EFFECT OF ACUTE HYPOXIA ON DEVELOPMENT OF METRASOL SEIZURES

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The study of functions of the body in hypoxia is interesting because any pathological state may be accompanied by hypoxia, the depth of which in many cases determines the severity and outcome of the pathological process. Acute hypoxia is known to cause seizures [11]. With lowering of the metabolic rate due to ischemia or hypoxia, excitability of nerve cells is increased and their responses to stimulation becomes excessive. However, this process is self-limiting, for the sharply increasing metabolic rate during the epileptic fit quickly exhausts the reserves of the nerve cells and they cease to respond to stimulation. The development of epilepsy after hypoxia may be due to selective degeneration of axon terminals arising from GABA-ergic neurons [12]. There is evidence that in some cases hypoxia has an inhibitory action on the development of seizures [9]. It has also been shown that adaptation to hypoxia depresses seizure manifestations in rats genetically predisposed to epilepsy, in response to acoustic stress [5], under the influence of metrazol [7] and of strychnine and penicillin [3], and that correlation exists between the resistance of rats to hypoxia and to the convulsant action of strychnine and penicillin [1].

The aim of this investigation was to study the effect of acute hypoxic hypoxia on the development of metrazol seizures.

EXPERIMENTAL METHOD

Experiments were carried out on 89 noninbred male rats weighing 150-250 g. Metrazol was injected subcutaneously in doses of 60, 80, and 100 mg/kg body weight immediately before the animal was decompressed in the pressure chamber. The effect of each dose of the drug was studied under a partial pressure of oxygen of 150, 110, 85, and 60 mm Hg. The animals remained under visual observation throughout the period of stay in the pressure chamber (1 h) and the latent period (the time from injection of the drug until the appearance of the first epileptic fit) and the number and duration of the seizures were determined. Statistical evaluation of the results was carried out by correlation analysis on the "Iskra-1256" computer.

EXPERIMENTAL RESULTS

The results are given in Table 1. Statistical analysis of the parameters reflecting seizure activity revealed significant positive correlation between the number of seizures and their total duration, and also between the mean duration of one seizure and the total duration of all seizures independently of the dose of metrazol and the experimental conditions, evidence that the method of evaluation of the results was appropriate. The latent period showed significant ($p < 0.05$) negative correlation with the total duration of the seizures and a tendency ($p < 0.01$) toward negative correlation with the number of seizures and the average duration of one seizure, irrespective of the dose of metrazol or the level of hypoxia. These correlations, which characterized the process of metrazol-induced seizures as a whole, can be extended by taking account of the correlation established previously between resistance to hypoxia and resistance to the action of epileptogens. Thus the higher the animal's resistance to

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TABLE 1. Effect of Hypoxia on Development of Metrazol Seizures in Rats ($M \pm m$)

Dose, mg/kg	pO_2, mm Hg	Latent period, sec	Number of seizures	Duration of one seizure	Duration of all seizures, sec
	150	590,0±61,00	1,33±0,21	32,50±8,31	40,83±9,52
60	110	636,7±75,50	2,00±0,51	89,58±37,40	275,8±155,7
	85	782,0±72,40	1,40±0,24	19,40±1,96	27,00±5,15
	60	1288,0±163,7	4,00±1,26	37,0±11,55	149,0±60,9
	150	630,8±91,70	2,17±0,30	39,22±9,94	90,83±36,20
80	110	648,3±139,2	2,33±0,49	84,67±23,16	254,2±99,90
	85	703,3±91,35	2,67±0,42	71,33±20,86	200,0±54,54
	60	1126,7±113,9	3,00±0,45	37,33±7,35	108,3±26,73
	150	615,5±26,00	3,20±0,47	729,0±258,6	1770,0±243,4
100	110	547,5±26,00	3,40±0,40	170,2±25,00	542,5±97,58
	85	582,2±92,40	4,22±0,40	213,4±77,54	693,0±162,5
	60	931,4±106,1	4,57±0,84	134,4±34,17	435,7±65,72

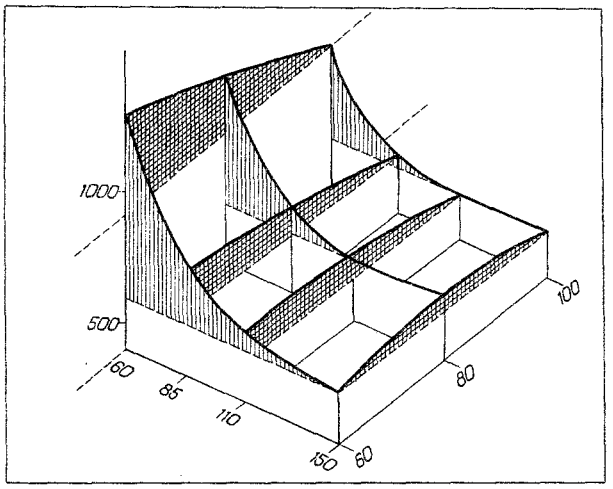

Fig. 1. Effect of hypoxia on latent period of onset of seizures after injection of different doses of metrazol. Abscissa, doses of metrazol (in mg/kg); ordinate, latent period (in sec); z axis, pO_2 in inspired air (in mm Hg).

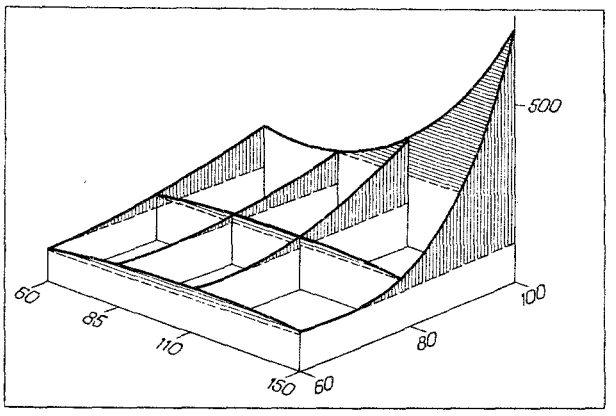

Fig. 2. Mean duration of one seizure depending on dose of metrazol and degree of hypoxia. Abscissa, pO_2 in inspired air (in mm Hg); ordinate, mean duration of seizure (in sec); z axis, dose of metrazol (in mg/kg).

hypoxia, the longer the latent period before it developed metrazol seizures, and the smaller their number and the shorter their duration. The results of the effect of a varied degree of hypoxia on the development of seizures induced by different doses of metrazol are illustrated in Figs. 1-3. It will be clear from Fig. 1 that all doses of metrazol under normoxic conditions induce seizures indistinguishable in the time of their onset after injection of the drug, but the duration of each of them (Fig. 2) and,

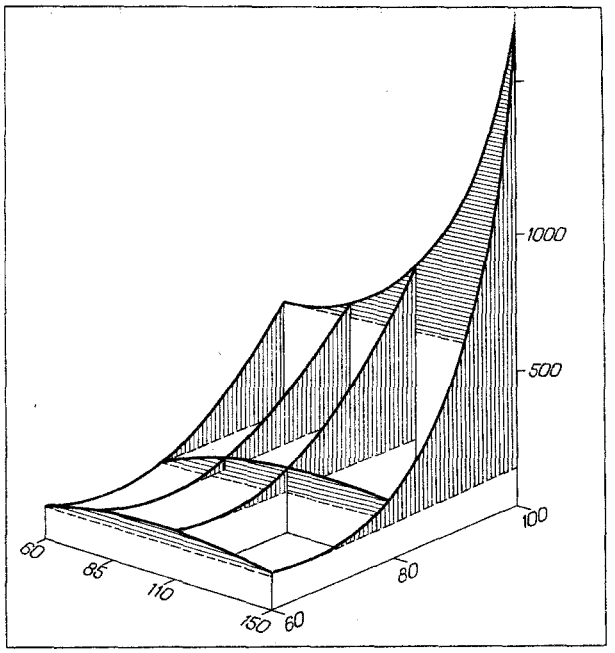

Fig. 3. Average total duration of seizures arising after injection of different doses of metrazol during exposure to hypoxia. Abscissa, pO_2 (in mm Hg); ordinate, total duration of seizures (in sec); z-axis, doses of metrazol (in mg/kg).

correspondingly, the total duration of all seizures, were greater in animals receiving the large dose of metrazol (Fig. 3). Hypoxia delays the development of metrazol seizures: the increase in the latent period itself increased with a decrease in pO_2. After injection of 60 mg/kg, LP began to increase when pO_2 was 110 mm Hg, after injection of 80 mg/kg it began after 85 mm Hg, and with a dose of 100 mg/kg this effect began when pO_2 was only 60 mm Hg (Fig. 1).

The effect of hypoxia on the mean duration of one seizure was exhibited only in a dose of 100 mg/kg, and the value of this parameter was significantly lower at pO_2 = 110 mm Hg. Hypoxia had a similar effect on the total duration of all seizures.

Thus the anticonvulsant action of hypoxia depends on its level and on the dose of the convulsant: the higher the level of hypoxia, the longer the latent period before development of the seizures, and for different doses of metrazol to have an identical effect, an increase in the dose requires a higher degree of hypoxia.

The anticonvulsant action of acute hypoxia may be associated with depression of cerebral cortical electrical activity by hypoxia with an increase in the GABA concentration. Hypoxia may also cause excitation of structures belonging to the anti-epileptic system of the brain [6]. Hypoxia is known to cause an increase in neuronal activity in the locus coeruleus [10], and an electrical stimulation of that structure depresses seizure activity [8].

The results are evidence of the protective action of hypoxia on the development of metrazol-induced seizures, and because the values of the parameters characterizing the seizure depend on the level of hypoxia and the relationship is described by a third power polynomial, the level of hypoxia required to be effective in suppressing metrazol-induced seizures can be calculated.

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EFFECT OF DESTRUCTION AND ACTIVATION OF SOME LIMBIC STRUCTURES ON DEVELOPMENT OF SEIZURES AND EMOTIONAL DISTURBANCES IN PICROTOXIN KINDLING

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Pharmacologic kindling, caused by repeated injections of picrotoxin in a subconvulsive dose, and characterized by an increase in severity of seizure manifestations, also has been shown to lead to the formation of a syndrome of pathologically enhanced defensive behavior [6]. The hippocampus has been shown to play the role of determinant structure of the epileptic pathological system (PS) lying at the basis of development of the seizure syndrome during pharmacologic kindling [3, 4]. Structures of the amygdala also play an important role in realization of aggressive-defensive forms of behavior and in the development of the enhanced emotional response during kindling evoked by electrical stimulation of this structure [8].

The aim of this investigation was to study the effect of destruction of the dorsal hippocampus and the basomedial amygdala and also their activation on the development of seizures and emotional disorders associated with picrotoxin kindling.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 220-250 g. Each group consisted of at least 10 animals. The rats were anesthetized with pentobarbital (40 mg/kg), fixed in a stereotaxic apparatus, and taking coordinates from the atlas [11], kainic acid [7], in a dose of 1 μg in 1 μl of phosphate buffer (pH 7.4), was injected by means of a "TOP" microsyringe (India) bilaterally into structures of the hippocampus (AP = −2.8, I = 1.5, H = 3.5) or amygdala (AP = −2.8, I = 4.5, H = 9.0) in order to destroy them. Activity of the hippocampus and amygdala was enhanced by microinjection of 5 μl of homologous blood [9], diluted 4:1 with distilled water, into these structures. Animals of the control groups received 1 μl respectively of phosphate buffer solution pH 7.4 or 5 μl of isotonic NaCl solution, diluted 4:1 with distilled water, under similar conditions. Daily for 3 weeks, 24 h after the injections of blood and 15 days after the microinjections of kainic acid, the animals received a single intraperitoneal injection of picrotoxin in a below-threshold dose of 1.0 mg/kg body weight [6]. The animals' behavior was observed for 90 min after the injections. The intensity of the seizures and of aggressive-defensive behavior was expressed in

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