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POSITIVE MODULATION OF DIAZEPAM ACTIVITY IN ALCOHOLIZED RATS BY CORTEXOLONE

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KEY WORDS: diazepam; cortexolone; ethanol

It was shown previously that glucocorticoids reduce, whereas antagonists of glucocorticoid receptors enhance the anxiolytic activity of diazepam [2]. Also we know that certain psychopathological disorders, including depressive states and chronic alcoholism, are accompanied by marked glucocorticoid hypersecretion with disturbance of regulatory feedback mechanisms [1, 4]. At the same time the effectiveness of tranquilizers of the benzodiazepine series is considerably weakened in rats with established physical dependence on ethanol and in the withdrawal state [1]. Doses of diazepam required to reduce the ethanol consumption in rats with physical dependence on it are correspondingly greatly increased by comparison with those for animals at the stage of formation of alcohol motivation [1].

To test the hypothesis of the antitranquilizing action of endogenous glucocorticoids in individuals with chronic alcoholism, experiments were carried out to study the effect of cortexolone — a glucocorticoid antagonist at the receptor level — on the effectiveness of diazepam, assessed on the basis of its tranquilizing activity and ability to reduce voluntary consumption of ethanol.

EXPERIMENTAL METHOD

Male rats weighing 450-500 g, consuming ethanol for 10 months, were used in the experiments. The anxiolytic activity of diazepam was studied by the method of motivated intraspecific aggression, which is a variant of the conflict situation, based on fighting between a pair of rats for the safe place on an electrode floor through which painful electric shocks are applied to the limbs [2]. Diazepam (Polfa) in a dose of 1 mg/kg and cortexolone (Calbiochem) in a dose of 20 mg/kg were injected intraperitoneally 30 and 45 min, respectively, before testing, in the form of a suspension with Tween-80. Animals of the control group received distilled water in equal volumes 30 min before the beginning of the experiment.

Before the experiments, animals consuming ethanol for not less than 10 months were placed in individual cages with free access to water and 15% ethanol solution, and for 14

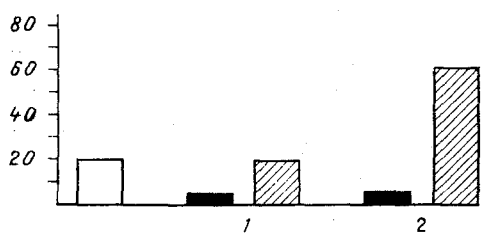

Fig. 1. Effect of acute (1) and chronic (2, for 5 days) administration of cortexolone on anxiolytic activity of diazepam in alcoholized rats. Abscissa: unshaded column — diazepam (1 mg/kg), black columns — cortexolone (20 mg/kg), shaded columns — diazepam (1 mg/kg) + cortexolone (20 mg/kg); ordinate, anxiolytic effect (in %).

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TABLE 1. Effect of Cortexolone and Diazepam on Voluntary Consumption of 15% Ethanol Solution by Rats Physically Dependent on Ethanol (M ± m)

Group of animals	Number of animals	Consumption of 15% ethanol solution, ml/kg/day							
		background consumption	during administration of preparations						
			as a whole	% of background	during 1st week	% of background	during 2nd week	% of background
Control	7	37,38±3,01	37,43±4,84	101,54±11,4	37,66±3,93	101,09±6,33	37,2±6,16	102,0±16,59
1	8	37,55±2,16	39,28±4,16	100,75±8,69	43,39±5,32	115,62±12,44	33,18±4,9	85,87±12,6
2	6	35,7±5,82	29,38±5,4	82,19±8,36	29,97±5,81	87,96±13,52	28,77±7,0	76,4±12,81
3	9	47,8±2,92	31,59±5,15*	65,38±9,75**	37,38±6,01	76,38±11,44	25,8±5,66*	54,37±11,4**

Legend. *p < 0.05 compared with background, **p < 0.05 compared with control.

days their background liquid consumption was recorded. Animals consuming not less than 35-50 ml/kg of 15% ethanol solution daily were divided into four groups. Rats of group 1 received diazepam daily for 14 days in a dose of 2 mg/kg, rats of group 2 received cortexolone in a dose of 20 mg/kg, and rats of group 3 received diazepam together with cortexolone in the same doses. Animals of the control group received distilled water by intraperitoneal injection in equivalent volumes. Consumption of ethanol solution and water was recorded daily.

EXPERIMENTAL RESULTS

It was shown first that after a single injection of cortexolone (20 mg/kg) into intact rats, an anxiolytic effect was obtained in 100% of animals receiving diazepam in doses of both ED_{50} and ED_{25}. Meanwhile a single injection of cortexolone in a dose of 20 mg/kg under analogous experimental conditions did not change the effectiveness of diazepam in rats with established physical dependence on ethanol. Chronic (for 5 days) administration of cortexolone modulated the effectiveness of diazepam in alcoholized rats. In a dose of 1 mg/kg, for instance, diazepam gave an anxiolytic effect in 20% of rats physically dependent on ethanol. Preliminary administration of cortexolone for 5 days increased this figure to 60% (Fig. 1).

There are indications in the literature of an anxiogenic and antianxiolytic action of stressor hormones, including glucocorticoids [3, 6, 7]. This suggested that the weakening of the effectiveness of diazepam in alcoholized rats may be based on an increase in secretion of glucocorticoids, which is a characteristic pathogenetic endocrine factor in chronic alcoholism.

If this suggestion is true and reducing the ability of diazepam to weaken alcohol motivation in rats physically dependent on ethanol is linked with the antianxiolytic action of glucocorticoids, chronic administration of glucocorticoid antagonists ought to restore the "antialcohol" activity of diazepam. For this purpose rats with established physical dependence on ethanol were given injections of cortexolone in a dose of 20 mg/kg daily for 14 days. Rats of another group received diazepam in a dose of 2 mg/kg. It was shown previously that in this dose diazepam gives neither an antialcohol nor an anxiolytic effect in rats with experimental alcoholism [1]. Animals of the third group received intraperitoneal diazepam together with cortexolone in the above-mentioned doses. It will be clear from the data in Table 1 that neither cortexolone nor diazepam alone could change ethanol consumption by comparison with either the initial or the control level.

Positive modulation by cortexolone of the effectiveness of diazepam may be connected, in our view, with prevention of the cytotoxic action of hormones of this type on hippocampal neurons. It is in the region of the hippocampus that the highest concentration of glucocorticoid receptors is found and damage to hippocampal neurons associated with endogenous hypercortisolemia may be responsible for age differences in psychoemotional disorders and changes in the memory process [7]. Since the septohippocampal system is a structure which plays a key role in the realization of the anxiolytic action of tranquilizers [5], increasing the effectiveness of the latter with the aid of cortexolone may be the result of the protective action of antagonists of glucocorticoid receptors at the hippocampal level.

On the other hand, glucocorticoids, through permissible regulation of activity of the enzymes involved in synthesis and degradation of serotonin, accelerate the development of tolerance to certain pharmacologic agents, including to ethanol [8-10]. It can be concluded that the real degree of tolerance and physical dependence on ethanol in individuals receiv-

ing the glucocorticoid antagonist cortexolone is lower than that in animals which have not had contact with this compound. The receptor and permissive mechanisms of the effect of glucocorticoids and their antagonists on the effectiveness of tranquilizers are not alternative, but rather they jointly determine the positive modulation by cortexolone of certain effects of tranquilizers in rats with experimental alcoholism.

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SUBSTANCE P AND EFFECT OF ETHANOL ON CENTRAL MECHANISMS OF AVOIDANCE IN RABBITS

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The polyfunctional nature of various endogenous peptide substances, observed by many workers, and their ability to normalize disturbed homeostatic parameters [2, 4, 12] suggest that these biologically active substances may be used to restore disturbed bodily functions. The first investigations in which, in particular, substances of peptide nature were used to evaluate animals predisposed to ethanol consumption [2] or to analyze the effect of oligopeptides on the central mechanisms of alcohol motivation [7, 14], have already been published.

The writers previously studied the action of ethanol on the formation of the avoidance reaction (AR) in animals [5] and also the effect of substance P (SP) on various motivation reactions. The aim of the present investigation was to discover to what degree SP can normalize the central mechanisms of AR, when disturbed by ethanol, in rabbits. Most attention was devoted to assessment of excitability of the ventromedial hypothalamus, and also to reticulo-hippocampal-hypothalamic interactions, during the development of defensive motivation, which is the basis of AR, in animals.

EXPERIMENTAL METHOD

Experiments were carried out on waking rabbits weighing 2.5-3 kg. Previously fed animals were used. Thin bipolar electrodes (0.1 mm) were inserted into the scalped rabbits in the ventromedial region of the hypothalamus, with the aid of the atlas of Sawyer et al. Threshold electrical stimulation of the center for "affective reactions" in order to obtain AR in the animals had the following parameters: 1.5-4 V, 50 Hz, pulse duration 1 msec. Bi-

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