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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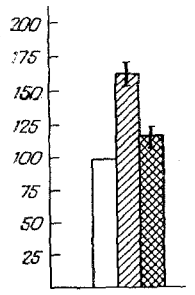


Fig. 1

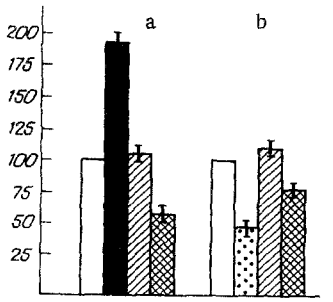


Fig. 2

Fig. 1. Changes in threshold of stimulation of ventromedial hypothalamus to obtain an AR in intact animals after injection of ethanol (0.5 g/kg) and of SP (30 μg/kg). Ordinate, threshold of stimulation of ventromedial hypothalamus to obtain avoidance reaction (in %). Unshaded column, threshold of stimulation of ventromedial hypothalamus in intact animals, oblique shading — after injection of ethanol, cross-hatching — injection of SP.

Fig. 2. Changes in latent period of AR to stimulation of ventromedial hypothalamus, conditioning stimulation of DH (a) and MRF (b) in intact animals, and also after injection of ethanol (0.5 g/kg) and of SP (30 μg/kg). Ordinate, latent period of AR (in %). Unshaded columns — latent period of AR to isolated stimulation of ventromedial hypothalamus, black column — after conditioning stimulation of DH, dotted column — after stimulation of MRF (in intact animals); oblique shading — after injection of ethanol, cross-hatching — after injection of SP.

polar electrodes also were implanted into the dorsal hippocampus (DH) and mesencephalic reticular formation (MRF). Conditioning stimulation of DH and MRF in experiments to study both the threshold of stimulation of the ventromedial hypothalamus and changes in the latent period of evoked AR had the following parameters: 5-7 V, 50 Hz, 1 msec for DH, and 2-4 V, 50 Hz, 1 msec for MRF. The duration of conditioning stimulation of the limbico-mesencephalic formation was 15 sec.

A 40% solution of ethanol in physiological saline was injected in a dose of 0.5 g/kg body weight into the marginal vein of the rabbit's ear. The behavioral reaction evoked by electrical stimulation of the ventromedial hypothalamus was analyzed 10 min after intravenous injection of ethanol.

SP (product of East Germany) in a dose of 30 μg/kg in 5 ml of physiological saline was injected slowly (1 ml/min) into the marginal vein of the rabbit's ear. Excitability of the ventromedial hypothalamus and the character of the reticulohippocampal influences were determined at the end of the intravenous injection of SP and thereafter at 15-min intervals for 1.5 h. The location of the subcortical electrodes was determined by a rapid method in brain sections cut to a thickness of 50-100 μ.

## EXPERIMENTAL RESULTS

Threshold stimulation of the ventromedial hypothalamus (the center for "affective reactions") evoked an AR in the animals after a short latent period. As in our previous investigations [5], conditioning stimulation of DH added significantly to the difficulty of AR formation in the animals, as shown both by elevation of the threshold of stimulation of the ventromedial hypothalamus ($p < 0.05$) and by lengthening of the latent period of AR ($p < 0.01$).

Intravenous injection of ethanol into the animals had a marked effect on the central mechanisms of AR, as shown by a decrease of 57.1% in excitability of the ventromedial hypothalamus ($p < 0.01$) and also by disturbance of reticulo-hippocampal-hypothalamic interactions. After injection of ethanol, both the inhibitory hippocampal ($p < 0.05$) and the facilitatory reticular influences ($p < 0.01$) on excitability of the ventromedial hypothalamus

were abolished. Data on the effect of a single injection of ethanol on the character of hippocampal-reticular influences during the development of AR in the animals are illustrated in Fig. 1. Against the background of modification by ethanol of the central mechanisms of AR, SP was injected into the animals. It was shown 10 min after intravenous injection of the undecapeptide that SP restored excitability of the ventromedial hypothalamus in 71.4% of cases. When assessing the intensity of stimulation of the ventromedial hypothalamus in order to obtain AR, we observed that whereas the threshold of stimulation of the ventromedial hypothalamus against the background of ethanol was 157.1% compared with the initial level, taken as 100%, after a single injection of SP this parameter had a value of 115.8% ($p < 0.05$).

The action of SP on reticulo-hippocampal influences, modified by ethanol, during the formation of AR in the animals was found to be selective. It was shown that SP in 71.4% of experiments did not restore the normally existing inhibitory influences of DH on excitability of the ventromedial hypothalamus. This is indicated, in particular, by the absence of any increase in the latent period of AR against the background of SP after conditioning stimulation of DH. Menawhile in 83.3% of experiments SP restored the facilitatory influences of MRF on excitability of the ventromedial hypothalamus, disturbed by ethanol, as is shown by the decrease in the latent period of AR after conditioning stimulation of mesencephalic structures (Fig. 2).

It can thus be concluded from the results of these experiments that SP has a partial normalizing effect on central mechanisms of AR in rabbits when modified by ethanol. A single injection of SP restored excitability of the ventromedial hypothalamus, disturbed by ethanol, and the normally existing facilitatory influences of MRF during AR formation in rabbits, but it was completely ineffective as regards normalization of the inhibitory effect of DH.

It was interesting to study the concrete neurophysiological mechanisms of partial normalization by SP of the process of AR formation when modified by ethanol. There is much evidence now that ethanol interferes with the metabolism of the generally accepted neurotransmitters: catecholamines [1, 8], GABA [8], etc.

Numerous investigations have shown that when processes taking place inside the brain are disturbed by alcohol it is the result of interaction between ethanol and opiate receptors [1, 9-11] and, in particular, with δ-receptors [15], and that naloxone must be regarded as an antagonist of alcohol intoxication [10, 11]. This explains the attempts of some investigators [7, 14] to use peptide substances which also affect neurotransmitter levels in the CNS, as factors capable of increasing the resistance of the body to ethanol.

We know that SP is closely connected with metabolism of various mediator systems [3, 12, 13]. This undecapeptide is regarded nowadays as a neurotransmitter, a neuromodulator, and a ligand of opiate receptors, properties which predetermine the regulatory functions of SP in the body [3, 12], evidently including during exposure to alcohol.

Our biochemical investigations [6], which demonstrated changes in neuronal metabolism in different brain formations after intravenous injection of SR, suggest that partial normalization of central mechanisms of AR, disturbed by ethanol, observed in the present experiments after injection of SP may also be the result of restoration of intracellular metabolism processed by this peptide.

The results of the experiments described above also showed that effects of SP on the central mechanisms of AR in rabbits previously receiving ethanol differed significantly ($p < 0.01$) from those observed by the writers previously [6] in intact animals.

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