VESTIBULOPROTECTIVE PROPERTIES OF SOME REGULATORY PEPTIDES

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It has previously been suggested that endogenous opioid peptides participate directly in the genesis of vestibulo-autonomic disorder in motion sickness (MS) [6, 7, 9]. The present writers showed subsequently that certain regulatory peptides (RP), such as substance P, γ- and des-Tyr-γ-endorphins etc., can prevent reflex vomiting arising in cats due to central injection of morphine or β-endorphin [8].

It can accordingly be postulated that these RP may exhibit vestibuloprotective properties in animals with an experimental model of MS. The aim of this investigation was to test this hypothesis experimentally.

EXPERIMENTAL METHOD

Twelve male cats were used. During the 3-5 days before the beginning of the experiment, the animals were anesthetized (pentobarbital sodium, 30-50 mg/kg intraperitoneally) and cannulas were implanted into the fourth ventricle in accordance with coordinates taken from the atlas [13]: P = 11, H = −4.5, L = 0. RP in doses of 10-100 μg were dissolved in sterile isotonic NaCl solution and 50-100 μl was injected by means of a microsyringe (Hamilton, Great Britain) 1-3 min before the beginning of the experiment. The model of MS was created by the method in [3] by exposure to vertical and horizontal accelerations for 1 h. The severity of MS was assessed in accordance with the scale in [14] in points.

The following RP were used: α-, γ-, and des-Tyr^1-γ-endorphins, hydra undecapeptide (N,N-diallyl-Tyr-Gly-Gly-ψ-CH_2-Phe-Leu-OH) (All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR, generously provided by Professor M. I. Titov), hog β-lipotrophin and $ACTH_{1-39}$ (Institute of Experimental Endocrinology and Hormone Chemistry, Academy of Medical Sciences of the USSR, generously provided by Academician of the Academy of Medical Sciences of the USSR Yu. A. Pankov), and substance P (generously provided by Professor K. Hecht, East Germany). To block opioid receptors the universal opioid antagonist naloxone (Endo Laboratories) and the selective δ-antagonist ICI 154, 129 (ICI Pharmaceuticals, Great Britan) were used. As the standard preparation, widely used for the prevention of MS in man [2], scopolamine was used.

EXPERIMENTAL RESULTS

The following RP had a statistically significant vestibuloprotective action, comparable with the effect of the standard preparation, scopolamine, when administered systemically (the absence of a positive effect of scopolamine when injected intraventricularly cannot yet be explained): γ- and des-Tyr^1-γ-endorphins, substance P, hydra undecapeptide, and naloxone (Table 1). Other RP (β-lipotrophin, ACTH, α-endorphin) did not prevent the development of vestibulo-autonomic disorders in cats with experimental MS (Table 1).

The effectiveness of naloxone when injected into the cerebral ventricles against MS is evidence that central opioid mechanisms play an important role in the pathogenesis of motion sickness. Diminution of the symptoms of MS under the influence of the selective δ-antagonist ICI 154,129, moreover, suggests that different types of opioid receptors are involved in this process. In this connection the absence of a positive effect of β-lipotrophin and ACTH in MS

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TABLE 1. Prophylactic Action of Regulatory Peptides and Opioid Receptor Blockers Compared with Scopolamine in Cats with Experimental Model of MS (M ± m)

Preparation	Dose	Severity of symptoms of MS, point
Placebo – Isotonic NaCl solution, μl	50	12,1±0,5 (6)
Scopolamine, μg	20—30	4,3±1,9** (5)
	0,1—1	11,7±2,3 (5)
Naloxone, μg	5—10	6,0±2,4** (5)
ICI 154, 129, μg	20—100	8,5±2,5 (4)
β-lipotropin, μg	10—100	10,5±1,4 (4)
ACTH, μg	10—100	15,0±2,1 (4)
γ-endorphin, μg	10—100	5,4±2,3** (5)
des-Tyr^1-γ-endorphin, μg	10—100	6,6±1,6* (5)
α-endorphin, μg	10—100	9,0±2,0 (4)
Substance P, μg	10—100	4,2±1,2* (5)
Substance, P, mg	0,75—1,2	2,1±0,6* (4)
Hydra undecapeptide, μg	10—50	2,5±0,5*

Legend. Preparations were injected intraventricularly except scopolamine in a dose of 20-30 μg, which was injected subcutaneously, and substance P in a dose of 0.75-1.2 mg, which was injected intraperitoneally. Number of experiments shown in parentheses. *$p<0.001$, **$p<0.05$ compared with placebo.

can probably be explained on the grounds that these RP have no antiemetic action relative to morphine and β-endorphin [8]. Conversely, γ- and des-Tyr^1-γ-endorphins, substance P [8], and hydra undecapeptide prevent vomiting induced by opioids, and this explains to a certain extent their positive prophylactic effect in motion sickness. Among the mechanisms of the protective action of peptides in MS, attention must also be paid to the antistressor properties of RP, for substance P, for example, exhibits them when admistered both centrally and peripherally [1, 4, 5]. Evidence in support of this view is given by the fact that substance P, in our experiments, when administered by both routes (directly into the cerebral ventricles and intraperitoneally) had a vestibuloprotective action (Table 1).

The efficacy of endorphins of the γ-type and the inefficacy of α-endorphin in MS can be explained both by the presence of neuroleptic properties in the former [10, 11], and by their antagonism with dopaminomimetics (by contrast with endorphins of the α-type), as shown by several tests [12, 15]. It has to be pointed out under these circumstances that the neuroleptic haloperidol, which can block dopamine receptors, has a prophylactic protective action against motion sickness in man [2].

Our data are thus evidence that several RP, namely endorphins of the γ-type, substance P, and hydra undecapeptide, possess vestibuloprotective properties in cats with a model of motion sickness. It can accordingly be postulated that, besides endogenous opioid peptides, other central peptidergic mechanisms also are involved in the pathogenesis of vestibulo-autonomic disorders associated with motion sickness.

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NEUROPHYSIOLOGICAL ANALYSIS OF NOOTROPIC CORRECTION OF ABNORMAL EEG FINDINGS DURING CHRONIC ADMINISTRATION OF ETHANOL TO ANIMALS

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Nootropic drugs are used in the modern treatment of alcoholism for the correction of functional and intellectual disturbances [5, 6, 8, 9]. Meanwhile, the manifestations and mechanisms of the protective action of nootropic drugs at the neurophysiological level have not yet been explained.

The aim of the present investigation was accordingly to study abnormalities of the EEG of the sensomotor cortex (SMC) and dorsal hippocampus (DH) of rats receiving ethanol by long-term administration, and the effect of drugs with nootropic activity on these changes.

EXPERIMENTAL METHOD

Experiments were carried out on 28 noninbred male rats weighing 300-350 g, divided into four groups: group 1) control (six intact rats); 2) six rats receiving daily intraperitoneal injections of 25% ethanol solution in a dose of 1.2 g/kg; 3) eight rats receiving daily injections of ethanol in the same dose + pyracetam (from Polfa, Poland) in a dose of 300 mg/kg, intraperitoneally, 50 min before injection of ethanol; 4) eight rats receiving an intraperitoneal injection of 2-ethyl-6-methyl-3-hydroxypyridine (3-HP), a substance with nootropic activity [1, 3, 10], in a dose of 100 mg/kg 30 min before the injection of ethanol. All substances were injected for 40 days. The animals were kept under animal house conditions on a standard diet. The experiments were carried out between 9 a.m. and 1 p.m.

Nichrome electrodes were implanted under sterotaxic conditions, under pentobarbital anesthesia (50 mg/kg, intramuscularly), into SMC and DH [14] 5-6 days before the electrophysio-

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