Precursors and metabolites of phenylethylamine, *m* and *p*-tyramine and tryptamine in human lumbar and cisternal cerebrospinal fluid

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SUMMARY Phenylacetic acid, *p*-hydroxyphenylacetic acid, *m*-hydroxyphenylacetic acid, phenylalanine, indoleacetic acid, 5-hydroxyindoleacetic acid and tryptophan were measured in lumbar and cisternal cerebrospinal fluid (CSF) taken during pneumoencephalography. The data suggest that the concentration of the acid metabolites of the trace amines tryptamine, phenylethylamine, *p*-tyramine and *m*-tyramine in lumbar CSF are influenced by the system that transports these acids out of CSF. In cisternal CSF this mechanism does not operate and more information can be obtained on the metabolism of the parent amines in the CNS. Our data indicate that (1) *m*-tyramine is relatively unimportant quantitatively (2) the rate of metabolism of phenylethylamine in human brain is similar to that of 5-hydroxytryptamine (3) the most important variable controlling the synthesis of phenylethylamine is the activity of aromatic amino acid decarboxylase (4) *p*-tyramine is synthesised at about half the rate of phenylethylamine and is thus quantitatively important in metabolic terms.

Studies on the metabolism of monoamines in the human CNS through measurement of amine metabolites in the cerebrospinal fluid (CSF) have concentrated on the catecholamines and 5-hydroxytryptamine (5HT). However, with increasing interest in the possible functions of the trace amines in the CNS, some studies have reported on trace amine metabolites in human CSF. Thus, the metabolite of tryptamine, indoleacetic acid (IAA), is present in CSF at a concentration which is positively correlated with that of CSF tryptophan.¹ This, and the fact that tryptophan administration increases CSF IAA in proportion to the size of the tryptophan load,² indicates that human CNS tryptamine metabolism is controlled in part by tryptophan availability. Another trace amine that is formed, like tryptamine, by the action of aromatic amino acid decarboxylase on an aromatic amino acid (in this case, phenylalanine) is phenylethylamine. Its acidic metabolite phenylacetic acid (PA) is present in CSF at a concentration that is

of the same order of magnitude as the catecholamine metabolites; it may be elevated in schizophrenia³ and low in depression.⁴ Of the other trace amines, the acidic metabolites of *p*-tyramine and *p*-octopamine are present in human ventricular and lumbar CSF.⁵ Their concentrations in lumbar CSF increase on administration of probenecid,⁶ indicating active CNS metabolism. This summarises most of what is known about trace amine metabolites in human CSF. In the present study we have measured IAA, PA, *p*-hydroxyphenylacetic acid (PHPA), a metabolite of *p*-tyramine, and *m*-hydroxyphenylacetic acid (MHPA), a metabolite of *m*-tyramine, as well as the amino acid precursors of those compounds, tryptophan and phenylalanine, in a series of CSF samples taken during diagnostic pneumoencephalography. This was done to provide more information on the metabolism of trace amines in human CNS and some of the factors that might influence it.

Methods

The study, performed on patients undergoing diagnostic pneumoencephalography (PEG) at the Montreal Neurological Hospital, was approved by the ethics committees of the Montreal Neurological Hospital and the

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Department of Psychiatry, McGill University. Some of the samples came from a previous study in which the patients received a tryptophan load before the PEG.² The procedure was done on the fasting patients, without premedication, between 9.00 a.m. and 12 noon. The first 2 ml of CSF was used for routine diagnostic purposes and the next 2 to 6 ml were collected for analysis of indoles. This sample was derived from the lumbar sac, which in humans has a volume of about 15 ml⁷ and will be referred to in this study as lumbar CSF. Oxygen was then injected until the lateral ventricles contained oxygen. Some CSF from this compartment was thus displaced down into the basal cisterns, and when most of the oxygen had been injected (average of 60 ml) a second sample of CSF (6 to 8 ml) was collected through the lumbar needle. This last sample consisted mainly of fluid that was originally in the basal cisterns and was displaced into the lumbar sac. It is referred to in this study as cisternal CSF. No more than 30 minutes separated the collection of lumbar and cisternal CSF. Both samples were allowed to drip directly from the needle into acid-washed tubes, and were stored at -70°C until the analyses were performed.

PA, PHPA and MHPA were measured in CSF by gas-chromatography-mass spectrometry.⁸ Indoles in CSF were measured by the method of Anderson and Purdy.⁹ This method involves direct injection of 10 to 50 µl of CSF into a high performance liquid chromatograph, separation of the various compounds on a reverse-phase column (30 cm × 3.9 mm column of 10 µ "µ-Bondapak C₁₈" from Waters Associates Inc, Milford, MA, USA) and measurement of the fluorescence of the indole ring using a modified Aminco-Fluoromonitor (American Instrument Co, Silver Spring, MD, USA). Phenylalanine in CSF was measured by an adaptation of the fluorometric method of McCaman and Robins.¹⁰ In the original method 20 µl of 0.3 N trichloroacetic acid is added to 100 µl plasma and 20 µl of the supernatant is taken for assay. In the adapted method 10 µl of 75% trichloroacetic acid is added to 150 µl CSF to precipitate any protein. The entire supernatant is taken and 10 µl of 4.5 N sodium hydroxide is added to bring the pH to 5.8 before proceeding with the assay as described by McCaman and Robins.

Patients

Measurements were made on samples from 39 patients. Of these, 16 had received a tryptophan load before their PEG, while 23 had not. Table 1 gives some of the patients'

characteristics, including the size and pretreatment time of the tryptophan loads, age, sex and some diagnostic categories. The majority of the patients were epileptics receiving anticonvulsants, although there were some whose anticonvulsant medication had been withdrawn at least one week before their PEG as part of their investigation in hospital, and some non-epileptic patients. All the epileptic patients were suffering from complex partial seizures, but none of them had had a seizure in the 24 hours preceding the PEG. The treated epileptics were receiving from one to three of the following drugs: carbamazepine, diphenylhydantoin, phenobarbital and primidone. Those not suffering from epilepsy had the following diagnoses: pituitary chromophobe adenoma, epidermoid tumour in the fourth ventricle, oculopharyngeal muscular dystrophy, spinal cerebellar degeneration, empty sella syndrome.

Results

EFFECT OF TRYPTOPHAN LOADS

As reported previously² tryptophan pretreatment increased CSF tryptophan, 5HIAA and IAA. Tryptophan administration did not have any effect on phenylalanine, PA, PHPA or MHPA in lumbar or cisternal CSF. This conclusion was arrived at by comparing, using a two-tailed Student's *t* test, the concentration of these compounds in the CSF of the 23 patients who received no tryptophan load, with their concentration in the CSF of the patients who received tryptophan loads. This comparison was done five ways, using each of the four groups in table 1 and also taking the 11 patients whose CSF tryptophan was greater than 1000 ng/ml. The mean lumbar CSF tryptophan for this latter group was 2303 ng/ml, 7.4-fold higher than the mean of 311 ng/ml for the 23 patients who did not receive tryptophan. When phenylalanine, PA, PHPA and MHPA concentrations in the CSF of patients not given tryptophan were compared with their concentrations in each of these five tryptophan-treated groups, none of the differences were found to be statistically significant. Thus, as tryptophan administration affected only tryptophan, 5HIAA and IAA, in analysing the results data from all 39 patients were pooled when the calculations did not

Table 1 Patient characteristics

Pretreatment with tryptophan (size of load and time of pretreatment)	No of patients	Age (mean and range) (yr)	Diagnosis		
			Epileptics		Others
			On anticonvulsants	Not on anticonvulsants	
None	23	25 (4-56)	19	3	1
3 g, 8 h	6	31 (17-46)	2	1	3
6 g, 8 h	3	30 (24-34)	3	0	0
3 g, 12 h	3	31 (24-42)	2	0	1
6 g, 12 h	4	37 (20-63)	3	1	1

include data on CSF indoles, while results from only the 23 patients who did not receive tryptophan loads were used when the calculations involved interrelationships between all the compounds measured.

GRADIENTS IN CSF

The relationship between the concentrations of all the compounds in lumbar and cisternal CSF was determined using a paired *t* test. As shown in table 2 5HIAA and PHPA were present at higher concentrations in cisternal CSF while phenylalanine was present at a higher concentration in lumbar CSF.

SEX AND AGE DIFFERENCES

Age and sex differences for the indoles have been discussed previously.¹ For phenylalanine, PA, PHPA and MHPA there was no difference between their concentrations in the CSF from the 17 males and 22 females for any of the compounds in either lumbar or cisternal CSF. As shown in table 3 both phenylalanine and MHPA showed positive correlations with the ages of the patients, but this effect was seen only in the lumbar CSF.

EFFECT OF ANTICONVULSANT DRUGS

This study included only a small number of patients not suffering from complex partial seizures and their diagnoses were very varied. Thus, it was not possible to make any comparison between the epileptics and the non-epileptics. However, it was possible to make a comparison between compounds in the CSF of

epileptics on anticonvulsants and the relatively small number not on anticonvulsants at the time of pneumocephalography. The only differences were that levels of PA and MHPA were higher in the lumbar CSF of patients on anticonvulsants (table 4).

INTERRELATIONSHIPS

Correlation coefficients between the various compounds were determined for both lumbar and cisternal compartments in two different ways. The correlations for all seven compounds were determined for those samples which came from the 23 patients who did not receive tryptophan loads (table 5). Correlations between phenylalanine, PA, PHPA and MHPA were also determined for the whole group of 39 patients (table 6), as tryptophan administration did not affect the levels of these compounds.

Discussion

SIGNIFICANCE OF COMPOUNDS IN CSF

CSF studies are useful only if the compounds measured reflect processes occurring in the brain. The origin of CSF tryptophan is unknown but this question is not relevant to the present study as the CSF tryptophan concentration does seem to reflect the brain tryptophan content.¹¹ Phenylalanine, like tryptophan, is carried into brain by a transport system which operates on all the large neutral amino acids.¹² Thus the influences on tryptophan and phenylalanine should be similar. This explains why we found a positive correlation between the concentrations of tryptophan and phenylalanine in CSF (table 5), and suggests that CSF phenylalanine reflects its level in brain in exactly the same way that CSF tryptophan tends to follow variations in brain tryptophan.¹¹

Among the acidic amine metabolites a wealth of data from many laboratories indicates that CSF 5HIAA is an index of CNS 5HT metabolism and we have shown that CSF IAA reflects metabolism of its parent amine tryptamine in the CNS.¹³ As far as the origin of PA, PHPA and MHPA in CSF is concerned the data are more limited. The two questions of importance are whether the acids are derived from the parent amine or via other pathways (for example transamination of an amino acid and the decarboxylation of the keto-acid) and whether the acids in CSF are from the CNS or from peripheral sources.

MHPA cannot, of course, be derived from *m*-tyrosine by transamination and decarboxylation as *m*-tyrosine does not occur naturally. Thus, MHPA could only be derived from *m*-tyramine. After *p*-tyrosine is transaminated to its keto-acid it is metabolised further to homogentisic acid. Thus

Table 2 Gradients of amine-related compounds in CSF

Compound	No of pairs	<i>t</i>	<i>p</i>
Tryptophan	39	0.25	NS
5HIAA	38	3.64	<0.001
IAA	38	0.15	NS
Phenylalanine	39	-2.73	<0.01
PA	38	1.63	NS
PHPA	38	2.13	<0.05
MHPA	38	-0.03	NS

The significance of the difference between the levels of the compounds in lumbar and cisternal CSF was determined using a paired *t* test. A positive value of *t* implies the concentration was higher in the cisternal CSF. NS = not significant.

Table 3 The correlation between age and the concentration of various amine-related compounds in CSF

Compound	Correlation coefficient (<i>r</i>)	
	Lumbar CSF (<i>n</i> = 38)	Cisternal CSF (<i>n</i> = 39)
Phenylalanine	0.34*	-0.12
PA	-0.11	-0.25
PHPA	0.12	-0.05
MHPA	0.43†	0.25

p < *0.05; †0.01.

Table 4 The effect of anticonvulsant treatment on the concentration of amine-related compounds in the CSF of patients with complex partial seizures

Compound	Lumbar (L) or Cisternal (C)	Not on anticonvulsants		On anticonvulsants	
		mean $\pm$ SE (ng/ml)	n	mean $\pm$ SE (ng/ml)	n
Phenylalanine	L	1580 $\pm$ 250	6	1520 $\pm$ 100	28
	C	1300 $\pm$ 180	6	1340 $\pm$ 37	28
PA	L	7.9 $\pm$ 0.7	6	18.1 $\pm$ 2.1*	27
	C	10.8 $\pm$ 1.6	6	20.1 $\pm$ 2.3	28
PHPA	L	6.47 $\pm$ 0.97	6	10.6 $\pm$ 1.1	27
	C	8.85 $\pm$ 0.97	6	13.2 $\pm$ 1.6	28
MHPA	L	0.35 $\pm$ 0.12	6	1.73 $\pm$ 0.32*	27
	C	1.35 $\pm$ 0.61	6	1.49 $\pm$ 0.22	28

*Significantly greater than value for patients not on anticonvulsants at $p < 0.05$.

Table 5 Correlation coefficients between tryptophan, 5HIAA, IAA, phenylalanine, PA, PHPA and MHPA concentrations in CSF

	Tryptophan	5HIAA	IAA	Phenylalanine	PA	PHPA	MHPA
Lumbar CSF (n = 22)							
Tryptophan		0.64†	0.33	0.33	0.08	-0.07	-0.15
5HIAA			0.40	-0.08	0.21	0.23	0.12
IAA				0.18	0.75†	-0.17	0.14
Phenylalanine					0.35	0.15	0.19
PA						0.70†	0.29
PHPA							0.37
MHPA							
Cisternal CSF (n = 23)							
Tryptophan		0.63†	0.57†	0.41*	0.29	-0.04	-0.03
5HIAA			0.14	0.17	0.10	0.13	0.13
IAA				0.33	0.58†	0.10	-0.17
Phenylalanine					0.32	-0.06	-0.44*
PA						0.09	-0.13
PHPA							0.20
MHPA							

Calculations were made using data from the 23 patients who did not receive a tryptophan load.
 $p < *0.05$; †0.01.

PHPA is probably derived from *p*-tyramine. The role of *m* and *p*-tyramine as precursors of MHPA and PHPA is also suggested by the distribution of the acids in rat brain which parallels that of *m* and *p*-tyramine.⁸ Transamination of phenylalanine is a minor pathway and the keto-acid that is formed can be reduced to phenylacetic acid or oxidised to o-hydroxyphenylacetate.¹⁴ Thus, for all three acids the relevant amine is probably the main precursor of the acids measured in this study. The evidence also indicates that the acids in CSF come from the CNS and not the periphery. Thus, in cats ¹⁴C-phenylacetic acid penetrates the blood-CSF barrier only with difficulty,¹⁵ and the hydroxy derivatives, which are more polar, would do so even less easily. If a compound diffuses from blood to CSF its concentration should be similar in different CSF compartments. Thus, we have suggested that the presence of a gradient within the CSF is strong evidence that a compound is derived from the CNS and not the

periphery.¹³ The presence of a gradient for 5HIAA, with higher levels in cisternal CSF than in the lumbar compartment (table 2), has been known for many years.¹⁶ We have seen a gradient for IAA in previous studies,^{1,13} but not in the present one (table 2). This difference may be due to the fact that some of the patients in the present study received a tryptophan load. The cisternal-lumbar gradient we found for PHPA is consistent with the ventricular-lumbar gradient reported previously,⁵ and indicates that PHPA is definitely of central origin. The absence of a gradient for PA and MHPA does not, of course, indicate peripheral origin, but may reflect active metabolism of the parent amines, phenylethylamine and *m*-tyramine, in the spinal cord.

The inverse gradient for phenylalanine, with higher levels in lumbar than in cisternal CSF (table 2) is a surprising finding. It may reflect the fact that phenylalanine is converted to tyrosine more readily

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Table 6 Correlation between phenylalanine, PA, PHPA and MHPA concentrations in CSF

	Phenylalanine	PA	PHPA	MHPA
<i>Lumbar CSF (n = 38)</i>				
Phenylalanine		0.22	0.12	0.07
PA			0.38*	0.17
PHPA				0.57†
MHPA				
<i>Cisternal CSF (n = 39)</i>				
Phenylalanine		0.23	-0.04	-0.38*
PA			-0.07	-0.12
PHPA				0.21
MHPA				

Calculations were made using data from the whole group of 39 patients.

p < *0.05; †0.01.

in the brain than in the spinal cord, thereby partially depleting phenylalanine in the CSF compartments adjacent to the brain. Although tryptophan and phenylalanine compete with one another for the same transport system, the rise of plasma tryptophan after a tryptophan load was not large enough to lower CSF phenylalanine, in this study, or CSF tyrosine in a previous report.¹⁷

METABOLISM OF THE MONOAMINES IN THE HUMAN CNS

The levels of PA we found in the CSF are high for the metabolite of a compound, phenylethylamine, that is found in brain at very low levels. Specifically the level in lumbar CSF of epileptics on anticonvulsants (18.1 ng/ml, table 4) is similar to the 5HIAA levels we found in the same type of patients.¹ Two other studies have reported PA concentrations of 16.9³ and 28.7⁴ ng/ml in the lumbar CSF of control patients. Thus, the values, although variable, do seem to be as high as those of the biogenic amine metabolites. This indicates that in the human CNS the rate of metabolism of phenylethylamine is as great as the rate of metabolism of 5HT, a conclusion that has already been made for the metabolism of phenylethylamine in rat brain.¹⁸

The concentration of PHPA we found in the lumbar CSF of treated epileptics (10.6 ng/ml, table 4) is a little higher than the value of 6.6 ng/ml reported for drug-free schizophrenics.⁶ The value is about half that of PA and indicates a rate of metabolism of *p*-tyramine in human CNS that is higher than that of tryptamine¹³ but somewhat less than that of the biogenic amines. The concentration of MHPA is only 16% of that of PHPA suggesting that the rate of metabolism of *m*-tyramine is small compared with phenylethylamine, *p*-tyramine and even tryptamine.

Some of the compounds measured were found to be influenced by age (MHPA, table 3) and by anticonvulsant drugs (PA and MHPA, table 4). These

effects were seen only in lumbar CSF and therefore may reflect more changes in the activity of the transport system which removes the acids from CSF than changes in the metabolism of the parent amines in the CNS. Aromatic acids are removed from the CSF by a probenecid-sensitive active transport system which is present in the choroid plexuses¹⁹ and in the cortical and spinal subarachnoid spaces.^{20, 21} There is no evidence of such a transport system in the basal cisterns. In a previous study we found that levels of IAA in lumbar CSF were influenced by this transport system and that IAA levels in cisternal CSF gave more information on the metabolism of the parent amine, tryptamine, in the CNS. Thus, the absence of any effect of age or anticonvulsant drugs on metabolite levels in cisternal CSF indicates that these factors probably do not influence brain metabolism of phenylethylamine, *p*-tyramine and *m*-tyramine.

The correlation coefficients between the various compounds shown in tables 5 and 6 point to some factors controlling synthesis of the amines. The positive correlations between tryptophan and 5HIAA, and between tryptophan and IAA, have been reported previously¹ and suggest that tryptophan availability is one factor controlling the synthesis of both 5HT and tryptamine in brain. Tryptamine is formed by the action of aromatic amino acid decarboxylase on tryptophan, and this enzyme seems to be far from saturation with its substrate tryptophan, as tryptophan loads increase tryptamine synthesis in proportion to the size of the load.² Aromatic amino acid decarboxylase also acts on phenylalanine to form phenylethylamine. Data from the rat indicate that the Km of the enzyme for phenylalanine is high (10⁻² M)²² and thus, that phenylethylamine synthesis should vary in proportion to phenylalanine availability. However, the data in table 5 shows no positive correlation between phenylalanine and PA. Obviously, differences between phenylalanine concentration between different individuals are not an important factor explaining the different rates of phenylethylamine metabolism in different individuals, although, of course, changes of phenylalanine levels over time may still produce important changes in phenylethylamine in any individual. Inspection of the correlations between the different acid metabolites suggests that differences in the levels of aromatic amino acid decarboxylase activity may be an important source of the variability of phenylethylamine metabolism. In lumbar CSF a variety of positive correlations are seen between the different metabolites, presumably because of differences in the activity of the transport system that removes all these acids from CSF. In cisternal CSF, where this transport system does not operate, the

only significant positive correlation is between PA and IAA. The parent amines, phenylethylamine and tryptamine, are the only two formed exclusively by aromatic amino acid decarboxylase. This enzyme is not very active towards tyrosine,²² and *p*-tyramine is formed mainly by the hydroxylation of phenylethylamine²³ and dehydroxylation of dopamine.²⁴ Thus, the relationship between PA and IAA could indicate that the main factor causing differences in their levels is the enzyme which is rate-limiting in their synthesis, aromatic amino acid decarboxylase. The levels of this enzyme in human brain is known to be very variable²⁵ and these variations may account for some of the variability in the synthesis of phenylethylamine and tryptamine.

Phenylethylamine and tryptamine share not only the enzymes involved in their metabolism but also an ability to diffuse across the blood-brain barrier.^{13, 26} Thus, it may be variability in the decarboxylation of the precursor amino acids in peripheral tissues as much as in brain that causes the wide range of concentrations of PA and IAA in CSF.

The only other correlation we found was a negative relationship between phenylalanine and MHPA which was seen only in cisternal CSF and thus, if it is real, probably reflects a metabolic relationship. However, we are not able to provide any explanation or interpretation of this finding.

Our data indicate that phenylethylamine is metabolised in human brain at a rate that is similar to that of the biogenic amines. This, and the fact that it has structural and behavioural similarities with amphetamine,²⁷ point to a need for further information about the role of this amine in human CNS. *p*-Tyramine is metabolised at a rate about half that of phenylethylamine and also deserves further study. Because the concentration of the acid metabolites of the trace amines in lumbar CSF seems to be influenced by the transport of these compounds out of CSF, further studies on these compounds would be best performed on cisternal CSF (which can be obtained during pneumoencephalography) or on lumbar CSF after administration of probenecid.

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