Decreased β -phenylethylamine in CSF in Parkinson's disease

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Abstract

Objective—To determine the concentrations of β -phenylethylamine (PEA) in CSF in patients with Parkinson's disease, and to evaluate the relation between concentration of PEA in CSF and severity of Parkinson's disease.

Methods—Using gas chromatography-chemical ionisation mass spectrometry, CSF concentrations of PEA were measured in 23 patients with Parkinson's disease (mean age, 64.0 (SD 8.2) years), of whom three were at Hoehn and Yahr stage II, 11 were at stage III, and nine were at stage IV. Comparison was made with eight patients with neuropathy (mean age, 57.0 (SD 19.2) years) and 12 controls without neurological disease (mean age, 57.6 (SD 4.8) years).

Results—Concentrations of PEA in CSF in Parkinson's disease were significantly lower (mean 205 (SD 131) pg/ml) than in patients with peripheral neuropathy (433 (SD 254) pg/ml) and controls (387 (SD 194) pg/ml). The concentrations of PEA in CSF correlated negatively with Hoehn and Yahr stage ($P < 0.01$).

Conclusions—There are decreased CSF concentrations of PEA in patients with Parkinson's disease.

(*J Neurol Neurosurg Psychiatry* 1997;63:754-758)

Keywords: β -phenylethylamine; cerebrospinal fluid; Parkinson's disease; Hoehn and Yahr stage

Parkinson's disease is a relatively common progressive nigrostriatal neuronal degeneration. Recently alterations of several neurotransmitters related to dopaminergic neurons have been emphasised in Parkinson's disease.^{1,2} Some studies have indicated that β -phenylethylamine (PEA) acts as a neurotransmitter or neuromodulator in the nigrostriatal dopaminergic pathway. PEA, which has been implicated in the pathogenesis of certain psychiatric and neurological diseases,³⁻⁵ was identified as a biogenic trace amine in mammalian tissues including brain in the 1960s.^{6,7} Since then, PEA has been investigated extensively in neurochemical, neuropharmacological, and neurophysiological contexts.⁸⁻¹²

The synthesis of PEA is by decarboxylation of phenylalanine¹³ and it is metabolised either first to phenylacetaldehyde by monoamine oxidase type B (MAO-B) and subsequently to phenylacetic acid (PAA) by aldehyde dehydrogenase, or alternatively to phenylethanolamine by

dopamine- β -hydroxylase (fig 1).¹⁴ Acting on presynaptic dopaminergic nerve terminals, PEA stimulates dopamine release.^{13,15} PEA also has an indirect sympathomimetic effect.¹⁶ Although some authors have reported altered PEA concentrations in psychiatric diseases,¹⁷⁻¹⁹ PEA concentrations in patients with Parkinson's disease have not been reported. We measured PEA in the CSF of patients with Parkinson's disease as the best reflection of its status in the CNS in vivo and examined relations between CSF concentration of PEA and severity of disease.

Patients and methods

CHEMICALS AND REAGENTS

Deuterium-labelled PEA (D4-PEA) was purchased from MSD Isotopes (Quebec, Canada). Pentafluoropropionic anhydride was obtained from TCI (Tokyo, Japan). PEA and other chemicals were purchased from Wako Pure Chemical Industries Ltd (Osaka, Japan).

SUBJECTS

Specimens of CSF were obtained from 23 patients with Parkinson's disease (11 men, 12 women; mean age, 64.2 (SD 8.2) years; mean duration of disease, 6.4 (SD 2.9) years, range 2 to 14 years). Specimens were also obtained from eight non-parkinsonian patients with peripheral neuropathy (five men, three women; mean age, 57.0 (SD 19.2) years), and from 12 controls without neurological disease, including eight orthopaedic patients, three urological patients, and one gynaecological patient (six men, six women; mean age 57.6 (SD 4.8) years). Severity of Parkinson's disease was rated according to Hoehn and Yahr stage.²⁰ All patients were receiving antiparkinsonian drugs including levodopa-benserazide and bromocriptine, but not the MAO-B inhibitor deprenyl, which affects concentrations of PEA in CSF. The amount of levodopa given was 200 to 400 mg per day, except in three patients (patients 1, 7, and 19 in the table). For patients 7 and 19, L-threo-DOPS was administered.²¹ Ten patients showed depression; some received antidepressant drugs. With the informed consent of the patients, lumbar puncture was performed between 8 30 and 11 00 am. No CSF samples visibly contaminated with blood were used. The first ml of CSF obtained was immediately frozen and stored at -80°C until assay.

EXTRACTION AND DERIVATISATION

The extraction of PEA from CSF was performed by a method described previously.²² Samples of CSF (0.5 ml) were placed in silicon

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Received 7 March 1997 and
in revised form 9 June 1997
Accepted 18 June 1997

Figure 1 Synthesis and catabolism of PEA and dopamine. "L-Dopa" at the top of the scheme represents exogenous levodopa administered to treat Parkinson's disease. DOPA=3,4-dihydroxyphenylalanine; L-Dopa=levodopa; AADC=aromatic amino acid decarboxylase; MAO-B=monoamine oxidase type B; DBH=dopamine β hydroxylase.

coated tubes. Then 5 ng D4-PEA were added to each tube as an internal standard. In addition, 5 ng D4-PEA was added to each of four tubes with 0.5 ml Ringer's solution. Then, 30 pg, 100 pg, 300 pg, or 1 ng PEA were each added to one of these four tubes as standards. All samples were kept at 0°C for 20 minutes to equilibrate. After the addition of 50 μ l 6 N NaOH, CSF was applied to an Extrelut column (2 cm $\times$ 2.5 cm, Merck, Darmstadt, Germany) left for five minutes, and eluted with 7 ml ethyl acetate. The eluate was collected in a tube which contained 100 μ l 1 mM HCL to prevent loss of PEA during evaporation in a concentrator (Savant, Farmingdale, NY). The residue was derivatised with 50 μ l pentafluoropropionate (PFP) anhydride at 100°C for 20 minutes. The solvent was evaporated to

dryness with dry nitrogen gas, and the sample was reconstituted with 20 μ l ethyl acetate.

GAS CHROMATOGRAPHY-CHEMICAL IONISATION MASS SPECTROMETRY (GC/CI/MS)

Sample volumes of 2 μ l were injected into a GC-CI mass spectrometer. The double-focused mass spectrometer was interfaced with a data acquisition system (Hitachi M-80B, Hitachi, Japan). Isobutane was used as the reagent gas (source pressure, 3×10^{-6} torr) and helium was the GC carrier gas (40 ml/min). The GS/MS interface oven and transfer line were set at 260°C. A Megabore column (0.56 mm internal diameter, 15 m long, J and W Scientific Co, Folsom, CA, USA) coated with DB-1 was used. The oven temperature was maintained isothermally at 100°C. The mass numbers used for quantitative analysis were m/z 268 corresponding to PEA-PFP and m/z 272 corresponding to D4-PEA-PFP. Peak area measurement was used for the estimation of ion currents. The calibration curve was highly correlated in standard samples ($r=0.970$) in the range of 30–1000 pg/ml PEA (fig 2).

MEASUREMENT OF HOMOVANILLIC ACID (HVA)

Specimens of CSF from 19 patients with Parkinson's disease and 12 controls were ultra-centrifuged for five minutes at 15 000 g at 4°C. HVA was determined in 20 μ l supernatant by high performance liquid chromatography (Gilson Model-231, Germany; Eicom ECD-100, Japan). Details have been reported previously.²³

STATISTICS

Data were expressed as mean (SD) and analysed with analysis of variance (ANOVA), and followed by Scheffe's *F* test or Student's *t* test (two tailed) to evaluate the significance of differences between each groups. The relation between severity of disease in Parkinson's disease and CSF PEA concentration was analysed with Pearson's correlation. A *P* value >0.05 was considered significant.

Results

The table shows the results of assays for PEA and HVA together with clinical characteristics of the patients with Parkinson's disease. No significant difference was evident for sex or age distribution between control and neuropathy patients and patients with Parkinson's disease. Mean concentrations of PEA in patients with Parkinson's disease ($n=23$), patients with peripheral neuropathy ($n=8$), and controls ($n=12$) were 205 (SD 131), 433 (SD 254), and 387 (SD 194) pg/ml, respectively, with the concentration in patients with Parkinson's disease being significantly lower than those in the neuropathy and control groups ($P<0.001$). No significant difference was noted between the peripheral neuropathy and control groups (fig 3). Concentrations of PEA in CSF from patients with Parkinson's disease with depression (163 (SD 72.8) pg/ml) were lower than those in patients with Parkinson's disease without depression (244 (SD 242) pg/ml), but not significantly ($P=0.07$). The present study did

Clinical characteristics and CSF concentrations of PEA in Parkinson's disease

Patient No	Age (y)	Sex	Disease duration (y)	Hoehn and Yahr stage	Depression	Levodopa* (mg/day)	PEA (pg/ml)	HVA (ng/ml)
1	62	F	2	II	–	0	395	ND
2	67	M	3	II	–	300	660	15
3	71	F	6	II	–	400	356	ND
4	68	M	3	III	–	300	170	ND
5	64	F	3	III	–	200	150	52
6	60	M	4	III	–	300	165	45
7	72	F	5	III	–	0	356	20
8	62	M	6	III	–	300	199	17
9	45	F	7	III	+	300	190	ND
10	63	M	9	III	–	200	111	32
11	45	M	9	III	+	300	150	71
12	58	M	9	III	–	300	170	24
13	70	F	10	III	–	200	160	28
14	57	F	14	III	+	300	170	58
15	76	F	3	IV	–	300	150	60
16	61	F	5	IV	–	400	82	ND
17	73	M	5	IV	+	300	111	33
18	65	F	5	IV	+	200	141	31
19	75	F	6	IV	+	0	82	31
20	62	M	7	IV	+	400	199	13
21	60	M	8	IV	+	300	199	11
22	66	F	8	IV	+	300	268	42
23	75	M	10	IV	+	300	82	53
Mean	64.2		6.4			257	205	35.3
SD	8.2		2.9			116	131	17.9

PEA=phenylethylamine; HVA = homovanillic acid; –=absent; +=present; ND = not done.

*Dose of levodopa received per day.

Figure 2 (A) Calibration curve for selected ion monitoring chromatographic analysis of PEA extracted from Ringer's solution. Vertical axis represents ion intensity ratio of m/z 268 to m/z 272. (B) Typical chromatogram, showing the recordings of pentafluoropropionic derivative of PAE (m/z 268, lower part) with a deuterium labelled internal standard (m/z 272, upper part), obtained from 0.5 ml CSF from a patient with Parkinson's disease (patient 1 in the table).

Figure 3 Concentration of PEA in CSF from patients with Parkinson's disease, patients with neuropathy, and subjects without neurological disease (controls). Horizontal bars represent the mean and vertical bars the SEM.

Figure 4 Significant negative correlation between the CSF concentration of PEA and Hoehn and Yahr stage in patients with Parkinson's disease (Pearson's correlation, $r = -0.67$, $P < 0.001$).

not show a significant relation between concentration of PEA in CSF and dose of levodopa, or between the concentrations and duration of Parkinson's disease. The concentration of PEA in CSF showed a significant negative correlation with Hoehn and Yahr stage ($P < 0.001$, fig 4).

The CSF concentrations of HVA did not differ significantly between Parkinson's disease (35.3 (SD 17.9) ng/ml, $n = 19$) and control groups (39.5 (SD 15.4) ng/ml, $n = 12$). No significant correlation was found between CSF concentrations of PEA and HVA.

Discussion

Our results showed lower CSF concentrations of PEA than those previously reported by Lauber and Waldmeier (mean 17.3 (SD 3.3) ng/ml, range 3–45 ng/ml, $n = 15$).²⁴ PEA readily permeates the blood brain barrier and plasma concentrations of PEA have been reported as ranging from 100 to 1000 pg/ml,^{22–25, 26} which is similar to the presently obtained concentrations in CSF. Experimental studies have found brain tissue concentrations of PEA in rats to be < 10 ng/g.^{3, 11, 25, 26} The present study is the first to show decreased CSF concentrations of PEA in patients with Parkinson's disease compared with neurological controls (patients with peripheral neuropathy) and with neurologically normal controls of comparable ages.

Three reasons could account for decreased CSF concentrations of PEA in patients with Parkinson's disease. (1) PEA may be decreased due to neuronal degeneration, as the amine may be synthesised by the nigral dopaminergic neurons which diminish in this disease.^{11, 27, 28} Greenshaw *et al*²⁹ have found degeneration involving the substantia nigra to result in both depletion of dopamine (DA) and a decrease in the rate of PEA accumulation in deprenyl pre-treated rats. (2) Postsynaptic PEA catabolism may be increased in Parkinson's disease. Changes in MAO-B activity are capable of altering catabolism of PEA. However, the activity of MAO-B in patients with Parkinson's disease has been a matter of controversy.^{30, 31} In a recent report, more 1-benzyl-1,2,3,4-tetrahydroisoquinoline (1BnTiQ), which is formed from PEA and its metabolite phenylacetaldehyde, was found in the CSF of patients with Parkinson's disease than in the CSF of

controls. Increased formation of 1BnTiQ in Parkinson's disease may result in reduction of CSF PEA concentrations.³² (3) Increased presynaptic DA concentrations are known to inhibit PEA synthesis at the decarboxylation step,¹¹ a phenomenon which may be relevant in patients with Parkinson's disease under treatment with levodopa (fig 1). Thus the low concentration of PEA in Parkinson's disease may be caused by antiparkinsonian drugs used for treatment. However, we found no correlation between CSF concentration of PEA and the dose of levodopa taken by each patient in our study.

Some researchers have suggested that the concentration of PEA or its metabolite phenylacetic acid (PAA) may be a useful biochemical marker in psychiatric and behavioural research.^{19–33} This may also be true in neurodegenerative disease, as we found a significant negative correlation between CSF concentration of PEA and severity of Parkinson's disease (Hoehn and Yahr stage). We think that CSF PEA concentrations reflect either the severity of nigrostriatal degeneration in patients with Parkinson's disease or a reduced modulatory effect of PEA on a postsynaptic receptor response to DA.

Reduced CSF concentrations of HVA in unmedicated patients with Parkinson's disease have been reported.³⁴ LeWitt *et al* have reported that concentrations of DA metabolites do not correlate with clinical severity of Parkinson's disease because HVA is known to be influenced by therapy with levodopa and other antiparkinsonian drugs.³⁵ We found no significant difference between the CSF concentration of HVA in Parkinson's disease and control groups, possibly because even patients at Hoehn and Yahr stage IV in our study were receiving comparatively small amounts of levodopa.

PEA may affect behaviour and even be important in psychiatric disease, as it is similar in structure to amphetamine and is able to evoke stereotyped behaviours. Decreased urinary concentrations of PEA have been reported in patients with depression,¹⁸ Depression is a common symptom in patients with Parkinson's disease,³⁶ and we found a marginally significant difference in concentration of PEA in CSF between patients with Parkinson's disease with depression and those without depression ($P=0.07$). The possibility remains that reduced PEA concentrations might participate in the pathogenesis of depression in Parkinson's disease.

We thank Professor Toshiharu Nagatsu, Department of Neurochemistry, Institute for Comprehensive Medical Science, Fujita Health University, for valuable comments; and Miss Yoko Kuroiwa and Miss Seiko Umezaki for their assistance in manuscript preparation.

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HISTORICAL NOTES

Tetanus after cranial trauma in ancient Egypt

Diagnostic features of tetanus (lockjaw) noted by ancient Hellenistic and Roman era medical writers¹ were also seen by Middle Egyptian physicians around 1550 BC. The Edwin Smith papyrus in the collection of the New York Academy of Sciences discusses 33 cases of cranial, facial, jaw, neck, and spinal cord injuries used as teaching exercises, possibly for military surgeons.²

Case 7 deals with a surgeon's second examination of a patient who had a gaping wound to the head, exposing the tepau, explained by a gloss as being something like leather between the bones of the skull, and previously identified as either the falx cerebri or frontal sinus, but perhaps most plausibly to be identified with protruding dura mater swollen by a subdural haematoma visible through broken pieces of the fractured skull, treated with topical analgesic and anointed or dusted with sterile dressing.³ Injuries to the dura mater, the outermost layer of the meninges (netnet),⁴ had a possibility of healing following debridement, but since the surgeon's first visit, the head wound has become infected and malodorous, and the patient cannot open his mouth because the risus sardonicus of lockjaw has set in.⁵

"If you find in that patient that his flesh has developed heat under the wound which is in the tepau of his skull. That man, he has developed toothache under the site of that injury.

You put your hand on him and you find his brow is wet with sweat. The muscles (metu) of his neck are taut, his face is flushed, his teeth and his back (sic). The odour inside his brain-case (hn, literally 'box, chest') is like sheep/goat excrement. His mouth is bound, his eyebrows drawn, his face as if he was weeping."

"Second diagnosis and prognosis: You shall then say concerning him 'one having a gaping wound in his head extending to the bone and penetrating the tepau of his skull. He has developed toothache; his mouth is bound; he suffers stiffness of his neck. Therefore do not treat the ailment'".

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