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# NEUROPEPTIDES IN MECHANISMS OF ACTIVATION OF VENTROMEDIAL HYPOTHALAMIC STIMULATION-INDUCED AVOIDANCE REACTIONS DURING SATIATION

S. K. Sudakov

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A dominant focus of avoidance as a rule inhibits food motivation. Meanwhile the demand for food has a modulating effect on the character of the avoidance behavior of animals. It has been shown, for example, that avoidance reactions of hungry mice [6, 7] and of the marine mollusk Aplysia [10] are considerably depressed compared with those of satiated animals. Shevelkin [4] showed that food sensory satiation activates avoidance reactions in snails. It can be postulated that neurochemical factors participating in the organization of animals' food behavior may also exert a modulating action on avoidance motivation. For instance, endogenous oligopeptides such as opioids and gastrointestinal peptides, involved in the formation of food behavior [1, 8], in particular inhibit the organization of avoidance behavior [3, 5, 12].

The aims of the present-investigation were accordingly as follows: 1) to determine the effect of satiation, starting from the first contact of hungry rabbits with food until complete refusal to eat any more, on the character of avoidance reactions induced by ventromedial hypothalamic stimulation; 2) to assess the role of β-endorphin, cholecystokinin, and gastrin in mechanisms of modulation of avoidance reactions during changes in the level of food motivation in rabbits.

## EXPERIMENTAL METHOD

Experiments were carried out on 25 male rabbits weighing 2.5 kg, allowed free access to food before the experiment, and on 25 rabbits deprived of food for 48 h before the experiment. Bipolar nichrome electrodes were implanted in all animals into the right ventromedial hypothalamus and a cannula was introduced into the left lateral cerebral ventricle. Stimulation of the ventromedial hypothalamus led to passive avoidance behavior of the animals. The parameters of the stimulating currents were: amplitude 20-80 μA, duration of square pulses 1 msec, frequency 20-100 Hz. After testing for avoidance reactions so that, at a frequency of stimulation of 100 Hz, the latent period of the reaction was 1 sec, 40 μliters of Ringer's solution for warm-blooded animals, 1 nmole pentagastrin in 30 μliters of Ringer's solution, 0.3 nmole of the octapeptide cholecystokinin in 30 μliters of Ringer's solution, and 1 mmole of β-endomorphin in 30 μliters of Ringer's solution were injected into the lateral cerebral ventricle of animals of 4 groups, respectively, each consisting of 5 hungry and 5 satiated rabbits; 1 μmole naloxone in 0.5 ml of Ringer's solution also was injected intravenously into 5 hungry and 5 satiated rabbits. Next, with an interval of 1-10 min, a series of stimulations was applied to the ventromedial hypothalamus in the form of square pulses of different frequency: from 20 to 100 Hz consecutively. The latent period of the avoidance reaction to stimulation of each

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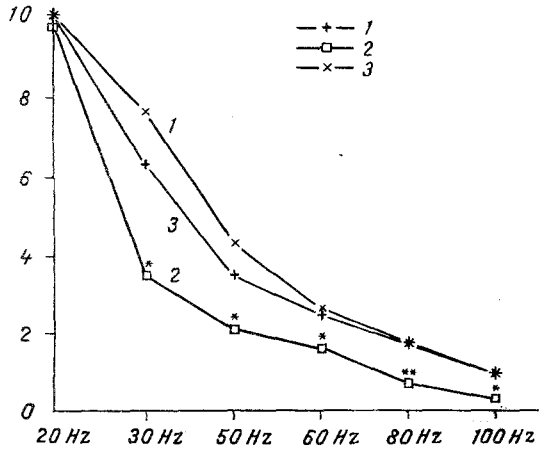


Fig. 1

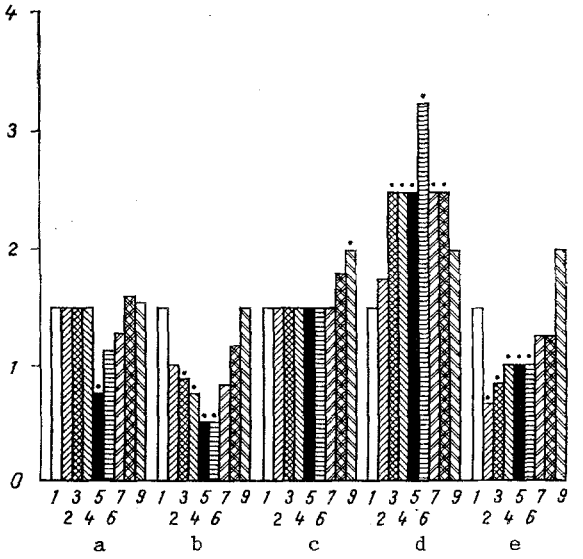


Fig. 2

Fig. 1. Changes in latent periods of avoidance reactions to electrical stimulation of ventromedial hypothalamus by current of varied frequency, in hungry rabbits (1), at beginning of eating (2), and on complete satiation (3). Ordinate, latent period (in sec). Abscissa, frequency of stimulation (in Hz). *p < 0.05, **p < 0.01.

Fig. 2. Changes in latent periods of avoidance reactions to stimulation of ventromedial hypothalamus with a frequency of 80 Hz in hungry rabbits receiving injection of Ringer's solution (a), pentagastrin (b), octapeptide cholecystokinin (c), or β-endorphin (d) into lateral cerebral ventricles or intravenous injection of naloxone (e). Ordinate, latent period (in sec); 1) background level; after injection of substance: 2) 1 min, 3) 10 min, 4) 20 min; after beginning of food consumption: 5) 1 min, 6) 5 min, 7) 10 min, 8) 20 min; 9) after complete satiation; *p < 0.01 (compared with background level).

frequency used (20, 30, 50, 60, 80, and 100 Hz) was determined. The rabbits were given combined food 20 min after injection of the substance. The latent period of beginning of eating and latent period of avoidance reactions to stimulation of the ventromedial hypothalamus at different frequencies were determined individually for each rabbit during 90 min after provision of the food.

The results were analyzed and Student's criterion determined by means of "Microstat" (Microsoft Corporation, USA) and "Supercalc-3" (Sortium Corporation, USA) program packs on an "Apricot" personal computer (Quest Automation, England).

## EXPERIMENTAL RESULTS

The experiments showed that the latent period of avoidance reactions of hungry rabbits into whose lateral ventricles Ringer's solution was injected were significantly reduced by the first minute of food consumption by the hungry rabbits ($p < 0.01$). Further food consumption led to gradual lengthening of the latent periods of the avoidance reactions. Changes of latent period were observed similar in direction and significance at all frequencies of stimulation of the ventromedial hypothalamus studied (Fig. 1). By the time of satiation (when the rabbits completely refused food) the latent periods recorded were a little longer than those in hungry animals (Fig. 2).

The experimental results indicate that physiological changes taking place on close contact of the animal with food and at the beginning of the act of eating may lead to activation of avoidance behavior. On the basis of our hypothesis that the organization of the behavioral act of feeding involves the direct participation of the genetic apparatus of nerve cells, expressed as the synthesis of specific peptide molecules [2], the following suggestion may be made. When hungry animals achieve the first stage of the result, namely the finding of food, peptide factors synthesizing in the nerve cells of the CNS of the hungry rabbit are secreted into the perineuronal space, and this evidently contributes to the further continuation of

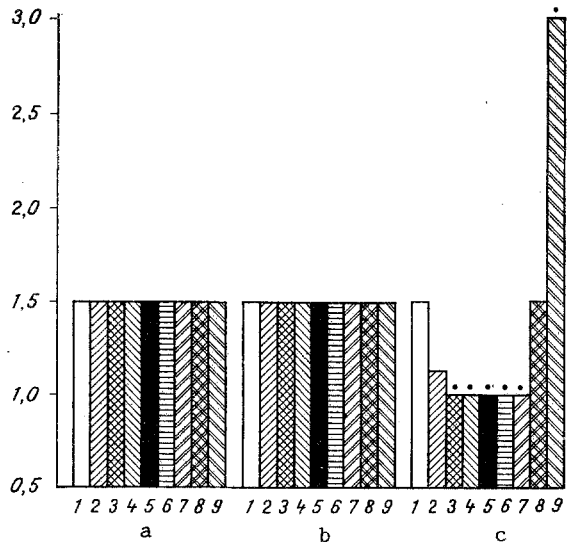


Fig. 3. Changes in the latent periods of avoidance reactions to ventromedial hypothalamic stimulation with a frequency of 80 Hz in fed rabbits receiving injections of Ringer's solution (a) or pentagastrin (b) into the lateral cerebral ventricles or intravenous injection of naloxone (c). Ordinate, latent periods (in sec); 1) background level; 2-9) 1, 10, 20, 21, 25, 35, 55, amd 90 min, respectively, after injection of the substance.

feeding behavior until the final adaptive result of satisfaction of the food metabolic need is achieved.

To test the hypothesis that activation of defensive reactions of hungry rabbits is connected with elevation of CNS levels of peptides involved in the formation of feeding behavior, special experiments were carried out. Latent periods of avoidance reactions induced by stimulation of the ventromedial hypothalamus were studied in hungry and fed rabbits following intraventricular injection of pentagastrin, cholecystokinin, and β-endorphin, and also after intravenous injections of naloxone. Injection of the octapeptide cholecystokinin in a dose of 0.3 nmole and of naloxone in a dose of 1 μmole was found to induce complete suppression of feeding behavior in rabbits deprived of food for 48 h before the experiment.

Injection of naloxone led immediately to shortening of the latent period of avoidance reactions similar to, or even more marked than that observed when eating began naturally (Fig. 2). Characteristically shortening of the latent periods of the avoidance reactions took place immediately after injection of naloxone both into the hungry rabbits and into the previously fed rabbits (Fig. 3). Intraventricular injection of the octapeptide cholecystokinin did not led to activation of avoidance reactions. On the contrary, some lengthening of latent periods of the avoidance reactions was observed 40-60 min after injection of the peptide.

Injection of 1 nmole β-endorphin and 1 nmole pentagastrin into the lateral cerebral ventricles of rabbits deprived of food for 48 h before the experiments led to activation of feeding behavior, which was manifested as quicker discovery of food by the animal and the beginning of food consumption.

Intraventricular injection of β-endorphin into both hungry and fed rabbits caused an increase in the latent periods of avoidance reactions to stimulation of the ventromedial hypothalamus. Food consumption by hungry animals against the background of the action of β-endorphin did not shorten the latent period of the avoidance reaction but, on the contrary, led to even stronger inhibition of avoidance behavior 5 min after the beginning of eating (Fig. 2).

Injections of pentagastrin shortened the latent periods of avoidance reactions of the hungry rabbits. Food consumption against the background of the effect of this peptide caused a further slight degree of shortening of the latent period. Injection of pentagastrin into the fed rabbits did not change avoidance reactions to lateral hypothalamic stimulation (Figs. 2 and 3).

It can thus be concluded that of the drugs tested only pentagastrin has a selective effect on the avoidance reactions of hungry rabbits. Injections of cholecystokinin and naloxone, simulating a state of satiation, either had no effect on avoidance behavior or their action on avoidance reactions is equally independent of the intensity of food motivation. Injection of β-endorphin, whose level in the CNS, as other investigations have shown [9, 11], is enhanced during hunger and falls sharply during feeding, gives the opposite effect – inhibition of avoidance behavior. This may indicate that physiological elevation of

the opioid levels in the CNS during food consumption has no marked action on avoidance behavior.

The experiments indicate that changes in the level of food motivation have a modulating effect on the intensity of avoidance behavior with the active participation of an endogenous gastrin-like factor secreted into the perineuronal space at the stage of contact of the animal with food and the beginning of its consumption.

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