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ORIGINAL ARTICLE

Cerebrospinal Fluid and Plasma Neurochemicals: Response to Cranial Electrical Stimulation

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Introduction

It is generally acknowledged that disturbances of neurochemicals are likely in patients with depression, and there have been many attempts to measure those abnormalities in various types of psychiatric illness. It is also reported that there are relationships between the levels of neurochemicals. The only known ratios actually reported in the literature before the current work are for catecholamines: that is, dopamine, norepinephrine, and epinephrine and their metabolic by-products (Karoum et al., 1987). It has also been stated that peripheral epinephrine, norepinephrine, metanephrine and normetanephrine do not pass the blood/brain barrier, so that elevations in blood and urine do not give direct metabolic evidence about central metabolism (Davis et al., 1988). In one study, 45% of severely depressed patients had increased cerebrospinal fluid levels of epinephrine and metanephrine with only 5% of healthy controls showing such elevation (Davis et al., 1988). On the other hand, serum dopamine, betahydroxylase activity, and homovanillic acid level in the cerebrospinal fluid have been reported in psychotically depressed patients (Schatzberg et al., 1985), and there are increasing numbers of references in which serum or plasma neurochemicals are studied (Hughes et al., 1984). To our knowledge there has not been any report relating the levels of cerebrospinal fluid neurochemicals with those in the serum plasma. The current study was undertaken for such a comparison.

Methods

Five asymptomatic, volunteer subjects who are nonsmokers and have no clinically diagnosed illness were included. The subjects ranged in age from 23 years of age to 60 years of age; there were four males and one female. Informed consent was obtained from all subjects after the nature of the procedure was explained. Each subject had a spinal tap done while lying at rest with a blood sample taken just prior to the insertion of a 25 gauge spinal needle into the lumbar subarachnoid space. The cerebrospinal fluid was then collected for a baseline measurement of neurochemicals. Each of the individuals then underwent 20 minutes of cranial electrical stimulation (CES) with a cranial electrical stimulator which has been studied extensively (Shealy, 1979; Shealy et al., 1989). Ten minutes following the stimulation a repeat blood sample was taken and cerebrospinal fluid was again collected.

In an additional five subjects, all female, similar CES was done with blood levels of neurochemicals before and ten minutes following 20 minutes of CES. Blood was centrifuged, plasma and serum separated, frozen and shipped overnight to a reference lab.

Results

The results of this study are shown in Tables 1 and 2.

In Figure 1 the percent changes from baseline are presented.

In five subjects who underwent cerebrospinal fluid and plasma studies, cerebrospinal fluid levels of melatonin are approximately 2.5 to 5 times those of blood.

Cerebrospinal fluid levels of serotonin are approximately one to two times those of blood.

Cerebrospinal fluid levels of beta-endorphin are approximately 1.5 to 3 times those of plasma.

Plasma levels of cholinesterase are approximately 10 times those of cerebrospinal fluid.

Plasma levels of norepinephrine are approximately 10 to 20 times those of cerebrospinal fluid.

Cerebrospinal responses to CES were most marked for serotonin and beta-endorphin.

Plasma responses to CES were greater for melatonin and slightly higher for norepinephrine.

Plasma responses to CES for beta-endorphin were considerable, with average increases of at least 50% over baseline.

In the five subjects who had only blood measurements before and after CES, responses were similar to those seen in the five subjects who had both cerebrospinal fluid and blood studies.

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TABLE 1

Changes in Plasma and Cerebrospinal Fluid Neurochemicals in Response to Cranial Electrical Stimulation

	MEL	NE	BE	ST	CE
		Patient 1			
Plasma					
Pre-CES	18.1	199	4.38	57.6	16.4
Post-CES	23.1	247	8.66	65.1	15.4
CSF					
Pre-CES	64.8	22.9	8.75	47.3	1.7
Post-CES	76.1	26.4	17.23	129.5	1.9
		Patient 2			
Plasma					
Pre-CES	21.3	208	8.43	36.2	14.3
Post-CES	30.2	255	10.17	49.2	16.4
CSF					
Pre-CES	48.3	18.6	12.25	69.1	1.2
Post-CES	57.2	19.1	39.11	187.2	1.2
		Patient 3			
Plasma					
Pre-CES	21.9	288	6.95	38.4	13.9
Post-CES	25.9	365	9.38	42.9	16.2
CSF					
Pre-CES	84.7	42.1	10.66	77.9	QNS
Post-CES	80.2	54.1	22.91	96.1	1.3
		Patient 4			
Plasma					
Pre-CES	26.2	299	4.11	64.1	13.1
Post-CES	32.2	371	6.78	76.5	14.8
CSF					
Pre-CES	98.3	11.9	14.81	136.1	1.9
Post-CES	94.3	13.2	16.26	199.0	1.8
		Patient 5			
Plasma					
Pre-CES	12.2	189	6.55	123.4	17.3
Post-CES	14.2	234	9.63	132.1	18.2
CSF					
Pre-CES	68.2	12.3	12.99	156.9	1.6
Post-CES	72.1	17.3	18.78	176.1	2.0

MEL = Melatonin ng/ml.

NE = Norepinephrine pg/ml.

BE = Beta-endorphin pg/0.1ml.

ST = Serotonin ng/ml.

CE = Cholinesterase u/ml.

TABLE 2
Changes in Plasma Neurochemicals in Response to Cranial Electrical Stimulation

	MEL	NE	BE	ST	CE
Patient 6					
Pre-CES	27.3	207	5.28	35.2	12.2
Post-CES	22.4	246	5.87	49.7	14.1
Patient 7					
Pre-CES	20.5	278	5.78	62.5	8.6
Post-CES	26.1	309	6.25	71.7	10.0
Patient 8					
Pre-CES	21.9	288	6.95	38.4	13.9
Post-CES	25.9	365	9.38	42.9	16.2
Patient 9					
Pre-CES	28.7	286	4.00	59.3	14.6
Post-CES	29.6	295	5.68	61.7	14.0
Patient 10					
Pre-CES	18.3	227	5.87	43.9	12.9
Post-CES	26.9	295	5.99	58.7	14.7

MEL = Melatonin ng/ml.
NE = Norepinephrine pg/ml.
BE = Beta-endorphin pg/0.1ml.
ST = Serotonin ng/ml.
CE = Cholinesterase u/ml.

Discussion

Some effects of CES on neurochemicals have been previously reported (Shealy et al., 1989). In the current study, serotonin and beta-endorphin responses to CES were considerably greater in the cerebrospinal fluid than they were in plasma. Melatonin showed a greater response in plasma than in cerebrospinal fluid; and there were relatively little differences between norepinephrine and cholinesterase responses in cerebrospinal fluid and blood. Despite the very considerably greater serotonin and beta-endorphin responses in cerebrospinal fluid, the increases in plasma which have been noted n a previous publication are consistent, and indeed the plasma eta-endorphin response is over 50% as great as it is in the erebrospinal fluid. It is not practical to do cerebrospinal fluid nalyses on all patients, but blood plasma studies are fairly asily done. Our studies suggest that significant changes in lasma levels of melatonin, serotonin, beta-endorphin, norepiephrine and/or cholinesterase following CES are consistent nd represent a reasonable view of sometimes more dramatic anges taking place in the cerebrospinal fluid.

It is also worth noting the baseline differences between ese neurochemicals. Melatonin levels in the cerebrospinal uid appear to be 2-4 times those in plasma. Melatonin levels the cerebrospinal fluid rise after CES only a modest amount of less than 20%, but in the plasma go up 28-40+%.

Pro-CES cerebrospinal fluid and plasma levels of norepinephrine are very similar. There is a very modest change in norepinephrine in the cerebrospinal fluid of 3-15% after CES, whereas in the blood norepinephrine increases 20-25% with CES. Presumably, CES leads to some central activation of the sympathetic system to release norepinephrine.

Pre-CES cerebrospinal fluid levels of beta-endorphin are one and one-half to twice that of plasma. Cerebrospinal fluid levels of beta-endorphin increase up to 219% after CES, whereas in the plasma they increase only up to 98%. A major question to be answered is whether the plasma increases come from the brain or peripherally through hypothalamic-autonomic activation.

Pre-CES levels of cerebrospinal fluid serotonin range from somewhat less than that of plasma to approximately twice plasma levels. Following CES the cerebrospinal fluid levels of serotonin increase approximately cone and one-half to twice baseline whereas in the blood they increase only 15-40%. Does this represent a release from the brain or activation of a peripheral mechanism?

There is relatively little cholinesterase in the cerebrospinal fluid with pre-CES plasma levels being approximately ten times those of cerebrospinal fluid. There is very modest or nonexistent response of cholinesterase in cere-

cerebrospinal fluid after CES, and very modest change in the plasma in CES, ranging from -6% to +15%.

It is not reasonable to attempt statistical analysis of data from such a small number of subjects. Nevertheless, the relationship of cerebrospinal fluid to plasma neurochemicals is of interest as is the response to CES. CES-induced plasma increases in melatonin, serotonin, beta-endorphin, and norepinephrine suggest that CES activates a broad hypothalamic response. This may account for its reported benefit in treatment of depression (Shealy, 1979; Shealy et al., 1989).

This latter suggestion is supported by an earlier report of lowered beta-endorphin levels in patients with chronic pain (Shealy, 1985).

Conclusion

Cerebrospinal fluid and plasma levels of five neurochemicals have been measured in five asymptomatic, normal subjects at rest and after cranial electrical stimulation (CES), with plasma levels obtained in an additional five subjects. Although cerebrospinal fluid levels of serotonin and beta-endorphin rise to a greater extent with CES, beta-endorphin, serotonin, and melatonin appear to change significantly in plasma and provide observations of clinical interest. Plasma levels of norepinephrine appear to change moderately after CES. Hypothalamic modulation may explain the reported antidepressant effect of CES.

Summary

Simultaneous cerebrospinal fluid and plasma levels of norepinephrine, cholinesterase, beta-endorphin, serotonin, and melatonin were measured in five asymptomatic adult subjects at rest and 20 minutes following cranial electrical stimulation (CES). Beta-endorphin, serotonin, and melatonin increase in plasma and cerebrospinal fluid after CES. Plasma levels of these neurochemicals provide a useful clinical tool for monitoring response to acute intervention.

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