The changes in the fractional composition and content of hemoglobin derivatives under the influence of glucocorticoids described above must consequently be taken into account when a hormone preparation is chosen.

LITERATURE CITED

1. V. I. Kalinicheva, in: Anemia in Children [in Russian], Leningrad (1978), p. 70.
2. M. S. Kushakovskii, Clinical Forms of Damage to Hemoglobin [in Russian], Leningrad (1968).
3. N. I. Lopatina and V. M. Shevchuk, Vopr. Med. Khim., No. 1, 42 (1972).
4. N. F. Starodub, Biokhimiya, No. 4, 757 (1974).
5. O. F. Tarasov, in: Anemia in Children [in Russian], Leningrad (1978), p. 191.

EFFECT OF CHRONIC ADMINISTRATION OF LITHIUM CHLORIDE ON DEVELOPMENT OF HYPERSENSITIVITY OF DOPAMINE RECEPTORS DURING MORPHINE WITHDRAWAL IN RATS

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KEY WORDS: morphine; abstinence syndrome; hypersensitivity of dopamine receptors; lithium.

Prolonged administration of narcotic analgesics increases tolerance to their action and also leads to mental and physical dependence on the drug. Discontinuation of the drug gives rise to a withdrawal syndrome, characterized by various behavioral effects. Meanwhile marked changes are observed in metabolism of CNS mediators.

There is evidence that aggressiveness arising in rats after withdrawal of morphine is connected with a change in the sensitivity of the dopamine receptors [7]. Administration of dopaminomimetic agents (apomorphine, amphetamine) after withdrawal of morphine sharply increase, whereas administration of substances blocking dopaminergic transmission (neuroleptics reduce, aggressive reactions in abstinent rats [5, 7].

Meanwhile hypersensitivity of dopamine receptors developing after withdrawal of chronically administered neuroleptics (haloperidol) can be prevented by giving lithium chloride at the same time [1, 6]. The stabilizing action of lithium chloride on dopamine receptors has been demonstrated in experiments with electrophysiological [4] and behavioral [1] tests and also in experiments on binding of ^{3}H-spiroperidol [6].

The object of this investigation was to study the action of chronic administration of lithium on manifestations of the withdrawal syndrome after discontinuing morphine in rats.

EXPERIMENTAL METHOD

Male Wistar rats weighing 250-280 g were divided into four groups (20 animals in each group). The rats of group 1 received morphine hydrochloride twice a day for 10 days in increasing doses (from 30 to 300 mg/kg intraperitoneally). The rats of group 2 received injections of 0.2M lithium chloride chloride solution in a dose of 2 meq/kg body weight intraperitoneally 1 week before the beginning of the morphine injections, after which the two preparations were given simultaneously for 10 days. Animals of group 3 were given a 0.2M solution of lithium chloride only for 17 days. The animals of group 4 (control) received physiological saline.

The threshold of nociceptive sensation was determined in some of the animals 60 h after administration of the substances ceased by pinching the tail with Hafner's forceps, and their spontaneous and apomorphine-induced (10 mg/kg, intraperitoneally) aggressiveness also was estimated [1]. In another group of animals the dopamine (DA), homovanillic acid (HVA), and 3,4-dihydroxyphenylacetic acid (DHPAA) content in the corpus striatum was determined spectrofluorometrically [3].

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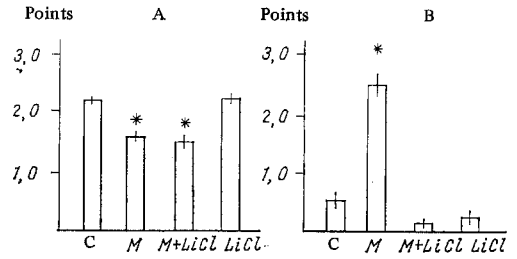

Fig. 1. Changes in threshold of nociceptive sensation (A) and intensity of apomorphine-induced aggressiveness (B) 60 h after stopping 10-day administration of morphine (M), morphine and lithium chloride (M + LiCl), and lithium. C) Control. Aggressiveness determined 45 min after injection of apomorphine. *$P \leqslant 0.05$.

TABLE 1. Content of DA, HVA, and DHPAA (in μg/g brain tissue) in Corpus Striatum of Rats 60 h after 10-Day Administration of Morphine, Morphine Together with Lithium Chloride, and Lithium Chloride Alone (M ± m)

Group of animals	DA	HVA	DHPAA
4 (control)	8,27±0,23	0,43±0,03	1,16±0,04
1	6,33±0,18*	0,29±0,07*	0,69±0,05*
2	8,50±0,52	0,45±0,07	0,83±0,09
3	7,97±0,32	0,37±0,05	1,02±0,07

*$P < 0.05$.

EXPERIMENTAL RESULTS

Lowering of the threshold of nociceptive sensation and high degrees of spontaneous and apomorphine-induced aggressiveness were found 60 h after stopping the administration of morphine (Fig. 1). Accompanying administration of lithium did not affect the hyperalgesia induced by morphine withdrawal. In the animals receiving lithium chloride simultaneously with morphine the aggressive reactions were depressed. At the same time the turnover of DA and its metabolites – HVA and DHPAA – was reduced (Table 1). Lithium prevented the decrease in the content of DA and its metabolites (HVA and DHPAA).

The results of this investigation confirm the hypothesis that withdrawal aggressiveness of rats is connected with increased sensitivity of dopamine receptors. Evidence in support of this conclusion is given by the reduction in DA turnover and potentiation of the behavioral effects of apomorphine, a direct stimulator of dopamine receptors.

Combined administration of lithium chloride with morphine prevents the development of hypersensitivity, as previous investigations with neuroleptics also showed [1, 6]. After witholding of morphine specific binding of ^{3}H-spiroperidol by membranes of the rat corpus striatum was significantly lower and affinity for the receptors was increased. It is suggested that this fact may be the explanation of the behavioral hypersensitivity to DA agonists [8].

The mechanism of the stabilizing action of lithium chloride on the development of hypersensitivity of the dopamine receptors is not clear. We know that morphine lowers the Ca^{++} ion level in the rat brain. Parallel administration of calcium salts with morphine considerably reduces the manifestations of withdrawal after discontinuing morphine. It is suggested that administration of calcium salts can prevent or largely reduce morphine dependence also in rats [9]. There is evidence that lithium ions can replace Ca^{++} ions in membranes [2]. It may be that this competitive action between Li^+ and Ca^{++} is one of the reasons why combined administration of lithium with morphine prevents the development of withdrawal aggressiveness. However, further investigations are necessary to explain the mechanism of the action of lithium on the dopaminergic system.

LITERATURE CITED

1. L. Kh. Allikmets (L. H. Allikmets), M. Stanley, and S. Gershon, Life Sci., 25, 165 (1979).
2. J. M. Birch, in: Medical Practice, Lancaster (1977), p. 89.
3. C. J. Earley and B. E. Leonard, J. Pharmacol. Methods., 1, 67 (1978).
4. D. W. Gallager, A. Pert, and W. E. Bunney, Nature, 273, 309 (1978).
5. G. Gianutsos and H. Lal, Mod. Probl. Pharmacopsych., 13, 114 (1978).
6. A. Pert, J. E. Rosenblatt, C. Sivit, et al., Science, 201, 171 (1978).
7. S. K. Puri and H. Lal, Psychopharmacologia (Berlin), 32, 113 (1973).
8. S. K. Puri, T. C. Spardling, and C. R. Mantione, Life Sci., 23, 637 (1978).
9. I. S. Sanghvi and S. Gershon, Biochem. Pharmacol., 26, 1183 (1977).

EFFECT OF GABA ISONICOTINOYLAMIDE ON THE CEREBRAL CIRCULATION

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KEY WORDS: GABA isonicotinoylamide; cerebral circulation; nervous regulation of the cerebral circulation.

Gamma-aminobutyric acid (GABA) has a marked effect on the cerebral circulation. It has been found that GABA can increase the blood supply to the brain by lowering the tone of the cerebral vessels [6]. Together with GABA, the walls of the blood vessels have been shown to contain enzymes concerned in its biosynthesis (glutamic acid decarboxylase) and activation (GABA transaminase) [7-9], and receptors sensitive to GABA have been discovered [10-12]. It has also been shown that central GABAergic mechanisms play a role in the regulation of the cerebral circulation [3].

It was accordingly decided to study the cerebrovascular properties of new GABA derivatives. For this purpose, GABA isonicotinoylamide was synthesized [2], and its effect on the cerebral circulation studied.

EXPERIMENTAL METHOD

Experiments were carried out on 27 cats weighing 3-4 kg under general anesthesia (urethane and chloralose), with artificial ventilation of the lungs, and on five waking cats. The cerebral blood flow in the carotid system was determined with the aid of ^{133}Xe on a VAV-100 apparatus and an electromagnetic flowmeter (Nihon Kohden, Japan). The EEG was recorded from the parietal region, the ECG in lead II, and the blood pressure in the femoral artery. Tonic activity and reflex responses in sympathetic nerves of the renal plexus and stellate ganglion were recorded [1]. The vascular component of the action of the compound on the cerebral hemodynamics was differentiated by a technique of separate bilateral perfusion of the carotid and vertebral arteries [4]. The partial pressure of carbon dioxide was determined in samples of arterial blood by the ABC-1 apparatus and it was maintained within the control limits (35-40 mm Hg). The animals were killed with a mixture of urethane and chloralose.

EXPERIMENTAL RESULTS

In the experiments to record the cerebral blood flow by means of an electromagnetic flowmeter and ^{133}Xe it was found that GABA isonicotinoylamide (GABA-INA) in a dose of 10 mg/kg, injected intravenously, increased the cerebral circulation by 34 $\pm$ 4.5%. The effect developed from the first few minutes after injection of the compound and the initial level of the blood flow was restored after 40-60 min. The blood pressure fell by 31 $\pm$ 3.3%.

The study of the effect of GABA-INA (10 mg/kg) on tone of the cerebral vessels by separate bilateral perfusion of the carotid and vertebrobasilar arteries showed that the compound can lower vascular tone equally in the two arterial systems of the brain. In the carotid system the fall in tone amounted to 20 $\pm$ 2.4%, and in the vertebral artery system to 21 $\pm$ 3.5%.

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