

SUBSTANCE P IN CENTRAL MECHANISMS OF THE FOOD RESPONSE  
TO STIMULATION OF THE LATERAL HYPOTHALAMUS IN RABBITSV. G. Zilov, S. K. Rogacheva,  
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UDC 612.391.3-06:612.822.1:577.175.82

KEY WORDS: substance P; food response; lateral hypothalamus; dorsal hippocampus; mesencephalic reticular formation.

Substance P (SP) is one of the first neuropeptides to be discovered and it is therefore the one which has been studied the most. However, there are only isolated publications on the effect of SP on individual behavioral responses of animals. The effect of SP has been described on grooming in mice [9], on facilitation and inhibition of passive avoidance learning in rats when injected into the brain [8, 16], and absence of changes in conditioned-reflex avoidance after injection of SP into the lateral ventricles [11].

The object of this investigation was to study the effect of SP on the formation of food motivation in animals and, in particular, on excitability of the hypothalamic "food center" and on reticulo-hippocampo-hypothalamic interrelations.

## EXPERIMENTAL METHOD

Experiments were carried out on 15 waking rabbits weighing 2.7-3 kg. The animals were fed before taking part in the experiments. Thin (0.1 mm) bipolar nichrome electrodes were implanted into the lateral area of the hypothalamus of a previously scalped rabbit in accordance with the atlas of Sawyer et al. (1957). The hypothalamic "food center" was stimulated by an electric current of threshold strength (1.5-4 V, 50 Hz, 1 msec). Bipolar electrodes also were implanted in the dorsal region of the hippocampus and the mesencephalic reticular formation. In experiments to study the threshold of stimulation of the lateral hypothalamus and changes in the latent period of the evoked food response the parameters of stimulation were 5-7 V, 50 Hz, and 1 msec for the dorsal hippocampus and 2-4 V, 50 Hz, and 1 msec for the mesencephalic reticular formation. The duration of stimulation of the limbicomesencephalic structures was 15 sec. The EEG was recorded from different areas of the cerebral cortex by means of needle electrodes on an 8-channel EEG-80 electroencephalograph (Medicor, Hungary). Powers of the principal EEG rhythms within the range from 1.7 to 70 Hz were analyzed on a wide-band EEG analyzer-integrator of ANIEG-8 type (Medicor). The ECG was recorded in standard lead II. SP 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 lateral hypothalamus and the character of reticulo-hippocampal influences were determined at the end of intravenous injection of SP and thereafter at 15-min intervals for 1.5 h. The results were subjected to statistical analysis by Student's test. The locations of the subcortical electrodes were verified by an express method in brain sections cut to a thickness of 50-100 µ.

## EXPERIMENTAL RESULTS

Threshold electrical stimulation of the lateral hypothalamus evoked behavior in the satiated animals directed toward seeking and eating food, which usually was preceded by a brief orienting-investigative response. Behavior evoked by stimulation of the lateral hypothalamus, based on ascending excitation of the hypothalamic "food center" was characterized by specific power patterns of the principal EEG rhythms in areas of the cortex studied.

The writers previously determined the character of hippocampal and reticular influences on excitability of the hypothalamic motivation centers [1]. In the present experiments

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P. K. Anokhin Research Institute of Normal Physiology, Academy of Medical Sciences of the USSR. I. M. Sechenov First Moscow Medical Institute. (Presented by the Academician of Medical Sciences of the USSR V. V. Zakusov,) Translated from *Byulleten' Éksperimental'noi Biologii i Meditsiny*, Vol. 97, No. 1, pp. 3-5, January, 1984. Original article submitted May 18, 1983.

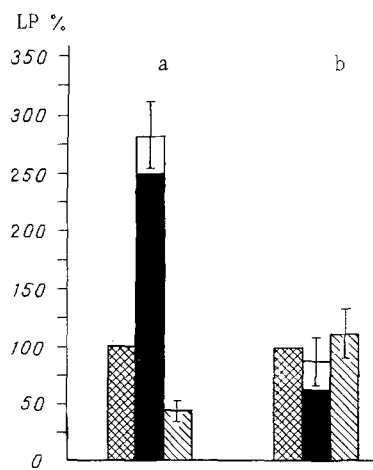


Fig. 1. Hippocampal-reticular influences on latent periods of evoked food response before (a) and after (b) intravenous injection of SP (30  $\mu\text{g/kg}$ ). Ordinate, deviation of latent period of food response (in %). Cross-hatched columns — latent periods of food response during isolated stimulation of lateral hypothalamus; black columns — after stimulation of dorsal hippocampus, obliquely shaded columns — after stimulation of MRF.

stimulation of the dorsal hippocampus significantly inhibited the formation of food behavior in the animals (Fig. 1), as shown both by elevation of the threshold of lateral hypothalamic stimulation ( $P < 0.05$ ) and by lengthening of the latent period of the food response ( $P < 0.01$ ). Stimulation of the mesencephalic reticular formation (MRF), causing activation of the neocortical EEG, on the other hand, lowered the threshold of lateral hypothalamic stimulation ( $P < 0.01$ ) and significantly reduced ( $P < 0.01$ ) the latent period of food behavior.

Intravenous injection of physiological saline containing SP (30  $\mu\text{g/kg}$ ) into the animals was followed by considerable autonomic responses: an increase in the frequency and amplitude of respiratory movements, changes in the cardiac rhythm with reversible disturbances of intracardiac conduction in some experiments, and also changes in the integral EEG of the neocortical areas and the patterns of its basic rhythms.

Profound changes were observed in relations between the hypothalamo-reticulo-hippocampal structures participating in the formation and realization of food behavior. Immediately after intravenous injection of SP the threshold of lateral hypothalamic stimulation required to evoke purposive food behavior was significantly increased ( $P < 0.01$ ). The degree of elevation of the threshold of stimulation of the hypothalamic "food center" differed in different experiments, but irrespective of the original parameters of stimulation of the hypothalamic motivation center it exceeded 200%. Analysis of the trend of the threshold of lateral hypothalamic stimulation in the animals after injection of SP showed that by the 45th-60th minute excitability of the hypothalamic "food center" had returned to its original level ( $P < 0.05$ ). Excitability of the hypothalamic food center was observed to be dependent on the dose of SP injected. For instance, an increase in SP concentration in some experiments to 50-70  $\mu\text{g/kg}$  led to inversions of food behavior, manifested as the complete absence of such behavior, the appearance of food behavior at the end of lateral hypothalamic stimulation, or replacement of the animal's food behavior by an avoidance reaction in response to a stimulating current with high parameters (up to 10 V).

Against the background of SP both inhibitory effects of the hypothalamus and facilitatory effects of MRF on excitability of the lateral hypothalamus were absent ( $P < 0.01$ ), as may be seen in the case of latent periods of the food response of the animals both to isolated stimulation of the hypothalamic "food center" and to stimulation of the same motivation center after stimulation of the hippocampus and MRF (Fig. 1).

The results indicate that SP can affect the formation of behavior based on excitation of food motivation in animals, and they agree with observations made by workers who found a high SP concentration in the lateral area of the hypothalamus in different animals [7, 8, 10]. High SP concentrations in the dorsal hippocampus [19] and mesencephalic formations [12] can explain the disturbances of hippocampal-reticular influences on excitability of the hypothalamic "food center" discovered after intravenous injection of SP, which altered the balance of this peptide which normally exists in the CNS.

The effect of SP, injected intravenously, on the central mechanisms of food behavior formation is extremely complex, in the writers' view, for the action of SP both directly on the CNS and indirectly on the brain through changes in the hormonal balance and activity of the autonomic nervous system has to be taken into account. Considering the possible neuro-mediator [6, 13, 15] and neuromodular [5, 14] functions of SP, and also data on the existence of receptors for SP in different organs and tissues [4, 17], the presence of SP in autonomic ganglia and autonomic nerve endings [18], determining activity of the cardiovascular system in particular [2, 3], it must be recognized that these are important parameters both for function and for purposive behavioral responses.

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