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ROLE OF PERIPHERAL ADRENERGIC STRUCTURES IN DISORDERS OF MOTOR COMPONENTS OF OPERANT BEHAVIOR IN RATS WITH EMOTIONAL STRESS

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KEY WORDS: adrenoreceptors; motor skills; emotional stress.

Disturbances of the fine motor skills in man during emotional stress are realized to some extent through activation of adrenergic structures of skeletal muscles [4]. It has been shown that substances activating peripheral β-adrenoreceptors (in doses without any central action) or stimulating release of endogenous catecholamines into the blood stream, can disturb reproduction of motor programs formed previously [3].

The aim of this investigation was to continue the study of the role of development of disturbances of precise movements during emotional stress.

EXPERIMENTAL METHOD

Experiments were carried out on male albino rats weighing 220-350 g. The effect of emotional stress and of the test substances on ability to reproduce precise motor skills was studied by a modified Sidman's operant activity method [12]. To avoid electric shocks applied through the electrode floor of the chamber, the animal had to press a pedal with a force of not less than 3 g and not more than 5 g. In that case the painful electrical stimulation (ac pulses, 50 Hz, stabilized amplitude 0.5 mA, duration 1 sec, following frequency once every 5 sec) was interrupted for 20 sec. If the pedal was not released during the 20-sec interval and pressed again with the required force, electrical stimulation was resumed. If the force of pressure on the pedal exceeded 5 g, at the beginning of the period of interruption of electric shocks the animal received extra punishment in the form of a series of dc pulses (1.5 mA, 5 msec, 50 Hz) for a duration of 2 sec. Experiments were carried out on 36 rats trained beforehand in this type of operant activity. Training was given in two stages: First the animals were taught operant activity in accordance with Sidman's usual program. During training the strength of pulses applied to the electrode floor was 1 mA. After the skill of avoiding electric shocks (allowing not more than 5-7% of shocks applied to the electrode floor) had been achieved the animals were taught to work according to a modified program. Experiments began on animals which, in the course of 60 min of activity by the modified program, did not press too strongly on the pedal more than 10 times. As the criterion of accuracy of reproduction of the preformed motor skill, the number of times the animal pressed too strongly during a 60-min experimental session was used.

To evaluate the central effects of the compounds, the method of recording electrical activity in the sensomotor cortex, lateral area of the hypothalamus, and the dorsal hippocampus through chronically implanted electrodes was used. The electrodes were inserted stereotaxically, taking coordinates from the atlas [8]. Experiments began 3-4 days after the operation. The EEG was analyzed by integration (epoch of analysis 10 sec) within frequency bands of 2-4, 4-8, 8-13, 13-20, and 20-30 Hz. The method of constructing histograms of distribution by number of intervals of different duration between pressings on the pedal during

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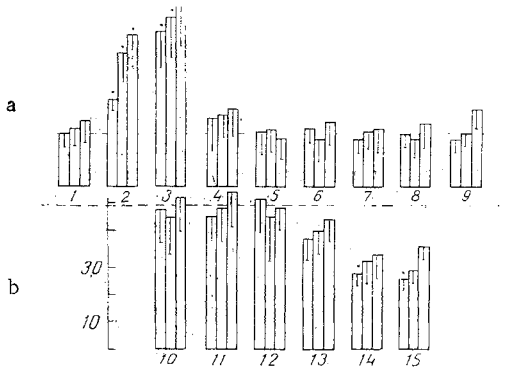

Fig. 1. Effect of adrenergic drugs on motor components of operant activity of rats under ordinary conditions (a) and when complicated by emotiogenic activity (b). Columns denote number (M ± m) of times the animal pressed too strongly on the pedal (three columns indicate one drug, three doses). Broken line — control level for the given conditions. *) Values differing statistically significantly from corresponding control. a: 1-3) Noradrenalin, adrenalin, and isoproterenol in doses of 0.1, 0.5, and 1 mg/kg, respectively; 4) phentolamine (5, 10, and 20 mg/kg); 5-9) atenolol, practolol, talinolol, oxprenolol, and propranolol (1, 5, and 10 mg/kg), respectively; b: 10) phentolamine (5, 10, and 20 mg/kg); 11-15) atenolol, practolol, talinolol, oxprenolol, and propranolol (1, 5, and 10 mg/kg), respectively.

activity, according to the ordinary Sidman program [10], also was used to assess the central action of the compounds tested. Experiments of this series were carried out on a separate group of animals (84 rats). The experimental technique and the method of plotting interval histograms were fully described previously [1, 2]. Experiments on animals of all three groups were repeated several times, but not more often than once every 5-6 days. The stress to which the animals were exposed consisted of immobilization for 1 h [1]. The substances used for analysis were noradrenalin and adrenalin (0.1-1 mg/kg), the β_1-adrenoblockers atenolol, talinolol, and practolol (1-10 mg/kg), the total β-adrenoblockers propanolol and oxprenolol (1-10 mg/kg), and also the α-adrenolytic phentolamine (5-20 mg/kg). Physiological saline was injected in control experiments. All the test substances were injected intraperitoneally 40-60 min before the experiment began.

EXPERIMENTAL RESULTS

Data on the effect of stress and the test substances on the accuracy of reproduction of the motor components of operant activity are given in Fig. 1. The emotiogenic procedure which was used considerably upset the accuracy of reproduction of preformed motor programs. An increase was observed in the number of times the rats pressed the pedal too strongly. Isoproterenol and adrenalin, within the dose range tested, also increased this parameter. However, after injection of noradrenalin this parameter increased only very little during activity under ordinary conditions. The α-adrenolytic phentolamine, even in large doses, did not abolish the adverse effect of emotional stress on reproduction of motor skills. Cardioselective (atenolol, practolol, talinolol) β-adrenoblockers, within the dose range studied, also had only a weak effect on this parameter during ordinary activity and after immobilization. The total β-adrenoblockers oxprenolol and propanolol, within the dose range tested, had a weak effect on the motor components of operant activity under ordinary conditions, but in small doses (1 mg/kg) they considerably reduced the number of times the animal pressed too strongly on the pedal after immobilization. In large doses this effect of oxprenolol and propranolol was somewhat reduced.

It can be tentatively suggested that in threshold doses causing disturbances of reproduction of precise motor skills (0.1 mg/kg) adrenalin and isoproterenol had minimal central action, for when injected in these doses, these drugs had virtually no effect on the power of electrical activity recorded from the test structures (Table 1). A similar conclusion can be drawn regarding the central action of propranolol in a dose of 1 mg/kg. Signs of a change

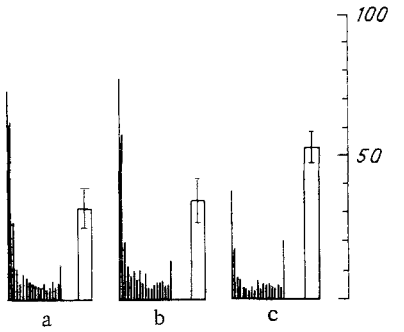

Fig. 2. Effect of propranolol on character of operant activity of rats. On left — interval histograms (number of 1-sec classes 20), on right — number of shocks getting through (M ± m). Common scale for interval histograms and number of shocks which got through. a) Initial activity, b) after injection of propranolol in a dose of 1 mg/kg, c) in a dose of 10 mg/kg.

TABLE 1. Effect of Adrenalin, Isoproterenol, and Propranolol on Rat Brain Electrical Activity (in % of total power of electrical activity for all frequency bands)

Drug	Dose, mg/kg	Sensomotor cortex					Lateral area of hypothalamus					Dorsal hippocampus				
		frequency band, Hz														
		2—4	4—8	8—13	13—20	20—30	2—4	4—8	8—13	13—20	20—30	2—4	4—8	8—13	13—20	20—30
Control	—	30,6	32,5	14,5	12,8	9,6	33,1	26,5	17,4	14,1	8,8	24,4	26,5	18,1	17,3	13,6
Adrenalin	0,1	33,3	29,6	14,1	12,5	10,5	35,3	30,1	12,5	12,7	9,4	23,7	29,8	17,3	15,9	13,2
Isoproterenol	0,1	31,2	29,0	14,6	12,7	12,5	33,4	27,9	15,4	13,8	9,5	24,2	28,3	17,4	16,8	13,3
Propranolol	1,0	31,6	29,9	14,9	13,0	10,6	33,0	28,3	16,5	13,9	8,3	24,9	27,1	17,0	16,9	14,1
"	5,0	32,9	27,2	13,8	13,3	12,7	24,9	29,3	17,2	16,9	11,6	24,5	27,0	17,1	16,7	14,7
"	10,0	23,7	32,1	19,6	14,7	9,8	18,3	29,3	24,3	19,0	9,1	26,9	28,2	16,6	15,0	13,2

in the power of electrical activity in the test structures in these experiments were observed after injection of propranolol in doses of 5 and 10 mg/kg. In a dose of 1 mg/kg propranolol evidently has no central neurotropic activity (Fig. 2), for it did not change the character of operant activity (judging from the interval histogram and the number of electric shocks which got through). In a dose of 10 mg/kg propranolol reduced the number of short intervals between pressing on the pedal (1-2 sec) and increased the number of electric shocks which got through during activity under ordinary conditions (Fig. 2). A similar but stronger effect on the character of the rats' operant activity was observed after injection of other drugs with central depressant action [1]. Data in the literature also indicate that propranolol and oxprenolol, in doses of 1-3 mg/kg, have no central neurotropic action [7, 10].

The facts described above suggest that an important role in the genesis of disturbances of precise motor skills during emotional stress is played by activation of peripheral β-adrenergic structures, most probably on account of an increase in endogenous catecholamines circulating in the blood [11]. It is quite possible that the disturbances of reproduction of the motor components of operant activity observed in these experiments are mediated through changes in the functional state of skeletal muscles which have β_2-adrenergic receptors [5, 6, 9]. In all probability, during emotional stress (such as frequently arises in complex types of operator activity) adaptive changes in the functional state of the skeletal muscles, developing to a certain extent because of increased activity of the sympathicoadrenal system, and aimed at preparing the muscular system for intensive activity under conditions of high speed and effort, prove inadequate to the situation and lead to disturbances of complex goal-directed activity, requiring precise reproduction of muscular efforts. The results of the present investigation can be used in the search for optimal ways of pharmacological correction of disturbances of reproduction of motor skills in man during emotional stress.

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EFFECT OF TSH RELEASING HORMONE AND ITS ANALOGS WITH DIFFERENT HORMONAL ACTIVITY ON SOME PHARMACOLOGICAL EFFECTS OF ETHANOL

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KEY WORDS: TSH releasing hormone and its analogs; ethanol; tolerance.

Thyroid stimulating hormone releasing hormone (TSHRH), the hypothalamic releasing hormone which induces liberation of thyroid stimulating hormone (TSH) and prolactin, has a broad spectrum of biological activity. It not only has purely hormonal properties, but also exhibits antagonism against the hypnotic and hypothermic effects of ethanol and barbiturates, and also against the cataleptic action of β-endorphin [3, 6]; a possible extrahypophyseal mechanism of realization of these effects, moreover, has been suggested [4].

To study relations between the hormonal and nonhormonal components in the spectrum of pharmacological action of TSHRH, a comparative study was made of the "antialcoholic" properties of TSHRH and its analogs with modified hormonal activity.

EXPERIMENTAL METHOD

The following peptides were studied in the experiments: TSHRH, L-pyroglutamyl-L-seryl-L-leucinamide (TSHRH-2), an analog with no effect on TSH secretion, but which reduces prolactin secretion, and the methyl ester of TSHRH (TSHRH-3), with sharply reduced releasing activity with respect to both hypophyseal hormones [2]. All compounds were synthesized in the laboratory of Protein Hormone Chemistry, Institute of Experimental Endocrinology and Hormone Chemistry, Academy of Medical Sciences of the USSR. Experiments were carried out on noninbred male albino mice weighing 20-25 g and kept on a pellet diet.

The narcotic action of ethanol was determined by measuring the length of time the mice spent in the side position after intraperitoneal injection in a dose of 4.75 g/kg in the form of a 25% solution. The rectal temperature (t°C) was measured by means of a thermometer (from Nihon Kohden, Japan) 10 min before and 30 min after intraperitoneal injection of 3.5 g/kg of

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