Phenylethylamine in Paranoid Chronic Schizophrenia

Abstract. *Phenylethylamine (PEA) is an endogenous amine that is structurally and pharmacologically related to amphetamine. Urinary PEA excretion is significantly higher in paranoid chronic schizophrenics than in nonparanoid chronic schizophrenics and normal controls. Diet, hospitalization, and medication do not account for differences in PEA concentrations. These findings offer some indication that PEA may be an endogenous amphetamine.*

Phenylethylamine (PEA), a naturally occurring amine that resembles amphetamine pharmacologically and structurally, has been hypothesized to be of etiological importance in some cases of schizophrenia (*1, 2*). Normal persons who ingest amphetamine in sufficient doses may develop symptoms that are clinically indistinguishable from paranoid schizophrenia (*3*). In fact, the misdiagnosis of amphetamine intoxication is not rare; frequently, the clinical symptoms of amphetamine intoxication are indistinguishable from those of paranoid schizophrenia (*4*). When schizophrenic patients are given small doses of amphetamine, their existing schizophrenic symptoms typically worsen (*5*). Both amphetamine intoxication and schizophrenia are somewhat successfully treated by the phenothiazines and other neuroleptics that block dopamine. Dopamine, which is central to many current hypotheses of schizophrenia, is also commonly thought to mediate amphetamine intoxication (*4*).

In the laboratory setting, the pharmacological effects of amphetamine on behavior have been well studied and widely used as an animal model of schizophrenia (*6*). Structurally, amphetamine and PEA are identical except for the presence of an α-methyl group on the amphetamine side chain (α-methyl-PEA). Amphetamine and PEA produce similar stereotypies, although PEA is less potent and has a shorter duration of action (*2, 7*). Both amphetamine- and PEA-induced stereotypies in animals are blocked (i) by neuroleptics that are clinically useful in treating schizophrenia and (ii) in doses approximately equal to the neuroleptics' relative clinical potencies (*2, 8*). Some differences in pharmacological and behavioral effects in animals do exist between PEA and amphetamine. Clozapine, a poor dopamine blocker, antagonizes stereotypies induced by PEA but not those induced by amphetamine (*9, 10*). While repeated self-administration of both PEA and amphetamine in animals occurs without the development of tolerance, pimozide, a strong dopamine blocker, antagonizes self-administration of amphetamine but not that of PEA (*11*). Tolerance to PEA administration in other schedules and paradigms, in general, does not occur (*12*).

Interest in a PEA hypothesis of schizophrenia is bolstered by PEA's presence in the human brain, with highest concentrations in the limbic system (*13*). It is also present in human cerebrospinal fluid, blood, and urine (*13, 14*). Fischer *et al.*, the first to look at urinary PEA in psychiatric patients, found elevated concentrations in seven schizophrenic subjects (*15*) and confirmed their initial report in four additional schizophrenics (*16*). However, Suzuki and Yagi (*17*), using spectrophotometric techniques, were unable to confirm Fischer *et al.*'s findings in five schizophrenics. Unfortunately, studies have been confounded by variability in PEA excretion for both normal and psychiatric patient populations. Schweitzer *et al.* (*18*) found normal PEA excretion in three acute schizophrenics. The investigators emphasized the methodological problems of lack of sensitivity and specificity and suggested that such difficulties might explain the disparity in the literature.

We have developed a mass fragmentography method for the assay of urinary PEA that is sensitive to 0.5 μg during a 24-hour period and is highly specific (*14, 19*). The assay is reliable, with intraclass correlation coefficients of greater than 0.9 for split samples run on different days.

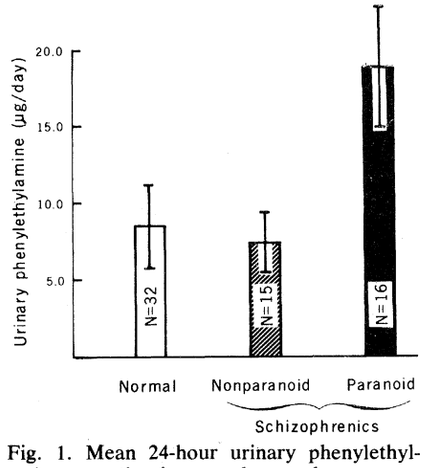

Fig. 1. Mean 24-hour urinary phenylethylamine excretion in normal controls, nonparanoid chronic schizophrenics, and paranoid chronic schizophrenics. Bars indicate standard errors.

We report the 24-hour urine excretion of free PEA in 31 chronic schizophrenic patients [diagnosed by RDC (*20*)] and in 32 normal subjects. Sixteen of the patients were paranoid and 15 nonparanoid, as determined by historical review, semistructured interview, and staff consensus diagnoses based on DSM III categories (*20*). All patients had been hospitalized for at least 1 year without having returned to premorbid functioning. Many were being treated with phenothiazines; however, phenothiazines did not consistently alter urinary PEA concentrations in eight patients we studied both with and without medication (at least 3 weeks without medication) [paired $t(7) = 0.37$, not significant]. All diagnoses and groupings were made prior to the PEA analysis. All analyses were performed on coded samples.

The PEA value for each individual was determined by calculating the mean of all urine collections for that individual. The one-way analysis of variance showed significant overall results [$F(2,60) = 3.36$, $P = .04$] (Fig. 1). The mean of the 16 paranoid chronic schizophrenics was significantly higher than that of the 32 normal subjects and that of the 15 nonparanoid schizophrenics (Newman Keuls's test, $P < .05$). The PEA excretion by the nonparanoid schizophrenic group was not significantly different from that by the normal group.

Of the 31 chronic schizophrenics studied, 12 were high excreters of PEA (more than 10 μg in 24 hours on at least two of three tests), compared with 3 of 32 normal subjects (Fisher exact probability test, $P = .008$). Of the 12 schizophrenic high excreters, 10 were subtyped paranoid (Fisher exact probability test, $P = .009$).

Finding increased PEA in the urine of paranoid chronic schizophrenic patients may represent a significant step forward in our understanding of the schizophrenic process; however, the possible contamination of nonspecific factors, such as diet, hospitalization, or adequacy of urine collection, must be considered.

To assess the acute dietary contribution of PEA, five normal subjects ingested 200 g of chocolate (containing 1.15 mg of PEA) during a 2-hour period. No increase in their 12-hour urine excretion of PEA was observed (paired t-test). Serial 12-hour urine samples collected from 15 normal, healthy adult volunteers demonstrated no diurnal variation (*21*). No significant correlation was seen between PEA excretion and pH (*22*).

The correlation between PEA excretion and length of hospitalization was

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also not significant. Both paranoid and nonparanoid groups were hospitalized on identical wards and were chronically ill for comparable time periods, so that chronicity and environmental factors did not account for the differences in PEA excretion seen in these two groups (*23*). Patient cooperation in urine collection is always a methodological problem, and the adequacy of collection can never be assured. Nevertheless, even with urine volumes that may have been inadequate, we found an increase in urinary PEA in schizophrenic patients.

Since monoamine oxidase (MAO), a major enzyme in PEA degradation, is decreased in the platelets of some chronic schizophrenics—perhaps, in particular, those with paranoid symptoms (*24*)—it is attractive to speculate that such a reduction might represent a decreased capacity to metabolize PEA and thereby lead to its accumulation. Demish *et al.* (*25*), in the only published study in which PEA was used as substrate for MAO, reported reduced MAO for the paranoid subgroup only (12.1 nmole per milligram of protein per hour versus 16 for normal subjects).

The finding of increased PEA in urine of paranoid chronic schizophrenics offers some indication that PEA may be an endogenous amphetamine. Nonetheless, results must be viewed with caution. Although PEA readily crosses the blood-brain barrier, the relationship of urinary 24-hour PEA excretion and circulating brain concentrations of PEA is unknown. The relationship between PEA excretion and changes in clinical state has not yet been studied. Most importantly, although much is known about amphetamine's ability to produce a paranoid psychosis and of the similarities of PEA to amphetamine in animal models, the potential psychotomimetic effects of PEA in humans are yet to be explored.

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13. Limbic system [R. L. Borison, M. Reyes, F. Lemus, H. S. Havdala, B. I. Diamond, *Res. Comm. Psych. Psychiat. Behav.* **2**, 193 (1977)]; cerebrospinal fluid, plasma, and urine (*14*).
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19. Urine was collected into refrigerated containers with 5 ml of 10 percent EDTA and stored at − 20°C until analyzed. In the analyses, 0.2-ml portions of the urine were mixed with 1 ml of 0.5 M phosphate buffer. Deuterated PEA was added as internal standard and the mixture was immediately extracted into ethyl acetate. The PEA was then converted to a pentafluoropropionyl derivative with 100 percent pentafluoropropionyl imidazole (PFPI) in ethyl acetate (25 μl). The extracted PEA was heated at 70°C for 10 minutes and cooled; 5 μl of 10 percent dry methanol was added, and the mixture was reheated at 70°C for 10 minutes. This last step was necessary to remove excess PFPI. Gas chromatography was carried out on an 0.8″ (outside diameter) column packed with 1 percent SE 54 + 0.5 percent OV + 0.2 percent OV_{210}. A quadrupole gas chromatograph mass spectrometer (Finnegan 3200) focused on ions of 104 and 107 atomic mass units to detect PEA and [$^2H_4$]PEA, respectively (*14*).
20. Research and Diagnostic Criteria (RDC) and Diagnostic and Statistical Manual of Mental Disorders (DSM III) have been discussed by R. L. Spitzer, J. K. Endicott, E. Robins [*Am. J. Psychiatry* **132**, 1187 (1975)]. All patients were interviewed according to a shortened version of the Present State Exam [J. K. Wing, J. E. Cooper, N. Sartorius, *The Measurement and Classification of Psychiatry Symptoms* (Cambridge University Press, New York, 1974)] and a paranoid dimensions checklist, which, based on suggestions by D. Rosenthal, includes measures of suspiciousness, hostility, grandiosity, rigidity, and evasiveness.
21. Consecutive 12-hour urine collections were begun at 9 a.m. No difference was observed between the morning and evening collections. Suzuki and Yagi (*17*) collected consecutive 8-hour urine samples from three normal subjects and found increased PEA excretion in the samples taken from 4 p.m. to midnight.
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Cholecystokinin Octapeptide: Continuous Picomole Injections into the Cerebral Ventricles of Sheep Suppress Feeding

Abstract. *Cholecystokinin octapeptide decreased food intake in a dose-related manner when injected continuously into the lateral cerebral ventricles of sheep that had been deprived of food for 2, 4, 8, or 24 hours. In sheep deprived of food for 2 hours, as little as 0.01 picomole per minute suppressed feeding 35 percent 1 hour after beginning injection. Pentagastrin also decreased feeding in the 2-hour group, but only at a much higher dose range. Secretin had no effect. These findings support the hypothesis that cholecystokinin octapeptide acts on central nervous system structures that are involved in control of food intake.*

The peptides in the gastrointestinal (GI) tract likely play some role in the control of food intake under normal conditions. They are secreted in response to the quality and quantity of ingested food, enter the bloodstream, and can be transported to the brain to act as signals to regulatory mechanisms. In the past few years, evidence has been accumulating for a role of cholecystokinin (CCK, 33 amino acids) as a satiety factor.

Originally it was hypothesized that CCK released by the GI tract acted on receptors that mediate the food intake response (*1*). The central nervous system (CNS) has been considered to be the probable site for these receptors. It was shown that the ventromedial hypothala-

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