

ROLE OF BETA-ADRENOBLOCKERS IN MODIFICATION OF THE HYPOTHALAMIC FEEDING CENTER BY SUBSTANCE P

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The role of peptides in the central mechanisms of motivation [5], which largely determines the goal-directed behavior of man and animals, has been demonstrated [5]. The ability of individual oligopeptides to modify temporarily the inborn properties of the hypothalamic motivation centers also have been established [4]. In particular, electrical stimulation of the lateral hypothalamus (LH), inducing feeding behavior in intact animals after injection of substance P (SP), began to induce an avoidance reaction from this center.

In the investigation described below a pharmacologic analysis of the phenomenon of modification of the hypothalamic feeding center by the action of substance P by means of beta-adrenergic antagonists and ketamine was attempted.

EXPERIMENTAL METHOD

Experiments were carried out on 14 unrestrained male rabbits weighing 2.5-3 kg. Satiated animals were used in the experiments. Bipolar nichrome electrodes 0.1 mm in diameter were implanted, in accordance with Sawyer's Atlas of the Rabbit Brain, into the lateral hypothalamic region of the previously scalped animal. Depending on the accuracy of targeting, threshold stimulation of the lateral hypothalamus in order to obtain feeding behavior in the animals required a current of between 1.5 and 4.0 V, a frequency of stimulation of 50 Hz, and pulse duration of 1 msec. Substance P (Germany) was injected as a single dose into the animals through a cannula implanted in the lateral ventricle, in a dose of 15 nmoles in 20 μ l physiological saline, by means of a microsyringe. To determine the specificity of action of substance P, in the control series of experiments physiological saline was injected in a volume of 20 μ l into the lateral ventricle. Ampul solutions of propranolol (Imperial Chemical Industries Limited, UK); Obsidan (VEB Arzneimittelwerk, Germany), droperidol, and kalipsol (both from Gedeon Richter, Hungary) were used. These preparations were injected intravenously into the animals in doses of 0.25 and 0.5 mg (Inderal, Obsidan), 0.25 mg (kalipsol), and 0.3 and 0.5 mg (droperidol). Excitability of the lateral hypothalamus and latent periods of behavioral reactions evoked from the lateral hypothalamus were estimated at the end of intraventricular injection of substance P and thereafter at 5-min intervals after intravenous injection of the antagonists for 1 h. The experimental results were subjected to statistical analysis by personal computer. The location of the subcortical electrodes was verified by the express method, in brain sections 50-100 μ thick.

EXPERIMENTAL RESULTS

As numerous experiments have shown electrical stimulation of LH of satiated animals led after a short orienting-investigative reaction to the search for and eating of food. In our previous investigations SP had different

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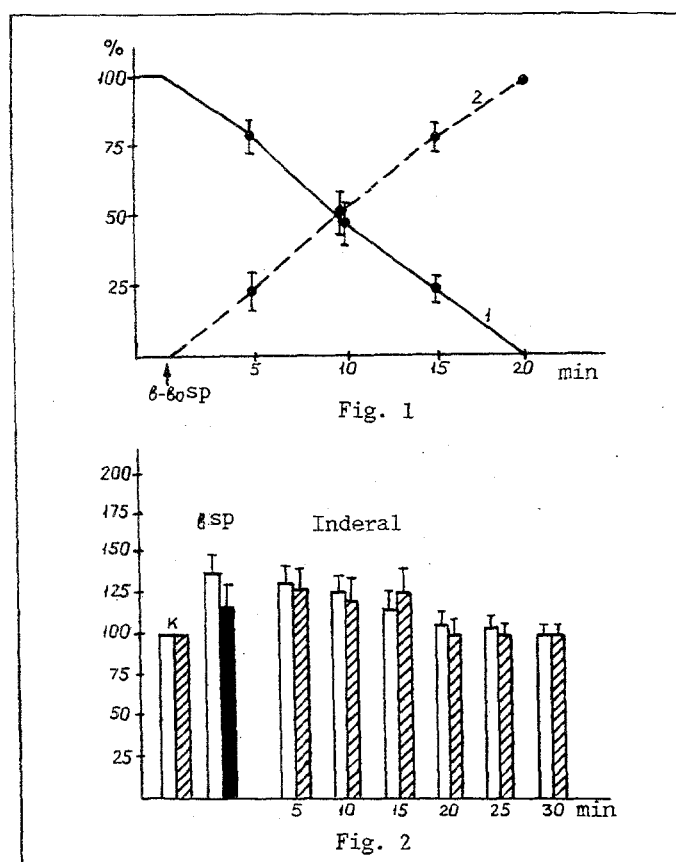


Fig. 1. Dynamics of replacement of feeding response by avoidance reaction to stimulation of lateral hypothalamus against the background of a single intraventricular injection of 15 nmoles substance P: 1) feeding reaction; 2) avoidance reaction.

Fig. 2. Dynamics of change in threshold of stimulation of lateral hypothalamus and of latent period of feeding reaction and avoidance reaction after a single injection of 15 nmoles substance P and intravenous injection of 0.5 mg Inderal. Legend: unshaded columns – threshold of stimulation of LH; obliquely shaded – latent period of feeding response; shaded black – latent period of avoidance reaction; C) control data, SP) effect of substance P. Abscissa, time (in min); ordinate, threshold of stimulation of LH and latent period of evoked reaction (in %).

effects on the central mechanisms of biological motivations, mainly by changing feeding behavior [3]. This was expressed initially as reduction of the excitability of LH for the formation of feeding behavior, disturbance of hippocampo-reticulo-hypothalamic relations, and later, the appearance of an avoidance reaction in the animals in response to stimulation of the hypothalamic feeding center.

In the present investigations the transition period of the change in functional properties of LH after a single injection of SP, which was found to be 20 min ($p < 0.05$) was analyzed. The dynamics of the decrease in frequency of appearance of a feeding response and, conversely, of an increase in the frequency of the avoidance reaction to electrical stimulation of the hypothalamic feeding center is illustrated in Fig. 1.

Just as for other oligopeptides, the effect of SP on inborn functional properties of LH was found to be reversible, with a total duration of 55-60 min after the end of intraventricular injection [4]. Thus a period of about 30 min was available for the experimenters, sufficient to study the chemical mechanisms of transformation of the functional properties of LH by SP.

In 14 experiments in which a substance with properties predominantly of a beta-adrenergic antagonist was used, complete restoration of the properties of the hypothalamic feeding center, previously modified by SP, was

observed. At the end of intravenous injection of Inderal and Obsidan in doses of 0.25 and 0.5 mg, electrical stimulation of LH again evoked a feeding reaction ($p < 0.001$), despite the preceding injection of SP (Fig. 2). We found no dose-dependent effect from the use of Inderal and Obsidan in the above concentrations. These two pharmacologic agents, similar in their chemical composition, were characterized by only slightly different patterns of recovery of feeding behavior in response to stimulation of LH, if the threshold of stimulation of LP and the latent period of the feeding reaction were used as criteria.

Different results were obtained when the animals were given kalipsol (ketamine), against the background of which the avoidance reaction evoked from the hypothalamic center modified by SP was preserved ($p < 0.01$).

The use of preparations with a different spectrum of effects on the CNS in these experiments led to differences in the mechanisms of realization of the cascade effects of the regulatory peptides [1]. In particular, extensive interaction of SP with classical mediators, with a variety of CNS receptors, and with other substances of peptide nature, with which SP exists in both synergic and antagonistic relations [2], has been described.

In our experiments kalipsol, an analgesic and corresponding in autonomic manifestations to a preparation weakening the tone of the parasympathetic division, proved ineffective in restoring the functional properties of LH when disturbed by SP. Under the influence of beta-adrenoblockers the avoidance reaction evoked from LH against the background of the action of SP ceased, after which electrical stimulation of this motivation center, just as in intact animals, was accompanied by a feeding reaction. Abolition of the avoidance reaction on stimulation of LH against the background of SP by means of beta-adrenergic antagonists can be explained by the involvement of catecholamines in the central architecture of this behavioral reaction [10] and numerous indications of the involvement of the adrenergic formations of the brain in the central effects of SP. However, adrenergic mechanisms play an important role also in the formation of feeding motivation [6, 9]. This, in turn, raises the question why, after eliminating the effect of SP on the functional properties of LH, beta-adrenoblockers did not affect the central mechanisms of the feeding reaction.

After many years of investigation of the role of catecholamines in the regulation of feeding behavior, Leibowitz [7] concluded that feeding behavior is initiated at the hypothalamic level predominantly by stimulators of alpha-, and not beta-adrenoreceptors. Excitation of beta-adrenoreceptors, just as of dopamine receptors, on the other hand, inhibits food consumption by animals [7]. However, this conclusion is contradicted by the results of experiments in which the use of beta-adrenoblockers suppressed, and did not enhance, the feeding behavior of animals in response to stimulation of LH [9].

The results of these experiments indicate an important role of beta-adrenergic mechanisms, possibly not alone, in the modification of the functional properties of the hypothalamic feeding center under the influence of SP, while at the same time they confirm the views of Leibowitz on the importance of beta-adrenoreceptors in the mechanisms of hunger and satiation.

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