg (193 males, 190 females) were screened for their platelet MAO activities. All of them were healthy and drug-free. In a second step, the 20 subjects of both sexes with the lowest and highest MAO values were asked to participate in a psychological test. Of the invited 80 students 72 were willing to cooperate. The day of psychological testing, blood was taken for a second MAO determination.

Biographic Data. To reexamine an eventual relationship between individual habits, psychosocial problems and platelet MAO activity, we developed a biographic questionnaire (Table 1).

Psychological Tests. For evaluation of personality factors which measure stable characteristics of a person (psychological "traits" or dispositions), the 16 PF of Cattell (1973) and Freiburger Persönlichkeitsinventar (personality inventory; FPI; Fahrenberg et al. 1978) were applied. Furthermore, the Eysenck Personality Questionnaire (EPQ; Eysenck 1975), a test that has been construed in a way comparable with the 16 PF, was used. This test gives only three personality factors ("second-order-factors") that have a particularly high stability in one individual over time.

MAO Determination. Venous blood (20 ml) was collected in EDTA vacutainer tubes, and platelets were immediately prepared by a modified method of Baenziger and Majerus (1974), as described by Winter et al. (1978). The platelets were stored frozen at −20° C. Later, the frozen platelet pellet was lysed by addition of bidistilled water, to give a protein concentration of about 2 mg/ml, and subsequent freeze-thawing. MAO activity was determined by the method of Wurtman and Axelrod (1963), slightly modified according to Winter et al. (1978), using tryptamine, which is a substrate for both MAO A and B. Platelet lysate of 50 µl was incubated for 30 min at 37° C with 150 µl of substrate solution at saturating conditions (80 µM/l). The samples were run in triplicate together with a standard (obtained by collecting platelets from 0.4 l blood, provided by the blood bank). Activity values were corrected for interassay variation, as measured by variation of the standard sample. Protein concentration was determined according to Lowry et al. (1951).

Statistical Evaluations. For comparison of the scores of the psychological tests Student's *t*-tests for independent samples were used. Since differences for 16 personality factors of the 16 PF and for 9 personality factors of the FPI had to be tested, the problem of multiple statistical tests arose. A way out of this difficulty is to multiply the *P*-values obtained by the number of personality factors (Bonferroni inequality). Whenever this empirical *P*-value ($P \times 16$ or $P \times 9$) remains below the level of significance assumed, i.e. remains below the level of $P = 0.05$, the outcome is significant and is adjusted for the number of possibilities (α-adjustment; Krauth and Lienert 1973).

For statistical comparison of biographic data, Fisher's exact test was applied and the *P*-values were corrected by the Bonferroni inequality.

Results

Figure 1 depicts the distribution of the platelet MAO activities in the 383 students. Figure 2 shows the values of enzyme activity for each individual for the first and second blood samples. There is a "regression to the mean": subjects who had been selected because of their low MAO tend to have higher activities, and subjects who had been selected because of their high MAO tend to have lower activities at the

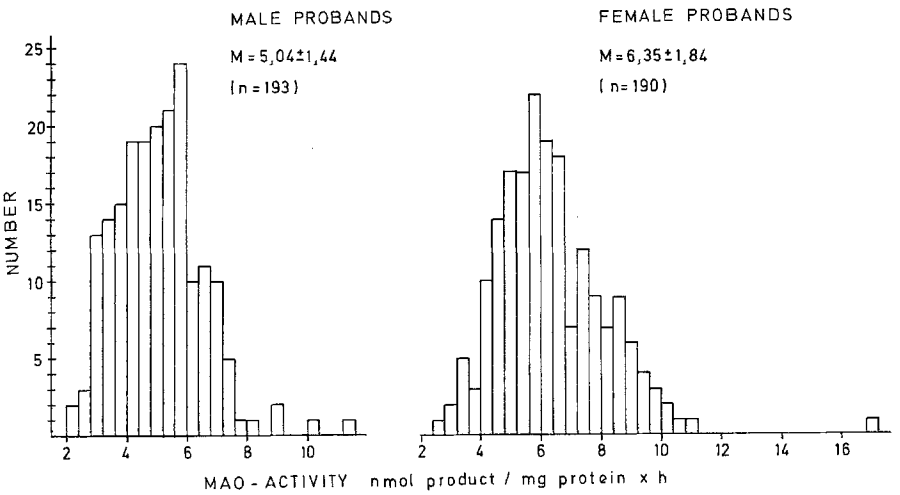

Fig. 1. Distribution of platelet MAO activity in 383 healthy individuals as measured at the first occasions of blood drawing. Substrate tryptamine; M = mean ± s.d.

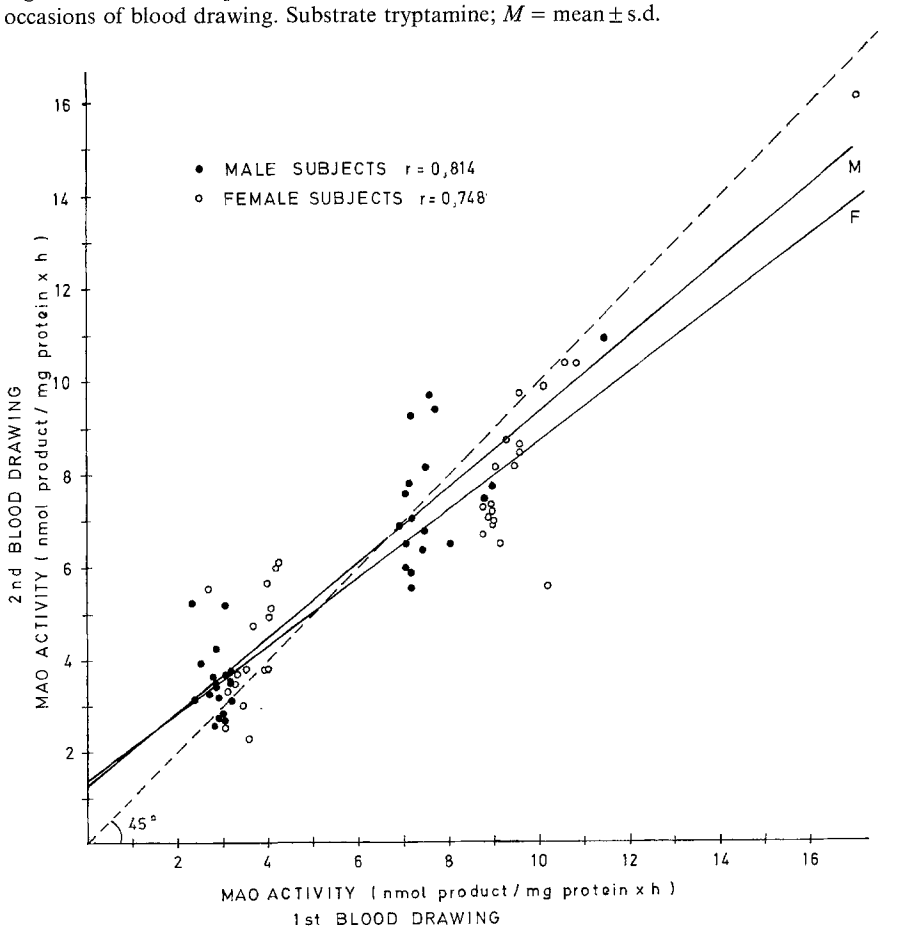

Fig. 2. Platelet MAO in subjects with low or high enzyme activities on the days of the first and second blood drawings. Substrate tryptamine; r = coefficient of regression

Table 1. Biographic data of the subjects who belonged to the low or high MAO groups

		Low MAO subjects			High MAO subjects		
		Males $n=19$	Females $n=16$	Both sexes $n=35$	Males $n=18$	Females $n=19$	Both sexes $n=37$
Probands:	married	7	2	9	7	4	11
	unmarried	11	14	25	11	15	26
	divorced	1	0	1	0	0	0
Parents:	married	19	14	33	18	18	36
	divorced	0	2	2	0	1	1
Probands:	operation	7	9	16	9	12	21
Probands:	accidents	5	5	10	7	6	13
Probands:	smokers	11*	6	17	3*	7	10
Probands:	usual alcohol intake	15	12	27	15	15	30
Probands:	sleep good	15	14	29	16	13	29
	medium	3	1	4	2	6	8
	bad	1	1	2	0	0	0
Probands:	suicidal thoughts[a] occasional	0	5	5	3	5	8
	rare	3 **	3	6 *	8 **	5	13 *
	never	16	8	24	7	8	15
Probands:	suicide attempts	1	0	1	0	1	1
Family:	suicide attempts[a]	1	1	2	1	0	1
Probands:	psychiatric contact[a]	0	0	0	1	1	2
Family:	psychiatric contact[a]	2	1	3	0	2	2
Probands:	penalties[a]	0	0	0	0	0	0
Family:	penalties[a]	3	1	4*	0	0	0*
Probands:	members of clubs[a]	12	4	16	9	7	16

[a] One female subject with high MAO did not answer these questions
* $P<0.05$; ** $P<0.01$

second examination. In the low MAO group, the mean activities were 2.90 (males) and 3.65 (females) at the first, 3.56 (males) and 4.23 (females) at the second examination. In the high MAO group, the mean values were 7.73 (males) and 9.87 (females) at the first, 7.55 (males) and 8.45 (females) at the second examination.

Table 1 demonstrates the biographic data and incidences of psychosocial problems in the low and high MAO groups, separately for males and females. Only in a few cases were the differences statistically significant. Low MAO males were more frequently smokers than their high MAO counterparts, but they had less suicidal thoughts than males with high MAO activity. There was a higher incidence of penalties among the relatives of low MAO probands as compared with the high MAO groups. The probands themselves, however, showed no difference; further-

Table 2. Mean 16 PF test profiles of the low MAO (---) (19 males, 16 females) and high MAO (———) (18 males, 19 females) groups

Factor	Low Score Description	Standard Ten Score 1 2 3 4 5 6 7 8 9 10	High Score Description
A	reserved, detached, critical, aloof, stiff		outgoing, warmhearted, easy-going, participating
B	less intelligent, concrete-thinking		more intelligent, abstract-thinking, bright
C	affected by feelings, emotionally less stable, easily upset changeable		emotionally stable, mature, faces reality, calm
E	humble, mild, easily led, docile, accommodating		assertive, aggressive, stubborn, competitive
F	sober, taciturn, serious		happy-go-lucky, enthusiastic
G	expedient, disregards rules		conscientious, persistent, moralistic, staid
H	shy, timid, threat-sensitive		venturesome, uninhibited, socially bold
I	tough-minded, self-reliant, realistic		tender-minded, sensitive, clinging, overprotected
L	trusting, accepting conditions		suspicious, hard to fool
M	practical, "down-to-earth" concerns		imaginative, bohemian, absent-minded
N	forthright, unpretentious, genuine but socially clumsy		astute, polished, socially aware
O	self-assured, placide, secure, complacent, serene		apprehensive, self-reproaching, insecure, worrying, troubled
Q_1	conservative, respecting traditional ideas		experimenting, liberal, free-thinking
Q_2	group-dependent, a "joiner" and sound follower		self-sufficient, resourceful, prefers own decisions
Q_3	undisciplined self-conflict, lax, follows own urges, careless of social rules		controlled, exacting will power, socially precise, compulsive
Q_4	relaxed, tranquil, unfrustrated, composed		tense, frustrated, driven, owerwrought

Table 3. Mean FPI test profiles of the low MAO (---) (19 males, 16 females) and high MAO (———) (18 males, 19 females) groups

FPI Scale			9 8 7 6 5 4 3 2 1	
1	Nervousness	psychosomatically disturbed		psychosomatically not disturbed
2	Spontaneous aggressivity	spontaneously aggressive, emotionally immature		not aggressive, disciplined
3	Depressivity	dysphoric, insecure		content, secure
4	Irritability	irritable, easily frustrated		calm, indifferent
5	Sociability	sociable, vivid		unsociable, reserved
6	Composedness / Self-reliance	self confident, well tempered		irritable, hesitating
7	Reactive aggressivity / Dominance	reactively aggressive, dominating		compliable, moderate
8	Inhibitedness	retarded, tense		easy going, communicative
9	Openness / Self-criticism	open-minded, self-critical		reserved, uncritical
E	Extraversion	extraverted		introverted
N	Emotional lability	emotionally labile		emotionally stable
M	Masculinity	typically masculine selfdescription		typically feminine selfdescription

Table 4. Mean scores of EPQ after transformation into *z*-values of the standard normal distribution for males, females and both sexes. No statistical significance was achieved in any of the comparisons

EPQ second-order factors	Males		Females		Both sexes	
	Low MAO	High MAO	Low MAO	High MAO	Low MAO	High MAO
Psychoticism	0.93	0.05	0.93	0.29	0.93	0.17
Extraversion	0.20	0.20	−0.21	−0.02	0.01	0.09
Neuroticism	−0.23	0.06	0.41	−0.04	0.06	0.01

more, the penalties among the relatives were exclusively due to traffic accidents. There were no indications for severe criminality in any case.

Table 2 shows the average 16 PF profiles of the two groups of low and high MAO probands, which are very similar. There was no statistically significant difference between any of the test scores, neither in males nor in females or when the sexes were combined. The profiles are typical for a student population; they lack extreme deviations from the average.

With respect to the FPI (Freiburger Persönlichkeitsinventar), the comparison of test scores between the two MAO groups does not lead to statistically significant differences (Table 3). The test profiles are nearly all within the "normal" range.

Table 4 gives the results of the EPQ: there is no significant difference between the scores of the low and the high MAO groups of the probands after transformation of the scores to *z*-values of the standard normal distribution. The *t*-values for comparison of both sexes are: psychoticism $t = 0.35$; extraversion $t = 0.15$; neuroticism $t = 0.65$.

Discussion

Genetic factors play an important role in determining such disorders as psychoses, neuroses and alcoholism (cf. Zerbin-Rüdin 1980; Heigl-Evers and Schepank 1980; Goodwin 1979). The development of medical genetics has convincingly demonstrated that inherited diseases that had so far been regarded as genetic entities can be split into different subtypes of diseases. It appears that genetic heterogeneity within inherited diseases is the rule rather than the exception. Thus, correlations between biochemical parameters and a certain disorder can be obscured because of the etiological heterogeneity. Furthermore, the rates of concordance in identical twins for psychiatric diseases are far from 100%. This suggests to us that there may be individuals who are disposed to a psychiatric disorder but who, for as yet unknown reasons, do not develop the illness. These subjects may show certain psychological deviations.

Using the same methodological approach as described by Buchsbaum et al. (1976) this study was designed to reexamine independently the associations described in normal subjects between psychological traits, biographic data and platelet MAO activity. In spite of a certain "regression to the mean" (Fig. 2), we could confirm that platelet MAO has a sufficient stability over time in a given individual so that this parameter is suitable for investigations into a possible

relationship with psychological dimensions. The regression to the mean has been observed by Francis Galton and is characteristic of a parameter influenced by both genetic and nongenetic (environmental, measurement errors) factors (cf. Vogel and Motulsky 1979). Furthermore, the genetic determination of interindividual variation of platelet MAO has repeatedly been shown (cf. Friedl et al. 1981).

To our surprise we could not find psychological differences between subjects with low MAO as compared with those with high MAO. Our failure to confirm the differences described by the NIMH group could have been for any of the following reasons:

1. Methodology of psychological testing;
2. Selection of probands;
3. There is no relationship between platelet MAO and psychological dimensions.

Ad 1. We applied three well-standardized psychological tests that measure predominantly stable personality factors. It is therefore unlikely that our results are at variance because of the tests applied. Furthermore, the biographic data that we explored do not point to a relationship between platelet MAO and psychological traits either. Of course we cannot exclude that our "normal" probands tended to give socially desirable responses. However, since absolute confidentiality had been promised and the lie-factors were low, this possibility is rather unlikely.

Ad 2. The students had been invited by mail to participate in a large-scale screening investigation on correlations between neurophysiological and psychological parameters. For external reasons only students of medicine and basic sciences were asked to cooperate. About 20–25% of all contacted students answered, so that our 383 subjects are only ¼–⅕ of an originally invited group. This may have led to a selection of "normality". On the other hand, voluntary participation in a study in which the results are made available to the probands does not automatically select for "normality". There may be additional reasons such as personal problems, interest in psychology, or psychiatric disorders in relatives that lead a student to participate in such an investigation. However, these influences are not restricted to our study, but—at least to a certain extent— are valid for every investigation that depends on volunteers.

Nevertheless, the proband sample of Buchsbaum et al. (1976) on which some further studies are also based may have been characterized by a higher heterogeneity. At least, the occurrence of psychological problems in the NIMH study—suicide attempts, contact with a psychiatrist, problems with the law—is unusually high in comparison with our German sample. Thus, we cannot exclude that our failure to replicate the correlations between platelet MAO and psychological dimensions is due to differences in selection of probands.

Ad 3. If there is a relationship between platelet MAO and psychopathology at all, it cannot be strong. In this study, the statistically significant differences in the biographic data go in the opposite direction, in comparison with Buchsbaum et al. (1976). This is in line with our findings in relatives of patients with schizophrenia (Propping and Friedl 1979) and of patients with affective psychosis (Maubach et al. 1981), who are expected to show more frequently psychological deviations from

normal, but who did not differ in their platelet MAO activities as compared with healthy controls. On the other hand, one of the authors (H. B.) reported a negative correlation between the score 'extraversion' of the EPQ and platelet MAO activity in an investigation with 20 healthy probands (Gattaz and Beckmann 1981); Murphy et al. (1977) also described mainly negative, though mostly not significant correlations between platelet MAO activity and the MMPI scores. Thus, still more studies are necessary to explain the divergent results.

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