Eur Arch Psychiatr Neurol Sci (1986) 236:83–87

European Archives of Psychiatry and Neurological Sciences

Urinary Phenylethylamine Correlates Positively with Hypomania, and Negatively with Depression, Paranoia, and Social Introversion on the MMPI

H. W. Moises[1], P. Waldmeier[2], and H. Beckmann[3]

[1]Psychiatrische Klinik des Zentralinstituts für Seelische Gesundheit, Postfach 5970, I5, D-6800 Mannheim, Federal Republic of Germany
[2]Pharmazeutische Forschungsabteilung der Ciba-Geigy AG, CH-4002 Basel, Switzerland
[3]Psychiatrische Klinik der Julius-Maximilians-Universität, Füchsleinstrasse 15, D-8700 Würzburg, Federal Republic of Germany

Summary. It has been suggested that phenylethylamine (PEA) may play a role in the modulation of affective behavior. The aim of the present study was to test this hypothesis. Urinary PEA excretion was determined in 32 drug-free healthy volunteers, and the MMPI was used for personality assessment. In support of this hypothesis, a significant positive correlation between PEA and hypomania ($r = 0.50$; $P < 0.05$) and a significant negative correlation between PEA and depression ($r = -0.58$; $P < 0.01$) was observed in the female subgroup. Furthermore, PEA correlated significantly negatively with hypochondriasis ($r = -0.65$; $P < 0.01$), paranoia ($r = 0.49$; $P < 0.05$), and social introversion ($r = -0.60$; $P < 0.05$). These results are the first evidence in normal individuals either that PEA itself might play a role in the modulation of affective behaviour, or alternatively that PEA could be related to mechanisms responsible for the modulation of affective behavior.

Key words: Phenethylamines – Personality disorders – Manic disorder – Depressive disorder – Monoamine oxidase inhibitors

Introduction

Phenylethylamine (PEA) is a trace amine whose chemical structure, and pharmacological and behavioral effects closely resemble those of amphetamine. It has been suggested that PEA may play a role in the etiology of psychiatric disorders. A decrease in PEA has been suggested in depression (Fischer et al. 1968; Sabelli and Mosnaim 1974), and an increase in schizophrenia (Sandler and Reynolds 1976), paranoid schizophrenia (Potkin et al. 1979) and aggressive personality disorders (Sandler et al. 1978).

Together these hypotheses postulate a relationship between PEA concentrations and psychopathological conditions. The PEA concentration in the brain is thought to influence psychological functions, and extreme deviations from normal could cause psychiatric disorders such as paranoid schizophrenia, aggressive personality disorder, and depression. However, nothing is known about the role of PEA in normal individuals.

Data in support of these hypotheses have been reported by several investigators, others however were unable to confirm these findings (for reviews: Reynolds 1979; Wolf and Mosnaim 1983). The conflicting results may have arisen from unrecognized differences in relevant variables of the control groups.

Some evidence suggests that personality differences may be such relevant variables. Personality factors are known to correlate with the activity of monoaminoxidase (MAO) B, an enzyme which degrades PEA (see e.g., Murphy et al. 1977; Gattaz and Beckmann 1981; Demisch et al. 1982). Furthermore, the postulated relationship between PEA concentration and psychological phenomena suggests a graded influence of PEA. For this reason one might expect, even in a normal population, some signs of depression in individuals with low PEA values and signs of hypomania, aggression, psychopathic, and paranoid tendencies in individuals with PEA concentrations higher than normal.

On the basis of this postulated dimensional model the following predictions were made: urinary PEA concentration correlates positively with hypomania, schizophrenia, paranoia, psychopathia scores, and negatively with depression on the Minnesota Multiphasic Personality Inventory (MMPI). The aim of our study was to test these predictions.

In view of the methodological problems involved in the determination of the low amounts of PEA in biological material (Reynolds 1979), a procedure with a particularly high selectivity and sensitivity was used for the determination of urinary PEA concentrations: capillary gas chromatography combined with chemical ionization mass spectrometry.

Moreover methodologically, we tried to maximize the magnitude of correlations between PEA and personality variables. It is well known that the magnitude of correlations is reduced by two factors (Barnes 1984). The first factor – the distance between the variables – is a problem in almost every investigation in biological psychiatry. The great number of variables intervening between the biological predictor and observed behavior tends to attenuate the magnitude of the correlations. As it was not possible to circumvent the first factor we tried to reduce the influence of the second – restricted ranges of variables – by selecting individuals in such a way as to cover a wide range of personality scores.

Offprint requests to: H. W. Moises at the above address

Material and Methods

Subjects

To cover a wide range of personality variables, 32 healthy volunteers (16 males and 16 females, mean age 26.06 SD 5.43 years) were selected on the basis of their extraversion and neuroticism scores from a sample of 424 individuals, tested in the Psychological Institute of the University Heidelberg by the Freiburger Personality Inventory (Fahrenberg et al. 1973). Diet, smoking and drinking habits, diseases, family history and psychopathology were evaluated in a standardized interview by an experienced psychiatrist. All subjects were free of concurrent diseases and drug-free according to their own information and to the results of urinary drug screening. Special attention was paid to differences in dietary intake, especially to food containing large quantities of PEA such as chocolate etc. However, no notable differences were observed. (Most of the subjects were students consuming the standard menu of the university canteen.)

Psychological Trait Measurements

For the evaluation of the psychological traits the German version by Blaser and Gehring (1972) of the MMPI (Hathaway and McKinley 1951) was used.

Procedure

Within a period of 10 days 24-h urine samples were collected on 3 different days. Creatinine clearance was determined for each sample to check for correct collection of the urine; incorrect collection would have led to pathological creatinine clearance values. The participants had been informed of the importance of correct collection and that this would be checked. Aliquots were kept frozen at −70°C until analyzed.

Biochemical Measurements

The concentration of PEA in urine was determined by a highly specific and sensitive method using capillary gas chromatography/chemical ionisation mass spectrometry as described recently (Lauber and Waldmeier 1984). In each sample, the concentration of PEA in urine was determined three times. The first value was discarded and the mean of the second and third value was corrected for creatinine values and used for further calculations.

Statistical Analysis

For PEA, the mean of the creatinine-corrected values from the 3 different days was used for further analysis. The significance of sex differences was tested by the Wilcoxon rank sum test ($P < 0.05$, two-tailed). Spearman rank correlation coefficients were calculated for the psychological and biochemical measurements. The variable of sex was controlled again by examining the correlations for males and females separately as well as for the total group. A two-tailed test of significance ($P < 0.05$) was used for the correlations.

Results

Table 1 shows the means and standard deviations of the variables under investigation for males and females separately. No significant sex differences were found except for the hypochondriasis and the masculinity/femininity scale of the MMPI. It is interesting to note that males excreted less PEA than females. This difference however was statistically not significant.

Table 2 displays the Spearman's correlation coefficients between the psychological measurements for females and males. It can be seen that some scales intercorrelated significantly. In the light of the significant correlations found be-

Table 1. Mean scores and standard deviations for urinary PEA and personality variables

Variable	Males ($n = 16$)		Females ($n = 16$)		P[b]
	Mean	SD	Mean	SD	
Urinary PEA[a]	28.83	21.06	40.42	35.68	N.S.
MMPI variables					
Lie (L)	41.50	6.00	40.21	6.25	N.S.
Validity (F)	52.87	8.20	51.00	11.17	N.S.
Correction (K)	53.50	9.95	55.36	11.57	N.S.
Hypochondriasis (Hs)	48.94	5.90	53.86	7.35	*
Depression (D)	54.12	9.94	52.64	10.33	N.S.
Conversion hysteria (Hy)	56.75	9.23	58.50	6.54	N.S.
Psychopathic deviate (Pd)	58.94	8.94	54.93	8.27	N.S.
Masculinity/feminity (Mf)	62.19	7.76	38.00	9.57	***
Paranoia (Pa)	48.56	8.09	48.21	12.07	N.S.
Psychasthenia (Pt)	57.37	11.87	51.57	8.95	N.S.
Schizophrenia (Sc)	53.12	10.78	52.14	6.91	N.S.
Hypomania (Ma)	48.75	9.51	48.36	10.19	N.S.
Social introversion (Si)	55.00	13.80	52.21	13.01	N.S.

[a] µg/g creatinine; [b] Wilcoxon rank sum test
* = $P < 0.05$; *** = $P < 0.001$; N.S. = not significant on the 5% level

Table 2. Spearman's correlation coefficients between psychological measurements

	D	Hs	Hy	Pd	Mf	Pa	Pt	Sc	Ma	Si	L	F	K
D	—	36	43	20	− 4	75***	69**	45*	−43*	81***	−36	26	−59**
Hs[a]	59**	—	54*	22	29	30	47*	27	−10	40	13	−56*	−48*
Hy	56**	41	—	55*	−29	54*	36	56*	20	5	−43	75***	−45*
Pd[a]	62**	26	77***	—	−10	34	16	34	4	− 4	−34	25	6
Mf	24	1	33	48*	—	−38	1	−31	−33	13	34	−17	43
Pa	79***	42*	69**	82***	42*	—	39	60**	−35	42	−25	26	−54*
Pt[a]	63**	37	55**	64**	63**	75***	—	78***	15	63**	−44*	50*	−59**
Sc[a]	72***	45*	65**	75***	62**	88***	78***	—	36	22	−54*	55*	−50*
Ma[a]	−12	−19	38	39	16	1	3	12	—	−48*	−42	48*	− 8*
Si	50*	15	−14	− 2	28	23	52*	26	−39	—	−17	13	−61**
L	− 8	42*	−18	−19	−51*	− 8	−15	−24	−21	−10	—	−40	23
F	13	−16	27	53*	20	42*	44*	47*	59**	2	1	—	−63**
K	−23	32	− 3	−31	−58**	−92	−50*	−43*	−32	−46*	40	−57**	—

Abbreviations of the MMPI scales are explained in Table 1.
[a] K-corrected. Females above the diagonal and males below. Decimal points omitted.
* = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$

Table 3. Spearman's correlation coefficients between urinary PEA and personality measurements

Personality measures	Females ($n = 16$)	Males ($n = 16$)	Total group ($n = 32$)
Hypomania[a]	50*	−29	12
Depression	−58**	−13	−39*
Hypochondriasis[a]	−65**	− 5	25
Conversion hysteria	−41	−18	−23
Psychopathic deviate	− 5	−22	−20
Masculinity/femininity	−10	−40	−34*
Paranoia	−49*	− 4	−32*
Psychasthenia[a]	−24	3	−18
Schizophrenia[a]	−14	−28	−20
Social introversion	−60**	14	−24

[a] K-corrected. Decimal points omitted
* = $P < 0.05$; ** = $P < 0.01$

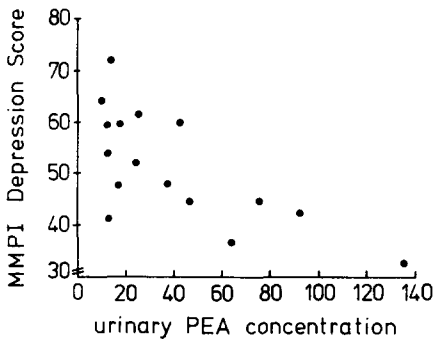

Fig. 1. Correlation between urinary PEA concentration (μg/g creatinine) and depression in females ($r = -0.58$; $P < 0.01$)

tween PEA and personality variables, it is noteworthy that in females the depression scale correlated significantly positively with paranoia, psychasthenia, schizophrenia, social introversion, and significantly inversely with hypomania.

Table 3 presents the Spearman rank correlation coefficients between urinary PEA and the MMPI scales. In the total group, PEA correlated significantly negatively with depression, paranoia, and masculinity/femininity scales. Most of the significant correlations in the total group were due to the female subgroup.

In the male subgroup, none of the correlations reached significance. In the female group, PEA correlated significantly positively with hypomania and negatively with depression (Fig. 1). Furthermore, a significant negative correlation was obtained with hypochondriasis, paranoia, and social introversion, which in turn correlated with depression as can be seen in Table 2.

Discussion

Of the 30 correlations between PEA and psychological variables, 8 were significant at the 0.05 level. As approximately 2 correlations might have been expected by chance, the results suggest that something more than chance is operating. Furthermore, the pattern of correlations – positive correlation with hypomania and negative with depression, hypochondriasis, paranoia, and social introversion (Table 3), which in turn intercorrelated (Table 2) – suggests systematic relationships between related variables rather than random ones.

If we accept this, two main components of our results remain to be explained: the sex differences and the correlations between PEA and personality variables.

With regard to the sex differences, females showed significantly higher values on the hypochondriasis and males on the masculinity/femininity scale of the MMPI (see Table 1). The first sex difference possibly reflects the higher incidence of psychosomatic disorders in females, the latter is not surprising since the masculinity/femininity scale of the MMPI has been constructed to differentiate between males and females. The finding of reduced urinary PEA levels in males is in aggreement with the results of Philips (1978). However, in our sample this difference was not statistically significant. In contrast to the female subgroup no significant correlations were obtained in our male subgroup. This could be due to the restricted range of PEA values in the male group or to a male-specific confounding variable, e.g., testosterone which might influence mood and possibly PEA metabolism. The significant inverse correlation between PEA and the masculinity/femi-

ninity scale, which in turn probably relates somehow to the action of testosterone, might be seen as indirect evidence for the latter assumption.

With regard to the correlations between PEA and personality variables, hypomania correlated significantly positively, whereas depression, hypochondriasis, paranoia, and social introversion correlated significantly negatively with urinary PEA concentrations in females (see Table 3). To our knowledge no comparable data have been published concerning PEA and personality traits. However, there have been studies concerned with PEA and related variables in psychiatric patients. Our finding of an inverse correlation between the MMPI depression scale and the 24-h urinary PEA excretion accords with studies indicating a significant reduction in the 24-h urinary PEA excretion in depressed patients (Fischer et al. 1972, 1973; Mosnaim et al. 1973; Sabelli and Mosnaim 1974). On the other hand, no positive correlation between PEA and the paranoia or psychopathic deviate scale of the MMPI was found. Our results do not agree with those of Potkin et al. (1979) and Jeste et al. (1981) reporting higher PEA excretion in chronic paranoid schizophrenics, or those of Sandler et al. (1978) suggesting PEA overproduction in aggressive psychopaths. It should be noted however that we were using the MMPI as a psychological measurement with a normal population while the above authors were concerned with a patient population and used clinical diagnoses.

The possible relationship of PEA to certain personality traits suggested here indicates that such traits should be controlled in studies comparing mental disorders with a healthy group. The variability of certain personality traits in so called normals may be extreme. Certain features may greatly increase the readiness of persons to serve as controls, thus leading to a bias. In the present study, since individuals most willing to participate scored high in extraversion and low in neuroticism considerable effort was required to find an adequate number of volunteers representing the other extremes of the scales (high neuroticism and low extraversion). Likewise, other researchers have found volunteers to be extraverted (McLaughlin and Harrison 1973). However, introversion and neuroticism are personality traits often encountered in psychiatric patients. In other words, studies comparing psychiatric patients with normal controls will probably often compare neurotic introverts (patients) with stable extraverts (controls). The conflicting results of the studies concerned with PEA in depression, psychopathy, and schizophrenia might be due to various factors such as age, sex, medication, and biochemical measurements, or personality variables of the control groups. For this reason, future studies of PEA in psychiatric patients should control for the personality variables social introversion and depression as measured by the MMPI, which have been found to correlate highly with urinary PEA excretion in females.

In conclusion, the results of our study confirm the essential predictions made at the beginning of the study, at least in females. As predicted, low PEA concentrations are associated with traits of depression and higher PEA levels with signs of hypomania even in a normal population. These findings could be accounted for by Sabelli and Mosnaim's PEA hypothesis of affective behavior. However, they cannot exclude the possibility that PEA itself does not modulate affective behavior but is related to mechanisms responsible for its modulation. Experimental evidence from pharmacological studies suggests that PEA may not be involved in neuromodulation (Waldmeier et al. 1985). This is in line with the results of a study suggesting that l-deprenyl (a MAO B inhibitor with PEA and dopamine as preferred substrates) is not effective as an antidepressant (Mendis et al. 1981). On the other hand, other investigators using l-deprenyl have found a significant improvement in depressive patients (e.g., Mendlewicz and Youdim 1983). Birkmayer et al. (1984) even observed strong clinical efficacy of l-deprenyl plus l-phenylalanine (a precursor of PEA) comparable only to that of electroconvulsive treatment. These authors concluded that the strong antidepressant effect of the combined treatment is based on the accumulation of l-PEA in the brain.

Finally, MAO inhibitors are known to be especially effective in 'atypical depression' and to increase PEA concentrations (Tyrer 1976; Quitkin et al. 1979). The depressive syndrome obtained by negative correlations between urinary PEA and the MMPI scales depression, hypochondriasis, paranoia, and social introversion closely resemble the descriptions of 'atypical depressions' characterized by 'somatization of symptoms', 'sensitivity to interpersonal rejection', and 'social phobias'. Further studies are needed to clarify whether the 'low PEA depressive syndrome' is identical with the 'atypical depression', and whether the MMPI scales depression, hypochondriasis, and social introversion might be a better predictor of the response to MAO B inhibitors than the unreliable diagnostic category 'atypical depressions'.

Acknowledgements. We thank Professor Dr. M. Amelang and Dr. P. Borkenau from the Institute of Psychology at the University of Heidelberg for their kind support in the acquisition of volunteers.

References

Barnes GE (1984) A brief note on two often ignored principles that tend to attenuate the magnitude of correlations. Person Individ Differ 5:361–363

Birkmayer W, Riederer P, Linauer W, Knoll J (1984) L-Deprenyl plus L-phenylalanine in the treatment of depression. J Neural Trans 59:81–87

Blaser P, Gehring A (1972) Ein programmierter Kurs zur deutschsprachigen Ausgabe des Minnesota Multiphasic Personality Inventory. In: Hathaway SR, McKinley JC (Hrsg). Hans Huber, Bern

Demisch L, Georgi K, Patzke B, Demisch K, Bochnik HJ (1982) Correlation of Platelet MAO Activity With Introversion: A Study on a German Rural Population. Psychiat Res 6:303–311

Fahrenberg J, Selg H, Hample R (1973) Das Freiburger Persönlichkeitsinventar. Hogrefe, Göttingen

Fischer E, Heller B, Miro A (1968) β-phenylethylamine in human urine. Arzneimittelforsch 18:1586

Fischer E, Spatz H, Heller B, Reggiani H (1972) Phenylethylamine content of human urine and rat brain. Its alterations in pathogenic conditions and after drug administration. Experientia 28:307–308

Fischer E, Spatz H, Fernandex Labriola R (1973) Quantitative gas chromatographic determination and infrared spectrographic determination of urinary phenylethylamine. Biol Psychiatry 7:161–165

Gattaz WF, Beckmann H (1981) Platelet MAO activity and personality characteristics. A study in schizophrenic patients and normal individuals. Acta Psychiat Scand 63:479–485

Hathaway SR, McKinley JC (1951) The Minnesota Multiphasic Personality Inventory Manual. The Psychological Corporation, New York

Jeste DV, Doonagaji DR, Panjwani D, Datta M, Potkin SG, Karoum F, Thatte S, Shet AS, Apte JS, Wyatt RJ (1981) Cross-cultural study of biochemical abnormality in paranoid schizophrenia. Psychiat Res 3:341–352

Lauber J, Waldmeier PC (1984) Determination of 2-Phenylethylamine in Rat Brain After MAO Inhibitors, and in Human CSF and Urine Capillary GC and Chemical Ionization MS. J Neural Trans 60:247–264

Mosnaim AD, Inwang EE, Sugerman JH, de Martini W, Sabelli HC (1973) Ultraviolet spectrometric determination of 2-phenylethylamine in biological samples and its possible correlation with depression. Biol Psychiatry 6:235–257

McLaughlin RJ, Harrison NW (1973) Extraversion, neuroticism and the volunteer subject. Psychol Rep 32:1131–1134

Mendis N, Pare CMB, Sandler M, Glover V, Stern G (1981) (−)Deprenyl in treatment of depression. In: Youdim MBH, Paykel ES (eds) Monoamine oxidase inhibitors. The state of the Art. Wiley, Chichester, pp 171–176

Mendlewicz J, Youdim MBH (1983) L-Deprenyl, a selective monoamine oxidase type B inhibitor, in the treatment of depression: a double-blind evaluation. Brit J Psychiatry 142:508–511

Murphy DL, Belmaker RH, Buchsbaum MS, Nichols A, Costa JL, Wyatt RJ (1977) Biogenic amine-related enzymes and personality variations in normals. Psychol Med 7:149–157

Philips SR (1978) β-Phenylethylamines: a metabolically and pharmacologically active amine. In: Mosnaim AD, Wolf ME (eds) Noncatecholic phenylethylamines. Part I. Phenylethylamines: biological mechanisms and clinical aspects. MDekker, New York, pp 113–138

Potkin SG, Karoum F, Chwang LW, Cannon-Spoor HE, Philips I, Wyatt RJ (1979) Phenylethylamine in paranoid chronic schizophrenia. Science 206:470–471

Quitkin F, Rifkin A, Klein DF (1979) Monoamine oxidase inhibitors. A review of antidepressant effectiveness. Arch Gen Psychiatry 36:749–760

Reynolds GP (1979) Phenylethylamine – a role in mental illness? TINS 2:265–268

Sabelli HC, and Mosnaim AD (1974) The Phenylethylamine Hypothesis of Affective Behavior. Am J Psychiatry 131:695–699

Sandler M, Reynolds GP (1976) Does phenylethylamine cause schizophrenia? Lancet 1:70–71

Sandler M, Ruthven CRJ, Goodwin BL, Field H, Matthews R (1978) Phenylethylamine overproduction in aggressive psychopaths. Lancet 2:1269–1270

Tyrer P (1976) Towards rational therapy with monoamine oxidase inhibitors. Br J Psychiatry 128:354–360

Waldmeier PC, Buchle AM, Lauber J (1985) Cerebral 2-phenylethylamine concentrations and turnover not influenced by various pharmacological treatments in rats. In: Bieck H, Boulton AA, Maitre L, Riederer P (eds) Proceedings of the IInd Trace Amines Symposium. Humana Press Inc, Clifton, New Jersey, pp 15–26

Wolf ME, Mosnaim AD (1983) Phenylethylamine in neuropsychiatric disorders. Gen Pharmac 14:385–390

Received January 14, 1986