18. J. T. Shepherd, Circulation, 33, 484 (1966).
19. M. P. Wiedeman and R. F. Tuma, Microvasc. Res., 12, 71 (1976).
20. H. N. Majorowitz and B. W. Zweifach, The Inflammatory Process, Vol. 2, New York (1973).

SUBSTANCE P IN CENTRAL MECHANISMS OF THE AVOIDANCE REACTION

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The contradictory results of investigations into the effect of substance P (SP) on the formation of active and passive avoidance in animals [10, 11, 14] served to motivate the present experiments in which an attempt was made to assess the role of SP in the development of the avoidance reaction (AR) in rabbits. Most attention was paid to the effect of SP on excitability of the ventromedial hypothalamus, and also on reticulo-hippocampal-hypothalamic interrelations during the formation of defensive motivation, which forms the basis of AR, in animals.

EXPEPIMENTAL METHOD

Experiments were carried out on 16 unanesthetized rabbits weighing 2.7-3 kg. The animals were fed before the experiments. Thin (0.1 mm) bipolar nichrome electrodes were implanted in accordance with Sawyer's atlas into the ventromedial hypothalamus of the scalped rabbit. Threshold electrical stimulation of the center for "affective reactions" (1.5-4 V, frequency 50 Hz, pulse duration 1 msec) was applied. Bipolar electrodes were also implanted into the dorsal region of the 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 a strength of 5-7 V at a frequency of 50 Hz, with pulse duration of 1 msec for the dorsal hippocampus and 2-4 msec with the same frequency and pulse duration for MRF. The duration of conditioning stimulation of the limbico-mesencephalic formations was 15 sec. The EEG was recorded from various regions of the cortex by means of needle electrodes on an eight-channel EEG-80 electroencephalograph (Medicor, Hungary). The power of the principal EEG rhythms within the range from 1.5 to 70 Hz was recorded and studied on a type ANIEG-8 wide-band EEG analyzer-integrator (Medicor). The ECG was recorded in standard lead II. SP (from Sigma, USA) in a dose of 30 μg/kg, diluted 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 reticulo-hippocampal influences were determined at the end of intravenous injection of SP and at 15-min intervals thereafter for 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 stimulation of the ventromedial hypothalamus (the center for "affective reactions"), after a short latent period, evoked AR in the animals. This reaction, based on defensive motivation, was accompanied by specific patterns of powers of the principal EEG rhythms in the frontal and occipital regions of the cortex.

The character of hippocampal and reticular influences on excitability of hypothalamic motivational centers was established previously [4]. In the present experiments conditioning stimulation of DH significantly impeded the formation of AR in the animals, as was shown both by elevation of the threshold of stimulation of the ventromedial hypothalamus ($P < 0.05$) and

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by lengthening of the latent period of AR ($P < 0.001$). Conditioning stimulation of MRF, inducing activation of the neocortical EEG, on the other hand, lowered the threshold of stimulation of the ventromedial hypothalamus ($P < 0.01$) and shortened ($P < 0.001$) the latent period of AR.

Intravenous injection of physiological saline containing SP (30 < g/kg) into the animals was followed by considerable autonomic responses: an increase in the frequency and amplitude (up to 65-100%) of respiratory movements, quickening of the heart rate, and new patterns both on the integral EEG for the cortical regions and of powers of the principal rhythms of its components. Against the background of SP the threshold of stimulation of the ventromedial hypothalamus was raised for a short time (up to 10 min); the degree of deviation of the voltage threshold did not exceed 50% ($P < 0.05$). Analysis of hippocampal-reticular influences on excitability of the ventromedial hypothalamus showed that in 11 (73.3%) of the 15 experiments SP abolished the inhibitory effects of DH. In 15 (93.8%) of the 16 experiments, facilitatory influences of MRF on the formation of AR in the animals were preserved (Table 1).

Comparison of the results of the present investigations with data obtained previously on the role of SP in the formation of food behavior in animals [5] suggests that SP plays a selective role in the central mechanisms of behavioral reactions, based on different biological motivations.

Analysis of the powers of the principal rhythms constituting the integral EP of the frontal and occipital regions of the cortex revealed definite correlation between changes in central mechanisms producing AR in animals, arising after administration of SP, and the relations of the limbico-mesencephalic formations studied with regions of the neocortex. A single intravenous injection of SP considerably modified the pattern of powers of the cortical regions (Fig. 1) in response to stimulation of DH ($P < 0.01$). Behaviorally, this was expressed as absence of inhibitory effects of DH on the development of AR in the animals against the background of SP. Meanwhile, preservation of the facilitatory effects of MRF on the formation of this particular motivational reaction, after intravenous injection of SP, was accompanied to a considerable degree by coincidences of the EEG power patterns in response to ascending influences of the activating formation of the brain.

The results of these experiments are evidence that SP participates in the mechanisms of AR formation in rabbits. Whereas excitability of the hypothalamic center of "affective states" was quickly restored after a single intravenous injection of this peptide, disturbance of limbico-mesencephalic interrelations and, in particular, the absence of inhibitory effects of DH, lasted for 1.5 h. Several observations [1, 8] indicate that SP may be involved in various behavioral reactions accompanied by a negative emotional state. However, the concrete mechanisms of participation of SP in the development of AR in animals still remain unexplained. The selective role of SP in the formation of food behavior and AR in animals, discovered in the present investigation, also requires an explanation.

There is now convincing proof of a connection between SP and catecholamine metabolism in various brain formations [13] and, in particular, with dopamine metabolism [2, 15]. Investigations have been published by authors who have observed that SP may be involved in serotoninergic brain mechanisms [9, 12]. The ability of SP to abolish inhibitory effects of DH on the

TABLE 1. Effect of SP on Excitability of Ventromedial Hypothalamus and also on Effects of MRF and DH during Formation of AR

Reaction	Type of effect		
	strengthens	abolishes (depresses), %	no effect %
Excitability of ventromedial hypothalamus	—	18,75 (3)	81,25 (3)
Facilitatory effects of DH	—	6,25 (1)	91,75 (15)
Inhibitory effects of DH	—	73,33 (11)	26,67 (4)

Legend. Number of experiments shown in parentheses.

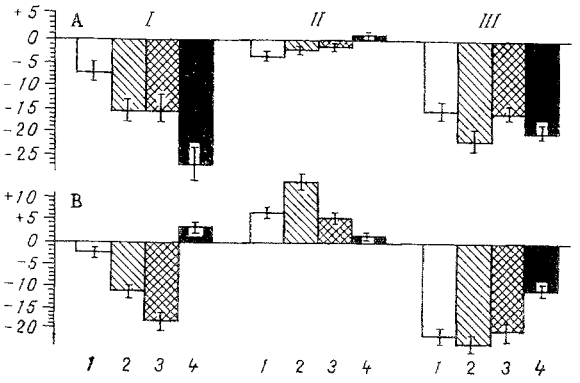

Fig. 1. Changes in powers of principal EEG rhythms in frontal cortex to threshold stimulation of ventromedial hypothalamus (I), and stimulation of DH (II) and MRF (III) before (A) and after (B) injection of SP. 1-4) β-, α-, θ-, and δ-rhythms, respectively. Ordinate, change in power (in %).

formation of food behavior [5] and AR in animals, observed in the present experiments, recalls the effect of the dopamine blocker, droperidol [4], on these behavioral reactions. Meanwhile, the changes observed in motivational behavioral reactions after administration of SP are not in harmony with views on interaction of this peptide exclusively with substances nowadays regarded as mediators. Among investigations which have established the presence of immunoradioactivity in different parts of the central and autonomic nervous system, similar to SP, the results of observations on interaction between SP and opiate receptors of the brain [6] and also on the ability of the peptide to change the cerebral blood flow [3], must be mentioned.

The selective effect of SP on the formation of food behavior and AR in animals confirms not only the hypothesis [7] that neuropeptides participate in the central mechanisms of biological motivations, but also the conclusion that every biological motivation is the result of specific integration of heterochemical brain structures [4].

LITERATURE CITED

1. K. Hecht, P. Oehme, E. A. Yumatov, et al., in: Systemic Mechanisms of Motivations [in Russian], Moscow (1982), p. 213.
2. A. V. Val'dman, in: Pharmacology of Neuropeptides [in Russian], Moscow (1982), p. 9.
3. V. G. Zilov, in: Problems in Physiology of the Hypothalamus [in Russian], No. 13, Kiev (1979), p. 53.
4. V. G. Zilov, S. K. Rogacheva, L. I. Ivanova, et al., Byull. Éksp. Biol. Med., No. 1, 3 (1984).
5. K. V. Sudakov, in: Proceedings of the 14th Congress of the I. P. Pavlov All-Union Physiological Society [in Russian], Vol. 1, Moscow (1983), p.141.
6. E. A. Yumatov, K. Hecht, Yu. G. Skotselyas, et al., in: Vasoactive Peptides [in Russian], Sofia (1980), p. 44.
7. J. Davis and A. Dray, Nature, 268, 351 (1977).
8. J. P. Huston and U. Staubli, Behav. Brain Res., 2, 264 (1981).
9. D. Luttinger, C. B. Nemeroff, and A. J. Prange, Brain Res., 237, 183 (1982).
10. R. Mitchell and S. Fleetwood-Walker, Europ. J. Pharmacol., 76, 119 (1981).
11. P. Oehme, K. Hecht, L. Piesche, et al., Acta Biol. Med. Germ., 39, 469 (1980).
12. U. Staubli and J. P. Huston, Neurosci. Lett., 13, Suppl. 3, 329 (1979).
13. K. Treptow, P. Oehme, E. Gäbler, et al., Regulatory Peptides, 5, 343 (1983).