EFFECT OF MESENCEPHALIC STIMULATION ON RESPONSES TO NOCICEPTIVE STIMULATION OF THE DENTAL PULP

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UDC 612.884-06:612.826.5

Chronic experiments on cats showed that stimulation of certain zones of the mesencephalon reduces or completely suppresses responses to pain caused by stimulation of the dental pulp. Depending on the parameters of brain stimulation the antinociceptive effect was manifested as differential changes in individual motor, autonomic, emotional, and behavioral components of the integral nociceptive response. After-analgesia was found and the dynamics of the return of the various manifestations of pain after cessation of brain stimulation was noted. The possible mechanisms of the antinociceptive effect are discussed.

KEY WORDS: pain; mesencephalon; analgesia; emotional behavior.

Recent investigations have shown that stimulation of the central gray matter and of certain other deep brain structures is accompanied by analgesia [3, 6, 7, 9-13]. In most of these investigations the antinociceptive effect was determined from the increase in the pain threshold or suppression of the generalized response to nociceptive stimulation, and virtually no attempt has been made to investigate changes in the individual components and manifestations which, as has been shown [1, 5], form the integral nociceptive response and are integrated at different brain levels.

The object of this investigation was to make a more detailed study of the antinocicpetive effect by studying changes in individual manifestations of the nociceptive response to graded stimulation of the dental pulp.

EXPERIMENTAL METHOD

Altogether 25 experiments were carried out on three cats. The dental pulp was stimulated in chronic experiments with square pulses (0.5 msec, 6 pulses/sec, 0.2-10 mA) through electrodes implanted into the pulp of an upper incisor by the method of [14] modified in the writers' laboratory [2]. The central gray matter was stimulated through nichrome electrodes implanted in accordance with sterotaxic coordinates taken from the atlas of the cat's brain [15]. The parameters of the stimuli varied within the following range: 0.5-1 msec, 15-100 pulses/sec, 1-10 V. The duration of stimulation was 20-30 sec. The "points" whose stimulation induced analgesia had the coordinates A2, R1, HO; A6, R1, H + 2, A6, R1, H + 2. The electrodes were inserted into the dental pulp and brain under pentobarbital anesthesia. The experiments were carried out 10-14 days after the operation.

EXPERIMENTAL RESULTS AND DISCUSSION

Three consecutive developing levels, characterized by certain manifestations and intensities, assessable conventionally on a point scale (Table 1), were distinguished in the integral nociceptive response of cats to gradually increasing stimulation of the dental pulp.

The first level was characterized by manifestations arising in response to stimulation with an intensity of 1-1.5 thresholds (stimuli with an intensity of 0.2-0.5 mA, inducing the mouth opening reflex, were taken as the threshold) and not accompanied by autonomic, emotional, or behavioral response to the pain. Since the

Department of Pharmacology, I. P. Pavlov First Leningrad Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR S. V. Anichkov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 82, No. 10, pp. 1158-1161, October, 1976. Original article submitted February 9, 1976.

TABLE 1. Manifestations of Nociceptive Response and Their Intensity during Gradually Increasing Stimulation of Dental Pulp

Level of response	Manifestations	Intensity of stimulation in thresholds				
		1	2	4	6	8
1st (perception of pain)	Mouth opening reflex	1	2	2	2	2
	Licking	1	2	2	2	2
2nd (tolerance to pain)	Piloerection	—	1	2	2	2
	Changes in respiration	—	1	1	2	2
	Uncontrolled movements, throwing back the head, stepping movements with the paws	—	—	1	2	2
3rd (generalized response)	Protective movements	—	—	—	1	2
	Scratching	—	—	—	1	2
	Running	—	—	—	1	2
	Crying	—	—	—	1	2
Total number of points for stimuli of each particular strength		2	6	8	14	19

Legend. 1) Point manifestation clearly observed, 2) very strongly observed.

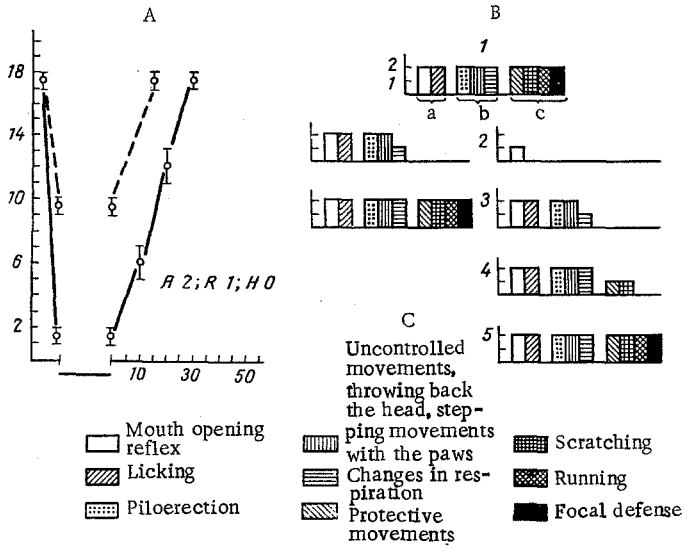

Fig. 1. Effect of mesencephalic stimulation on generalized nociceptive response to stimulation of dental pulp in cats. A) Combined data (10 experiments) on change in itensity of nociceptive response to brain stimulation with an intensity of 3 V (broken line) and 4 V (continuous line). Abscissa, time (in sec); ordinate, magnitude of response in points (according to Table 1). Numbers show time after cessation of brain stimulation. Line beneath abscissa shows period of brain stimulation (30 sec). Stereotaxic coordinates of stimulated point shown on right of graph; B) changes in individual manifestations of combined nociceptive response during brain stimulation with intensity 3 V (diagrams on left) and 4 V (diagrams on right). 1) Structure of nociceptive response to stimulation of dental pulp with intensity of 8 thresholds (normal); 2) against background of mesencephalic stimulation; 3, 4, 5) 15, 20, and 30 sec after brain stimulation. Diagrams: ordinate, conventional rating of intensity of each manifestation of nociceptive response, in points; a, b, c) 1st, 2nd, and 3rd levels of nociceptive response (according to Table 1); C) conventional representation of individual manifestations of nociceptive response given in Table 1.

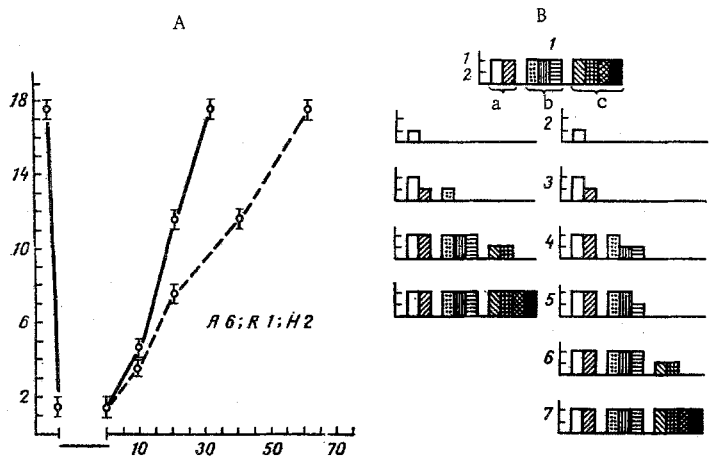

Fig. 2. Dynamics of recovery of pain response to stimulation of dental pulp after mesencephalic stimulation: A) combined data (10 experiments) for restoration of generalized nociceptive response after brain stimulation for 30 sec (continuous line) and 5 min (broken line); B) recovery of individual manifestations of generalized response after brain stimulation for 30 sec (diagram on left) and 5 min (diagrams on right). 1) Structure of nociceptive response to stimulation of dental pulp with intensity of 8 thresholds, under normal conditions, 2) with accompanying brain stimulation, 3, 4, 5, 6, 7) 10, 20, 30, 40, and 60 sec after stimulation respectively. Remainder of legend as in Fig. 1.

leading features of this level were very specific for nociceptive stimulation of the pulp [12, 14], it was called the level of pain perception. Level 2 occurred from the time of appearance (stimulus intensity 2-3 thresholds) of piloerection, changes in respiration, throwing back the head, uncontrolled movements, and other features (salivation, dilation of the pupil on the side opposite to stimulation, which were not assessed in points) during a further increase in the intensity of the manifestation of pain perception. All the features of the second level mentioned above can be regarded as analogs of the emotional-behavioral response to tolerable pain [1, 5].

Characteristically during this period the animal was strained; it made energetic stepping movements with its paws, turned around, tried to find a comfortable position, and "pressed itself" into the floor of the experimental chamber. With an increase in stimulus strength (up to 8-10 thresholds) responses indicating strong and unendurable pain appeared, accompanied by generalized reactions. During this period the cats made sudden protective movements and attempted to pull out the electrodes; they became aggressive or they responded by running and crying. Autonomic manifestations were strong: apnea, marked piloerection, micturition, etc.

During mesencephalic stimulation with a strength of 1-2 V, a duration of under 0.5 msec, and a frequency of under 30 pulses/sec virtually no change was found in the structure of the original nociceptive response. During stimulation under different conditions (3 V, 1 msec, 30-60 pulses/sec) an antinociceptive effect now developed, in which the manifestations of the third level disappeared from the combined nociceptive response (Fig. 1). In this case it can be surmised that the influences of the antinociceptive structures were oriented primarily toward brain systems forming emotional and behavioral components of pain, and that the antinociceptive effect developed as a result of disturbance of the mechanisms responsible for generalized manifestations of pain [1, 3]. Under these conditions of stimulation, influences restraining the development of the generalized response and increase in the period of tolerance to pain were effective only during stimulation of antinociceptive structures, for all the features of the third level were restored immediately after stimulation ceased (Fig. 1).

Increasing the intensity of stimulation to 4-4.5 V was accompanied by deep analgesia during stimulation, i.e., by total inhibition of all features of the second and third levels, and the intensity of responses of the first level was sharply reduced. Whereas normally stimulation of the dental pulp with an intensity of 6-8 thresholds evoked a generalized response, during concurrent stimulation of the antinociceptive points it was accompanied by features of the first level only, corresponding to pain perception. Only during very strong stimulation of the pulp (18-20 thresholds), applied against the background of brain activation, did a generalized response similar in quantity and intensity of its features to the initial generalized response to a stimulus of 8 thresholds arise.

The results of these experiments indicate that the antinociceptive effect was manifested also by a sharp increase in the threshold of pain perception. It has been suggested that elevation of the pain threshold is due to inhibition of activity of neurons which form the ascending high-threshold afferentation [3, 9].

After cessation of stimulation, features of the nociceptive response were restored in the opposite order to their disappearance: first the manifestations of the first level increased, then followed the autonomic responses, and it was only after 15-20 sec that a generalized response to stimulation of the dental pulp appeared (Fig. 1). This order of increase of the components of the nociceptive response is evidence, in the writers' opinion, of the existence of antinociceptive aftereffects, oriented mainly toward inhibition of systems integrating generalized responses to pain. These influences were discovered in a more differentiated form when the dynamics of recovery of the structure of the nociceptive response were studied after prolonged stimulation of antinociceptive points (Fig. 2).

As Fig. 2 shows, longer activation of antinociceptive structures was not accompanied by deepening of analgesia in the course of stimulation. However, with an increase in the duration of brain stimulation the intensity and duration of the antinociceptive action also increased in the poststimulation period.

In one particular experiment, for instance (Fig. 2B), the generalized nociceptive response was restored as early as 30 sec after the end of brain stimulation for 30 sec, but after brain stimulation for 5 min the features of the third level did not appear until 60 sec had elapsed.

These results show that the analgesic action persists after cessation of stimulation of antinociceptive structures. It is in the poststimulation period that the component of antinociceptive action which determines inhibition of the generalized response to pain is clearly revealed and that tolerance to pain is increased. After-analgesia can arise only as a result of the reverberation of excitation in neuronal circuits of antinociceptive structures or on account of a change in the content of neurochemical mediators in those structures [11]. The possibility cannot be ruled out that an important role in the origin of the after-antinociceptive action is played by neurohumoral shifts and readjustments of the systems integrating the manifestations of the generalized response to pain.

The differential nature of the changes in the combined nociceptive response to stimulation of antinociceptive structures revealed by these experiments suggests that the antinociceptive effect, as a psychophysiological phenomenon, is due not only to the primary inhibition of the high-threshold flow ascending from relay neurons connected with high-threshold "nociceptive" afferentation, but also to a disturbance of the mechanisms involved in the emotional and behavioral response to pain. If the antinociceptive effect is examined from this aspect, it is clearly most useful to investigate its pharmacological modulation by the use not only of specific pain-relieving agents, but also of psychotropic drugs.

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