Short report

Cerebrospinal fluid GABA levels in various neurological and psychiatric diseases

HIROO KURODA, NORIO OGAWA, YASUHIDE YAMAWAKI, ITARU NUKINA, TADASHI OFUJI, MITSUTOSHI YAMAMOTO,* SABURO OTSUKI*

From the Third Department of Internal Medicine and the Department of Neuropsychiatry,* Okayama University Medical School, Okayama, Japan

SUMMARY Cerebrospinal fluid gamma-aminobutyric acid (CSF-GABA) was analysed by radioreceptor assay in 16 normal controls and 84 patients with various neurological and psychiatric diseases. In patients with spinocerebellar degeneration, neuro-Behçet’s syndrome and Parkinson’s disease, CSF-GABA levels were decreased. On the other hand, increased CSF-GABA levels were detected in patients with meningitis.

Gamma-aminobutyric acid (GABA), a putative inhibitory neurotransmitter, is distributed throughout the brain and spinal cord.1-4 Recent studies suggest that a disorder of GABA metabolism may exist in certain neurological and psychiatric diseases.5-9 Since cerebrospinal fluid (CSF) is believed to be formed in the choroid plexus and is in contact with both the brain and spinal cord, it may reflect disorders of central nervous system (CNS). To gain further insight into various neurological and psychiatric diseases, we have measured GABA concentrations in CSF by radioreceptor assay.

Methods

Controls The control group consisted of normal volunteers and patients in hospital without neurological or psychiatric disease and who were not receiving drugs. In the normal controls there were 8 men and 8 women; the mean age was 44 ± 17 yr (mean ± SEM).

Patients Eighty-four patients with various neurological and psychiatric diseases were investigated in this study. The figure shows the diagnoses of the patients.

Address for reprint requests: Dr Hiroo Kuroda, Third Department of Internal Medicine, Okayama University Medical School, Okayama 700, Japan.

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Procedures All individuals were maintained on absolute bed rest and oral intake was avoided for the previous 15 hours. Some of these patients were not medicated. In the others drug therapy was stopped for at least 14 days preceding lumbar puncture with the exception of those with epilepsy. Lumbar puncture were performed at 9 am in the standard fashion with the patients in the lateral decubitus position. Ten ml of CSF was withdrawn and the final 5 ml was immediately frozen in an acetone dry ice tube and kept at −70°C until assay.

Assay GABA radioreceptor assay was performed primarily by the method of Enna et al.10 For the receptor preparation, crude synaptic membrane was prepared from whole rat brain using a modification of the method of De Robertis et al.11 Briefly, Sprague-Dawley rats (200-250 g) were decapitated and the whole brains were immediately removed. The tissue was homogenised in 10 vol of ice-cold 0·32 M sucrose by Brinkman Polytron PT-10 homogeniser for 20 s and the homogenate was centrifuged at 900 g for 10 min. The supernatant was further centrifuged at 11 500 g for 20 min, and the pellet was resuspended in 10 vol of Tris-HCl buffer (50 mM Tris-HCl buffer, pH 7·6) and kept at −70°C until used. Before analysis, this preparation was thawed and homogenised with a glass-homogeniser in 100 vol of Tris-HCl buffer, then centrifuged at 50 000 g for 20 min. The supernatant was discarded and the pellet was resuspended in 100 vol of Tris-HCl buffer containing 0·05% Triton X-100 and incubated in shaking water bath at 37°C for 30 min, then centrifuged at 50 000 g for 20 min, twice. The pellet was resuspended in 20 vol of Tris-HCl buffer to make a tissue concentration of approximately 0·6 mg protein/ml. For the GABA radioreceptor assay, 0·5 ml...
portion of this membrane suspension was placed into glass containing 0-2 ml of CSF, 0-2 ml of Tris-HCl buffer and 0-1 ml of 6-4 nM \(^{3}H\)-GABA (Amersham, specific activity 57 Ci/nmol). The samples were incubated in ice for 30 min and the reaction was terminated by filtration through glass fibre filters (Whatman GF/C) under reduced pressure. Finally, each filter was washed twice with 5 ml of cold Tris-HCl buffer and then placed into a scintillation vial with 10 ml of scintillation fluor for counting. All samples were analysed in duplicate.

Results

With the radioreceptor assay, as little as 5 pmoles/ml of GABA could be measured reliably. The results of this study are shown in the figure. In normal controls, the mean (± SEM) GABA level in CSF was 143 ± 16 pmoles/ml. The mean CSF-GABA level in females was 159 ± 23 pmoles/ml (N = 8) and that in males was 127 ± 22 pmoles/ml (N = 8), which were not different. There was no correlation (r = 0.16) between age and CSF-GABA level in normal controls. Among the patients tested, the lowest GABA level in CSF was observed in patients with olivopontocerebellar atrophy and late cortical cerebellar atrophy, which were 46 ± 2 pmoles/ml and 55 ± 11 pmoles/ml respectively. The next lowest CSF-GABA level was seen in patients with neuro-Behçet’s syndrome which was 57 ± 8 pmoles/ml. In patients with Parkinson’s disease, Alzheimer’s disease and Pick’s disease, the CSF-GABA levels were also quite low, which were between 60 and 70 pmoles/ml. On the other hand, we found an increased CSF-GABA level in patients with meningitis, which was 309 ± 65 pmoles/ml. In all other diseases tested, CSF-GABA levels did not differ from normal controls.

Discussion

As described above, we could measure CSF-GABA level down to 5 pmoles/ml by radioreceptor assay; the CSF-GABA level in normal controls was slightly lower than that which some other groups have reported.7,12,13 The lowest CSF-GABA level was seen in patients with olivopontocerebellar atrophy and late cortical cerebellar atrophy. Both these illnesses are characterised by degeneration of the cerebellum. The GABA concentration in the
cerebellum is low but the total GABA content is high. Therefore, the destruction of cerebellum causes a decrease of total cerebellar GABA content. The low CSF-GABA level in these two diseases, therefore, may be associated with the degeneration of cerebellum, and the CSF-GABA level may suggest the severity of these diseases. Indeed, the CSF-GABA level was correlated with the degree of atrophy of the cerebellum on CT scans. Manyam et al have reported decreased CSF-GABA levels in cerebellar degeneration.14 The CSF-GABA level in neuro-Behçet's syndrome was low, so we could differentiate this type of Behçet's syndrome from other types. Furthermore, measuring CSF-GABA level might be a useful method to diagnose neuro-Behçet's syndrome at an early stage.

The CSF-GABA level in Parkinson's disease was low, about 43% of normal controls. Glutamic acid decarboxylase (GAD) catalyses the decarboxylation of glutamic acid to GABA, and GAD regulates the steady-state concentration of GABA. The highest concentrations of GAD and GABA are in substantia nigra and globus pallidus.15 The activity of GAD is decreased in certain areas of the brain in patients with untreated Parkinson's disease and is almost normal in brains of patients treated with levodopa, whereas brain levels of GABA are unchanged in both groups of Parkinson's disease.16 17 The CSF-GABA level in Parkinson's disease in the present study was very low compared with that in Enna et al's report, which analysed levodopa-treated patients.18 The decrease of CSF-GABA in Parkinson's disease may be due to the change of GABA turnover because patients in this study were not treated with levodopa for at least 14 days.

Alzheimer's disease and Pick's disease are characterised by dementia and severe cerebral cortical degeneration. The CSF-GABA level in these diseases was quite low, almost the same as in Parkinson's disease. In cerebral cortex, the GABA concentration is low and is about 40% of that in substantia nigra and globus pallidus. But the total GABA content is high because of the total weight of the cerebral cortex. The total GABA content in cerebral cortex thus becomes lower with the progress of these diseases. There was an increase of CSF-GABA level in patients with meningitis, which was about twice as high as that of normal controls. These data suggest that inflammation of the meninges caused by the infection may change the function of the blood-brain-barrier, so that GABA can be easily transported from brain to CSF or change the function of GABA metabolism in brain. Buryakova et al have reported that CSF-GABA was detected in patients with bacterial meningitis, but not found in the CSF with serous meningitis and normal controls in childhood. They suggested that the detection of CSF-GABA might be used as a test to differentiate between serous and bacterial meningitis.18 In the present study, almost of all patients were adults with viral infection. It will be necessary to analyse many more patients with various types of meningitis before definite conclusions can be drawn.

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