Effects of GABAmimetics on Chemoreceptor Regulation of Respiration

I. A. Tarakanov, L. N. Tikhomirova, and V. A. Safonov

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 128, No. 9, pp. 274-278, September, 1999
Original article submitted March 16, 1999

Changes in chemosensitivity of the respiratory system to oxygen and carbon dioxide induced by a GABAmimetic lithium hydroxybutyrate were studied on narcotized rats. In the majority of animals (56%), this activation of GABA receptors caused periodic apnea. The sensitivity of the respiratory system to hypercapnia sharply decreased (or completely disappeared) 30-45 min after intravenous injection of lithium hydroxybutyrate, while the sensitivity to oxygen was preserved. In rats, as well as in cats, GABAmimetics can readjust the chemoreceptor circuit from respiratory CO_2-dependent to O_2-dependent regulation.

Key Words: *hypoxia; hyperoxia; hypercapnia; chemoreflex regulation of respiration; GABAergic system*

Chemoreception circuit is the main component of metabolic autoregulation of respiration, which is responsible for the adequacy of lung ventilation to metabolic requirements of the body [1,2] and stable arterial gas composition (tension of oxygen and carbon dioxide). In some diseases, the composition of blood gases is altered, which indicates considerable effects of some factors on the chemoreceptor system. The GABAergic system plays the major role in modulation of chemoreflexes in cats [3-5] and rats [7]. Comparative analysis reveals similar and different reactions of the respiratory system to GABAmimetics in cats and rats [6].

Here we studied the role of the GABAergic system in sensitivity of the respiratory center to changes in arterial blood gases and pH in rats. To this end, the respiratory responses to hypercapnia and hypoxia before and after injection of the GABAmimetic lithium hydroxybutyrate were studied.

MATERIALS AND METHODS

Experiments were performed on 3-month-old albino male and female rats (n=16) weighing 340-500 g and narcotized with sodium pentobarbital (Spofa, 40-50 mg/kg intraperitoneally+low doses intravenously). The GABAergic system was stimulated with the GABAmimetic lithium hydroxybutyrate injected intravenously in a dose of 750 mg/kg and concentration of 40% [7]. Body temperature was maintained at 37.0-38.5°C (accuracy 1°C) using a screened electric heater. Tracheotomy was performed at the level of the upper third of the trachea; endotracheal plastic tube of the corresponding diameter fixed in the trachea was connected to a transducer equipped with an inlet valve for recording respiration parameters. The main indexes of respiration (minute volume, respiratory rate, and pneumotachogram) were recorded using an MKh-01 polygraph (Russia) under BTPS conditions. Hypoxic and hypercapnic gas mixtures (10% O_2 in nitrogen and 5% CO_2 in air, respectively) were prepared from air, nitrogen, and CO_2 based on the ratio of gas flow to air flow determined by a standard set of rotameters for an anesthesia apparatus. Taking into account our previous findings that stabilization of gas tension of the blood after the onset of gas mixture inhalation takes about 3 min, all measurements were performed for 5 min. Blood samples were taken, and parameters of respiration and systemic circulation were determined on the 4th min of inhalation. The interval between consecutive exposures to gas mixtures was no less

Laboratory of Pathophysiology of Respiration, Research Institute of General Pathology and Pathophysiology, Russian Academy of Medical Sciences, Moscow

0007-4888/99/0009-0895$22.00

than 10 min. The contents of O_2 and CO_2 in gas mixture, acid-base equilibrium indexes, and blood gases were monitored using an ABL-330 device (Radiometer International AG). Blood pressure and heart rate were recorded using a catheter introduced into the femoral artery and connected to an MKh-01 tensiometer. Blood samples (85 μl) for pH analysis and gas composition were also taken through this catheter. The catheter equipped with an elastic balloon filled with water and connected to an MKh-01 transducer was introduced into the esophagus to monitor the esophageal pressure. The pressure in this system during passive expiration was set at 0 mm Hg. All indexes were recorded by an N3031-6 ink automatic recorder (Russia) and recorded in an analog form using an EAM-500 14-channel magnetograph (Tesla). The results were analyzed by Student's t test. The differences were considered to be significant at $p<0.05$.

RESULTS

We used rats at the age above 3 months to verify our assumption that the respiratory reaction depends on the age of experimental animals [6]. The probability of the development of periodic breathing in response to lithium hydroxybutyrate in rats of this age was 56%, which 2-fold surpassed this parameter in young animals [6]. These data indicate that the mechanisms of transmitter regulation in the CNS (for example, GABAergic regulation of respiration) are developed with age. This should be taken into account when analyzing the mechanisms of GABAmimetic-induced respiratory disturbances.

The respiratory reaction in rats (compared with that in cats) to lithium hydroxybutyrate consists in monophasic changes in the respiratory rate. Taking this fact into account we tested chemosensitivity of the respiratory system to hypercapnic and hypoxic stimuli before and 30 min after injection of the GABAmimetic inducing periodic breathing. Additionally, 100% O_2 was used for analyzing the sensitivity of the respiratory system to hyperoxic stimuli.

Figure 1 shows characteristic reactions of the respiration and systemic hemodynamics to hypercapnia before and after injection of lithium hydroxybutyrate against the background of periodic breathing. GABA-

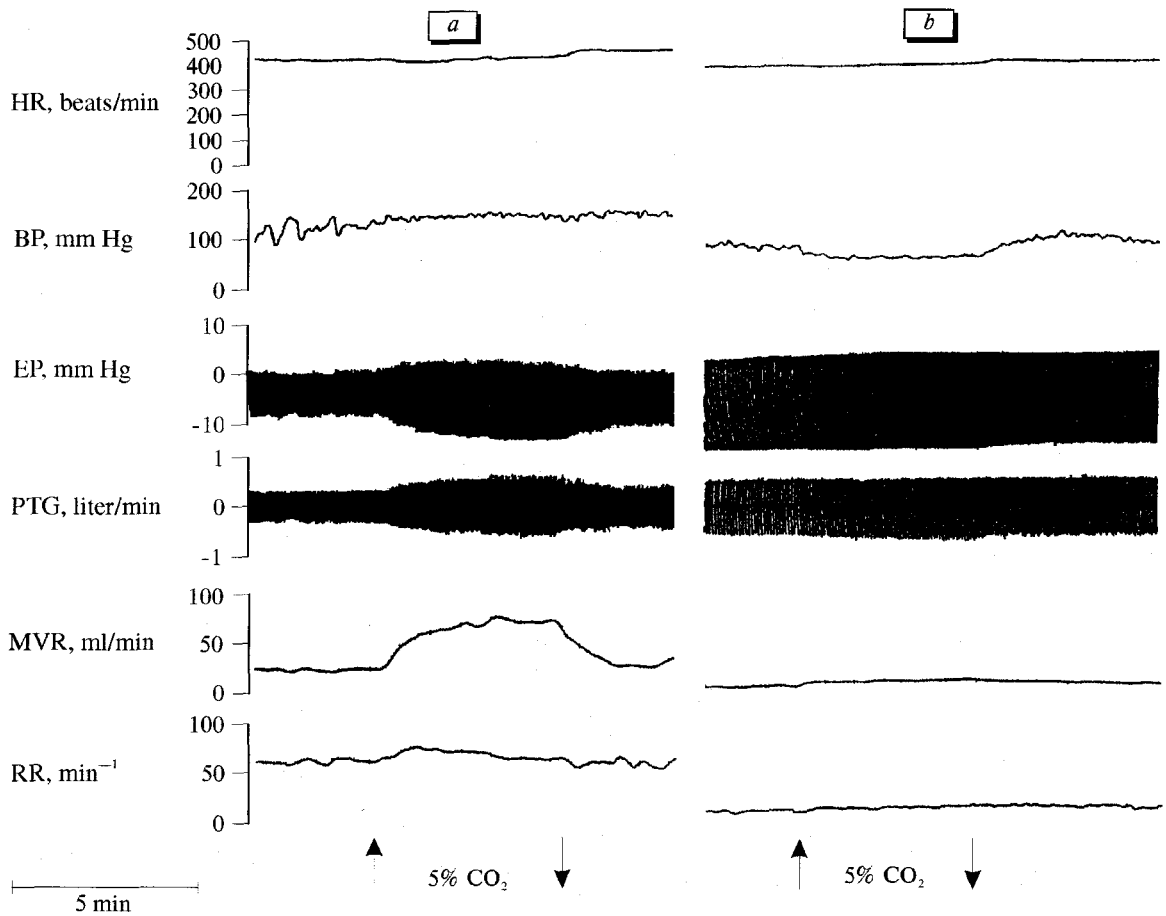

Fig. 1. Changes in respiration and hemodynamics in rats during breathing with 5% hypercapnic mixture before (*a*) and after (*b*) injection of lithium hydroxybutyrate. Here and in Fig. 2: HR, heart rate; BP, average systemic blood pressure; EP, esophageal pressure; PTG, pneumotachygram; MVR, minute volume of respiration; and RR, respiratory rate. Time is shown below; arrows designate the start and end of gas mixture inhalation.

mimetic abolished the increase in lung ventilation. Although in some rats this reaction was observed, it was less pronounced than in the control.

There was a decrease in the sensitivity of the respiratory system to hypercapnic stimuli in rats displaying no respiratory arrhythmia after administration of lithium hydroxybutyrate. These findings suggest that the mechanisms of generation of the respiratory rhythm and chemoreceptor regulation are not closely interrelated in the pathogenesis of respiratory arrhythmia.

Figure 2 shows reactions of the respiratory and cardiovascular systems to hypoxic hypoxia before and after injection of lithium hydroxybutyrate. In the initial state, inhalation of hypoxic mixture was generally accompanied by a weak reaction (Fig. 2, *a*). GABAmimetic did not abolish, but even potentiated the reaction to hypoxia (Fig. 2, *b*). Thus, the respiratory system adequately responded to reduced O_2 content. The respiratory reaction to hyperoxia was also analyzed. Although lithium hydroxybutyrate decreased the respiratory rate, transition to hyperoxia also suppressed breathing under these conditions. This confirms the fact that the action of GABAmimetics on receptors of the GABAergic system does not reduce the sensitivity of the respiratory system to oxygen deficiency or excess [3].

Arterial blood gases also served as an additional criterion in the analysis of respiratory reactions to hypoxia and hypercapnia. This parameter was chosen due to the fact that routine statistical methods (averaging of the respiratory rate and minute respiratory volume) provide no adequate information about differences or similarities, because GABAmimetics induce irregular and periodic breathing. Thus, blood gases is the integral parameter of the efficiency of lung ventilation, which minimizes the influence of respiratory changes and reflects gas exchange in the lungs. Changes in this parameter include passive (changes in blood gases determined by modulation of air gas contents) and active (changes in some other gas reflecting active reaction of the respiratory system to changes in air gas composition) components (Fig. 3).

In the initial state, hypercapnia always increases tension of CO_2 (passive component) and O_2 (active

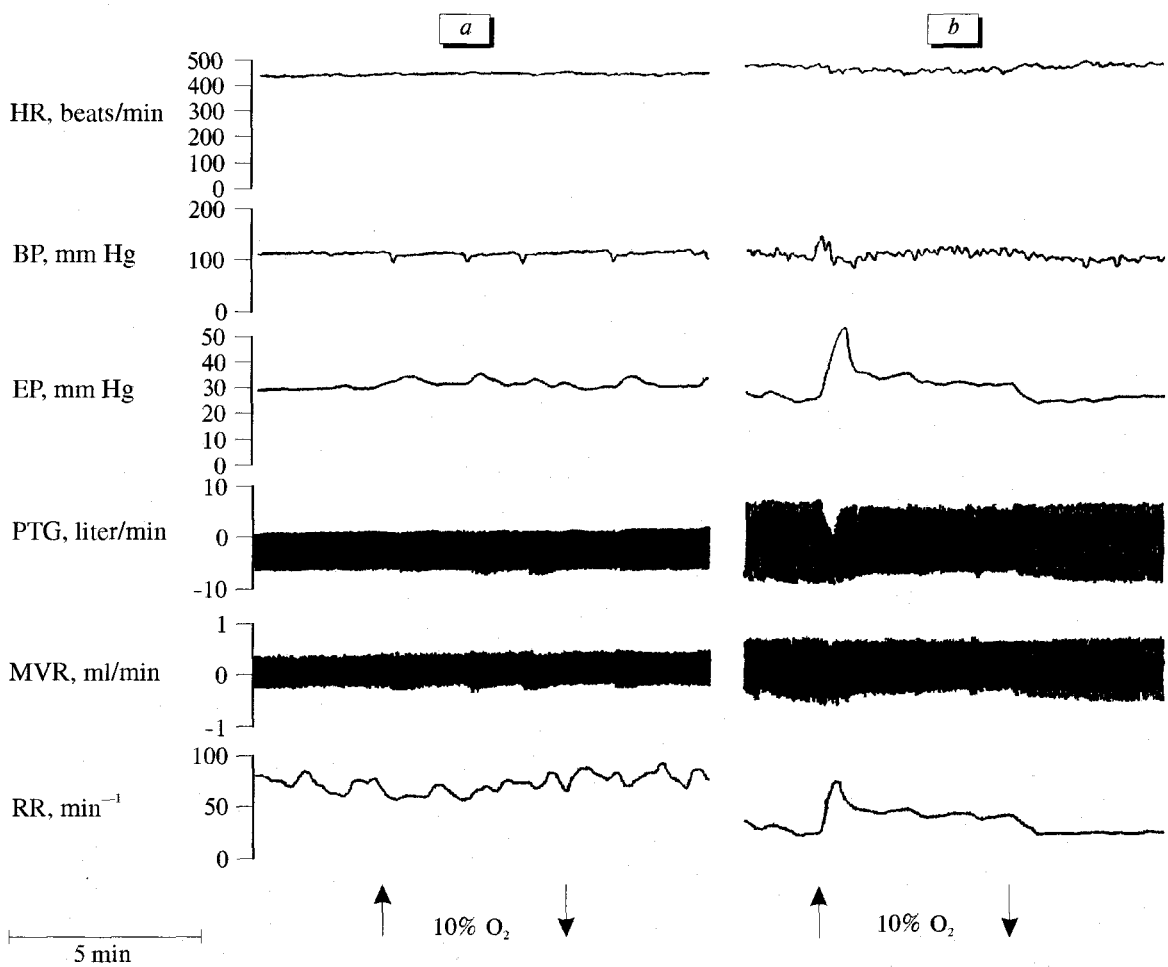

Fig. 2. Changes in respiration and hemodynamics in rats during breathing with 10% hypoxic mixture before (*a*) and after (*b*) injection of lithium hydroxybutyrate.

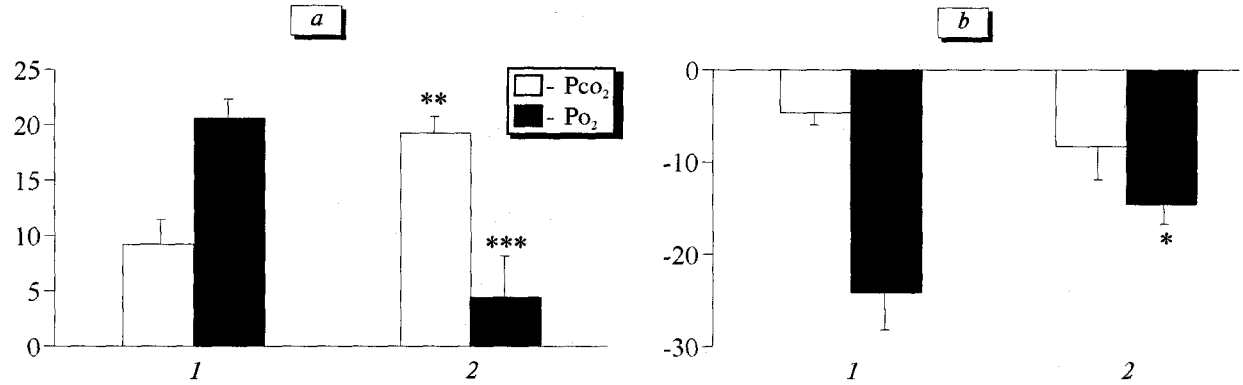

Fig. 3. Changes (Δ) in arterial blood gases (compared with the initial levels) in narcotized rats on the 5th min of breathing with hypercapnic (*a*, 5% CO_2 in air) and hypoxic (*b*, 10% O_2 in nitrogen) mixtures before (*1*) and after (*2*) injection of lithium hydroxybutyrate. Ordinate: gas tension, mm Hg. *$p<0.05$, **$p<0.02$, and ***$p<0.01$ compared with *1*.

increase in lung ventilation). Lithium hydroxybutyrate considerably increased Pco_2, but attenuated the increase in Po_2 (Fig. 3, *a*). Such differences confirm the fact that GABAmimetics sharply decrease or abolish the response of the respiratory system to excessive CO_2. This is in good agreement with the data obtained on cats [4].

We also analyzed changes in arterial blood gases during hypoxia before and after injection of lithium hydroxybutyrate (Fig. 3, *b*). In the initial state, tension of O_2 (passive component) and CO_2 (active component) decreased upon transition to inhalation of O_2-deficient mixture. After administration of lithium hydroxybutyrate, the passive component of the respiratory reaction continued to decrease, while the active component tended to increase. These data confirm that GABAmimetics do not impede active reaction of the respiratory system to hypoxic hypoxia. Our findings attest to readjustment of the chemoreceptor circuit of the respiratory regulation from CO_2-dependent to O_2-dependent regulation so that the effects of hypo- and hyperoxia on respiration become more pronounced after the injection of lithium hydroxybutyrate.

Our studies performed on rats confirm the results obtained on cats [3-5]. In spite of some differences in the type of GABAmimetic-induced periodic apnea in rats and cats, these data indicate that the GABAergic system is involved in chemoreceptor regulation of respiration and determines the reaction of lung ventilation to changes in CO_2 content. This similarity of changes in chemoreflex regulation of respiration in cats and rats that belong to various classes of mammals suggests the presence of analogous GABAergic regulation of chemosensitivity in other mammals.

REFERENCES

1. A. A. Petrov, V. A. Safonov, V. M. Nekrasova, *et al.*, *Biol. Nauki*, No. 2, 43-46 (1970).
2. V. A. Safonov, V. N. Efimov, and A. A. Chumachenko, *Neurophysiology of Respiration* [in Russian], Moscow (1980).
3. I. A. Tarakanov, *Byull. Eksp. Biol. Med.*, 123, No. 3, 264-268 (1997).
4. I. A. Tarakanov, *Ibid.*, 123, No. 4, 385-390 (1997).
5. I. A. Tarakanov, *GABAergic Mechanisms of Formation of Pathological Respiratory Rate*, Abstract of Doct. Biol. Sci. Dissertation, Moscow (1997).
6. I. A. Tarakanov and V. A. Safonov, *Ros. Fiziol. Zh.*, No. 4, 300-308 (1998).
7. J. A. Hedner, J. Jonason, and D. Lundberg, *J. Neural Transm.*, 49, 179-186 (1980).