Cerebrospinal Fluid γ Aminobutyric Acid Levels in Migraine

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British Medical Journal, 1975, 3, 516-517

Summary

γ -Aminobutyric acid (GABA) levels in cerebrospinal fluid were measured in seven patients with tension headache and 12 patients with migraine. GABA was detected only during the migraine attack. The results suggest disordered GABA metabolism in migraine.

Introduction

Numerous biochemical studies on migraine have failed to establish its cause. Mostly, researchers have been concerned with biochemical values in the systemic circulation, there having been comparatively few studies on the cerebrospinal fluid (C.S.F.) during an attack. In a study to evaluate the possible importance of disordered metabolism of γ -aminobutyric acid (GABA) in neurological disease in the past two years we have estimated GABA levels in the C.S.F. of every patient admitted to our neurological unit in whom lumbar puncture has been performed as part of the essential clinical investigation. We report here our findings in patients with muscle contraction (tension) and migraine headache and, as far as we are aware, offer for the first time evidence of disordered GABA metabolism during the migraine attack.

Patients and Methods

Nineteen patients admitted to the neurology service of the Methodist Hospital and Baylor College of Medicine were diagnosed as suffering from tension headache (7 patients) and either classical or common migraine (12 patients). C.S.F. from these patients was obtained when lumbar puncture was performed as part of the essential clinical investigation to exclude other central nervous system (C.N.S.) disorders.

A 1-ml sample of C.S.F. was collected in chilled, acid-washed glass tubes and immediately frozen at -20°C . Tubes were transferred within 24 hours to storage at -85°C . Samples were analysed within 10 days of collection. Previous studies had shown no fall in GABA levels during this period.

GABA was analysed by an enzymatic fluorometric method¹ modified to allow satisfactorily sensitive and reproducible measurement in C.S.F. The procedure permits detection of GABA at a concentration of 10^{-12} mol per assay tube. The confidence level for reproducibility of the method at concentration from 10^{-9} mol/l was $\pm 6.8\%$ to 95% when calculated by duplicate analysis.

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Results

The results are shown in the fig. Lumbar puncture was performed during a headache-free period in seven patients with tension headache, and in no case was C.S.F. GABA detected. In seven patients with classical or common migraine C.S.F. obtained during a headache-free period also contained no GABA. When lumbar puncture was performed in six other patients during the headache phase after the spontaneous onset of a well documented migraine attack, however, C.S.F. GABA was measurable in all cases. One patient in this group had a second lumbar puncture during pneumoencephalography, performed because of the detection of ventricular dilatation by scanning. Though this patient proved to have evidence of cerebral atrophy, no C.S.F. GABA was detected in the second sample, taken when the patient was free of headache.

Rise in C.S.F. GABA levels in all patients when lumbar puncture was performed during migraine attack. ○ = Lumbar puncture performed twice in same patient.

Discussion

Compared with the concentrations of other amino-acids in C.S.F., GABA levels are of the lowest order.² This is apparently due in part to cellular transport mechanisms that have a high affinity for GABA uptake³ as well as possible GABA removal from C.S.F. by active transport at the choroid plexus.⁴ Therefore, though concentrations in the brain are high,⁵ GABA is generally not detected in C.S.F.⁶ In a previous series⁷ no C.S.F. GABA was detected in 19 patients without evidence of C.N.S. disease designated as controls. Thus for the purpose of this study the detection of GABA in C.S.F. is considered abnormal and thought to reflect disordered C.N.S. GABA metabolism.

Based on our earlier finding in control patients, the absence of detectable C.S.F. GABA in patients free of tension and migraine headache was expected. Measurable GABA levels during the migraine attacks in all the patients was surprising and is considered particularly convincing since samples were analysed blind.

The changes in cranial flow during a migraine attack are well established, with a decrease in cerebral blood flow during the prodromal phase and an increase during the headache phase.⁸ Increased concentrations of lactate have been found in the C.S.F. within 24 hours of the attack,⁹ suggesting a shift towards anaerobic cerebral metabolism during the prodromal ischaemia. Raised brain tissue concentrations of GABA have been noted in animals subjected to cerebral anoxia¹⁰ and are thought to result

from a decreased rate of oxidative metabolism, thereby decreasing utilization through the GABA shunt.¹¹ Increased C.S.F. GABA levels during a migraine headache may therefore reflect an increase in tissue GABA levels occurring coincidentally with the anoxic ischaemic phase of the attack. To support this, increased C.S.F. GABA levels have also been found in patients with cerebral ischaemia and infarction due to cerebrovascular disease.⁷

An increase of GABA in the C.S.F. is most likely the result of increased GABA concentrations in brain tissue extracellular fluid. Whether this is entirely secondary to a rise in intracellular GABA content or due to anoxic ischaemic conditions that encourage neuronal GABA release cannot be established by this study. Extraneuronal release and eventual intraneuronal depletion of dopamine, noradrenaline, and serotonin in ischaemic brain has been shown in other studies,^{12 13} so that GABA could be similarly affected.

GABA now seems well established as a major inhibitory neurotransmitter in the C.N.S.¹⁴ Indeed, it has been strongly identified with the natural inhibitory neurotransmitter producing hyperpolarization after neuronal depolarization.¹⁵ Its action is brief and rapidly reversed, mainly by avid cellular reuptake.³ If excess GABA release is assumed to take place during the prodromal ischaemia of migraine it seems not unreasonable to relate this in part to depression of cortical neuronal function clinically manifest by the rapidly and spontaneously reversible types of neurological deficit that frequently occur in this phase of the attack.¹⁶ In view of the frequency of migraine prodromes affecting visual function it should be pointed out that GABA is also present in large concentration in the retina,¹⁷ where it also functions as an inhibitory neurotransmitter.¹⁸

In conclusion, the surprisingly clear-cut results in our small series seem to indicate the need for a larger study to confirm the disorder of C.N.S. GABA metabolism during migraine. What

pathogenetic role such a disorder has in the syndrome, however, can be only speculative.

This work was supported in part by grant NS 09287 from the National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, Maryland.

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References

- Baxter, C. F., in *Methods of Neurochemistry*, ed. R. Fried, vol. 3, p. 1. New York, Dekker, 1972.
- Bitto, L., et al., *Journal of Neurochemistry*, 1966 **13**, 1057.
- Elliott, K. A. C., and Van Gelder, N. M., *Journal of Neurochemistry*, 1958, **3**, 28.
- Snodgrass, S. R., and Lorenzo, A. V., *Journal of Neurochemistry*, 1973, **20**, 761.
- Robinson, N., and Wells, F., *Journal of Anatomy*, 1973, **114**, 365.
- Perry, T. L., and Jones, R. T., *Journal of Clinical Investigation*, 1961, **40**, 1363.
- Welch, K. M. A., et al. Submitted for publication.
- Skinhoj, J. E., and Paulson, O. B., *British Medical Journal*, 1969, **3**, 569.
- Skinhoj, E., *Archives of Neurology*, 1973, **29**, 95.
- Lovell, R. A., et al., *Journal of Neurochemistry*, 1963, **10**, 479.
- Wood, J. D., *Experimental Brain Research*, 1962, **4**, 81.
- Meyer, J. S., et al., *Brain*, 1974, **97**, 655.
- Welch, K. M. A., et al., *Abstracts of Proceedings of the 6th meeting of the American Society for Neurochemistry*, 1975, vol. 1, p. 157.
- Krnjevic, K., *International Review of Neurobiology*, 1964, **7**, 41.
- Krnjevic, K., *Physiological Reviews*, 1974, **54**, 418.
- Milner, P. M., *Electroencephalography and Clinical Neurophysiology*, 1958, **10**, 705.
- Kuriyama, K. B., et al., *Brain Research*, 1969, **16**, 479.
- Woell, W. K., and Lasanky, A., in *Inhibition in the Nervous System and Gamma Amino Butyric Acid*, ed. E. Roberts, and C. F. Baxter, p. 482. New York, Pergamon, 1966.

Value of Infarct-specific Isotope (^{99m}Tc-labelled Stannous Pyrophosphate) in Myocardial Scanning

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British Medical Journal, 1975, **3**, 517-520

Summary

With the use of ^{99m}Tc-labelled stannous pyrophosphate scans positive for myocardial infarction were obtained from 28 patients in the acute stage of the disease. In some cases the scan was positive when the initial electrocardiogram gave equivocal results. Negative scans were obtained from a control group of patients and from eight patients in hospital with chest pain but with no other evidence of recent myocardial infarction.

Introduction

The diagnosis of myocardial infarction is based on clinical, electrocardiographic, and enzymatic abnormalities. Some or

all of these indices may be equivocal with a resultant delay in giving treatment. The use of myocardial scanning as an aid to establishing an earlier diagnosis has been limited mainly by the lack of an infarct-specific isotope suitable for routine use; ⁴⁰K (ref.¹) and ¹³¹I-labelled oleic acid,² used to show the infarct as a void against a background of normal activity, are unsatisfactory.³ Though ^{99m}Tc-labelled tetracyclines concentrate specifically in the acutely infarcted myocardium, their value in identifying myocardial infarcts⁴ is limited by both the poor target:background ratio and the interference from hepatic uptake.

The observation that calcium ions located in the mitochondria of irreversibly damaged myocardial cells are deposited in a crystalline hydroxyapatite structure⁵ resulted in the successful experimental⁶ and clinical⁷ use of the bone-seeking radionuclide ^{99m}Tc-labelled stannous pyrophosphate in visualizing acute myocardial infarcts. This added a new dimension to myocardial scanning, and we report here our results with the technique in cases admitted to a coronary care unit.

Patients and Methods

Forty patients with no clinical or electrocardiographic evidence of myocardial infarction who had been referred for bone scans were used as controls. After an intravenous injection of 15 mCi ^{99m}Tc-

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