REFLEX RESPONSES IN THE CARDIAC SYMPATHETIC NERVES AND THEIR CHANGES UNDER THE INFLUENCE OF MORPHINE

(UDC 612.833.178.2.014.46:615.783.12)

N. V. Kaverina and Yu. B. Rozonov

Laboratory for the Pharmacology of the Cardiovascular System (Head, Professor N. V. Kaverina), Institute of Pharmacology and Chemotherapy (Director, Active Member AMN SSSR, Professor V. V. Zakusov), AMN SSSR, Moscow

(Presented by Active Member AMN SSSR, V. V. Zakusov)
Translated from Byulleten' Éksperimental'noi Biologii i Medisiny, Vol. 61, No. 2, pp. 60-64, February, 1966
Original article submitted June 29, 1964

In the production of the syndrome of stenocardia, reflex reactions play an important role leading to constriction of the coronary vessels. We established earlier that reflexes arising from stimulation of the afferent fibers of somatic nerves have a constricting effect on the coronary vessels brought about through the sympathetic innervation of the heart. Further, it appeared that the application of a number of pharmacological substances, analgesics in particular, led to an inhibition of reflex action on the coronary vessels and the blood pressure. In special experiments, it was demonstrated that this effect was dependent on the central action of the analgesic substances.

The problem in the present research work was to make a further study of the mechanism of the effect of analgesic agents on the central processes responsible for the formation of reflexes occurring in the sympathetic nerves of the heart.

For solving this question most expeditiously, one needs to consider the electroneurographic method for recording reflex responses in the cardiac sympathetic nerves.

According to the observations of Sell and co-authors [7], stimulation of the afferent fibers of somatic nerves leads to the appearance of short bursts of impulses in the sympathetic nerves of the kidney and heart and to a subsequent longer inhibition of tonal activity. Judging from the parameters of the irritating stimulus and from the duration of the latent period (0.08-0.1 sec), the given response is dependent on the afferent impulses of the rapid-conducting, low-threshold fibers of the A group. Kutunskii and others [2] have confirmed that, on stimulation of the tibial and intestinal nerves with an intensity sufficient to stimulate both the A- and C-fibers, there appears in the sympathetic nerve of the kidney a secondary discharge with a latent period of 0.4-0.6 sec immediately after the initial discharge evoked by impulses of the A-fibers. This secondary discharge appears to be a response to stimulation of the afferent C-fibers. Superficial narcosis is a condition which can affect the appearance of a secondary discharge by the impulses of the C-fibers. The development of a response by stimulation of the C-fibers is accompanied by a considerable pressor reflex.

As is well known, signals of painful stimulations are transmitted in the central nervous system along the afferent C-fibers. It is just on that account that it seems particularly important to determine whether the reflex responses arise on stimulation of the C-fibers and also to examine the changes in those responses under the influence of analgesic agents.

EXPERIMENTAL METHODS

The experiments were conducted on cats narcotized with urethane and chlorolose. In order to obtain a light narcosis, the dose of narcotic agent varied from experiment to experiment corresponding to the individual sensitivity of the animals. Urethane was used at doses of 200-300 mg/kg and chlorolose at 20-50 mg/kg. Muscular movements were suppressed by dilitine applied internally at a dose of 30 mg in the course of an hour. After the thoracic cavity was opened, the left inferior cardiac nerve was teased out over a distance of 3-4 cm from the stellate ganglion and

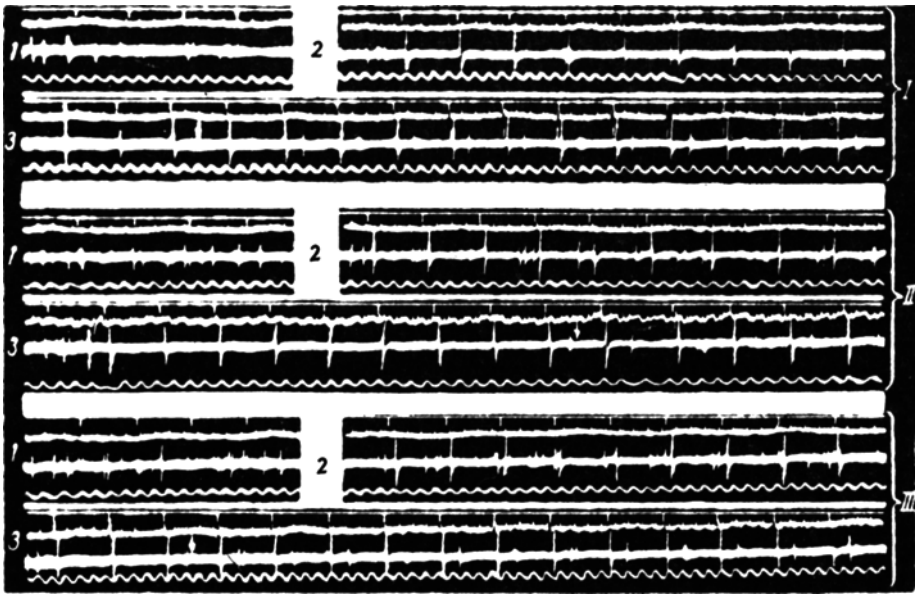

Fig. 1. Reflex responses in the inferior cardiac nerve under stimulation from the afferent A- and C-fibers of the tibial nerve and their changes under the influence of morphine (0.75 mg/kg). From above downwards; time intervals of stimulation (1 sec); ECG, impulses in the cardiac nerve; pulsations of arterial pressure. I) Tonal activity (1) and reflex responses in the inferior cardiac nerve on stimulation of the afferent A- (2) and C-fibers (3) before the administration of morphine. Reflex discharges to impulses of C-fibers appear in response to the 3rd irritating stimulus (|); II) inhibiting effect of morphine on the reflex responses from the afferent C-fibers. Weakening of the summation of stimuli 5 min after the administration of morphine (3). Reflex discharge from the afferent C-fibers appears as a response to the 10th irritating stimulus (|). III) Restoration of the original background 35 min after the introduction of morphine. Symbols the same.

then cut through near the heart. Potentials from the central segment of this nerve were led off through bipolar, platinum electrodes to a differential amplifier, type UBP 1-02 having a frequency character which was linear within the limits of 10-1000 cycles/sec. The inferior cardiac nerve was flooded with vaseline oil warmed to 37°. Parallel measurements were made of the pressure in the femoral artery by an electric manometer and the ECG. The recording was carried out with the aid of a smoothed oscillograph.

The central end of the cut tibial nerve was stimulated by electric stimuli. The parameters of the irritating stimuli were chosen so that they affected only the A group of afferent fibers (0.5-1msec, 1-5 v) or that they adequately stimulated not only the A-fibers but also the C-fibers of the tibial nerve (2-3 msec, 20-30 v). The frequency of the irritating stimulus was 0.5-1 per sec. The application of such frequencies permitted an analysis of the character of the separate components of the reflex responses.

EXPERIMENTAL RESULTS

If the tibial nerve was irritated by stimuli of an intensity of 1-5 v for 0.5-1 msec, there arose in the inferior cardiac nerve a response consisting of a short burst of impulses followed by a longer inhibition of tonal activity (Fig. 1, I and 2). The latent period of this response amounted to 0.07-0.1 sec. The duration and intensity of the response depended on the tonal activity. Since these data were in complete agreement with the observations of Sell and coauthors [7] given above, it may be considered that the reflex response in the cardiac sympathetic nerve, within the given parameters for stimulation of the tibial nerve, was dependent on the impulses of the A-fibers.

On increasing the intensity of the stimulation to 20-30 v and the duration of the stimulus to 2-3 msec, a secondary discharge occurred in the cardiac nerve immediately after the initial discharge evoked by impulses from the A-fibers. The latent period was 0.35-0.4 sec. The secondary burst of impulses usually had a lower amplitude

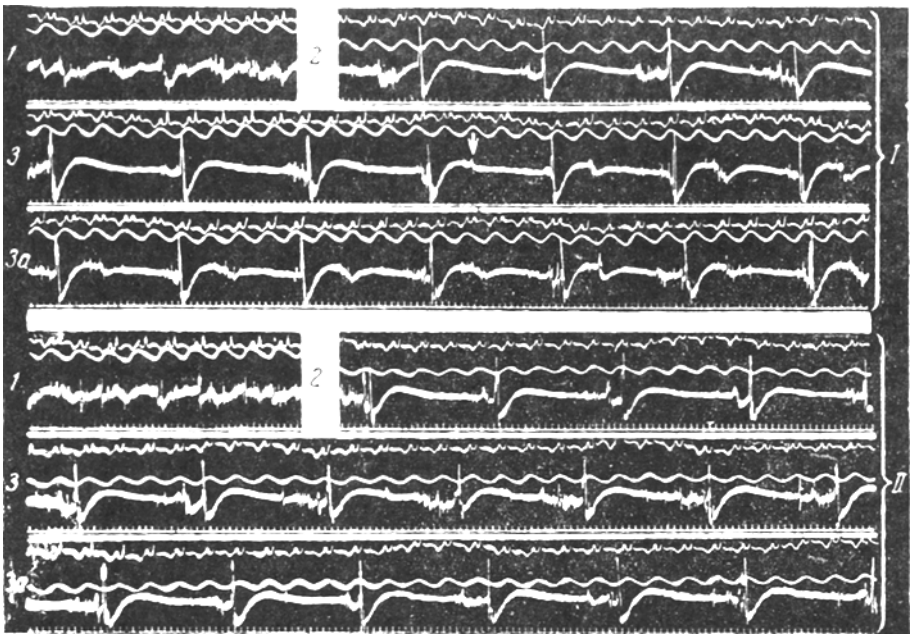

Fig. 2. Complete inhibition by morphine (1mg/kg) of the reflex responses in the inferior cardiac nerve on stimulation of the afferent C-fibers of the tibial nerve. From above downwards; ECG, pulsations of arterial pressure, impulses in the inferior cardiac nerve, time intervals 50 msec. I) Tonal activity (1) and reflex responses to impulses of afferent A- (2) and C-fibers (3, 3a) before administration of morphine. Reflex discharge from afferent C-fibers appears as response to the 4th irritating stimulus (|) (denoted by arrow). II) Five min after introduction of morphine. Reflex discharge from afferent C-fibers absent (3, 3a).

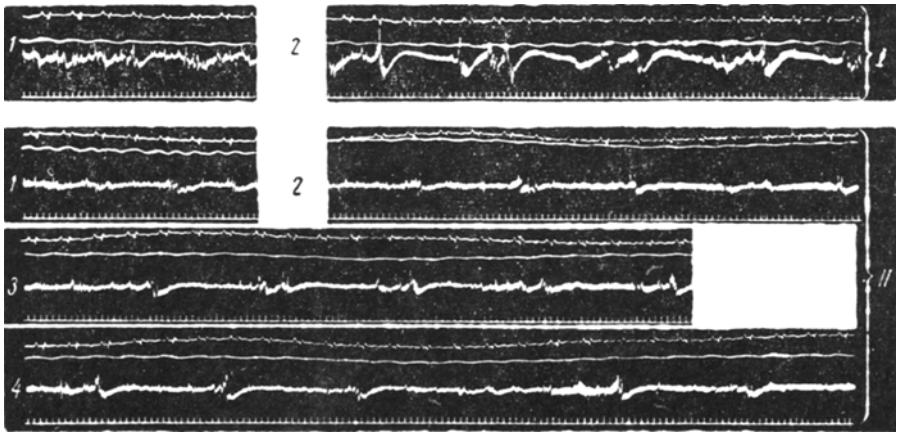

Fig. 3. Inhibition by morphine (3 mg/kg) of the reflex discharges from the afferent A-fibers at the threshold strength of stimulation. Sequence as before in Fig. 2. I) Before administration of morphine; 1) tonal activity; 2) reflex responses from A-fibers (1 v, 0.5 msec, one stimulus per sec); II) 5 min after administration of morphine; 1) tonal activity; 2) inhibition of reflex responses from A-fibers; 3) appearance of reflex responses from A-fibers on increasing the strength of the stimulation (5 v, 0.5 msec, one stimulus per sec); 4) reflex responses from A-fibers on further increasing the strength of stimulation (10 v, 0.5 msec, one stimulus per sec).

but was more prolonged than the first. It was also characteristic that, at the threshold for the given animal, the stimulation of the secondary discharge usually followed in response to the 2nd-4th stimulus and, therefore, appeared to be the result of a summation of stimuli (Fig. 1, I and 3). For the emergence of the secondary reflex discharge in response to an intensive stimulation in narcotized animals, an extended latent period was needed,also a summation of stimuli. All this is typical of a reflex discharge from afferent C-fibers [2-4,6].

The results of the experiments conducted revealed also that morphine in doses of 0.5-1 mg/kg inhibited the reflex responses in the inferior cardiac nerve evoked by discharges from the afferent C-fibers. If, prior to the administration of morphine, the secondary discharge in the cardiac sympathetic nerve appeared as a response to the 2nd-4th stimulus then, after morphine had been introduced,it appeared much later. Already, after the administration of morphine at a dose of 0.5 mg/kg, the discharge from the afferent C-fibers appeared at the 7th-8th stimulus instead of at the 2nd-4th. On raising the dose to 0.75 mg/kg this discharge usually appeared not earlier than the 10th-15th stimulus (Fig. 1, II and 3). The effect lasted for 30-35 min. Thus, its inhibiting effect on the summation of stimuli serves as the first manifestation of the effects of morphine. In this connection, our results confirm the observations of Zakusova [1] who, in experiments on intact animals, found that one of the first signs of the effects of morphine given in small doses was a weakening of the capacity of the nervous system for summation of stimuli.

An increase in the dose of morphine to 1 mg/kg, even with a stimulation lasting for 25-30 sec, did not bring about the appearance of the secondary reflex discharge (Fig. 2, II, 3a). Under these conditions, the duration of the effect amounted to 50-60 min.

Thus, morphine led to a complete inhibition of the reflex discharge evoked by the afferent impulses of the C-fibers. It is especially interesting to note that, on administration of morphine in small doses, no changes were observed in the character of the reflex responses caused by stimulating the A-fibers. When the dose was increased to 3-4 mg/kg,only the responses of the A-fibers, evoked by the threshold stimulation intensity, were inhibited (1-2 v, 0.5-1 msec). On raising the intensity of stimulation, the reflex responses from the afferent A-fibers were no different from those recorded initially (Fig. 3).

Since the reflex discharges of the A- and C-fibers recorded in our experiments have a common end path through the preganglionic neurons of segments T_1-T_{4-5} of the spinal cord, it is evident that morphine administered at the doses referred to has no effect on the sympathetic efferent paths. Consequently, it may be assumed that its inhibiting action on the reflex discharges from the C-fibers appears to be the result of a difficulty in the conduction of stimuli through the neurons of the spinal cord (which transmit the impulses of these fibers).

Such an assumption is confirmed by the observations of Haase and co-authors [5]. According to their data, morphine in doses of 0.2-0.3 mg/kg inhibits the nociceptive component of the polysynaptic response in the anterior roots of the spinal cord at levels L_7-S_1 evoked by stimulation of the afferent C-fibers of the fibular nerve. At the same time, the transmission of impulses from the A-fibers does not alter under the influence of morphine. Thus, morphine in very small doses, suppresses the reflex responses of the motor neurons of the lumbar segments of the spinal cord and of the sympathetic preganglionic neurons of the thoracic segments arising through stimulation of the afferent C-fibers. The responses of this same group of neurons to impulses of the A-fibers do not alter under the influence of morphine introduced at the given doses. These data permit it to be concluded that morphine inhibits the passage of stimuli in the spinal sensory system which transmits impulses from the afferent C-fibers. Evidently, the action of morphine is developed at the level of the lumbar segments of the spinal cord. We pointed out above that the first appearance of the effects of morphine was a weakening of the capacity for summating stimuli. It may be assumed, therefore, that the mechanism of the inhibiting action of morphine on the reflex responses of the afferent C-fibers is linked with its effect on the summation processes taking place in the sensory system of the spinal cord.

LITERATURE CITED

1. V. V. Zakusov, Farmakol. i toksikol., 6, 3, 10 (1943).
2. A. Ya. Katunskii, A. Michani, L. Fedina, et al., Physiology and Pathology of the Nervous System [in Russian] (1964), p. 51.
3. W. F. Collins and C. T. Randt, J. Neurophysiol., 21, 345 (1958).
4. W. F. Collins and C. T. Randt, Arch. Neurol. (Chicago), 5, 202 (1961).
5. J. Haase, G. Block, W. Koll, et al., in the book: 20th International Physiological Congress, Abstracts of Communications, Brussels (1956), p. 382.
6. J. Laporte and P. Bessou, C. R. Soc. Biol., 152, 161 (1958).
7. R. Sell, A. Erdely, and H. Schaefer, Pflüg. Arch. ges. physiol., 267, 566 (1958).