SUBSTANCE P INCREASES RESISTANCE OF THE AVOIDANCE REACTION TO ETHANOL

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The writers previously demonstrated the ability of substance P (SP) to partially restore the central mechanisms of defensive motivation, constituting the basis of the avoidance reaction (AR) in rabbits, when disturbed by ethanol [5].

This paper describes an attempt to discover to what extent SP can prevent the disturbance by ethanol of the central mechanisms of AR. Attention was concentrated on assessment of excitability of the ventromedial hypothalamus, and also on reticulo-hippocampo-hypothalamic interrelations during the formation of this motivational response.

EXPERIMENTAL METHOD

Experiments were carried out on conscious rabbits weighing 2.5-3 kg. The animals used in the experiments had previously been fed. Thin bipolar electrodes (0.1 mm) were inserted in accordance with the atlas of Sawyer and co-workers into the ventromedial region of the hypothalamus of the scalped rabbit. The threshold of stimulation of the center of "affective reactions" by an electric current to obtain AR in the animals was 1.5-4 V, with a frequency of stimulation of 50 Hz and pulse duration 1 msec. Bipolar electrodes also were implanted in the dorsal region of the hippocampus (DH) and the mesencephalic reticular formation. Conditioning stimulation of DH and the mesencephalic reticular formation (MRF) in experiments to study both the threshold of stimulation of the ventromedial hypothalamus and changes in the latent period of the evoked AR was 5-7 V for a frequency of 50 Hz and pulse duration of 1 msec for DH, and 2-4 V for the same frequency of stimulation and pulse duration for the mesencephalic reticular formation. The duration of conditioning stimulation of the limbico-mesencephalic formations was 15 sec.

SP (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. The behavioral reaction to electrical stimulation of the ventromedial hypothalamus was analyzed 10 min after intravenous injection of SP.

The character of hippocampal and reticular influences on excitability of the ventromedial hypothalamus was determined at the same times.

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. Excitability of the ventromedial hypothalamus and the character of reticulo-hippocampal influences were determined at the end of intravenous injection of ethanol and at intervals of 15 min for a period of 1.5 h. The location of the subcortical electrodes was determined by an express method in brain sections cut to a thickness of 50-100 μ.

EXPERIMENTAL RESULTS

Threshold electrical stimulation of the ventromedial hypothalamus (the center for "affective reactions") after a short latent period induced AR in the animals. Just as in our previous investigations [4], conditioning stimulation of DH significantly

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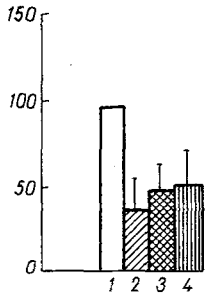

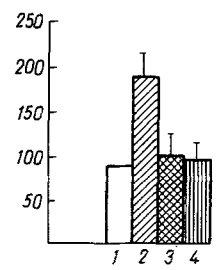

Fig. 1 Fig. 2

Fig. 1. Facilitatory influences of conditioning stimulation of MRF on AR formation, as reflected in latent period in intact animals after preliminary intravenous injection of SP (30 μg/kg) and subsequent intravenous injection of ethanol (0.5 g/kg). 1) Intact animals, isolated stimulation of ventromedial hypothalamus; 2) intact animals, conditioning stimulation of MRF followed by testing stimulation of ventromedial hypothalamus; 3) the same, preceded by SP; 9) the same preceded by ethanol. Here and in Fig. 2: ordinate, latent period of AR (in per cent).

Fig. 2. Inhibitory influences of conditioning stimulation of dorsal hippocampus on AR formation as reflected by latent period in intact animals after preliminary intravenous injection of SP (30 μg/kg) and subsequent intravenous injection of ethanol (0.5 g/kg). 1) Intact animals, isolated stimulation of ventromedial hypothalamus; 2) intact animals, conditioning stimulation of dorsal hippocampus and testing stimulation of ventromedial hypothalamus; 3) the same, preceded by SP; 4) the same, preceded by ethanol.

impaired AR formation in the animals, as shown by an increase in the threshold of stimulation of the ventromedial hypothalamus ($p < 0.05$) and by an increase in the latent period of AR ($p < 0.01$). Meanwhile, conditioning stimulation of MRF, on the other hand, facilitated the onset of AR in the animals, as shown mainly by shortening of the latent period of AR ($p < 0.01$) in response to stimulation of the center for "affective reactions."

The central mechanisms of AR, unlike those of behavioral reactions based on other biological motivations, were affected to a lesser degree by injection of SP [4]. In 66.7% of cases ($p < 0.05$) excitability of the ventromedial hypothalamus was unchanged, in 13.3% ($p < 0.05$) it was increased, and in 20.0% ($p < 0.05$) it was depressed after injection of SP. We also noted that in 86.7% of cases ($p < 0.01$) the facilitatory influences of MRF on excitability of the ventromedial hypothalamus were preserved whereas inhibitory influences of DH on excitability of the center for "affective reactions" were abolished in 73.3% of experiments ($p < 0.05$).

Against the background of the minor changes in central mechanisms of AR induced by SP, ethanol was given to the animals. It was found 15 min after intravenous injection of ethanol that the excitability of the ventromedial hypothalamus remained at its previous level in 66.7% of cases ($p < 0.05$), it was increased in 26.6% ($p < 0.05$), and reduced in fewer than 6.7% ($p < 0.01$). For comparison it is worth noting that injection of the same quantity of ethanol into intact animals was accompanied in 83.7% of cases ($p < 0.01$) by elevation of the threshold of stimulation by 57.1% ($p < 0.01$).

However, a preceding injection of SP increased the resistance of the central mechanisms of AR to ethanol not only by preserving the former level of excitability of the ventromedial hypothalamus. Against the background of SP, facilitatory influences of MRF on excitability of the ventromedial hypothalamus were preserved, despite the intravenous injection of ethanol. This result is all the more important because injection of ethanol abolished facilitatory influences of MRF on AR formation in intact animals ($p < 0.01$) [5].

Although SP under normal conditions abolishes existing inhibitory influences of DH on the hypothalamic motivational center, it nevertheless did not enable the character of the effect of ethanol on hippocampal-hypothalamic relations to be evaluated reliably.

This view was confirmed by concrete analysis of the latent period of AR in experiments with conditioning stimulation of DH and MRF (Figs 1 and 2). For instance, whereas conditioning stimulation of MRF was accompanied by facilitation of AR, as shown by reduction of the latent period compared with that of AR in intact animals, injection of ethanol after SP increased the latent period only very slightly (Fig. 1).

Meanwhile, as will be clear from Fig. 2, the inhibitory effect of DH on the formation of AR in the animals, as reflected in an increase in the latent period of AR in the intact animals up to 226.8 ± 26.4% ($p < 0.01$) compared with the initial value, taken as 100%, was absent both after injection of SP and after injection of ethanol.

It can thus be concluded from the results of these experiments that SP increases the tolerance of the central mechanisms of AR to ethanol.

This conclusion does not appear out of the ordinary if the ability of certain substances of peptide nature either to partially abolish the negative effects of ethanol or to increase the resistance of the body to its action is taken into account. For example, injection of Leu-enkephalin, enkephalin-like tetrapeptide, and delta sleep-inducing peptide into rats reduced the quantity of ethanol consumed by 30-50% on average [6]. Positive effects, reducing both the pathological motivation toward ethanol and the action of ethanol on the body, are given by bradykinin [7], neurotensin, and bombesin [10]. Injection of vasopressin or of its separate fragments increased the resistance of both rats [11] and mice [12] to the effects of ethanol.

The effect of certain tachykinins and, in particular, of neurokinin A, expressed as an increase in resistance of the gastric wall to ulcer formation under the influence of ethanol [8], is an interesting observation.

Profound changes in the classical neurotransmitter systems and opiate receptors have now been established [1] in response to the action of ethanol on the CNS. Meanwhile, substances of peptide nature have a similarly broad spectrum of action on the CNS [2], so that they may attract interest as possible drugs for the treatment of alcoholism [3].

The results of the present investigations, demonstrating the ability of SP to increase the tolerance of AR to ethanol, combined with our data showing partial normalization of the central mechanisms of this behavioral reaction, when disturbed by ethanol, under the influence of this undecapeptide [5], indicate that further intensive study of SP will be worthwhile.

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