COMPARISON OF THE EFFECT OF NOOTROPIC DRUGS ON THE EMETIC ACTION OF MORPHINE

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Besides the characteristic properties of nootropic drugs, namely improving memory and learning, these compounds also can have a protective action against various forms of poisoning of the nervous system due to alcohol, morphine, barbiturates, etc. [2, 4, 6]. Several analogs of piracetam have now been synthesized, which in their effect on animal behavior and, in particular, their ability to protect animals against amnesia induced by electric shock, are superior to the prototype [7].

The aim of this investigation was to compare the antiamnesic effect of piracetam, oxciracetam [7], and N-acetylglycinamide, with the effect of these compounds on the emetic action of morphine.

EXPERIMENTAL METHOD

The piracetam used in the experiments was manufactured at the Latvbiofarm Combine, oxiracetam and N-acetylglycinamide were synthesized at the Research Institute of Biomedical Technology, Ministry of Health of the USSR. All preparations were of 98% purity, as shown by IR- and NMR-spectroscopy. The nootropic activity of the preparations was studied on male and female Wistar rats weighing 150-200 g by the passive avoidance conditioning (PCA) test [9]. Between 80 and 100% of the rats in these experiments were trained and electric shock evoked retrograde amnesia in 80-90% of the animals. The substances were injected intraperitoneally 40 min before the animals were placed in the experimental chamber for training. Groups of control animals received the equivalent volume of isotonic sodium chloride solution, which was used as the solvent for the preparations. Between 10 and 30 rats were used in each experiment. The significance of differences was estimated by Student's test and by Fisher's exact method. The effect of the nootropic agents on morphine-induced vomiting was studied in unanesthetized male cats weighing 2.2-4.5 kg, which were unrestrained. Cannulas were inserted into the 4th ventricle of the brain 3-5 days before investigation of the animals began, under general anesthesia (pentobarbital sodium, 30-40 mg/kg, intraperitoneally), taking coordinates from the stereotaxic atlas [8]. The position of the cannula in the 4th ventricle was verified with the aid of Evans' blue at autopsy. In the course of the experiment the ECG and respiration were recorded on an RM-150 polygraph (Nihon Kohden, Japan), after which the heart rate and respiration rate per minute were calculated from these parameters. Morphine, in doses of 10-100 μg, and the test drugs were dissolved in sterile isotonic sodium chloride solutions and injected into the 4th ventricle by means of a microsyringe (Hamilton, USA) in a volume of 50-100 μl.

EXPERIMENTAL RESULTS

The study of the antiamnesic action of piracetam, oxiracetam, and N-acetylglycinamide within the dose range from 0.1 to 100 mg/kg (Table 1) showed that in this particular model the protective properties of piracetam and oxiracetam are quite similar. In both cases dependence of the effect on the dose of the drugs used has extrema.

The effective action of N-acetylglycinamide (NAGA), a compound not hitherto classed in this group, will be noted.

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TABLE 1. Antiamnesic Effect (in %) of Nootropic Drugs during Electroconvulsive Shock in Rats by the PCA Test

Preparation	Dose of drug, mg/kg					
	100	50	25	10	1	0.1
Piracetam	75**	10	50*	80*	20	30
Oxiracetam	85**	30	44*	74*	37*	20
NAGA	60**	70*	40*	50*	80*	0

Legend. *$p < 0.05$, **$p < 0.025$.

To study the effect of the test drugs on morphine-induced vomiting, morphine was injected into the 4th ventricle of the cats in a dose inducing a single or multiple episodes of vomiting, which were not observed after control injections of isotonic sodium chloride solution. Changes in heart rate were observed in the animals but no change in respiration rate. Depending on the animals' sensitivity to morphine, its dose was varied from 10 to 100 μg. Piracetam, injected 5 min before morphine in the ratio of 1:1 relative to it, did not alter the latent period of the vomiting response in five cats. Increasing the piracetam:morphine dose ratio tenfold completely blocked the emetic action of the morphine (five cats). The heart and respiration rates were unchanged after injection of a combination of piracetam and morphine. Unlike piracetam, oxiracetam exhibited a complete protective action in doses starting 100 times smaller than the dose of morphine, which likewise had no effect on the heart and respiration rates (12 cats). Thus, on the model used, activity of oxiracetam was 1000 times greater than that of piracetam – a difference not previously observed in any physiological or biochemical test. NAGA in the ratio of 10:1 to morphine gave no significant antiemetic effect (six cats).

The results of this investigation show that cyclic nootropic compounds are antagonists of morphine in tests of its emetic action. Introduction of a hydroxy group in position 4 of the piracetam molecule leads to a thousandfold increase in the antiemetic activity of the compound, accompanied by a negligible increase in its nootropic properties. Meanwhile NAGA, which has a marked nootropic action, does not exhibit antiemetic activity. This fact is evidence that, just as in the case with the antihypoxic properties of nootropic drugs [1], their antiemetic activity does not correlate with nootropic activity. The effectiveness of oxiracetam evidently cannot be explained by its direct antagonism to the opiate, for specific binding of nootropic drugs with brain membranes has not yet been identified [5].

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