# EFFECT OF MORPHINE ON CARDIOVASCULAR RESPONSES TO STIMULATION OF THE DIENCEPHALIC CENTER FOR PAIN INTEGRATION

M. M. Kozlovskaya and A. V. Val'dman*

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Morphine in analgesic doses inhibits the pressor responses evoked by stimulation of the periventricular system, and this is responsible for its effect on the diencephalic center for integration of visceromotor manifestations of the emotional response to pain.

Analgesics block vascular reflexes arising from "nociceptive" afferent fibers of group C [3]. The cardiovascular response to this stimulation is the autonomic component of the emotional response to pain [2]. Integrative centers of the autonomic equivalents of emotions and the zone of overlapping of the "nociceptive pathways" lie at the meso-diencephalic level. Diffuse pathways of conduction of nociceptive sensation pass through the central gray matter of the mesencephalon to the nuclei of the third ventricle [11]. The writers have shown [5] that manifestations of a generalized nociceptive response to electrodermal stimulation are identical with manifestations of the emotional response of aggressive-defensive type evoked by stimulation of nuclei of the third ventricle.

The effect of morphine was studied on cardiovascular responses to direct activation of the system of periventricular hypothalamic nuclei and, for comparison, of other diencephalic nuclear complexes. The object of the investigation was to determine whether morphine has a selective action on the cardiovascular responses associated with an emotional state of the aggressive-defensive type accompanying severe nociceptive stimulation, or whether the effect of the analgesic is the same on the other cardiovascular responses associated with other forms of behavior.

## EXPERIMENTAL METHOD

Several unipolar electrodes were implanted into rabbits, mainly into the nuclei of the hypothalamic periventricular system. In long-term experiments the parameters of stimuli required to evoke an emotional response of aggressive-defensive type were determined. In an acute experiment on unanesthetized animals the functional characteristics [1] of the cardiovascular responses evoked in the same animals by stimulation of the previous parameters were recorded. Other types of behavioral responses and the accompanying cardiovascular manifestations to stimulation of dorsal and lateral hypothalamic nuclei were recorded similarly. The position of the active tip of the electrode was determined histologically and identified by reference to the atlas of the rabbit's diencephalon [6]. Observations were made on 30 animals.

## EXPERIMENTAL RESULTS AND DISCUSSION

Activation of the nuclear complexes of the hypothalamic periventricular zone, with which the development of an emotional aggressive-defensive response to pain is connected, evoked cardiovascular responses

*Corresponding Member, Academy of Medical Sciences of the USSR.

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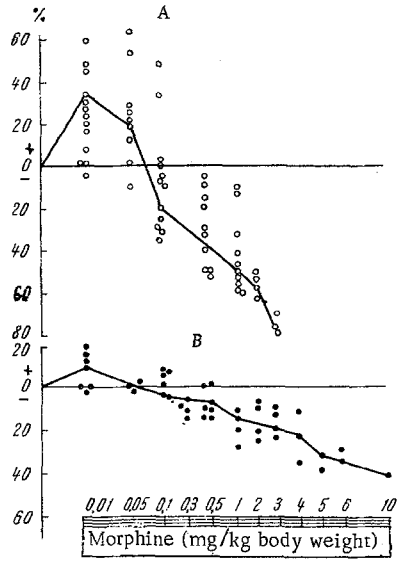


Fig. 1. Amplitude of pressor responses versus dose of morphine. A) Stimulation of nuclei in wall of third ventricle (periventricular, dorsomedial, paraventricular); B) stimulation of dorsolateral hypothalamus and subthalamus. Abscissa, dose of morphine (in mg/kg); ordinate, change in amplitude of pressor phase (in % of initial level). Upward – facilitation, downward – inhibition. Each point is the result of a single observation.

characterized by a low threshold and by a rapid and steep rise of the pressor phase. The functional characteristics and structures responsible for these responses have been analyzed in detail by the writers previously [1]. Responses of this type were very sensitive to the action of morphine. The relationship between the change in amplitude of the pressor response and the dose of morphine is shown graphically in Fig. 1A, reflecting aggregated experimental results. In small doses morphine caused facilitation, while in analgesic doses it caused a sharply increasing inhibition of the pressor response.

Dynamics of changes in the response produced by increasing doses of morphine is illustrated in Fig. 2A. The facilitatory action of small doses of morphine on the amplitude (h) of the pressor response, slight reduction in the latent period, and, with a gradual increase in the dose, a subsequent decrease in amplitude of the response with no distinct changes in the parameters of the rising slope (t, angle $\alpha$) can be seen. Morphine had a similar biphasic effect on the respiratory responses and the changes in muscle tone recorded in the same animals, which, like the vascular responses, are somato-autonomic correlates of the nociceptive and aggressive-defensive responses.

The dynamics of development of the inhibitory effect of morphine on the cardiovascular response of this type and on the various components of the aggressive-defensive behavioral response observed in the same animals under long-term experimental conditions with stimulation of the periventricular nuclei with the same parameters of stimulation shows that in small doses (0.05-0.1 mg/kg) morphine modified the emotional and purposive direction of behavior [7]. Defensive movements remained intact or were even increased to some extent, correlating with the facilitatory action of morphine on the pressor phase of the vascular response. In doses of 0.3-0.5 mg/kg morphine prevented the development of a generalized emotional pain response to electrodermal stimulation, which was analyzed in a special series of observations [5], while in slightly larger doses (0.5-2 mg/kg) it reduced the intensity of the motor manifestations in responses of aggressive-defensive type, both in long-term [7] and in acute [8] experiments. The amplitude of the pressor phase of the vascular response showed a parallel decrease.

In some cases of more intensive or repeated stimulation of the periventricular nuclei the cardiovascular response was protracted in character, with a long, drawn-out falling phase (Fig. 2B). This corresponded in behavior to prolonged after-excitation of the rabbit. Morphine in small doses considerably reduced the duration of this protracted falling phase or cut it short, but caused virtually no change to the initial segment of the pressor phase.

Under stereotyped experimental conditions the effect of morphine also was studied on cardiovascular responses corresponding to nonnociceptive, nonemotional, motivated forms of behavior (of the searching type) or motor responses of undirected character. They occurred in response to stimulation of the dorsal hypothalamus, the subthalamus, and lateral zones of the rostral hypothalamus, and they differed from the first type in their functional characteristics [1]. Responses of this type were very resistant to the action of morphine (graph in Fig. 1B). Only in response to total doses of between 4 and 6 mg/kg of morphine was the amplitude of the response reduced by 20-30%. Differences in the action of morphine on different types of cardiovascular responses recorded in the same animal were particularly marked. A fragment of one such experiment is illustrated in Fig. 3. The response arising to stimulation of the rostral zones of the periventricular nucleus (A) was considerably inhibited by morphine in a dose of 0.3-0.5 mg/kg, and parallel inhibition of the respiratory response and changes in muscle tone occurred. The responses arising to stimulation of the subthalamus (B) show little change even after injection of 5 mg/kg morphine. The respiratory responses and muscle contractions accompanying stimulation of these zones likewise were not inhibited.

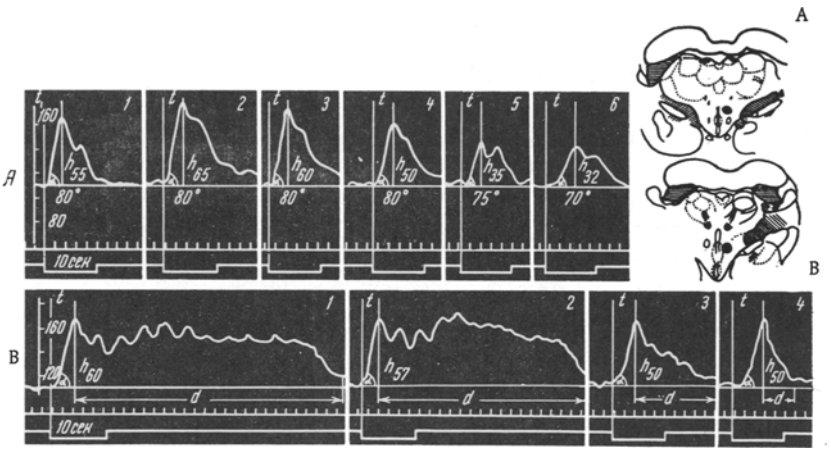


Fig. 2. Changes in parameters of cardiovascular responses evoked by stimulation of periventricular nuclei by increasing doses of morphine. A) Stimulation of periventricular nucleus: 1) normal, 2, 3, 4, 5, and 6) after administration of morphine in doses of 0.01, 0.05, 0.3, 0.5, and 1 mg/kg respectively; B) stimulation of lateral zones of dorsomedial nucleus: 1) normal, 2, 3, 4) after administration of morphine in doses of 0.05, 0.3, and 0.5 mg/kg respectively. From top to bottom: arterial pressure, time marker (2 sec), marker of stimulation; h) amplitude of pressor phase (in mm Hg); t) time of rising phase of pressor response (in sec); $\alpha$) angle of rising phase; d) falling phase of response. Diagrams on right show localization of electrodes.

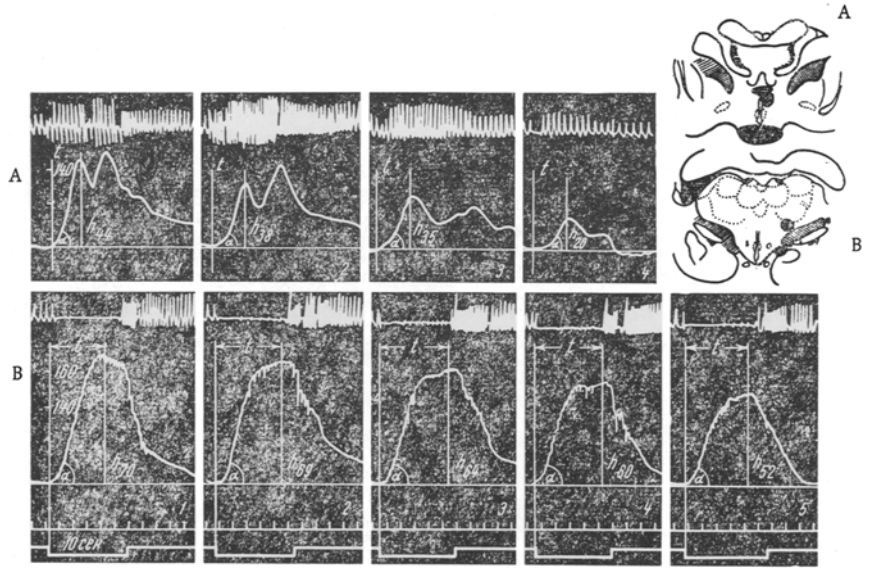


Fig. 3. Different actions of morphine on different types of cardiovascular responses in the same animal. A) Stimulation of rostral zones of paraventricular nucleus: 1) normal, 2, 3, and 4) after injection of morphine in doses of 0.3, 0.5, and 1 mg/kg respectively; B) stimulation of subthalamic zone: 1) normal, 2, 3, 4, and 5) after injection of morphine in doses of 0.3, 0.5, 1, and 5 mg/kg respectively. Localization of electrodes is shown in diagrams on the right. Remainder of legend as in Fig. 2.

The fact that cardiovascular reflexes to stimulation of nociceptive C-fibers are suppressed by morphine if it is injected into the ventricles also [3], when judging from the distribution of radioactive $C^{14}$-labeled morphine the drug penetrates only for 1-1.5 mm into the brain tissue [10], is evidence of the participation of nuclei of the periventricular system, i.e., of those structures which in the present experiments underwent direct activation. The ease of suppression of the cardiovascular responses due to direct stimulation of the periventricular system, suppression of the motor and autonomic manifestations of the generalized nociceptive response, and inhibition of reflexes to stimulation of the "nociceptive" C-fibers, while at the same time there was no disturbance (even when large doses were used) of the cardiovascular responses associated with other hypothalamic structures and accompanied by other types of motivated (non-nociceptive) behavior, are evidence that the action of morphine on these nuclear complexes is in fact more selective.

Impulses from the nuclei of the third ventricle spread along the periventricular system of fibers to the central gray matter of the mesencephalon, pons, and medulla. Multiple diffuse connections exist between the gray matter and the tectum, and these serve to activate a large number of effector elements responsible for the visceromotor and somatomotor manifestations. The efferent systems of the cardiovascular responses both to stimulation of nuclei of the third ventricle and to stimulation of hypothalamic ventro- and dorsolateral nuclei are oriented on the same components: preganglionic sympathetic neurons and the "pressor zone" of the bulbar vasomotor center. According to observations made in the writers' laboratory morphine in analgesic doses does not inhibit (or, indeed, it facilitates) pressor responses to direct activation of the reticular nuclei forming the "pressor" components of the vasomotor center [4], and does not disturb discharges of sympathetic nerves (recordings from the renal nerve) arising in response to direct activation of the lateral columns of the spinal cord, which carry fibers from the "pressor" zones of the vasomotor center [9]. All these facts indicate that morphine does not disturb the bulbar and bulbospinal centers of cardiovascular reflexes.

Facilitation of pressor responses by small doses of morphine, during stimulation both of the hypothalamus and of the bulbar level, is in agreement with observations [9] showing a decrease in the inhibitory phase (postactivation depression) of discharges of a sympathetic nerve evoked by activation of the ventral columns. These phenomena are evidently of similar nature: weakening of inhibitory effects aimed at the descending systems of control of vascular tone.

It can be assumed that the pharmacotherapeutic effect of morphine, in particular, suppression of autonomic and motor manifestations of nociceptive responses, is associated with its effect on the level of the periventricular system.

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