GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Sensitivity of the Respiratory System to Pulmonary Mechanoreceptor Impulses during GABAergic System Activation

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Acute experiments on narcotized cats show that systemic administration of the GABA receptor agonist sodium hydroxybutyrate and fenibut (phenylbutyrate) during periodic apneustic breathing and subsequent engine-like breathing reduces sensitivity of the respiratory system to afferentation from lung stretch receptors. Preliminary vagotomy does not promote the transformation of periodic apneustic breathing to engine-like breathing in response to injection of GABA agonists.

Key Words: *GABAergic system; respiration; mechanoreceptors; vagotomy; cat*

When studying regulatory effects of the brain GABAergic system on the respiration rhythm and pattern we have demonstrated that sodium hydroxybutyrate and baclofen reduce respiratory response to bilateral vagotomy [1]. This effect was explained by the interaction of the GABA agonists with $GABA_B$ receptors on neurons in the nucleus of the solitary tract [1]. The interaction of hydroxybutyrate with $GABA_B$ receptors was then proved by physiological and pharmacological methods [5-7]. It has been also demonstrated that microinjection of the $GABA_B$ agonist baclofen to the nucleus of the solitary tract inhibited the Hering-Breuer reflex in narcotized rats [8]. However, later experiments showed that GABA agonists induce biphasic changes in the respiratory rhythm in narcotized cats: periodic apneustic breathing (PAB) is then transformed into regular engine-like breathing [4].

Our aim was to study the effect of bilateral vagotomy, i.e., interruption of the afferent pathway from lung mechanoreceptors (MR) to the respiratory center, on the respiratory system and hemodynamic parameters during periodic and engine-like breathing and evaluate the role of pulmonary stretch receptors in the development of PAB.

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MATERIALS AND METHODS

Experiments were carried out on 16 mongrel cats of both sexes weighing 2.0-3.9 kg narcotized with Pentobarbital (40 mg/kg intraperitoneally). The GABA agonists sodium hydroxybutyrate and fenibut were injected intravenously in doses of 200 and 100 mg/kg, respectively. Since sodium hydroxybutyrate and fenibut produced similar effects, experimental data of these two groups were combined. Both vagus nerves were transected on the neck. The surgery and the procedure of recording of the respiratory and hemodynamic parameters are described in detail [1,3]. Experimental data in Figs. 1-4 show most typical dynamics of the studied parameters in vagotomized animals.

RESULTS

Since vagotomy is a routine approach in studies of the regulation of respiration, we do not describe the reaction to vagotomy in control animals. Vagotomy was

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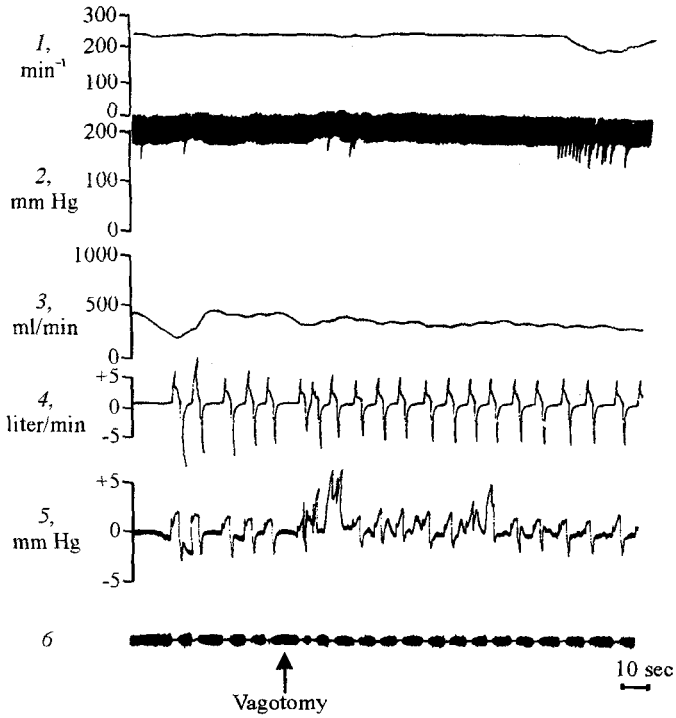

Fig. 1. Effect of vagotomy on respiration, hemodynamics, and EMG of the diaphragm in cat injected with sodium hydroxybutyrate. *1*) heart rate; *2*) systemic blood pressure; *3*) minute ventilation; *4*) pneumotachogram; *5*) esophageal pressure; *6*) EMG of diaphragm.

performed during phases I and II of GABAergic system activation. We expected that vagotomy during PAB (phase I) will aggravate respiratory rhythm disturbances and/or decrease respiration rate. However, two unexpected reactions were observed.

The first reaction was normalization of the respiration rhythm: inspiratory delays decreased or disappeared due to shortened periodicity of inspiratory muscle activity, while respiratory motions became more regular (Fig. 1).

The second reaction was the absence of the rapid (within 1 min) respiratory response (or negligible response). In these cases we observed typical PAB with inspiratory delays (Fig. 2).

Irrespectively of administered GABA agonist (fenibut or sodium hydroxybutyrate), vagotomy during engine-like breathing produced only a short-term increase in the respiration amplitude (2-5 respiratory cycles), after which the respiration volume returned to the baseline values. The most important finding was unchanged respiration rate (Fig. 3). Thus, during phase II of activation of the GABAergic system, vagotomy produced only a transient increase in lung ventilation due to a short-term increase in the amplitude of respiratory motions.

Analysis of hemodynamic parameters showed that vagotomy during phases I and II of GABAergic system activation had practically no effect on the cardiovascular functions. Hence, vagotomy during PAD and engine-like breathing little affected heart rate and systemic blood pressure. However, in some experiments marked increase in heart rate and less pronounced elevation of systemic blood pressure were observed immediately after vagotomy during phase II of GABAergic system activation (Fig. 3) probably due to elimination of vagal efferent inhibitory influences. Some authors reported that these influences can be potentiated by GABA and baclofen [9].

Our experiments demonstrated a progressive loss of sensitivity of the respiratory system to afferent signals from pulmonary MC in cats against the background of GABAergic system activation. During phase I of GABAergic system activation vagotomy more and more rapidly normalized breathing by eliminating apneustic delays, thus accelerating the development of

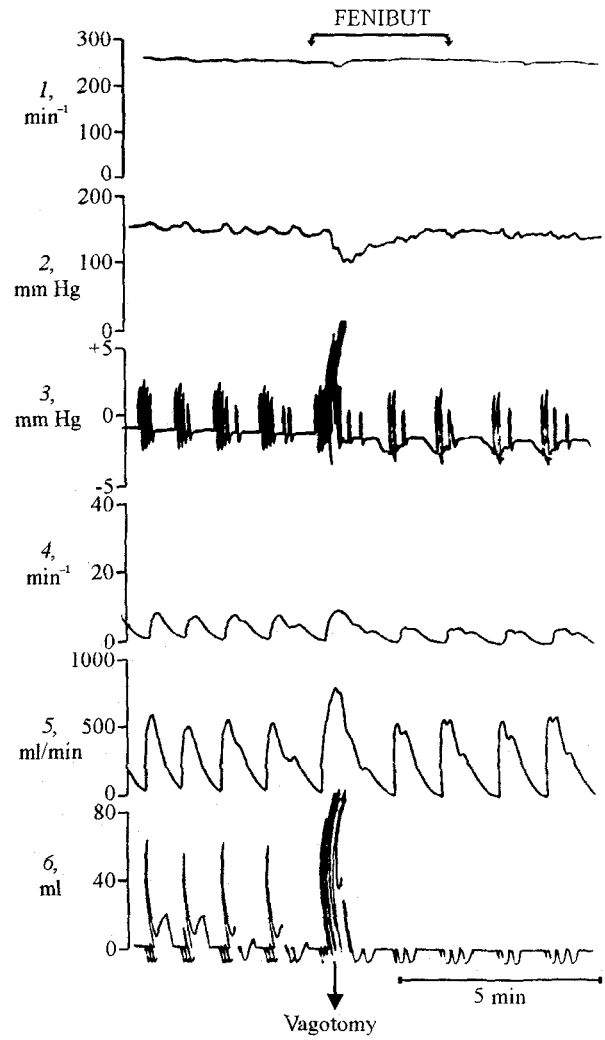

Fig. 2. Effect of vagotomy on respiratory and hemodynamic parameters in cat injected with fenibut (phase I of GABAergic system activation). Here and in Fig. 3: *1*) heart rate; *2*) mean systemic blood pressure; *3*) esophageal pressure; *4*) respiration rate; *5*) minute ventilation; *6*) respiration volume.

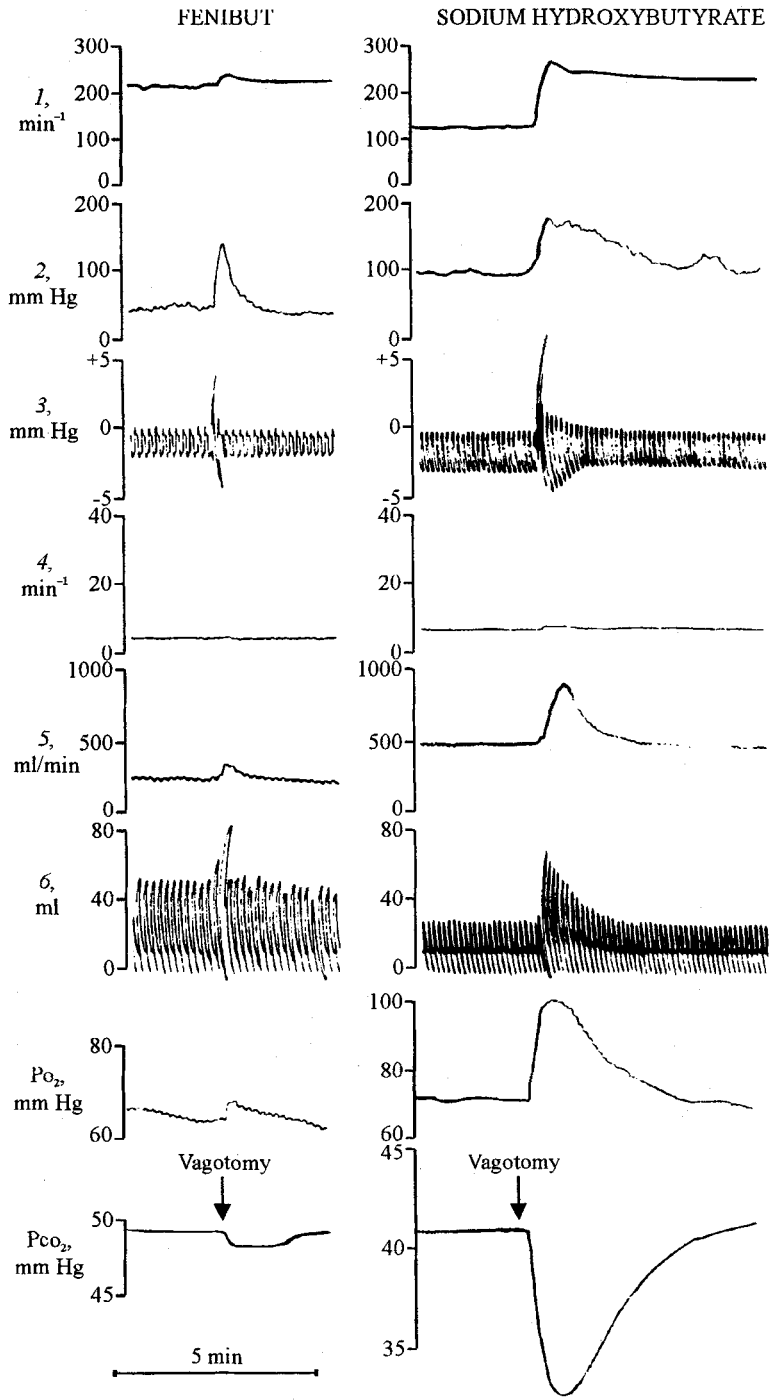

Fig. 3. Effect of vagotomy on respiratory and hemodynamic parameters and arterial blood gases in cat injected with fenibut and sodium hydroxybutyrate (phase II of GABAergic system activation).

phase II (engine-like breathing). During phase II of GABAergic system activation the respiratory system does not respond to vagotomy.

These findings suggest that the GABAergic system is actively involved in information transfer from pulmonary MC to the respiratory center in the medulla oblongata on stretching of the lung and respiratory pathways. This effect is probably achieved through presynaptic block of the vagal afferents in their primary projections via activation of $GABA_B$ receptors [1]. However, the role of the MC circuit of the respiratory center in the formation of PAB under conditions of GABAergic system activation remains unclear. It was found that vagotomy accelerates transition from PAB (phase I) to engine-like breathing (phase II), thus promoting normalization of the respiration

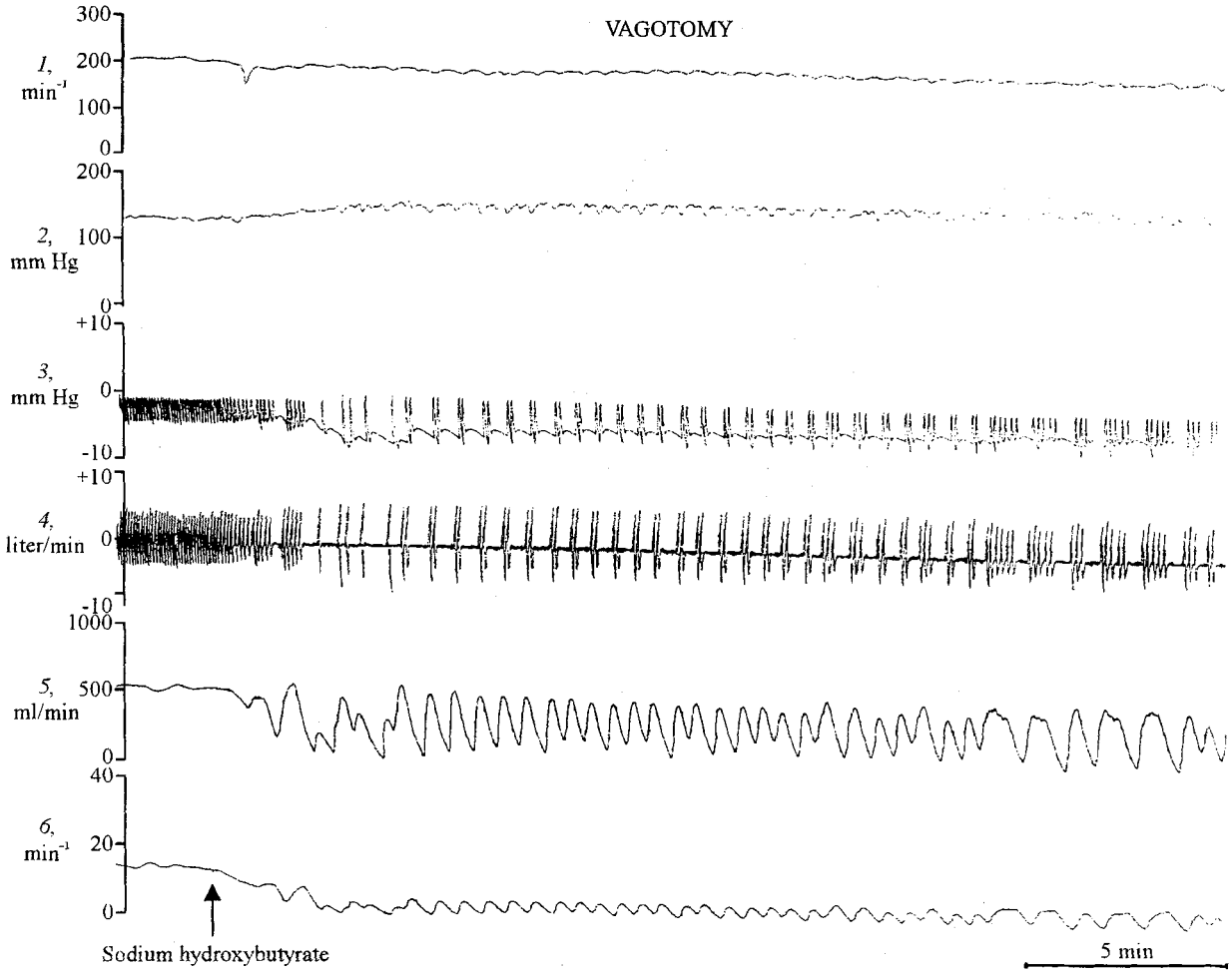

Fig. 4. Effect of sodium hydroxybutyrate on respiratory and hemodynamic parameters in vagotomized cats. *1*) heart rate; *2*) mean systemic blood pressure; *3*) esophageal pressure; *4*) pneumotachogram; *5*) minute ventilation; *6*) respiration rate.

rhythm in cats after injection of GABA agonists. It was interesting to find out whether irregular breathing developed in animals after elimination of MR afferentation.

In special experiments sodium hydroxybutyrate was injected to vagotomized cats. Typical PAB with marked inspiratory delays observed in these experiments proved that elimination of MR afferentation is not the only and/or critical factor causing disturbances in the respiratory rhythm with inspiratory arrests under conditions of GABAergic system activation.

Thus, activation of GABA receptors is associated with block of MR afferentation and readjustment of the respiratory chemoregulatory circuit [2]. Moreover, our findings suggest that afferentation from lung MR participate in the pathogenesis of respiratory rhythm disturbances, but does not play a critical role in the development of PAB.

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