ROLE OF OPIOIDERGIC AND ADRENERGIC MECHANISMS IN ANALGESIC ACTION OF GABA-POSITIVE DRUGS

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Two views are currently held on the character of interaction between the GABA system and opioidergic processes in the formation of analgesia and tolerance to the analgesic action of GABA-positive drugs. According to some authorities, the analgesic action of GABA-ergic drugs is effected independently of the opioidergic system, for the analgesic effect of GABA-agonists and of GABA-transminase inhibitors is unchanged in animals tolerant to morphine, whereas subchronic administration of baclofen causes no changes in the analgesia and analgesia arising [8, 11]. Other investigators consider that opiate analgesia and analgesia arising during activation of GABA-ergic transmission are realized through a common adrenoreceptor stage, as is confirmed by crossed tolerance to the analgesic action of the GABA-agonist THIP and of morphine, and the increase in density of α_2-adrenoreceptors in the brain of animals tolerant to morphine and THIP [3, 5]. However, the contradictions which exist, in our view, are due to the use of different models of nociceptive stimulation and also to the use of GABA-agonist with different affinity for $GABA_A$- and $GABA_B$-receptors.

In the investigation described below changes in the analgesic effect of morphine and of the adrenomimetic clofelin were studied after subchronic administration of depakine and baclogen, which act selectively on $GABA_A$- and $GABA_B$-receptors respectively [2, 10, 13], in tail-flick and vocalization tests, differing in the level of integration of the nociceptive response in the brain [4, 6, 7].

EXPERIMENTAL METHOD

Experiments were carried out on 140 male albino rats weighing 160-210 g. The analgesic action of the preparations was evaluated in tail-flick and vocalization tests by the standard method [1, 9]. GABA-positive drugs baclofen (from Polfa, Polane) and depakine (Labaz, France) were injected intraperitoneally twice a day (at 10 a.m. and 6 p.m.) for 7 days, baclofen in doses of 10 and 10 mg/kg, depakine in doses of 400 and 200 mg/kg. Sterile water for injection was injected into the control groups at the same times. Morphine (2.5 mg/kg) or clofelin (Boehringer Ingelheim, West Germany) was injected 16, 72, and 120 h after discontinuation of the GABA-positive drugs. The analgesic effect of morphine, chofelin, and depa-

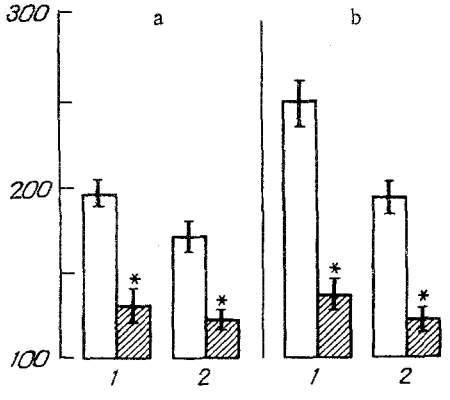

Fig. 1. Changes in analgesic effect of baclofen (1) and depakine (2) in vocalization (a) and tail-flick tests (b) during subchronic administration. Ordinate, changes in parameters of nociceptive sensation (in % of control level, taken as 100%). Unshaded columns — effect of drugs on 1st day of experiment, shaded — analgesic action of drugs on 7th day of experiment. *p < 0.05.

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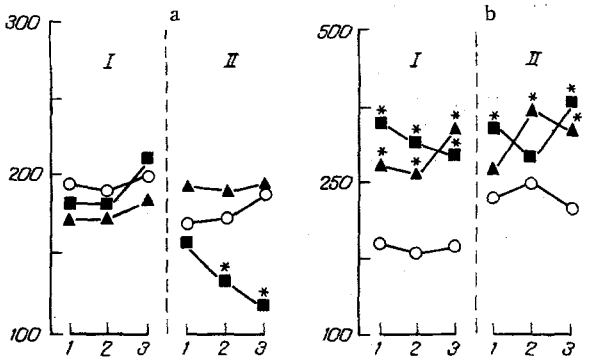

Fig. 2. Analgesic effect of clofelin (I) and morphine (II) in vocalization (a) and tail-flick (b) tests at various times after withdrawal of baclofen and depakine. Empty circles — analgesic effect of preparations in control animals; triangles and squares — analgesic effect of preparations in rats tolerant to baclofen and depakine, respectively, 16 h (1), 72 h (2), and 120 h (3) after cessation of administration of baclofen and depakine. Remainder of legend as to Fig. 1.

kine was evaluated 30 min, and that of baclofen 60 min after injection. The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

Subchronic administration of baclofen and depakine was accompanied by the development of tolerance to their analgesic action, as shown by a significant decrease by 40-55% in the results of the tail-flick and vocalization tests (Fig. 1). The analgesic action of morphine in animals tolerant to baclofen in the vocalization test did not change significantly, but it was significantly reduced in rats tolerant to depakine, especially 72 and 120 h after discontinuation of injection of depakine (Fig. 2a). Distinct strengthening of the analgesic effect of morphine was observed in the tail-flick test 16 h after discontinuation of baclofen and depakine, and it lasted for 120 h, i.e., for 5 days (Fig. 2b).

Clofelin in a dose of 0.05 mg/kg caused no analgesic effect either in the control group or after subchronic administration of GABA-positive substances. In a dose of 0.5 mg/kg clofelin had a distinct analgesic action in the control animals, which was unchanged in the vocalization test on rats tolerant to baclofen and depakine (Fig. 2a). Meanwhile, in the tail-flick test, clofelin-induced analgesia was potentiated after withdrawal of baclofen and depakine (Fig. 2b).

The results of these experiments are in agreement with data in the literature according to which the analgesic effect of morphine is not reduced after subchronic administration of baclofen, a $GABA_B$-receptor agonist, whereas after withdrawal of the $GABA_A$-agonists, the effectiveness of morphine analgesia is reduced [5, 8]. Meanwhile, in contrast to existing views, the results suggest that the role of opiate and adrenergic systems in the analgesic effect of $GABA_A$- and $GABA_B$-agonists differs at the suprasegmental and segmental levels. At the suprasegmental level (vocalization test) the analgesia arising during activation of $GABA_B$- and opiate receptors evidently has relatively independent mechanisms of realization. Meanwhile analgesia and tolerance to the analgesic effect mediated through $GABA_A$-receptors take place with the involvement of the opioidergic system. Yet the direct participation of an α-adrenoreactive component in this process is, in our opinion, doubtful for withdrawal of baclofen and depakine did not lead to any change in the analgesic effect of clofelin in the vocalization test.

At the segmental level (the tail-flick test) opioidergic and adrenergic mechanisms probably participate equally in the development of tolerance to the analgesic action of GABA-positive preparations, as is shown by potentiation of morphine and clofelin analgesia in the tail-flick test after subchronic administration of baclofen and depakine. Moreover, it can be postulated that the α_1-adrenergic component plays the more important role in processes of tolerance to the analgesic effect of GABA-ergic drugs, for potentiation of clofelin analgesia was observed in the present experiments only when the drug was used in a dose of 0.5 mg/kg, but not in a dose of 0.05 mg/kg, and these doses differ in the degree of their selective action on different typtes of α-adrenoreceptors [12].

LITERATURE CITED

1. B. V. Andreev, Yu. N. Vasil'ev, V. P. Kosinskii, and I. V. Marusov, Neuropharmacologic Aspects of Emotional Stress and Drug Dependence [in Russian], Leningrad (1978), pp. 38-48.

2. Yu. D. Ignatov and B. V. Andreev, Farmakol. Toksikol., No. 1, 5 (1987).
3. T. Andree, D. A. Kendall, and S. J. Enna, Life Sci., 32, 2265 (1983).
4. M. N. Carroll and R. K. S. Lim, Arch. Int. Pharmacodyn., 125, 383 (1960).
5. L. G. Costa and S. D. Murphy, J. Pharmacol. Exp. Ther., 229, 363 (1984).
6. F. Hoffmeister and G. Kroneberg, Methods in Drug Evaluation, Amsterdam (1966), pp. 270-277.
7. T. S. Jensen, H. D. Schro, and D. F. Smith, Neuropharmacology, 23, 149 (1984).
8. R. A. Levy and H. K. Proudfit, J. Pharmacol. Exp. Ther., 202, 437 (1977).
9. S. O. Orgen and A. C. Holm, J. Neurol. Transmiss., 47, 253 (1980).
10. K. J. Rasmussen, H. H. Schneider, and E. N. Petersen, Life Sci., 29, 2163 (1981).
11. S. P. Sivam and I. K. Ho, Neuropharmacology, 22, 767 (1983).
12. U. Strömhom, Naunyn-Schmiederbergs Arch. Pharmacol., 292, 167 (1976).
13. M. K. Ticku and W. C. Davis, Brain Res., 223, 218 (1981).

EFFECT OF PRENATAL ALCOHOL EXPOSURE ON ^{3}H-DIAZEPAM BINDING TO CEREBRAL CORTICAL SYNAPTIC MEMBRANES AT VARIOUS STAGES OF POSTNATAL DEVELOPMENT

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According to clinical observations, alcoholism in the parents leads to the appearance of cerebral developmental disturbances in children, including oligophrenia and delayed mental development [16]. Experiments on animals have shown that intrauterine alcoholization induces a combination of disturbances in postnatal development. The animals concerned are retarded in growth and weight [12], development of various parts of their brain is delayed [11], and metabolic changes arise [2], and all these disturbances are accompanied by impairment of formation and preservation of conditioned reflexes [4].

One possible cause of the effects of ethanol may be its interaction with the benzodiazepine system of the brain. In the first place ethanol, like benzodiazepines, has an anxiolytic, sedative, and hypnotic action [8]; the development of behavioral cross-tolerance between ethanol and benzodiazepines has been noted in animals [5]. Second, it has been shown that changes at the benzodiazepine receptor level in the brain of pregnant rats lead to specific changes in the analogous receptor system and behavior of the offspring [7, 15].

It was accordingly decided to study the effect of prenatal exposure of rats to ethanol on ^{3}H-diazepam binding with synaptic membranes of the brain in the offspring.

EXPERIMENTAL METHOD

Pregnant albino rats from the 5th to the 20th days of pregnancy were given 2.5-3 ml of 40% ethanol daily by gastric tube. Instead of alcohol, control animals received the equivalent volume of water. When the offspring of both groups (males) reached the age of 14 days (or 2 months) they were decapitated between 10 a.m. and 12 noon, the cerebral cortex was removed and homogenized in a Potter's homogenizer with Teflon pestle (25-30 transmissions) in 20 volumes of isolation medium, consisting of 0.32 M sucrose, 0.05 M Tris-HCl (pH 7.4), and 1 mM EDTA. The homogenate was centrifuged for 10 min at 1000g, the residue was discarded, and the supernatant was centrifuged for 20 min at 20,000g. The residue was suspended in 20 ml of 0.05 M Tris-HCl (pH 7.4) and frozen overnight at −8°C. Next day the material was sedimented by centrifugation at 20,000g for 20 min and the residue was again washed with 0.05 M Tris-HCl (pH 7.4) under the same conditions. The coarse fraction of synaptic membranes thus obtained was resuspended in 18 ml of 0.05 M Tris-HCl (pH 7.4).

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