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ANALYSIS OF THE EFFECT OF MORPHINE AND TRIMEPERIDINE ON THE UPTAKE AND LIBERATION OF NORADRENALIN BY MYOCARDIAL TISSUE

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The effect of morphine and trimeperidine on the concentration, uptake, and liberation of noradrenalin (NA) in the rat myocardium was investigated. Trimeperidine lowers the NA level in the myocardium. Morphine does not affect the liberation of NA-^{14}C from the isolated perfused heart, whereas trimeperidine significantly increases it, affecting both the "slow" and the "rapid" release of the mediator. Trimeperidine does not affect the uptake of NA-^{14}C by the perfused heart but morphine significantly lowers it. Competition between morphine and NA is characterized by an incomplete inhibition effect: Morphine and NA mutually affect the affinity of each other for the receptor and their interaction depends on their relative concentrations.

KEY WORDS: *Noradrenalin; morphine; trimeperidine; myocardium.*

Morphine and trimeperidine are frequently used for the relief of the pain syndrome in ischemic heart disease and myocardial infarction. The central depriming effect of analgesics on tonic and reflex activity in the sympathetic nerves of the heart is connected with an increased concentration of functionally active forms of noradrenalin (NA) in the brain tissue [2]. The writer showed previously [3] that morphine lowers the NA level in the myocardium of rats and increases the concentration of free NA in perfusion fluid from the isolated rabbit heart. However, the question of whether trimeperidine influences NA metabolism

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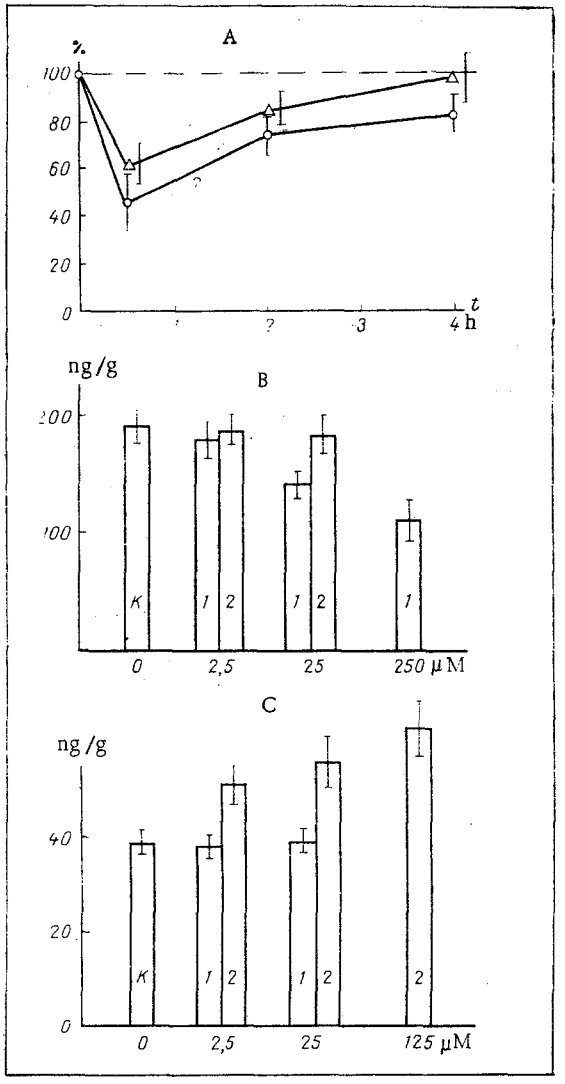

Fig. 1. Effect of morphine (1) and trimeperidine (2) on content (A), uptake (B), and liberation (C) of NA by myocardial tissue. A) Ordinate, NA content (in % of control); abscissa, time after injection of preparation (in h). B and C: Ordinate, quantity of NA taken up (B) and liberated (C) during perfusion for 10 min; K) control; abscissa, concentration of test substances. Values of M ± m given.

in the myocardium and the identify of the processes whereby morphine exerts its effect described above have not yet been investigated.

In this investigation the effect of morphine and trimeperidine on the dynamics of NA in the rat myocardium was studied.

EXPERIMENTAL METHOD

Trimeperidine (2 mg/kg) or physiological saline was injected into the caudal vein of rats. The animals were decapitated 30 min or 2 or 4 h later, the heart was removed, and its NA content determined [4, 5]. The uptake of NA-^{14}C by the rat heart, isolated by Langendorf's method, was determined [7] without chromatography of the supernatant, for during perfusion of the heart for 10 min with a solution of NA-^{14}C in a concentration of 10 ng/ml the quantity of NA metabolized does not exceed 4-7% [8]. The liberation of NA-^{14}C was investigated

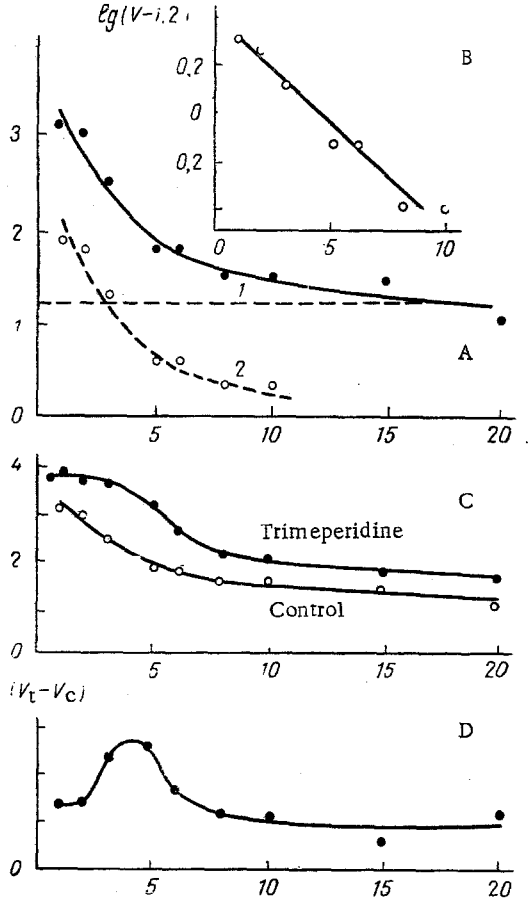

Fig. 2. Effect of trimeperidine on kinetics of NA release by the myocardium. Ordinate: A) rate of liberation of NA (in μg/min/g tissue) in control; 1) slow, 2) rapid release; B) rate of rapid release in control on semilogarithmic scale [log (V − 1.2) is logarithm of difference between total rate and rate of slow release]; C) rate of NA release (in μg/min/g) during perfusion with trimeperidine solution; D) difference between rate of release under influence of trimeperidine (V_t) and rate of release in control (V_c); abscissa, duration of perfusion (in min).

by the following method: The heart was first perfused for 10 min with a solution of NA-^{14}C in a concentration of 10 ng/ml; after rinsing of the heart perfusion was continued with a solution without NA-^{14}C (in the control experiments) or with a solution of morphine or trimeperidine. The NA-^{14}C concentration in the perfusion fluid flowing from the heart was determined by means of a scintillation counter.

EXPERIMENTAL RESULTS

As will be clear from Fig. 1A, trimeperidine and morphine lowered the NA concentration in the rat heart 30 min after injection. The NA content was close to its initial level after 4 h.

However, trimeperidine did not affect the reassimilation of NA-^{14}C by the myocardium, whereas morphine inhibited this process (Fig. 1B). Conversely, morphine did not affect the liberation of NA-^{14}C whereas trimeperidine appreciably increased it ($P < 0.05$).

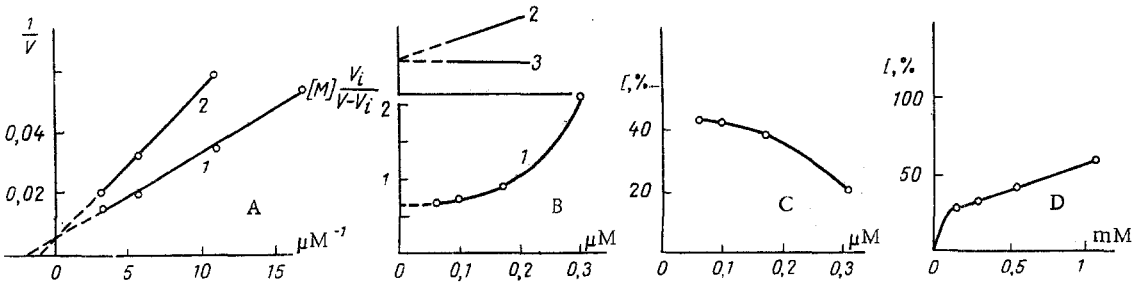

Fig. 3. Effect of morphine on kinetics of NA uptake by myocardial tissue. Ordinate: A) reciprocal of rate of uptake (1 — control, 2 — experiment); B) parameter of Hunter and Downs (V and V_i — rates of NA uptake in absence and presence of morphine, respectively); 1) experimental curve; 2 and 3) theoretical straight lines in case of competitive (2) and noncompetitive (3) inhibition; C and D) degree of inhibition of NA uptake (in % of its uptake in control). Abscissa, concentrations of NA (A, B, C) and morphine (D).

It will be clear from Fig. 2 that the rate of liberation of NA-^{14}C initially varied with time, but later became stabilized at a constant level. Liberation of NA took place at two speeds: at a constant rate — the "slow" release (Fig. 2A, curve 1), and at a rate changing with time — the "rapid" release (Fig. 2A, curve 2). If the curve of change of the rapid release is plotted on a semilogarithmic scale (Fig. 2B) the rate of the rapid release can be seen to change exponentially. The time constant of the rapid release was 6 min. The process can be expressed by the following equation:

$$N_t = 0{,}91 \cdot (1 - 0{,}01 \cdot t) + 0{,}09 \cdot e^{-t/6},$$

where N_t is the content of NA-^{14}C in the myocardium t minutes after the beginning of perfusion of the heart with solution not containing NA.

Under the influence of trimeperidine the velocity of slow release increased by 1.4 times (Fig. 2C) whereas the velocity of rapid release no longer changed exponentially (Fig. 2D). The maximal increase in the rate of release of NA-^{14}C took place 4 min after the beginning of perfusion of the heart with trimeperidine. By the eighth minute this increase in velocity was reduced, although the rate of release of NA-^{14}C under the influence of trimeperidine was still higher than in the control.

During perfusion of the heart with NA-^{14}C solution the rate of its accumulation by the tissue obeyed the Michaelis—Menten equation (Fig. 3A). The intercepts formed by continuation of the straight line (Fig. 3A) on the vertical and horizontal axes were equal to the reciprocals of the maximal rate of uptake (V_{max}) and the Michaelis constant (K_m), respectively. In these experiments V_{max} was 250 ± 40 ng/min/g tissue and K_m was 0.77 ± 0.12 μM, in agreement with data in the literature [7]. Addition of morphine to the perfusion fluid led to a decrease in the rate of NA-^{14}C uptake by the myocardium. The efficiency of inhibition of the process depended on the concentrations of both NA and morphine. With an increase in the NA concentration the efficiency of the inhibitory action of morphine was reduced (Fig. 3C), indicating the possibility of competitive interaction between morphine and NA. The curve of inhibition of NA uptake as a function of morphine concentration was biphasic in character (Fig. 3D): With low concentrations considerable inhibition of NA-^{14}C uptake (by about 25%) was observed, but with an increase in its concentration morphine inhibited the process much less strongly.

To determine the character of the effect of morphine on the NA uptake more precisely special methods of analysis of the kinetic curves were used [1, 6]. It will be clear from Fig. 3A that interaction between morphine and NA was competitive in character, for the experimental points in the presence and absence of morphine plotted in Lineweaver—Burk coordinates lay on straight lines intersecting on the vertical axis. The constant of inhibition of NA-^{14}C uptake by morphine was determined by calculation [1]. Its value was 0.62 nM.

However, further analysis [6] showed that the inhibition of NA-^{14}C uptake by morphine was more complex in character than simple competition. The experimental points in coordinates of Hunter and Downs in the case of competitive and noncompetitive inhibition must lie on straight lines (Fig. 3B). The hump found on the curve in this case is evidence of com-

petition between morphine and NA distinguished by an incomplete inhibition effect [1]. In competition of this type a triple complex (receptor—NA—morphine) may be formed. Morphine and NA probably bind with different neighboring groups of the receptor, and this determines their mutual influence on the affinity of the other for the receptor (Fig. 3C, D).

It can be concluded from the results of these experiments that morphine and trimeperidine act on peripheral adrenergic processes in the myocardium. Morphine, however, blocks the uptake of NA whereas trimeperidine stimulates its liberation. In both cases there is an increase in the free NA content in the synaptic space, i.e., the ultimate effect is the same.

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EFFECT OF LEVODOPA ON THE HEALING OF NEUROGENIC DEGENERATIVE LESIONS OF THE GASTRIC MUCOSA IN RATS

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Neurogenic degeneration of the gastric mucosa was produced in rats by immobilizing the animals for 3 h and by electrical stimulation. At the end of stimulation hemorrhagic erosions had developed in the gastric mucosa and they were still present 48 h later. Macroscopic and microscopic investigations showed that injections of levodopa into the rats in a dose of 10 mg/kg for 2 days after the end of stimulation accelerated the healing of hemorrhagic erosions of the mucosa.

KEY WORDS: *Neurogenic degeneration; healing; levodopa; gastric ulcers.*

An important role in the development of experimental neurogenic degeneration of the gastric mucosa is played by the sympathetic nervous system and its mediator, noradrenalin [1, 3, 7, 10, 12]. For instance, after electrical stimulation of rats leading to the development of degeneration of the stomach, the noradrenalin level in the organ falls [2]. Administration of the noradrenalin precursor, levodopa, after the end of electrical stimulation led to earlier restoration of the noradrenalin level in the stomach and disappearance of the hemorrhagic erosions.

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