EFFECT OF DALARGIN AND NALORPHINE ON PITUITARY–ADRENOCORTICAL SYSTEM FUNCTION IN THE VESTIBULOVEGETATIVE SYNDROME

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KEY WORDS: vestibulovegetative syndrome; ACTH; cortisol; β-endorphin; dalargin; malorphine.

The absence of any effective means of prevention and treatment of the vestibulovegetative syndrome (VVS) has led to attempts to use the most recently introduced therapeutic substances for its treatment [4, 6, 13]. The failure of most of these attempts is due to the absence of any all-embracing theory of the pathogenesis of VVS [8]. The "sensory conflict" theory is the one most widely held at present [12, 13]. According to the latest data in the literature [6], naloxone, a blocker of opiate receptors, has a vestibuloprotective action in VVS. The mechanism of its action is linked with blockade of opioid receptors of the chemoreceptor trigger zone of the vomiting center, with the result that nausea and vomiting, the most unpleasant symptoms for the patient and characteristic of VVS, appear much later.

The aim of this investigation was to study the mechanisms of action of dalargin and nalorphine, drugs interacting with opiate receptors, in VVS. Dalargin, a synthetic Leu-enkephalin analog, has a protective action in duodenal ulcers and arterial hypertension [1, 3]. Nalorphine blocks opiate receptors, and also possesses weak agonistic activity [5].

Since we know that persons predisposed to VVS have a lower level of the main stressor hormones in extremal states [14], it was decided to study the effect of the above-named agents on the time course of the ACTH, cortisol, and β-endorphin levels associated with vestibular stress in subjects with an initial low level of vestibulovegetative resistance (VVR).

EXPERIMENTAL METHOD

A model of VVS was created by cumulative exposure to Coriolis and precessional accelerations (Bryanov's CCPA test) in subjects spun on a VU-4m chair [2]. The subjects were nine clinically healthy male volunteers with a low VVR level (the limit of their tolerance of the CCPA test was 1-5 min). Dalargin (1-4 mg), nalorphine (5 mg), or the placebo (isotonic sodium chloride solution, 2 ml) were injected intravenously 5-15 min before spinning. All drugs were used under double blind control conditions. Blood samples were taken 4 times from the cubital vein for hormone radioimmunoassay 1 h before spinning, after injection of the drug at the height of its action immediately before spinning, immediately after spinning, and 1 h after spinning. Blood was taken into plastic tubes containing EDTA (7.5 mg to 5 ml of blood). After centrifugation the plasma was frozen and kept at −70°C until needed. For radioimmunoassay, kits from Immuno Nuclear Corp. (USA) and CIS (France) were used.

EXPERIMENTAL RESULTS

It will be clear from Table 1 that after injection of dalargin the plasma β-endorphin level fell somewhat (from 41.7 ± 5.3 to 33.4 ± 7.2 mg/ml), and this may be attributed to a compensatory increase in peptidase activity. Immediately after the CCPA test a considerable increase in ACTH, cortisol, and β-endorphin levels was observed. The highest β-endorphin activity (up to 259.1 ± 50.2 pg/ml), incidentally, was observed after CCPA and administration of nalorphine. This suggests that opiate receptor blockade makes the subjects less susceptible

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TABLE 1. State of the Pituitary–Adrenocortical System in a Model of VVS after Administration of Drugs Interacting with Opioid Receptors

Parameter		Drug		
		placebo	dalargin	nalorphine
β-Endorphin, pg/ml	I	41,6±10,6	41,7±5,3	37,4±12,2
	II	40,4±7,4	33,4±7,2	41,6±10,3
	III	184,8±42,1*	120,0±24,0*	259,1±50,2**
	IV	43,6±6,9	56,6±12,2	56,0±10,2
ACTH, pg/ml	I	26,5±1,4	35,9±9,5	30,9±12,4
	II	25,3±4,2	40,5±14,7	25,3±2,9
	III	114,8±30,2*	156,3±43,6*	112,0±37,5
	IV	26,4±8,5	33,2±6,5	31,0±6,1
Cortisol, ng/ml	I	216,0±14,0	170,0±22,0	174,0±12,0
	II	190,0±16,0	192,0±24,0	188,0±12,0
	III	264,0±28,0	259,0±28,0*	232,0±26,0*
	IV	266,0±47,0	272,0±21,0*	251,0±36,0
Coefficient of correlation (r)				
ACTH– β -endorphin (after spinning)		−0,21	+0,64	−0,06
ACTH – cortisol (after spinning)		+0,32	+0,69	+0,24
ACTH/ β-endorphin ratio (after CCPA)		0.62	1,30	0,43

Legend. I) Before spinning, II) after injection of drug, at the height of its action, immediately before spinning, III) immediately after spinning, IV) 1 h after spinning. *$p < 0.05$, **$p < 0.01$.

to β-endorphin. The greatest increase in ACTH activity after the CCPA test was observed after administration of dalargin, in agreement with data in the literature [9], according to which ACTH release is controlled through opioid receptors with which dalargin interacts. Calculation of the coefficient of correlation (r) between the ACTH and β-endorphin and ACTH and cortisol levels after the CCPA test showed that an average positive correlation was present only after administration of dalargin. ACTH and β-endorphin are secreted into the blood stream during stress simultaneously and in equimolar proportions [10]. In the present experiments this classical ratio was disturbed after administration of the placebo and nalorphine. Thus in VVS it is logical to speak not only of "sensory" but also of "hormonal conflict," i.e., by some as yet unknown mechanism the release of hormones and neurotransmitters from the pituitary gland into the blood stream in adequate quantities is disturbed. Similar disturbances also are observed in the pituitary–adrenocortical system.

Disturbance of the ACTH/β-endorphin ratio toward an increase is characteristic of chronic stress and leads to increased sensitivity to pain [7]. In the present experiments this ratio was highest after administration of dalargin and lowest after nalorphine (Table 1). In this respect, therefore, nalorphine has advantages over dalargin.

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PHARMACOLOGIC ANALYSIS OF THE ROLE OF INDIVIDUAL ETHANOL-OXIDIZING ENZYME SYSTEMS IN ETHANOL METABOLISM AT DIFFERENT STAGES OF EXPERIMENTAL ALCOHOLISM

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Investigations of the pharmacokinetics of ethanol in the blood of rats at different stages of experimental alcoholism have shed light on the character of the pharmacokinetic parameters reflecting the quantitative aspect of the course of ethanol metabolism [3].

However, the degree of involvement of each of the ethanol-oxidizing enzyme systems has received little study.

In the investigation described below a pharmacologic analysis was made of the role of ethanol-oxidizing enzyme systems in the metabolism of ethanol (by recording its elimination from the blood) at different stages of experimental alcoholism.

EXPERIMENTAL METHOD

There were four series of experiments on 78 noninbred male albino rats. The animals were selected by the stage of experimental alcoholism by the method in [1]; the weight of the rats with stage I of alcoholism was 180-200 g and their mean daily ethanol intake was 17.8 ± 1.3 ml; the corresponding figures for rats in stages II and II were 450-535 g and 26.2 ± 5.3 ml, and 500-600 g and 38.2 ± 3.8 ml.

The first three series of experiments were conducted on rats in the three different stages of experimental alcoholism. The scheme of all the series was the same: the animals were divided into four groups with six rats in each group and the pharmacokinetics of ethanol in the

TABLE 1. Pharmacologic Parameters of Ethanol in Blood of Rats Treated with Pyrazole at Different Stages of Experimental Alcoholism (M ± m)

Period of contact with ethanol	Experimental conditions n = 6	Elimination constant (K_e)	Absorption constant (K_a)	Maximal Time (T_{max}), h	Maximal concentration (C_{max}), μ moles/ml	Partition volume (V_p), ml/kg	Clearance (CIT) ml/kg/h	Area beneath curve, μmoles/ml/h
10 days	Expt.	0,19 ± 0,09***	0,88 ± 0,1***	3,4 ± 0,8***	11,7 ± 0,9***	1327 ± 216***	180 ± 23***	230 ± 89**
	Control	0,36 ± 0,04	3,0 ± 0,2	0,8 ± 0,02	5,4 ± 0,7	3036 ± 360	967 ± 83	22,3 ± 1,8
4 mo.	Expt.	0,2 ± 0,08*	3,2 ± 0,6***	1,13 ± 0,4**	9,93 ± 0,6*	1807 ± 264	233 ± 78***	145 ± 46***
	Control	0,8 ± 0,09	3,0 ± 0,1	0,56 ± 0,05	7,2 ± 0,5	1870 ± 122	1552 ± 309	15,0 ± 2,3
8 mo.	Expt.	0,05 ± 0,01***	2,2 ± 0,4	1,98 ± 0,1***	16,5 ± 0,12**	1156 ± 31*	54,4 ± 17,2***	633 ± 282***
	Control	0,34 ± 0,02	3,3 ± 0,4	0,8 ± 0,04	11,4 ± 1,2	1476 ± 195	430 ± 56	45,5 ± 4,7

Legend. Here and in Table 3: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ compared with control.

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