LITERATURE CITED

1. É. A. Bendikov and V. G. Butuzov, in: Pharmacology of Monoaminergic Processes [in Russian], Moscow (1971), p. 24.
2. R. S. Mirzoyan, Fiziol. Zh. SSSR, No. 6, 966 (1973).
3. R. S. Mirzoyan, Farmakol. Toksikol., No. 4, 5 (1984).
4. K. Aukland, Acta, Neurol. Scand., Suppl. 14, 42 (1965).
5. D. S. Baskin and Y. Hosobuchi, Lancet, 2, 272 (1981).
6. A. I. Faden, J. M. Hallenbeck, and C. O. Brown, Neurology (Minneapolis), 32, 1083 (1982).
7. S. Goldman, M. J. B. Cordonnier, and J. Sztencel, J. Neurosurg. Psychiat., 47, 77 (1984).
8. Y. Hosobuchi, D. S. Baskin, and S. K. Woo, Science, 215, 69 (1982).
9. J. Jabaily and J. N. Davis, Stroke, 15, 36 (1984).
10. R. Levy, P. Feustel, J Severinghaus, and Y. Hosobuchi, Life Sci., 31, 2205 (1982).

EFFECT OF CHLORGYLINE ON THE GABA LEVEL IN HYPEROXIA

I. A. Goroshinskaya and K. B. Sherstnev

UDC 612.822.1:547.466.3/-06:612.273.1/014.46:615.214.32

KEY WORDS: hyperoxia; γ-aminobutyric acid; chlorgyline.

A fall in the γ-aminobutyric acid (GABA) concentration, discovered in the brain of rats, mice, rabbits, chickens, and hamsters at different stages of hyperoxia, is an important step in the mechanism of development of oxygen poisoning during exposure to hyperbaric oxygen [3, 6, 8, 9]. GABA performs the function of inhibitory mediator [5]. Lowering of its level in the brain is regarded as one cause of the development of oxygen convulsions [10]. The writers showed previously that in hyperoxia qualitative changes take place in the catalytic properties of mitochondrial monoamine oxidase (MAO) [amine: oxygen-oxidoreductase (deaminating), flavin-containing, EC 1.4.3.4], as a result of which the enzyme becomes capable of deaminating several substances that normally are not MAO sustrates, including GABA [2]. Ability to modify substrate specificity during exposure to various factors and, in particular, to hyperoxia, is a feature of type A MAO (whose natural substrates are serotonin and noradrenalin) [1]. Chlorgyline, a selectively acting inhibitor of type A MAO, prevents transformation of the enzyme under the influence of hyperoxia and has a protective effect on the body, delaying the onset of oxygen convulsions and increasing the survival rate of the animals [7].

To study the mechanism of the protective action of chlorgyline, its effect on the GABA level was studied in the brain of animals exposed to hyperoxia.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred adult rats of both sexes weighing 150-180 g. The effect of oxygen under a pressure of 0.7 MPa. An intact animal and an animal receiving an intraperitoneal injection of clorgyline in a dose of 5 mg/kg 30 min before the session of hyperoxia, were placed in a pressure chamber simultaneously. The experiments ended in one series with the onset of convulsions in the intact rat (on average after 30 min, limits of variations 19-42 min). Animals protected with chlorgyline did not develop convulsions at this time. In the other series of experiments decompression was carried out after convulsions had begun in the rat protected with chlorgyline. Intact animals and animals taken 60 min after injection of clorgyline served as the control. An alcohol (10%) homogenate of the brain was centrifuged for 10 min at 400g, the residue was discarded, and the supernatant was evaporated on a rotary evaporator and its GABA content was determined on an AAA-881 automatic amino acid analyzer (Microtechna, Czechoslovakia) on a small column in 0.2M Na-citrate buffer, pH 4.25. Chlorgyline (M and B 9302), obtained from Dr. G. D. Barber (May and Baker, England), was generously supplied by Professor V. Z. Gorkin.

Laboratory Mechanisms of Adaptation of Animals to Extremal Environmental Factors, Biological Research Institute, M. A. Suslov Rostov-on-Don University. (Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 101, No. 1, pp. 45-46, January, 1986. Original article submitted February 11, 1985.

 0007-4888/86/0001-0056$12.50

TABLE 1. GABA Concentration (in μmoles/g tissue) in Rat Brain during Hyperoxia and after Injection of Chlorgyline (M ± m)

Control (1)	Chlorgyline (2)	0.7 MPa, convulsions (3)	Chlorgyline + 0.7 MPa, without convulsions (4)	Chlorgyline + 0.7 MPa, without convulsions (5)
1,683±0,146	1,162±0,069 $P_{1-2}<0,01$	1,017±0,041 $P_{1-3}<0,01$	1,586±0,056 $P_{1-4}>0,05$ $P_{3-4}<0,001$	1,48±0,020 $P_{1-5}>0,05$ $P_{3-5}<0,001$

EXPERIMENTAL RESULTS

Intraperitoneal injection of chlorgyline into rats in a dose of 5 mg/kg doubled the day before the onset of convulsions during hyperoxia; activity of type A MAO (substrate serotonin) under these circumstances was inhibited by 87% (Table 1).

Injection of chlorgyline into intact animals reduced the GABA concentration in the brain by 31%, probably due to the effect of chlorgyline on the intensity of inhibition in the CNS. In the convulsive phase of oxygen poisoning the GABA concentration in the brain fell by 40%. A fall in the GABA level by 20-60% in the rat brain during hyperoxia also was found by other workers [3, 4, 6, 9]. Injection of chlorgyline into the animals before they were placed in the pressure chamber completely prevented any fall in the GABA level induced by hyperoxia. The GABA concentration under these circumstances did not differ significantly from the control, either in animals in the preconvulsive state or in animals with established oxygen convulsions. This indicates that the normalizing effect of chlorgyline on the GABA level is associated with its direct action on the GABA system and not with any improvement in the animals' general state.

Lowering of the GABA level in the brain in hyperoxia is usually explained by inhibition of glutamate decarboxylase, an enzyme involved in GABA synthesis. A marked decrease in the activity of this enzyme during the development of oxygen poisoning, most distinctly observed in the convulsive phase, has been demonstrated by many workers [3, 6, 9]. However, the results of the present investigation suggests that an essential contribution to the fall in the GABA concentration is due to its deamination by type A MAO, modified under conditions of hyperoxia. The inhibitor of this form of the enzyme normalizes the GABA concentration in hyperoxia and has a general protective action, by considerably delaying the time of onset of hyperoxic convulsions.

LITERATURE CITED

1. V. Z. Grokin, in: Catecholaminergic Neurons [in Russian], Moscow (1979), p. 202.
2. I. A. Goroshinskaya, L. L. Grabovskova, Z. G. Bronovitskaya, and A. A. Krichevskaya, Fiziol. Zh. SSSR, 67. 1611 (1981).
3. A. A. Krichevskaya, V. S. Shugalei, L. A. Shcherbina, and G. G. Ermolenko, Vopr. Med. Khim., 20, 294 (1974).
4. L. G. Mendzheritskaya, A. A. Krichevskaya, and S. A. Lisovskaya, Kosmich. Biol. Aviakosmich. Med., 12, No. 4, 68 (1978).
5. I. A. Sytinskii, γ-Aminobutyric Acid in Activity of the Nervous System [in Russian], Leningrad (1972).
6. G. V. Shcherbakova, Dokl. Akad. Nauk SSSR, 146, 1213 (1962).
7. I. A. Goroshinskaya, Z. G. Bronovitskaya (J. A. Goroshinskaya, J. G. Bronovizkaya), and V. Z. Gorkin, Commun. Psychopharmacol., 1, 39 (1977).
8. J. D. Wood, J. Neurochem., 17, 573 (1970).
9. J. D. Wood, W. J. Watson, and A. J. Ducker, J. Neurochem., 14, 1067 (1970).
10. J. D. Wood, W. J. Watson, and G. W. Murray, J. Neurochem., 16, 281 (1969).