Effect of Opioids on Mechanoreflexive Respiration Control

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The effects of opioids (morphine and fentanyl) on the function of mechanoreceptive respiration regulatory loop were demonstrated. In most opioid-treated rats (74% cases) vagotomy was followed by apneustic respiration with inspiration pause. Excess of opioids in rat CNS produced minor disturbances in the respiration rhythm, but in the absence afferent input from the mechanoreceptors of respiratory pathways and lungs, pronounced periodic apneustic respiration with inspiration pauses developed. The opioidergic system is involved in the formation of respiratory rhythm, but had no appreciable effect on transmission of mechanoreceptive nerve pulses from respiratory pathways and the lungs to the respiratory center.

Key Words: *vagotomy; morphine; fentanyl; periodic apneustic respiration; rat*

An important role in the formation of the respiratory rhythm is played by inhibitory transmitters [5,6,8,9]. Opioid peptides are the most important inhibitory transmitters in CNS. Cerebral hypoxia and ischemia accompanying many pathological cases enhance the level of endogenous opioids in CNS [4]. The use of narcotic analgesics in clinical practice is usually limited by their inhibitory respiratory side effects: overdose of these agents provokes Cheyne—Stokes respiration (periodic breathing) [1]. Surely, the endogenous opioid peptides affect the work of the respiratory center, especially under extreme conditions characterized by accumulation of opioids in the extracellular cerebral liquid. The respiratory mechanoreceptive control loop determines the degree of respiratory muscle contraction providing the necessary respiratory volume according to the signals from the respiratory center. In our experiments, GABA-positive agents blocked transmission of mechanoreceptor input to respiratory center and provoked periodic apneustic breathing [3].

Our aim was to test whether activation of opioidergic system affects transmission of nerve impulses from the mechanoreceptors in the lungs and airways to the respiratory center. To this end, we compared the effect of bilateral vagotomy on respiratory pattern in control rats and in experimental rats treated with morphine or fentanyl.

MATERIALS AND METHODS

The rats weighing 300-500 g were intraperitoneally narcotized with sodium pentobarbital (Spofa, 40-50 mg/kg). The core temperature was maintained at 37.5-38.5°C. The opioid system was modulated with μ-opioid receptor agonists morphine and fentanyl. The drugs were injected intravenously in doses of 10 mg/kg (1% solution) and 0.025 mg/kg (0.005% solution), respectively. Vagus nerves were cut at the median portion of the neck. The parameters of basic respiration such as minute respiratory volume (MRV), respiration rate (RR), and pneumotachogram (PTG) were recorded with an MX-01 polygraph under BTPS conditions. Systemic blood pressure (BP) and heart rate (HR) were measured with a catheter introduced into the femoral artery and connected to an MX-01 tensiometric transducer. Intraesophageal pressure (IEP) was measured with another catheter with a water-filled elastic balloon introduced into the esophagus and connected to an MX-01 transducer. Pressure in the esophageal catheter was set in such a way that during passive expiration it was 0 mm Hg. The data were recorded on

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an H3031-6 pen-ink recorder and analyzed statistically using Student's t test at $p<0.05$.

RESULTS

According to some authors who studied the effect of opioids on the respiratory system, the agonists realizing their effects via μ-receptors produce the most pronounced effects. [7,9]. Therefore, we used μ-receptors agonists morphine and fentanyl [2]. After systemic application, these agents easily penetrate the blood-brain barrier and can efficiently activate μ-receptors in the opioidergic system thereby simulating terminal conditions characterized by accumulation of opiates in the cerebrospinal fluid (CSF).

Systemic administration of morphine rapidly and markedly inhibited pulmonary ventilation: 3 min post-injection MRV decreased by 1.5 times (Table 1). The morphine-induced changes in RR varied: in some cases RR decreased, but more frequently RR remained at the initial level. Slow injection of morphine in most cases insignificantly prolonged the inspiratory phase. The tidal volume (TV) decreased as early as 1 min postinjection and then dropped to 58% of the control.

Our findings agree with published data on the inhibitory action of opioid receptor agonists. They showed that injection of morphine to narcotized rats inhibited ventilation by decreasing the amplitude of respiratory excursions, but not due to inhibition of the respiratory rhythm.

Intravenous infusion of fentanyl often induced rapid (within 1-5 min) and critical inhibition of respiration followed in most cases by respiratory arrest. Artificial ventilation rapidly restored rhythmic respiration. After artificial respiration, RR was below the control level, but MRV returned virtually to the initial level due to increase in TV. Then we observed disturbances in the respiration rhythm manifested in short-term periodic inspiratory delay. These abnormalities were observed for 10-15 min, because fentanyl has a short-term action period. Thus, fentanyl can induce a rapid pronounced, but short-term inhibition of respiration.

Vagotomy was performed 30 min after morphine injection. It induced a response, which is most specific for rats (Fig. 1). Immediately after vagotomy, RR dramatically dropped, and this bradypnoe was accompanied by pronounced respiratory rhythm disturbances manifested as periodic apneustic breathing with inspiratory pauses. The later could be observed in the curve of intraesophageal pressure, which was arrested in the low position corresponding to the inspiratory phase. Despite such pronounced moderation of RR (by two and more times: Table 2), MRV decreased negligibly due to a significant increase in TV (by two times). This periodic apneustic respiration was maintained for 30-40 min. During this period, the inspiratory pauses became shorter and their incidence decreased. However, RR did not restore in contrast to vagotomy performed under standard conditions. The described type of periodic respiration developed only in rats with initially elevated RR. When morphine significantly decreased RR, which was low before surgery, vagotomy induced no significant decrease in RR and MRV. Moreover, it did not disturb the respiration rhythm. In 17 of 19 experiments in this series, vagotomy induced periodic apneustic respiration with inspiratory pauses. Thus, the probability of respiratory disturbances under these conditions was 74%.

TABLE 1. Effect of Intravenous Morphine on External Respiration in Rats ($M\pm m$, n=14)

Parameter	Time, min						
	0	1	3	5	10	15	30
MRV, ml/min	25.2±1.7	15.6±1.2****	13.7±0.9****	13.9±0.8****	13.4±0.6****	14.0±0.6****	15.4±0.9****
RR, min^{-1}	58.4±1.8	53.6±2.8	56.4±3.7	57.1±3.3	56.6±3.3	56.6±3.2	58.2±3.8
TV, ml	0.43±0.02	0.30±0.03***	0.26±0.02****	0.26±0.02****	0.25±0.02****	0.26±0.02****	0.28±0.02****

Note. Here and in Table 2: ****$p<0.001$; ***$p<0.002$; **$p<0.01$; *$p<0.05$ compared to initial value at minute 0.

TABLE 2. Effect of Vagotomy on External Respiration in Rats Injected with Morphine ($M\pm m$, n=19)

Parameter	Time, min						
	0	1	3	5	10	15	30
MRV, ml/min	20.1±1.6	20.3±1.9	21.4±1.9	15.5±1.4*	15.5±1.4*	16.1±1.5	16.6±1.5
RR, min^{-1}	60.0±2.4	26.7±2.3****	27.6±2.3****	28.9±2.2****	29.4±2.1****	29.7±2.0****	30.4±1.6****
TV, ml	0.34±0.03	0.83±0.10****	0.82±0.09****	0.57±0.07**	0.56±0.06**	0.57±0.07**	0.56±0.06***

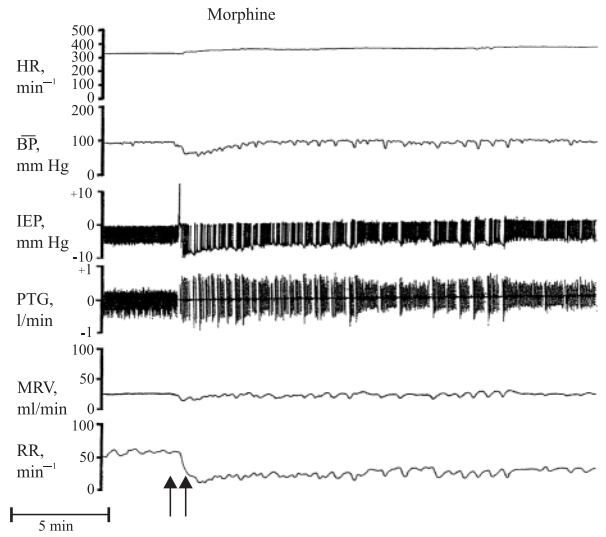

Fig. 1. Effect of bilateral vagotomy on external respiration and hemodynamics in rats injected with morphine. Here and in Fig. 2: HR, heart rate; BP, mean blood pressure; IEP, intraesophageal pressure; PTG, pneumotachogram; MRV, minute respiratory volume; RR, respiration rate. Arrows mark the moments of vagotomy.

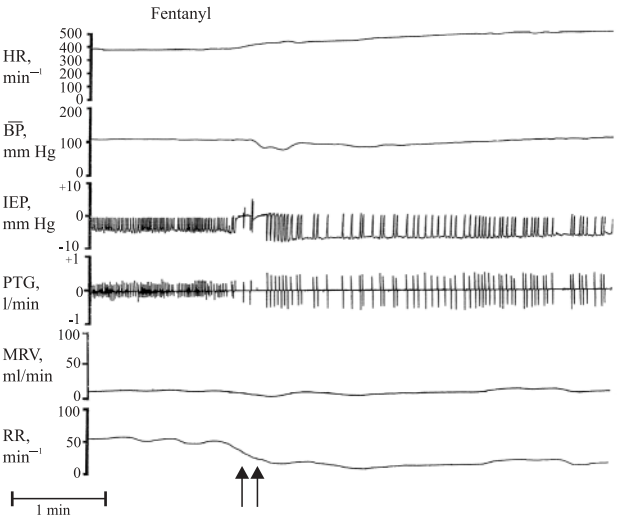

Fig. 2. Effect of bilateral vagotomy on external respiration and hemodynamics in rats injected with fentanyl.

Fentanyl often provoked respiratory arrhythmia within 10 min after injection. Vagotomy aggravated this abnormality, and respiration became apneustic (Fig. 2). RR markedly decreased, but MRV did not significantly change due to the compensatory increase in TV. If the interval between vagotomy and fentanyl injection was long and the respiration parameters returned to normal, no disturbances in respiration rhythm were observed and the surgery produced similar respiratory changes as in control rats. Thus, vagotomy against the background of activation of the opioidergic system can aggravate abnormalities of the respiration rhythm.

Activation of μ-opioid receptors with morphine or fentanyl produces no significant effect on mechanoreceptive input from the airways and lungs to the respiratory center. In case of inhibition of stabilizing vagal influence on respiratory rhythm, for example, during concurrent increase of GABA content in CSF, increased content of opioid peptides in the liquor can trigger the development of respiration rhythm abnormalities.

Thus, exogenous activation of opioidergic system does not significantly change the function of mechanoreceptive respiratory regulatory loop. Vagotomy deprives the respiratory center of stabilizing influence of the mechanoreceptive input. Vagotomy performed after administration of μ-opioid agonists usually induces periodic apneustic respiration with inspiratory pauses. Only in 2 of 19 morphine-injected rats vagotomy had no effect on respiration. We hypothesized that in these rats the blood-brain barrier was more permeable for opioids or opioid receptors in their respiratory center were more sensitive to the agonist than in rats.

Therefore, the opioidergic system is involved in the development of respiratory rhythm, but it produces no significant effect on transmission of the mechanoreceptive nerve impulses from the airways and lungs to the central respiratory regulator.

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