METRAZOL KINDLING IN ANIMALS DIFFERING IN SENSITIVITY TO THE CONVULSANT

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KEY WORDS: epilepsy; pharmacologic kindling; metrazol

Kindling is widely used as a model of epileptogenesis, learning, memory, and psychosislike and emotional-behavioral disorders [2, 3, 5, 8-10]. During kindling produced both by electrical stimulation and by drugs, not only species-specific [11], but also individual differences are observed in the sensitivity of animals to the action of a convulsant [6, 12-14]. Great variability has been found in the number of electrical stimulations of brain structures [7, 13] and systematic injections of convulsants [1, 4] necessary to obtain generalized tonicoclonic convulsions in animals. In investigations to study the effect of different antiepileptic agents on the development of seizure predisposition in rats during metrazol-induced kindling [1], we also found considerable differences in individual reactivity of animals receiving daily injections of metrazol. These differences in individual sensitivity make it difficult to assess the development of seizure predisposition during kindling in the general population of experimental animals on the basis of averaged parameters, and also, consequently, in assessing the efficacy of antiepileptic drugs used.

Hence the importance of preliminary determination of the approximate level of sensitivity of animals to the convulsant with the aim of forming relatively uniform experimental and control groups. In the investigation described below an attempt at such determination was made on the basis of the response of animals to a single preliminary injection of convulsant in the minimal active dose.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats initially weighing 170-190 g. The animals were kept under ordinary animal house conditions on a standard diet. The severity of the convulsions during kindling (daily intraperitoneal injection of metrazol) was assessed in points: 1) shaking (nodding) of the head; 2) infrequent (single) clonic convulsions of the whole body; 3) a series of clonic convulsions of the whole body or clonus of the forelimbs; 4) tonicoclonic convulsions with rearing on the hind limbs (the "kangaroo" posture); 5) clonicotonic convulsions with the animal falling on its side; 6) repeated tonicoclonic convulsions and (or) death of the animal.

Preliminary investigations with titration of doses of metrazol given by single intraperitoneal injection (over 100 animals were used) showed that a dose of 30 mg/kg does not induce seizure reactions under the experimental conditions used. This dose was adopted for chronic injection in order to produce kindling. In a dose of 40 mg/kg metrazol induced a seizure response rated at 1-3 points in 1-3 rats from each 10 animals tested. Animals giving a seizure response to this minimal effective dose could be considered to be relatively more sensitive to the convulsant action of metrazol, and these rats were conventionally described as metrazol-sensitive, and placed in group 1 (15 rats). Animals which did not give a seizure reaction to this dose could be considered to be less sensitive to the convulsant action, and they were described conventionally as animals with low sensitivity to metrazol (group 2; 15 rats). Kindling began 1 week after testing, by daily injection of metrazol in a subconvulsive dose of 30 mg/kg. The severity of the seizure reaction to injection of metrazol was estimated daily. The significance of differences was determined by Student's test.

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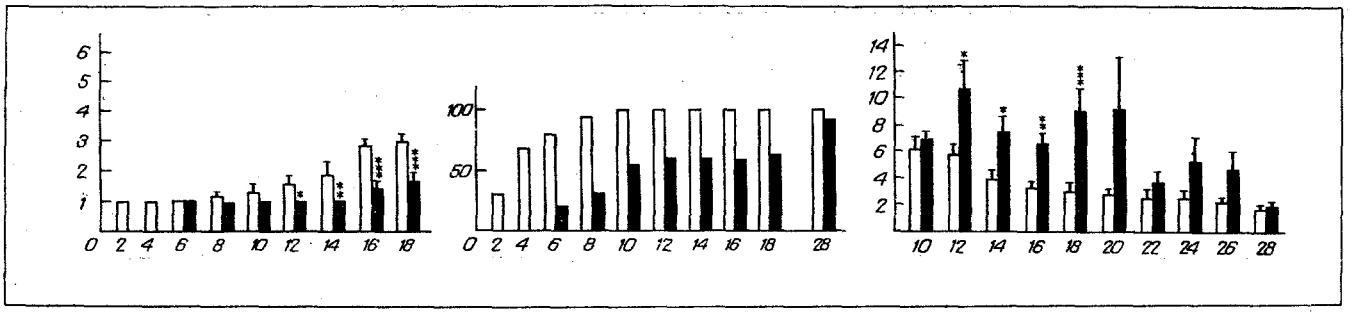

Fig. 1 Fig. 2 Fig. 3

Fig. 1. Severity of seizure response in relatively sensitive (empty columns) animals and in animals with low sensitivity (black columns) to metrazol, during kindling induced by daily injection of metrazol in a subconvulsive dose. Abscissa (here and in Figs. 2-3) – days of metrazol injection; ordinate – average severity of seizures (in points). Here and in Fig. 3, significance of differences during convulsions in animals of different groups: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Fig. 2. Number of animals in groups 1 (empty columns) and 2 (black columns) in which a seizure response appeared during metrazol kindling. Ordinate, number of animals (in %); total number of animals (15) in each group taken as 100%.

Fig. 3. Latent period of first seizure manifestations after each injection of metrazol in animals relatively sensitive (empty columns) and with low sensitivity (black columns) to metrazol during kindling. Ordinate, latent period of first seizure manifestations after each injection of metrazol (in min).

EXPERIMENTAL RESULTS

In the animals of group 1, receiving a daily intraperitoneal injection of metrazol in a subconvulsive dose (30 mg/kg) seizures with a severity of 1 point appeared as early as after the second injection (26% of rats). In group 2, the same reaction was observed only after the sixth injection (20% of rats) (Fig. 1). On the 8th-10th day of injection of metrazol, differences in the severity of the seizure reaction in the animals of these two groups were not significant. Later, beginning with the 12th day, these differences became steadily more marked and reached a maximum on the 16th day of metrazol administration.

In all rats of group 1 seizure reactions occurred by the 10th day. Meanwhile, in group 2, seizures were found in 53% of rats, and these differences persisted on the subsequent days of metrazol injection (Fig. 2).

The latent period of onset of the first seizures after each daily injection of metrazol from the 12th through the 18th day was significantly less in animals sensitive to metrazol than in those with low sensitivity (Fig. 3).

Thus testing with a threshold dose of metrazol may provide a comparatively easy method of predicting the sensitivity of animals to this convulsant, with the aim of forming groups of sensitive and resistant animals. For a more accurate separation of animals repeated testing is advised, with an interval of 5-7 days. This method can also probably be used with other convulsants.

LITERATURE CITED

1. G. N. Kryzhanovskii, M. N. Karpova, and O. Yu. Pankov, Byull. Éksp. Biol. Med., No. 10, 348 (1990).
2. G. N. Kryzhanovskii, A. A. Shandra, L. S. Godlevskii, and R. F. Makul'kin, Usp. Fiziol. Nauk, **19**, No. 4, 12 (1988).
3. A. A. Shandra, L. S. Godlevskii, and A. M. Mazarati, Usp. Fiziol. Nauk, **21**, No. 4, 50 (1990).
4. A. A. Shandra, L. S. Godlevskii, and N. D. Semenyuk, Byull. Éksp. Biol. Med., No. 4, 20 (1983).
5. G. V. Goddard, D. C. McIntyre, and C. K. Leech, Exp. Neurol., **25**, No. 2, 295 (1969).
6. C. K. Leech and D. C. McIntyre, Behav. Biol., **16**, 439 (1976).
7. G. Le Gal La Salle, Kindling 2, ed. by J. A. Wada, New York (1981), pp. 31-44.

8. J. Majkowski, Acta Neurol. Scand., Suppl. 109, 97 (1986).
9. R. M. Post and J. C. Ballenger, Handbook of Biological Psychiatry, Vol. 2, New York (1981), pp. 609-651.
10. R. M. Post and R. T. Kopanda, Am. J. Psychiat., **133**, No. 6, 627 (1976).
11. R. Racine, Neurosurgery, **3**, 234 (1978).
12. R. Racine, W. Burnham, J. Gartner, and D. Levitan, Electroenceph. Clin. Neurophysiol., **35**, 553 (1973).
13. P. R. Sanberg and K. P. Ossenkopp, Physiol. Behav., **20**, 205 (1978).
14. J. Ziade, Physiol. Behav., **12**, 527 (1974).

EFFECT OF PHOSPHOENOLPYRYVATE ON THE COURSE OF THE ACUTE PERIOD OF EXPERIMENTAL MYOCARDIAL INFARCTION

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KEY WORDS: phosphoenolpyruvate; acute myocardial ischemia; zone of necrosis

The compounds 1,3-diphosphoglycerate and phosphoenolpyruvate (PEP) belong to the category of very high-energy substrates of glycolysis, involved in the phosphorylation of ADP. However, despite evident preference for these compounds as potential agents supplying energy for survival of the myocardium under conditions of acute ischemia, there is virtually no information on research in this direction. The only exceptions are a few publications [4-7] describing the results of the use of PEP during cardioplegia and total ischemia of the rat heart.

The aim of this investigation was to study the effect of PEP on some parameters of bioenergetics, blood supply, cardiohemodynamics, and the formation of the zone of necrosis in experimental myocardial infarction.

EXPERIMENTAL METHOD

Experiments were carried out on mongrel male and female dogs weighing 6-17 kg and noninbred male albino rats weighing 250-300 g, anesthetized with pentobarbital sodium (40 mg/kg, intraperitoneally). In experiments on dogs the regional vein of the heart was catheterizod, and after ligation of the coronary artery, its distal segment also was catheterized by the method described previously [1]. Concentrations of lactate and glucose were determined by enzymic methods in samples of blood flowing from the ischemic zone, and the pH of the blood also was monitored. The blood supply to the ischemic region of the heart muscle was judged from the retrograde pressure (RP) and the collateral coronary blood flow (CCBF) in the distal part of the coronary artery. The first derivative of the intraventricular pressure (dp/dt) was recorded by means of a differentiator, and the average blood pressure (ABP) was measured in the femoral artery by means of "Bentley" pressure transducers. PEP ("Sigma") was injected intravenously in fractions of a total dose of 1 mg/kg (25% of the dose every 15 min) 5 min after occlusion of the coronary artery (OCA). A model of a myocardial infarct was produced in the rat by ligation of the descending branch of the left coronary artery at the level of the lower border of the auricle of the atrium. After the end of the manipulation the wound was closed in layers and the rats were artificially ventilated. The experimental animals were killed 4 h after OCA and the dimensions of the zone of ischemia and zone of necrosis were determined by the differential indicator method [2]. PEP was injected immediately after OCA in doses of 10, 1, and 0.1

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