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

Tetsuji INAGAWA

Department of Neurosurgery, Shimane Prefectural Central Hospital, Izumo 693, Japan

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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)[7,10,12,13,20,22]. Determination of the ventricular CSF values of HVA and 5-HIAA wich are the main metabolites of dopamine (DA) and 5-hydroxytryptamine (5-TH) respectively may be more useful than the lumbar CSF values, because HVA originates at the lateral ventricular level[15,16,19,20], but 5-HIAA is produced also at the spinal level[4,7,11,12,20,23]. 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 flow[10-12]. Parallel variation of HVA and 5-HIAA values may be due to the activity of the reabsorption system[2,5,8], 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-monophosphate[3,12], which are absorbed by active

*) 鰺川哲二：脳室内髄液の HVA, 5-HIAA, cAMP 濃度の経時的並行変動

transport to blood from CSF as in the case of HVA and 5-HIAA[8,14], 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.

MATERAL 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°C until analysis, which was performed within a few weeks.

HVA was determined fluorimetrically with a modified method of Curzon et al.[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 cAMP 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 HVA, 5-HIAA and cAMP concentrations in ventricular CSF #

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

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. * : $p<0.05$, ** : $p<0.01$

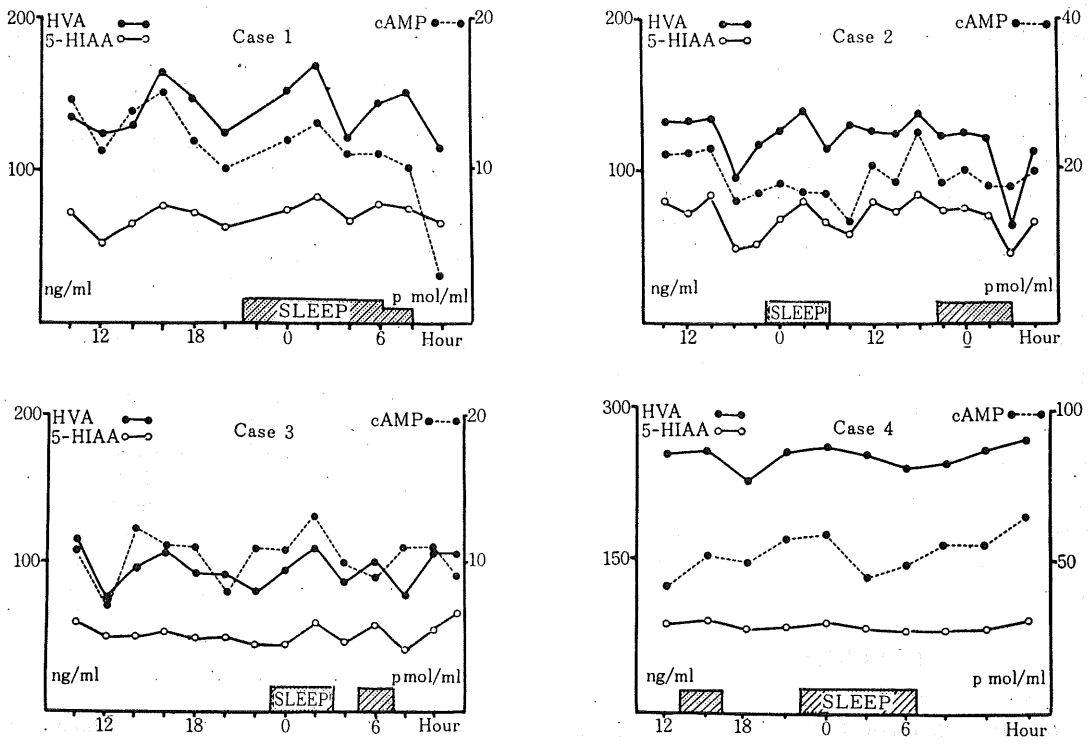

Fig. Variations of HVA, 5-HIAA and cAMP in ventricular CSF in Case 1-4.

cAMP and HVA values and cAMP and 5-HIAA values in 2 cases each. It has been reported that no relationship could be established between HVA and 5-HIAA values of ventricular CSF and sleep-awake cycle, and these values vary in parallel with one another over time[9-12], but it is of great interest to learn that it is possible the cAMP value may also vary in parallel with the other values. Perlow et al.[17,18] report that the HVA and cAMP values of ventricular CSF of rhesus monkeys showed such daily fluctuationd as being of high concentration during the light hours and of low concentration during the dark hours. Further, Wyatt et al.[24] reported that ventricular CSF 5-HIAA concentrations during non-rapid eye movement sleep were higher than when awake, while the values when awake were higher than during rapid eye movement sleep in patients with presenile dementia. Whatever the case, Perlow et al.[17,18] and Wyatt et al.[24] believe that the daily fluctuations of HVA, 5-HIAA and cAMP values of ventricular CSF are variations which occur at the site where these substances are produced.

It is assumed that HVA and 5-HIAA originate from the caudate nucleus[15,16,19,20] and the periventricular parencyma of the third ventricle[12] respectively, while cAMP probably reflects the activity of structure bordering the lateral ventricle, such as the caudate nucleus[18]. Perlow et al.[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[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

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 variatiofi exists.

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 CSF to blood[3,8,14,12].

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