5. A. R. Cools, Psychopharmacologia (Berlin), 36, 17 (1974).
6. A. Dahlström and K. Fuxe, Acta Physiol. Scand., 62, Suppl. 232 (1964).
7. R. Hassler and I. J. Bak, in: 3rd Symposium on Parkinson's Disease, edited by J. Gillingham and I. M. L. Donaldson, London (1969), pp. 29-37.
8. R. B. Holman and M. Vogt, J. Physiol. (London), 233, 243 (1972).
9. U. J. Hoyland, E. E. Shillito, and M. Vogt, Br. J. Pharmacol., 40, 659 (1970).
10. K. Y. Ng, T. N. Chase, R. W. Colburn, et al., Brain Res., 45, 499 (1972).
11. L. J. Poirier and T. L. Sourkes, Pharmac. Therap. B., 2, 19 (1976).

EFFECT OF ETHIMIZOLE ON CHANGES IN BRAIN METABOLISM CAUSED BY OVERSTIMULATION

E. V. Moreva and V. V. Bul'on

UDC 615.214.31.015.42:612.82

During overstimulation (electrical stimulation for 3 h) of rats considerable changes are observed in their brain metabolism. These changes are manifested as exhaustion of the noradrenalin reserves and disturbance of energy metabolism, leading to a fall in the creatine phosphate level. Preliminary (before electrical stimulation) administration of ethimizole prevented the noradrenalin and creatine phosphate deficiencies in the brain tissue of the overstimulated animals.

KEY WORDS: prolonged electrical stimulation of the brain; energy metabolism; noradrenalin; ethimizole.

Analysis of reflex dystrophies of the internal organs has shown that the development of tissue injuries is connected with a disturbance of the regulatory influences of the CNS. This is shown by the protective action of neurotropic drugs blocking cholinergic and adrenergic systems in the CNS and by the sharp decrease in the concentration of mediators – acetylcholine and, in particular, noradrenalin (NA) – in the brain tissue [1, 9, 10].

The invariable participation of the CNS in the transmission of noxious impulses during stimulation of reflexogenic zones was the motivation for the present investigation to determine whether metabolic changes take place under these circumstances in the brain tissue and whether they can be regulated by neurotropic drugs such as are used for the treatment of experimental neurodystrophies.

For this purpose, some indices of energy metabolism of the brain were studied and the NA concentration determined. The neurotropic drug used was ethimizole, an alkylamide of imidazoledicarboxylic acid with a marked central action on the energy metabolism of the CNS. The writers showed previously that ethimizole, 20 min after injection into normal animals, increases glycolysis, oxidative phosphorylation, and the creatine phosphate (CP) concentration, but reduces the inorganic phosphorus content [2, 5, 11].

EXPERIMENTAL METHOD

Experiments were carried out on male albino rats weighing 180-200 g. For overstimulation, leading to the development of neurogenic dystrophies, the animals were stimulated electrically for 3 h through needle electrodes implanted into the muscles of the forelimbs [3]. Ethimizole was injected intraperitoneally in a dose of 25 mg/kg 20 min before electrical stimulation began. Immediately after the end of stimulation the rats were killed by immersion in liquid oxygen, the brain was removed, and the content of NA [6], pyruvic acid [16], lactate [13], glycogen [17], CP [14], and inorganic phosphorus [15] was determined in the cerebral hemispheres. Intact animals served as the control.

Laboratory of Experimental Pharmacology, Department of Pharmacology, Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR S. V. Anichkov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 85, No. 3, pp. 299-301, March, 1978. Original article submitted June 10, 1977.

0007-4888/78/8503-0315$07.50 © 1978 Plenum Publishing Corporation

TABLE 1. Effect of Ethimizole on Changes in Some Indices of Brain Metabolism in Rats after Electrical Stimulation for 3 h (M ± m)

Substrates	Experimental conditions		
	control	stimulation	ethimizole + stimulation
Glycogen, mg%	74,0±3,2, n=6	45,0±3,8, n=6	29,0±2,3, n=6
Pyruvic acid, mg%	0,78±0,01, n=6	1,06±0,05, n=6	1,25±0,05, n=6
Lactate, mg%	20,0±1,0, n=6	26,0±0,8, n=6	28,0±2,0, n=6
CP, mg%	22,0±1,3, n=6	16,0±1,4, n=6	31,0±1,6, n=6
Inorganic phosphorus, mg%	24,0±1,2, n=6	35,0±2,3, n=6	20,0±1,5, n=6
NA, μg/g tissue	0,56±0,03, n=9	0,03 , n=8	0,31±0,04, n=10

Legend: n) number of experiments.

EXPERIMENTAL RESULTS

The results given in Table 1 show that after overstimulation for 3 h, causing the development of neurogenic lesions of the internal organs, definite changes took place in the energy metabolism of the CNS. These changes were manifested as a decrease in the energy reserves of the brain tissue, namely, a decrease in the glycogen and CP content. The decrease in glycogen and CP 3 h after the beginning of electrical stimulation of the animals amounted to 39 and 27% respectively. Meanwhile the content of pyruvic acid was increased by 36%, of lactate by 30%, and of inorganic phosphorus by 46%. The changes observed in the energy metabolism of the CNS were in full agreement with data obtained by other workers who found a reduction in the glycogen and CP reserves with a simultaneous increase in the lactic acid and inorganic phosphorus content in the brain of animals in a state of stress [12].

The disturbances of energy metabolism of the CNS during overstimulation were accompanied by a sharp fall in the NA content in the brain tissue of the rats (Table 1), confirming previous observations [1, 10].

Injection of ethimizole 20 min before the beginning of overstimulation of the animals had a protective action on metabolism of the brain tissue (Table 1). For instance, in the animals receiving ethimizole the deficiency in the content of the high-energy compound CP did not arise. Under these experimental conditions the CP level not only reached normal, but actually exceeded it by 40% compared with the control animals: 31.0 ± 1.6 and 22.0 ± 1.3 mg% respectively. It is interesting to note that the prevention of the CP deficit in the animals receiving ethimizole was not accompanied by normalization of the indices of glycolysis. On the contrary, a further decline was observed in the glycogen concentration (by 60% compared with the control), and the pyruvic and lactic acid content were increased by 60% and 40% respectively. Since the writers showed previously that ethimizole stimulates the energy metabolism of the brain (glycolysis and tissue respiration), it can tentatively be suggested that ethimizole induces stimulation of glycolysis and the effective utilization of pyruvate in the Krebs cycle under conditions of overstimulation of the CNS.

Besides the protective action of ethimizole on the energy metabolism of the CNS, it also had a preventive effect on the decrease in the NA concentration in the brain tissue. Ethimizole appreciably inhibited exhaustion of the NA reserves in the brain tissue and restored its level by 55% compared with the control.

The results of these experiments thus indicate that overstimulation of animals, leading to the development of neurogenic dystrophies of the internal organs, causes metabolic changes in the brain tissue which are manifested as exhaustion of the reserves of the adrenergic mediator and disturbance of energy metabolism in the CNS. Preliminary administration of ethimizole partly prevents these changes in the NA balance and prevents the disturbance of the energy metabolism of the brain by abolishing the CP deficit in overstimulated animals.

It is interesting to compare these results with those of the investigation of the cyclic AMP concentration in the brain tissues during overstimulation. Experiments in the writers' laboratory have shown that the cyclic AMP level in brain tissue falls considerably during electrical stimulation of rats for 3 h [7]. Since, as the writers have shown [4, 8], the biochemical effects of ethimizole in the brain are due to its activating effect on adenylate cyclase and to the accumulation of cyclic AMP, a biological regulator of cell metabolism, this aspect of the action of the compound might well explain its protective effect on the energy metabolism of the brain.

LITERATURE CITED

1. S. V. Anichkov, I. S. Zavodskaya, E. V. Moreva, et al., Neurogenic Dystrophies and Their Pharmacotherapy [in Russian], Leningrad (1969).

2. V. V. Bul'on and E. V. Moreva, Byull. Éksp. Biol. Med., No. 2, 185 (1977).
3. O. N. Zabrodin, Transactions of the Institute of Experimental Medicine, Academy of Medical Sciences of the USSR [in Russian], Vols. 7-8, Leningrad (1963), p. 212.
4. I. S. Zavodskaya, É. D. Migas, and V. V. Bul'on, Byull. Éksp. Biol. Med., No. 3, 54 (1975).
5. I. S. Zavodskaya, E. V. Moreva, and V. V. Bul'on, in: The Pharmacology and Toxicology of New Products of Chemical Synthesis. Proceedings of the 3rd Republican Conference [in Russian], Minsk (1975), p. 97.
6. É. Sh. Matlina and T. B. Rakhmanova, in: Methods of Investigation of Some Systems of Humoral Regulation [in Russian], Moscow (1967), p. 136.
7. É. A. Migas, Byull. Éksp. Biol. Med., No. 5, 541 (1976).
8. É. A. Migas and V. V. Bul'on, Farmakol. Toksikol., No. 6, 710 (1974).
9. E. V. Moreva, Farmakol. Toksikol., No. 1, 43 (1967).
10. E. V. Moreva, Farmakol. Toksikol., No. 6, 661 (1967).
11. E. V. Moreva and V. V. Bul'on, Farmakol. Toksikol., No. 6, 693 (1975).
12. K. I. Pogodaev and N. F. Turova, Biochemistry of the Brain during Fatigue and Exhaustion [in Russian], Moscow (1972).
13. S. B. Barker and W. H. Summerson, J. Biol. Chem., 138, 535 (1941).
14. A. Ennor and H. Rosenberg, Biochem. J., 51, 606 (1952).
15. G. H. Fiske et al., J. Biol. Chem., 66, 375 (1925).
16. T. E. Friedemann and G. E. Haugen, J. Biol. Chem., 147, 415 (1943).
17. S. E. Kerr, J. Biol. Chem., 116, 1 (1936).

NEUROTROPIC ACTIVITY OF PHENYLPYRROLIDONE-2 ISOMERS

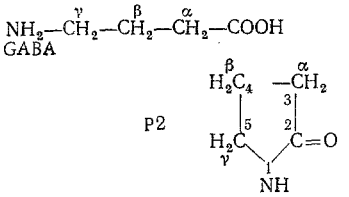
R. A. Khaunina

UDC 615.21:547.745].015.11

Pyrrolidone-2 (P2) is a cyclic form of gamma-aminobutyric acid (GABA). In experiments on mice and rats the pharmacological activity of three isomers of phenyl derivatives of P2 was investigated. All the compounds inhibited motor activity, lowered muscle tone and body temperature, potentiated the action of hexobarbital, and possessed anticonvulsive (electrical shock, strychnine, metrazol, thiosemicarbazide, audiogenic convulsions) and narcotic activity. The most active isomer was 4-phenylpyrrolidone-2 (phepyron). Comparison of the pharmacological activity of phenyl derivatives of P2 and analogous derivatives of GABA showed that the GABA derivatives have no anticonvulsive or narcotic activity and are less toxic. It is suggested that the phenyl derivatives of P2 are not converted into the analogous GABA derivatives in vivo.

KEY WORDS: gamma-aminobutyric acid; phenylpyrrolidone-2; neurotropic activity.

Pyrrolidone-2 (P2) can be regarded as the cyclic form of gamma-aminobutyric acid (GABA):



The suggestion that P2, which is a nonpolar molecule, is more soluble than GABA in lipids, and so penetrates in greater quantity through the blood–brain barrier, after which it is converted by hydrolysis into GABA, has led many workers to study its pharmacological action. Comparison of P2 with GABA has revealed that it has somewhat greater or less pharmacological activity than P2 depending on the index used [11-13, 15, 16].

Laboratory of Psychopharmacology, V. M. Bekhterev Leningrad Psychoneurological Research Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 85, No. 3, pp. 301-304, March, 1978. Original article submitted September 9, 1977.

0007-4888/78/8503-0317$07.50 © 1978 Plenum Publishing Corporation