ROLE OF ENDOGENOUS OPIOID PEPTIDES IN THE PATHOGENESIS OF MOTION SICKNESS

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The pathogenesis of motion sickness (MS) is complex and has not been fully studied. In particular, the role of the various neurochemical systems of the body in the genesis of MS is not quite clear. It has recently been shown that the endogenous opioid system participates in the genesis of several pathological processes [2, 6, 9, 13, 14]. This was the motivation for the study of the possible role of endogenous opioids in the pathogenesis of MS.

EXPERIMENTAL METHOD

The investigation was conducted on 19 clinically healthy male volunteers with initial low vestibulo-autonomic resistance (VAR), aged from 24 to 47 years, and weighing from 59 to 94 kg. MS was modeled by cumulative exposure to Coriolis and precessional accelerations – Bryanov's PKUK test [1], while the subjects were rotated in a VU-4m chair at a speed of 30 rpm. The blood pressure (BP; by Korotkov's method), pulse rate (PR), respiration rate (RR), intensity of vestibulo-autonomic reactions (the following basic symptoms of MS were taken into account: dizziness, illusory sensations of movement, perspiration, pallor, nausea, vomiting, and so on), and the duration of tolerance of the PKUK test. The investigation comprised not more than 10 rotation sessions (the first rotation session lasted 1 min), but if vestibulo-autonomic reactions of the II-III degree (according to Khilov's classification [5]) developed during rotation, the test was immediately stopped. Investigations of ability to tolerate the PKUK test were conducted at intervals of not less than 10-14 days.

The specific antagonist of opiates and opioids, naloxone, was used as pharmacologic indicator for indirect determination of the role of endogenous morphine-like substances in the genesis of MS. Naloxone hydrochloride ("Narcan") was injected intravenously in a dose of 0.4 mg before rotation and during rotation. The effectiveness of naloxone was estimated by comparison with the action of isotonic NaCl solution (placebo). Scopolamine, which is used for the prevention of MS, also was used in the investigations as a standard preparation. Scopolamine in a dose of 0.6 mg, and also the placebo, were taken internally 1.5 h before rotation. All drugs were used in accordance with the double blind control method.

To obtain direct proof of the participation of endogenous opioid peptides in the genesis of MS, the subjects' blood plasma was tested for β-endorphin before and after the PKUK test. Blood from the cubital vein of six subjects was collected in plastic test tubes containing EDTA (7.5 mg per 5 ml of blood). After centrifugation, the plasma was frozen and kept at −70°C until required for use. The plasma β-endorphin level was determined by radioimmunoassay, using a kit (intended for assay of β-endorphin in blood plasma) from Immuno Nuclear Corporation (USA).

EXPERIMENTAL RESULTS

All 19 subjects were characterized by a low vestibulo-autonomic index (VAI) with a duration of tolerance of the PKUK test in the control from 1 to 6 min (average 3.9±0.4 min). From 6 to 10 min (on average (8±1 min)

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TABLE 1. Effect of Naloxone, Taken 6-10 min before Rotation and during Rotation, on Subjects' Ability to Tolerate PKUK test (M±m)

Series of investigation	Ability to tolerate PKUK test, min
Control (n = 11)	3,8±0,5
Placebo (n = 11)	4,1±0,7
Naloxone 6-10 min before rotation (*n*=11)	5,8±0,8
Control (n = 6)	4,6±0,5
Placebo (n = 6)	5,1±0,7
Naloxone during rotation (n = 6)	7,8±1,0

Legend. n) Number of subjects tested.

before exposure to acceleration, 11 volunteers were given naloxone. Naloxone did not change (in three subjects) or raised (in eight) the VAI. The duration of tolerance of the PKUK test was significantly increased ($P < 0.01$ by Wilcoxon's paired criterion) by naloxone by 1.7±0.6 min, or by 55±21%, compared with the value obtained when the placebo was used (Table 1). Naloxone, which blocks opiate receptors, thus has a definite protective effect against MS.

The next series of investigations was undertaken to show whether naloxone possesses therapeutic properties in MS. Six volunteers were given naloxone during rotation (after exposure to acceleration for 1-3 min). The therapeutic effect of naloxone was found to be comparable with its prophylactic effect. For instance, in one subject naloxone did not change VAI, whereas in five subjects it increased VAI. The duration of tolerance of the PKUK test after administration of naloxone was significantly ($P < 0.05$, Wilcoxon's paired criterion), increased by 2.7±1.0 min, or by 60±24% relative to that under the influence of the placebo (Table 1). No statistically significant differences in the effect of naloxone and the placebo on BP, PR, and RR were obtained during rotation (Tables 2 and 3), although during the action of naloxone a tendency was observed toward stabilization of BP (Table 3).

The fact will be noted that, despite the use of naloxone, in some cases (when the drug was given both before and during rotation) the subjects vomited. This may be evidence either that the dose of the drug was too small to block the opiate receptors, and in particular, those located in the chemoreceptor trigger zone of the vomiting center [7, 8], or that naloxone has low affinity for these receptors. We know, for example, that naloxone is predominantly a blocker of μ-opiate receptors [11, 12], and besides them, other types of opiate receptors (α-, δ-, and $\varkappa$-receptors), for which the affinity of the antagonist is 10-30 times weaker [11, 12], may also be present in this zone. Most probably, however, many neurochemical systems participate in the genesis of vomiting during MS [3] and the use of one drug with a rather selective type of action may probably therefore not prevent it.

The standard drug scopolamine, under the conditions of these investigations, was less effective than naloxone. Of 16 subjects tested, in five it did not change VAI, and in 11 it raised it. The duration of tolerance of the PKUK test was significantly ($P < 0.01$, Wilcoxon's paired criterion) increased by 1.3±0.3 min (from 4.0±0.5 to 5.3±0.8 min) under the influence of scopolamine, or by 29±7% compared with the effect of the placebo.

Considering the positive prophylactic and therapeutic effect of naloxone against MS it can be postulated that endogenous opioid peptides participate in the genesis of the vestibulo-autonomic disorders in MS. This hypothesis was confirmed by the results of biochemical investigation of human blood plasma in order to determine the concentration of the opioid peptide β-endorphin.

The subjects' initial plasma β-endorphin level was 8.3±2.9 femtomoles/ml. Immediately after the PKUK test a significant ($P < 0.05$, Student's test) increase in the concentration of this peptide to 52.4±16.9 femtomoles/ml, or by 891±333%, was observed. The β-endorphin level 1 h after rotation was 11.3±3.0 femtomoles/ml, falling after 3 h to 3.3±0.7, and after 5 h to 3.0±1.4 femtomoles/ml.

TABLE 2. Effect of Naloxone, Given 6–10 min before Rotation, on Dynamics of BP, PR, and RR of Volunteers (M ± m)

Parameter	Preparation	Before rotation		Duration of rotation, min										5 min after rotation
		before administration of drug	5–10 min after administration	1	2	3	4	5	6	7	8	9	10	
BP, mm Hg	Placebo	119±5 / 78±3	116±4 / 77±3	121±5 / 84±4	119±4 / 84±2	121±3 / 86±3	123±5 / 91±2	121±6 / 83±3	122±2 / 78±2	130±10 / 90	140 / 90	—	—	114±3 / 77±3
	Naloxone	115±2 / 73±2	112±3 / 72±2	114±2 / 76±2	115±3 / 77±2	118±3 / 78±2	118±4 / 79±3	118±4 / 81±2	123±3 / 83±1	129±3 / 83±1	130±5 / 85±5	130±5 / 85±5	130±5 / 85±5	111±3 / 71±2
PR, beats/min	Placebo	68±2	70±4	71±4 (n=11)	76±3 (n=10)	80±2 (n=9)	79±3 (n=5)	78±3 (n=5)	77±11 (n=3)	94±26 (n=2)	72 (n=1)	—	—	67±3
	Naloxone	71±2	72±2	79±4 (n=11)	85±6 (n=10)	86±5 (n=10)	89±4 (n=9)	83±4 (n=8)	83±6 (n=6)	84±7 (n=4)	78±2 (n=2)	78±2 (n=2)	74±2 (n=2)	70±2
RR, cycles/min	Placebo	17±1	18±1	19±2	20±1	23±2	22±2	23±1	21±2	22±2	20	—	—	17±1
	Naloxone	16±1	16±1	18±1	19±1	19±2	19±2	19±2	20±2	19±2	15±3	14±2	14±2	17±1

Legend. Eleven volunteers took part in each series of the investigation. Here and in Table 3: n) number of subjects who continued rotation.

TABLE 3. Effect of Naloxone Taken during Rotation on Dynamics of BP, PR, and RR of Volunteers (M±m)

Parameter	Preparation	Before rotation	Duration of rotation, min										5 min after rotation
			1	2	3	4	5	6	7	8	9	10	
BP, mm Hg	Placebo	123±4 / 80±2	125±6 / 78±4	126±6 / 79±4	114±2 / 78±4	121±7 / 82±3	125±8 / 85±3	108±8 / 75±5	100 / 70	105 / 80	—	—	113±5 / 75±4
	Naloxone	120±3 / 80±3	124±6 / 83±4	123±6 / 81±3	118±5 / 78±3	122±4 / 79±3	121±4 / 81±3	122±4 / 79±5	114±2 / 76±5	113±4 / 75±3	117±4 / 75±5	113±4 / 77±7	117±4 / 78±2
PR, beats/min	Placebo	72±4	83±5 (n=6)	88±5 (n=6)	89±7 (n=6)	82±9 (n=6)	89±12 (n=3)	94±26 (n=2)	64 (n=1)	64 (n=1)	—	—	71±6
	Naloxone	69±1	75±4 (n=6)	77±4 (n=6)	78±4 (n=6)	76±3 (n=6)	74±2 (n=5)	78±5 (n=5)	72±3 (n=4)	69±1 (n=3)	71±1 (n=3)	72±2 (n=3)	69±2
RR, cycles/min	Placebo	15±1	16±1	18±2	18±2	19±2	17±3	14±2	12	12	—	—	16±2
	Naloxone	15±1	17±2	17±1	18±1	19±2	20±3	22±4	18±2	19±1	19±1	—	17±1

Legend. Six volunteers took part in each series of the investigation.

Considering the results of this investigation and also data published previously, indicating that endogenous opioid peptides cause vomiting and changes in various autonomic parameters in animals (BP, PR, RR, etc.) [2, 4, 7, 10], it can be postulated that endogenous opioid peptides (and β-endorphin, in particular) are directly involved in the genesis of the vestibulo-autonomic disorders in motion sickness.

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ACCELERATION OF VERTICAL MIGRATION OF CORNEAL EPITHELIAL CELLS IN ALBINO RATS DURING CHRONIC IMMOBILIZATION STRESS

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In previous investigations the writers showed that repeated exposure to stress (sublethal hyperthermia, hypoxia, and fixation in the supine position, five times) causes activation of cell division and DNA and RNA synthesis in the corneal epithelium of albino rats [1].

In this investigation the effect of chronic immobilization stress on the kinetics of corneal epithelial cells from the basal layer into higher layers was studied.

EXPERIMENTAL METHOD

Experiments were carried out on 49 male albino rats weighing 160-190 g. The animals were exposed for 1 h daily to fixation in the supine position for 5 days. After the final exposure to stress the animals were given an intraperitoneal injection of ^{3}H-thymidine (0.6 μCi/g body weight). Because the cornea has no blood supply, an additional application of 5 μCi of ^{3}H-thymidine was made to its surface.

The animals were killed and the cornea removed for investigation from the animals of group 1 one hour after the end of the final fixation and injection of ^{3}H-thymidine, from the animals of group 2 after 24 h, and of group 3 after 72 h. For each experimental group there was a corresponding control group of intact animals.

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