Parallel Variation of Homovanillic Acid, 5-Hydroxyindoleacetic Acid and Cyclic Adenosine-3, 5-Monophosphate in Ventricular Cerebrospinal Fluid of Man*1

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ABSTRACT

Ventricular cerebrospinal fluid (CSF) values of homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA) and cyclic adenosine-3, 5-monophosphate (cAMP) were determined every 2 or 3 hours over a period of 1 to 3 days in 4 patients, consisting of two cases of meningitis, one case of head injury and one case of cerebral aneurysm. Ventricular CSF samples were collected through a drainage tube inserted into the lateral ventricle in all cases. Concentrations of HVA, 5-HIAA and cAMP in ventricular CSF varied with time in all cases. Significant correlations were noted between HVA and 5-HIAA values in all cases, and between cAMP and HVA values and cAMP and 5-HIAA values in 2 cases each. However, no relationship of HVA, 5-HIAA and cAMP values to the sleep-awake cycle and meals could not be established in any cases.

These data may suggest that HVA, 5-HIAA and cAMP values in the ventricular CSF vary in parallel with each other with time.

INTRODUCTION

In recent years, attempts have been made to investigate the brain monoamine metabolism in various pathological conditions by measurement of homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) values in cerebrospinal fluid (CSF)7,10,11,15,19,20,22. Determination of the ventricular CSF values of HVA and 5-HIAA which are the main metabolites of dopamine (DA) and 5-hydroxytryptamine (5-TI) respectively may be more useful than the lumbar CSF values, because HVA originates at the lateral ventricular level15,16,19,20, but 5-HIAA is produced also at the spinal level4,7,11,15,19,20,23. However, as reported earlier by us that the HVA and 5-HIAA values of the ventricular CSF vary in parallel with each other over time, patients should not be evaluated on the basis of a single determination. The mechanism for this parallel variation is considered to be that these amine metabolites are equally regulated during their respective courses of 1) production, 2) circulation together with the CSF flow, and 3) process of absorption. However, points (1) and (2) can be ruled out because there was a significant correlation between the values of HVA and 5-HIAA even in comatose patients in whom one or both HVA and 5-HIAA values showed decreases and in a patient in whom there was complete blockage of the CSF flow10-12. Parallel variation of HVA and 5-HIAA values may be due to the activity of the reabsorption system2,5,8, which is said to be located in the choroid plexus. If this hypothesis is correct, it is felt that other substances, such as cyclic adenosine-3, 5-monophosphate5,18, which are absorbed by active

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transport to blood from CSF as in the case of HVA and 5–HIAA\(^{6,14}\), will vary in parallel with HVA and 5–HIAA. Thus, the author determined the HVA, 5–HIAA and cAMP concentrations in the ventricular CSF over time to ascertain as to whether there was a significant correlation between cAMP and HVA values, and cAMP and 5–HIAA values.

**MATERIAL AND METHODS**

Studies were performed on 4 patients, including 2 cases of meningitis, 1 case of head injury and 1 case of cerebral aneurysm. The ventricular systems of all cases were dilated. CSF was drawn from Cases 1 and 2 beginning 1 month after onset of meningitis, but no inflammatory findings in CSF were observed at the time. In Case 3, CSF was taken 1 month after head injury, and 4 months after the episode of subarachnoidal hemorrhage in Case 4. In Cases 1 to 3, meals were taken orally, whereas liquid diet by gastric tube was provided for Case 4 three times daily at 8 a.m., 12 noon and 7 p.m. Also sleep-awake cycle was checked in all cases.

Ventricular CSF samples were collected through a drainage tube inserted into the lateral ventricle every 2 or 3 hours over a period of 1 to 3 days. The fluid in the tube was discarded, and only that drawn from the ventricle was analyzed. The volume of CSF collected ranged from 8 to 10 ml per patient, but care was taken to draw the same amount each time. Each sample of CSF was centrifuged immediately after collection and then stored at \(-20^\circ C\) until analysis, which was performed within a few weeks.

HVA was determined fluorimetrically with a modified method of Curzon et al.\(^1,6,12\), and 5–HIAA with the method of Ashcroft et al.\(^1\), using 5 ml and 3 ml of CSF respectively. cAMP was measured in duplicate by radioimmunoassay using Yamasa cAMP assay kit (YAMASA SHOYU Co., Japan).

**RESULTS**

Concentrations of HVA, 5–HIAA and cAMP in ventricular CSF varied with time in all cases. Table shows the correlations between HVA, 5–HIAA, and cAMP. Significant correlations were noted between HVA and 5–HIAA values in all cases, and between cAMP and HVA values and 5–HIAA values in 2 cases each. Mean values of HVA, 5–HIAA and cAMP during each 24 hour period were almost constant in Cases 1, 2, 3 and 4. However, no relationship of HVA and 5–HIAA values to the sleep-awake cycle and meals could be established in any case.

Figure shows the variations with time in HVA, 5–HIAA and cAMP values in ventricular CSF in 4 cases.

**DISCUSSION**

In the present study, the HVA, 5–HIAA and cAMP values varied with time in all cases, and significant correlations were noted between HVA and 5–HIAA in all cases, and between

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Diagnosis</th>
<th>Delay (days)</th>
<th>HVA (ng/ml)</th>
<th>5–HIAA (ng/ml)</th>
<th>cAMP (p mol/ml)</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>50</td>
<td>Meningitis</td>
<td>11</td>
<td>139±5(13)</td>
<td>70±2(13)</td>
<td>11±1(13)</td>
<td>0.840** 0.557* 0.367</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>40</td>
<td>Meningitis</td>
<td>3</td>
<td>120±4(18)</td>
<td>69±3(18)</td>
<td>19±1(18)</td>
<td>0.780** 0.301 0.660*</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>49</td>
<td>Brain contusion</td>
<td>4</td>
<td>96±4(14)</td>
<td>52±2(14)</td>
<td>10±1(14)</td>
<td>0.780** 0.373 -0.065</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>62</td>
<td>Cerebral aneurysm</td>
<td>30</td>
<td>252±3(10)</td>
<td>85±1(10)</td>
<td>52±2(10)</td>
<td>0.753* 0.701* 0.714*</td>
</tr>
</tbody>
</table>

\# HVA=homovanillic acid, 5–HIAA=5-hydroxyindoleacetic acid, cAMP=cyclic adenosine-3, 5-monophosphate. Cerebrospinal fluid (CSF) samples were obtained through a drainage tube every 2 hours in Cases 1 and 3, and at 3 hours in Cases 2 and 4. \# Delay indicates length of time between ventricular drainage and start of CSF sampling. \# Mean±standard error. Numbers in parentheses indicate number of measurements. *: p<0.05, **: p<0.01
Parallel Variation of HVA, 5-HIAA and cAMP in CSF

It is assumed that HVA and 5-HIAA originate from the caudate nucleus\textsuperscript{15,16,19,20} and the periventricular parenchyma of the third ventricle\textsuperscript{12} respectively, while cAMP probably reflects the activity of structure bordering the lateral ventricle, such as the caudate nucleus\textsuperscript{18}. Perlow et al.\textsuperscript{17,18} report that the daily fluctuations of cAMP and HVA values of ventricular CSF show a 6-hour lag in attaining highest concentration, and explain this delay to be due to the fact that HVA which is produced in the corpus striatum requires this amount of time to appear in the CSF as a result of diffusion transport. Therefore, if the variations in HVA and cAMP values in the ventricular CSF had occurred at the site of production, there should naturally be a lag in the phase of variations of HVA and cAMP values, that is, a time lag between the highest HVA and cAMP values, and thus, there could not be parallel variation as observed in this study. Further, as reported previously\textsuperscript{10,12}, even in comatose patients in whom one or both HVA and 5-HIAA values showed decreases, there was parallel variation between the two. Thus, it is considered that

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figures.png}
\caption{Variations of HVA, 5-HIAA and cAMP in ventricular CSF in Case 1–4.}
\end{figure}
the variations with time in HVA, 5-HIAA and cAMP values in ventricular CSF are due to regulation in the process of absorption. However, it is unknown as to why such variations exist.

Further, although a significant correlation was observed between HVA and 5-HIAA in all cases, such a relationship was noted in only 2 cases each between cAMP and HVA values and cAMP and 5–HIAA values. Possible explanations for this are that the amplitude of cAMP values is smaller than HVA and 5–HIAA or there are quantitative or time differences in absorption by active transport between cAMP, and HVA and 5–HIAA. In order to clarify these points, it is necessary to study the HVA, 5–HIAA and cAMP values over time after the administration of probenecid which blocks active transport from blood to the cerebral origin of 5–hydroxyindole compounds in the cerebrospinal fluid of patients with psychiatric or neurological diseases.

REFERENCES


