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BRIEF COMMUNICATION

Lack of Protection by Pyridoxine or Hydrazine Pretreatment Against Monosodium L-Glutamate-Induced Seizures

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NEMEROFF, C. AND F. D. CRISLEY. *Lack of protection by pyridoxine or hydrazine pretreatment against monosodium l-glutamate-induced seizures.* PHARMAC. BIOCHEM. BEHAV. 3(5) 927–929, 1975. – Pretreatment of rats with hydrazine (100 mg/kg), a compound which raises brain gamma-aminobutyric acid (GABA) 175 percent in 12 hr was not able to prevent the occurrence of seizures induced by monosodium L-glutamate (MSG). Pyridoxine (50 mg/kg), the cofactor essential in the conversion of glutamate to GABA, also failed to prevent convulsions induced by parenteral MSG administration. It is concluded that the mechanism of action of MSG-induced seizures is neither by decreasing brain GABA levels or interfering with the pyridoxine cofactor.

Monosodium L-glutamate GABA Hydrazine Seizures Pyridoxine

IT has been reported [2] that parenteral administration of monosodium L-glutamate (MSG), a common food additive, induces seizures in experimental animals. Furthermore, it has been determined that MSG administration results in decreased brain levels of gamma-aminobutyric acid (GABA), a putative neurotransmitter in the mammalian central nervous system [7,8]. In the course of an investigation of changes in cerebrovascular permeability of plasma proteins during MSG-induced seizures [6], we attempted to evaluate the relationship between whole brain GABA levels and seizures induced by MSG. We attempted to prevent the occurrence of these MSG-induced convulsions by the administration of (1) hydrazine, which raises rat brain GABA levels by 175 percent in 12 hours [5] and (2) pyridoxine, the necessary cofactor in the maintenance of the glutamate-GABA-succinate pathway.

METHOD

Timed pregnant Sprague-Dawley rats were fed laboratory chow and water ad lib. The offspring, at various ages, were injected intraperitoneally with 4 g/kg of MSG (Sigma Chemical Co., St. Louis, Mo.) in normal saline. In order to determine whether decreased GABA levels per se, are responsible for the seizures induced by MSG, young rats were injected with hydrazine dihydrochloride (100 mg/kg) after the method of Maynert and Kaji [5]. This dose effectively raises GABA levels 175 percent in 12 hr; therefore these animals received a single dose of MSG (4 g/kg) 12 hr after receiving the hydrazine. In order to determine whether an inhibition of the cofactor, pyridoxal phosphate, is involved in the etiology of MSG-induced seizures, we injected young rats with pyridoxine HCl (50 mg/kg) just prior to the appearance of convulsant activity after the method of Baxter [1]. Controls initially received MSG but only received sham injections at the time of administration of the above-mentioned drugs to experimental animals. The incidence of seizure activity in each group was then recorded.

RESULTS AND DISCUSSION

As can be seen from Tables 1 and 2, neither the hydrazine nor the pyridoxine pretreatment was effective in

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TABLE 1

SEIZURE ACTIVITY IN MSG-TREATED RATS PRETREATED WITH PYRIDOXINE*

Age (Days)	Number Injected	Number Showing Seizures	Percent Showing Seizures
		MSG-Treated	
5	8	8	100
13	6	5	83
25	8	6	67
28	6	3	50
37	4	1	25
		MSG + Pyridoxine-Treated	
5	8	8	100
13	6	6	100
25	8	7	88
28	6	4	67
37	6	3	50

*Just prior to the occurrence of seizure, the MSG-treated rats received 50 mg/kg of pyridoxine HCL intraperitoneally.

reducing the incidence of MSG-induced seizures. Chi-square analysis revealed no statistically significant reduction in seizure activity between the experimental and control groups. As reported previously [6] the incidence of MSG-induced seizures is inversely proportional with the age of the animal. This may in part be due to the fact that neonates administered MSG show higher fasting glutamate levels in plasma than do adults [3].

As early as 1961, it was felt by many workers [10] that there was sufficient evidence to present a hypothesis that interference with normal maintenance of the glutamate-GABA pathway results in neuronal hyperactivity and seizures. Strong evidence for this theory was provided when it was reported that seizures induced by thiosemicarbazide or methoxy-pyridoxine could be arrested not only by pyridoxine supplementation but also by the administration of GABA. Furthermore, the intravenous administration of GABA to chicks before the development of the blood-brain barrier protected them against pentylenetetrazol-induced convulsions [10].

These results might be explained by a report [4] that has indicated that parenterally administered MSG causes a brief but significant depression of the uptake of glucose by the brain. If this is correlated with studies on the binding of GABA to mouse brain preparations [9] in which it is reported that the omission of glucose from the medium markedly decreases the ability of brain slices to take up or retain GABA, then an hypothesis can be formed concerning the results reported here. Even in the brains of rats treated with hydrazine (high GABA levels), the uptake of GABA might functionally be reduced due to the decrease in glucose uptake. The fact that the pyridoxine pretreatment was ineffective in reducing the incidence of MSG-induced seizures suggests that interruption of this cofactor is not involved in the etiology of these seizures. Perhaps the ratio of GABA to glutamate as suggested by Van Gelder [11] is the critical factor in the control of neuronal excitability. It is concluded that neither decreased GABA levels per se nor an interruption in the action of the cofactor, pyridoxal phosphate, is the causal factor underlying the occurrence of MSG-induced convulsions.

TABLE 2

SEIZURE ACTIVITY IN MSG-TREATED RATS PRETREATED WITH HYDRAZINE*

Age (Days)	Number Injected	Number Showing Seizures	Percent Showing Seizures
		MSG-Treated	
2	6	6	100
16	12	8	67
19	6	4	67
32	6	2	33
55	6	0	0
		MSG + Hydrazine-Treated	
2	6	5	83
16	12	8	67
19	12	7	58
32	10	3	30
55	6	0	0

*Twelve hr after the injection of Hydrazine dihydrochloride, 100 mg/kg intraperitoneally, the animals were injected with MSG, 4 mg/g.

REFERENCES

1. Baxter, C. F. The nature of gamma-aminobutyric acid. In: *The Handbook of Neurochemistry III,* edited by A. Lajtha. New York: Plenum Press, 1970, pp. 289–353.
2. Bhagavan, H. N., D. B. Coursin and C. N. Stewart. Monosodium glutamate induces convulsive disorders in rats. *Nature* **232:** 275–276, 1971.
3. Boaz, D. P., L. D. Stegink, W. A. Reynolds, L. J. Filer, Jr., R. M. Pitkin and M. C. Brummel. Monosodium glutamate metabolism in the neonatal primate. *Fedn Proc.* **33:** 651, 1974.
4. Creasy, W. A. and S. E. Malawista. Monosodium L-glutamate: inhibition of glucose intake in brain as a basis for toxicity. *Biochem. Pharmac.* **20:** 2917–2920, 1971.
5. Maynert, E. W. and H. K. Kaji. On the relationship of brain gamma-aminobutyric acid to convulsions. *J. Pharmac. exp. Ther.* **137:** 114–121, 1962.
6. Nemeroff, C. B. and F. D. Crisley. Temporary alteration in blood-brain barrier permeability to plasma proteins during monosodium L-glutamate-induced seizures. *Fedn Proc.* **33:** 233, 1974.
7. Prosky, L. and R. G. O'Dell. Biochemical changes of brain and liver metabolites in neonatal offspring of rats fed monosodium L-glutamate. *Experentia* **28:** 260–263, 1972.
8. Prosky, L. and R. G. O'Dell. Lack of an effect of dietary monosodium L-glutamate on some glutamate-metabolizing enzymes in developing rat brain. *J. Neurochem.* **19:** 1405–1408, 1972.
9. Sano, K. and E. Roberts. Binding of gamma-aminobutyric acid by mouse brain preparations. *Biochem. Pharmac.* **12:** 489–502, 1963.
10. Tower, D. B. The neurochemistry of convulsive states. In: *The Chemical Pathology of the Nervous System,* edited by J. Folch-Pi. New York: Pergammon Press, 1961, pp. 307–346.
11. Van Gelder, N. M. Brain weight and growth of mice fed gamma-aminobutyric acid, glycine or l-glutamic acid diet. *Brain Res.* **33:** 571–577, 1971.