Effect of Phenibut on the Formation of the Respiratory Rhythm

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In experiments with Nembutal-anesthetized cats of both sexes, the drug phenibut administered intravenously was found to elicit periodic apneic respiration and to rank between baclofen and sodium oxybutyrate in terms of the ability to disrupt the respiratory rhythm. It is suggested that these three activators of the gamma-aminobutyric acid (GABA) system produce differential effects on $GABA_B$ receptors (baclofen>phenibut>oxybutyrate in order of decreasing effectiveness) and participate in the formation of the respiratory rhythm, and that in activating this system they can give rise to irregular slowed respiration with pauses at inspiration.

Key Words: *cat; regulation of respiration; respiratory rhythm; phenibut; sodium oxybutyrate; baclofen; GABA-ergic system*

The structure and function of the brain's GABA-ergic system remain a subject of sustained interest in view of the important role this system plays in directing a variety of bodily functions. As studies continue to appear, more and more substances are found to be involved in regulating the metabolism and actions of GABA. The GABA-ergic system is of paramount importance for ensuring normal operation of the mechanisms regulating respiration [5,6]. In particular, as we have shown [1], GABA agonists such as sodium oxybutyrate and baclofen, administered systemically or centrally, impede the formation of the respiratory rhythm and the transmission of afferent impulses from pulmonary mechanoreceptors via the vagus nerves to neurons of the respiratory center.

The purpose of the present study was to see how selected respiratory parameters and the associated systemic hemodynamic parameters might be affected by phenibut - a substance that shares with sodium oxybutyrate and baclofen the property of being a GABA-ergic system stimulator but differs from them in molecular structure and affinity for specific receptors.

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MATERIALS AND METHODS

The study was conducted on Nembutal-anesthetized (40 mg/kg intraperitoneally) mongrel cats of both sexes weighing 2.2-3.6 kg. Phenibut was injected intravenously at 100 mg/kg. Dissection details and the procedure used to measure vital parameters are described in our earlier articles [1,4].

RESULTS

Phenibut, like the other two stimulants of the GABA-ergic system (sodium oxybutyrate and baclofen), led to a periodic apneic respiration with pauses at inspiration. Typical time courses of the respiratory and systemic hemodynamic parameters after phenibut administration are shown in Fig. 1; it can be seen that respiratory movements became slowed shortly postinjection, this being followed by the appearance of an abnormal respiratory rhythm by minutes 10-15. Respiratory pauses in places where respiratory movements were slowed became increasingly more frequent and reached their maxi-

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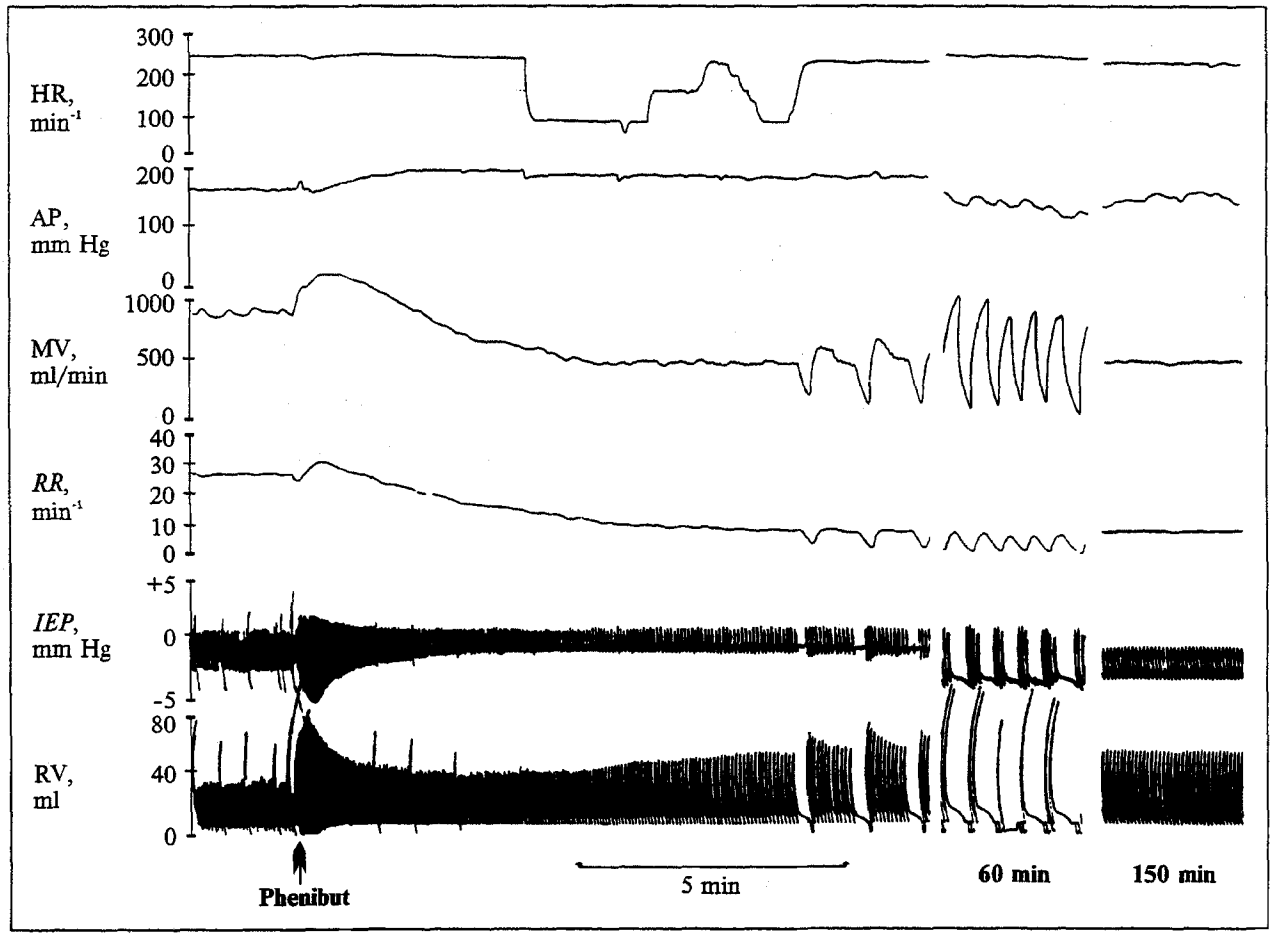

Fig. 1. Respiratory and systemic hemodynamic parameters in an anesthetized cat after phenibut injection. Here and in Figs. 2 and 3: *HR* — heart rate; *AP* — mean arterial pressure; *MV* — minute volume; *RR* — respiratory rate; *IEP* — intraesophageal pressure; *RV* — respiratory volume. The arrow marks the time of phenibut injection; 60 min and 150 min are recording times. A period of temporary cardiac arrhythmia after phenibut injection is evident on the HR curve.

mum approximately 40 to 60 min postinjection, at which time they lasted 30 sec or longer and alternated with 2-3 respiratory movements. This breathing pattern persisted for 90-120 min.

Systemic arterial pressure (AP) showed periodic fluctuations, sometimes combined with heart rate fluctuations. The AP and heart rate tended to rise when respiratory movements ceased and to fall as they were resumed.

A similar interrelationship of respiratory and cardiac periodicities was observed in our previous experiments where sodium oxybutyrate or baclofen were used to activate the GABA-ergic system [1,3,4]. Figures 2 and 3 depict typical tracings for the latter two drugs so that their effects on respiration and hemodynamics can be compared with those of phenibut. The similarities observed with regard to the emergence of apneic respiration and the linkage between responses of the respiratory and cardiovascular systems suggest that the changes mentioned above were brought about by a single mechanism. The linkage between breathing periodicity and AP is likely to be primarily due to cyclic variations in the composition of the blood (in its pH and the tension of its gases) which are detected by chemoreceptors. The increase of cardiovascular tone during apneic periods appears to be of a compensatory nature and underscores the functional unity of the respiratory and cardiovascular systems which act in harmony to supply the tissues with oxygen [2].

Since similar respiratory patterns emerged upon stimulation of the GABA-ergic system with the three agonists we tested, the alterations in the composition of arterial blood occurring under such stimulation may be illustrated by referring to our previous experiments [1,4]. These showed that the amplitudes of oscillations in Po_2, Pco_2, and pH and the shifts in their values relative to baseline (normal) levels during apneic respiration are sufficiently great to account for the observed increase in cardiovascular tone when respiration is inhibited.

The pauses between respiratory movements became progressively less frequent 90-120 min af-

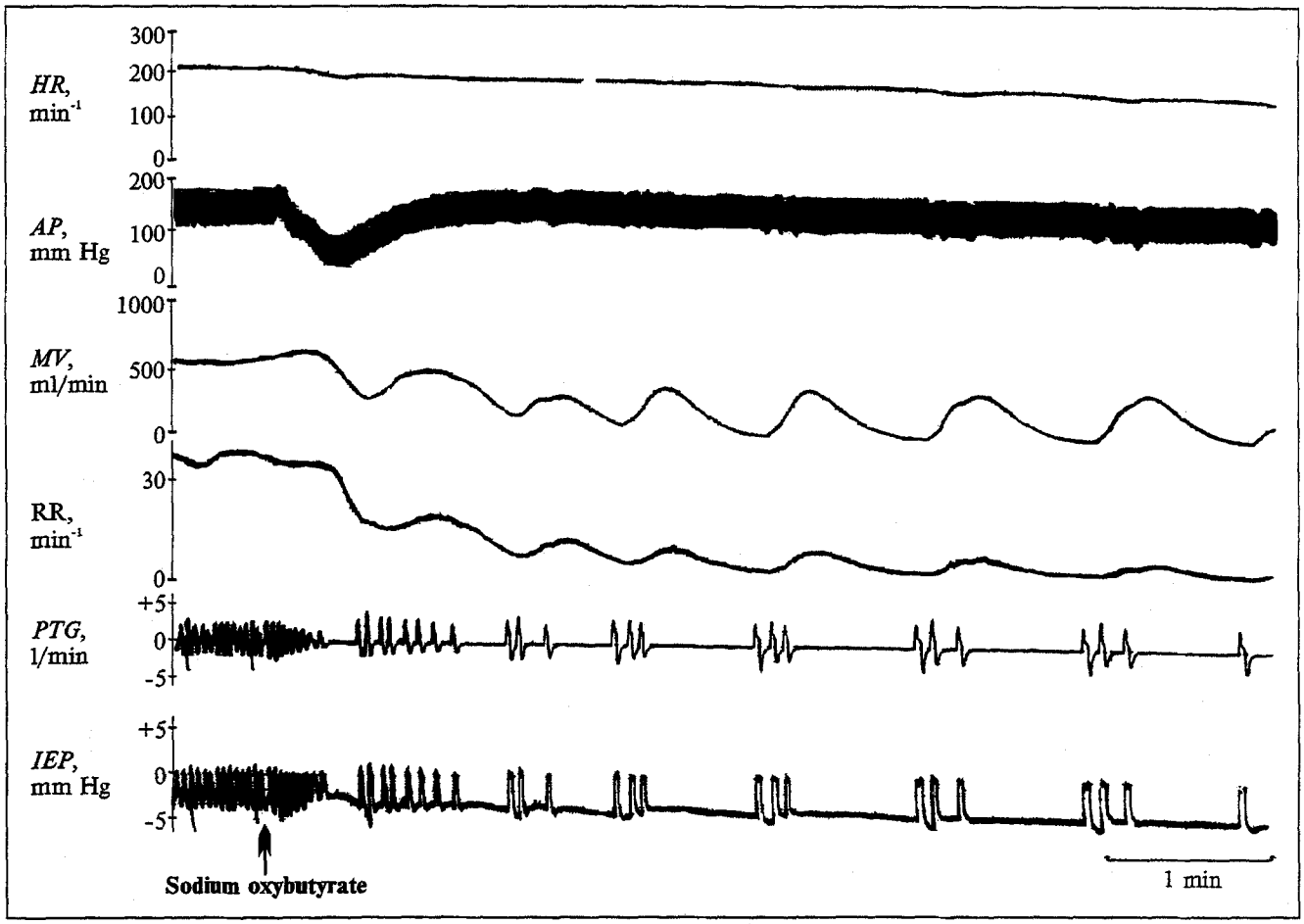

Fig. 2. Respiratory and systemic hemodynamic parameters in an anesthetized cat after sodium oxybutyrate injection. Here and in Fig. 3: *AP* – arterial pressure in the systemic circulation; *PTG* – pneumotachogram.

ter phenibut injection and disappeared completely 30-60 min later (the respiratory rhythm returned to "normal"). During that time a slow and deep breathing was maintained, which was characterized by a constant volume and frequency ("machine-type" respiration, Fig. 1). It differed from the normal (baseline) breathing in smaller minute volume (MV) values and unresponsiveness of respiratory movements. As respiratory pauses disappeared, the AP and heart rate curves smoothed out.

The GABA-ergic system agonists we tested can be ranked as follows in order of decreasing ability to disrupt the respiratory rhythm when injected intravenously: baclofen (1-5 mg/kg), phenibut (50-100 mg/kg), and sodium oxybutyrate (100-200 mg/kg). As we suggested earlier, the major mediators of respiratory disturbances following activation of the GABA-ergic system are $GABA_B$ receptors, in which case the ability of the above drugs to cause periodic apneic respiration is presumably determined by their affinity for these receptors.

Along with the similarities indicated above, the three drugs showed certain differences in their respiratory and cardiovascular effects. First, whereas the injection of sodium oxybutyrate was immediately followed by transient inhibition of respiration and cardiac activity, phenibut, on the contrary, initially stimulated respiration (increased its frequency and depth). This difference has to do with the opposite reactions of oxybutyrate and phenibut solutions (alkaline with the former and acid with the latter) which undoubtedly also have opposite effects on the chemoreceptors when administered systemically. Also, as the baclofen doses used were much lower than those of phenibut or sodium oxybutyrate, injection of this drug did not elicit substantial reactions from the respiratory or cardiovascular system. Second, phenibut injection was followed in some tests by a rise of systemic AP, which was not observed with oxybutyrate or baclofen. Phenibut, however, impaired the respiratory rhythm in all tests irrespective of its effect on AP. This further bolsters our contention that the respiratory distur-

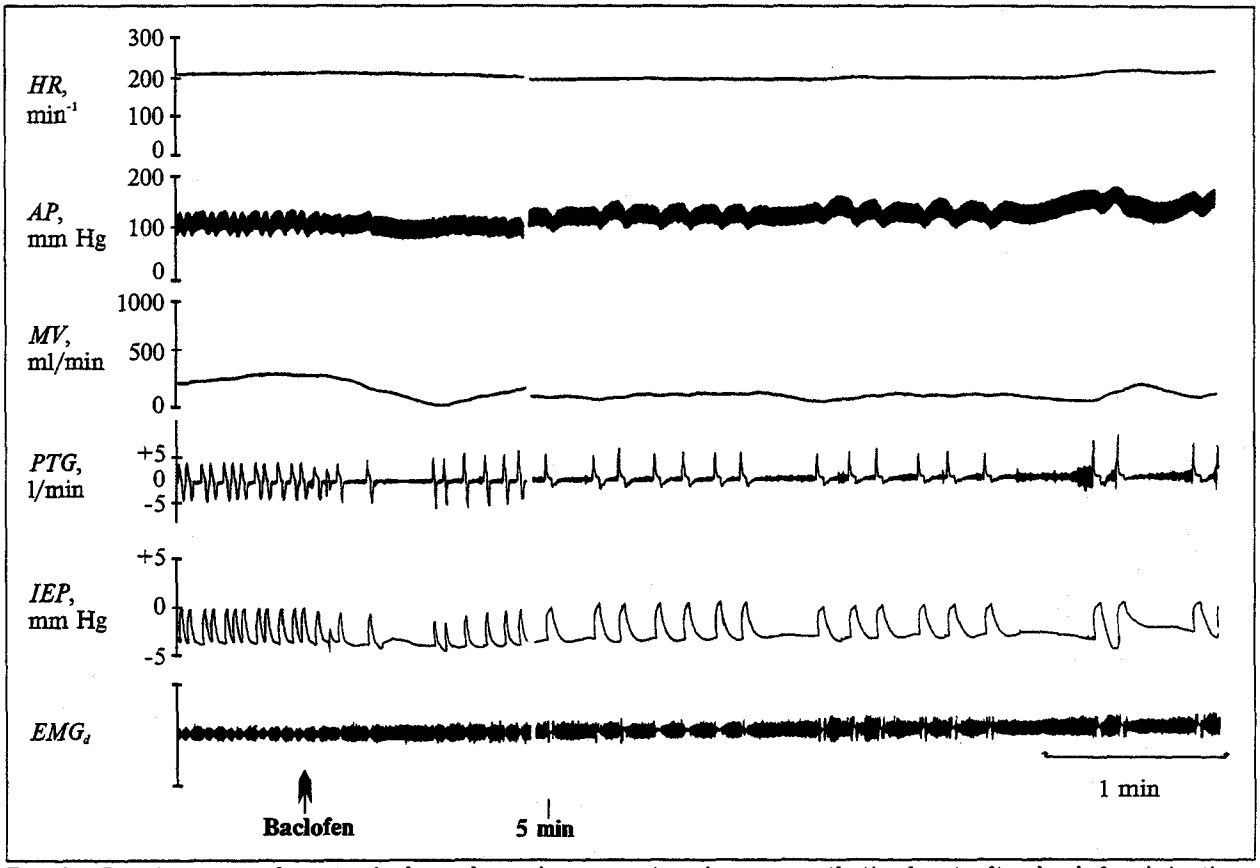

Fig. 3. Respiratory and systemic hemodynamic parameters in an anesthetized cat after baclofen injection. EMG_d – electromyogram of the diaphragm.

bances observed upon activation of the GABA-ergic system are not a consequence of AP depression [4].

REFERENCES

1. G. N. Kryzhanovskii, I. A. Tarakanov, and V. A. Safonov, *Fiziol. Zh.*, № 11, 13-23 (1993).
2. M. V. Sergievskii, R. Sh. Gabdrakhmanov, A. M. Ogorodov, *et al., Structure and Functional Organization of the Respiratory Center* [in Russian], Novosibirsk (1993).
3. I. A. Tarakanov, V. A. Safonov, and G. A. Semkina, *Byull. Eksp. Biol. Med.*, **114**, № 7, 24-27 (1992).
4. I. A. Tarakanov, E. A. Golovatyuk, E. R. Turskaya, and V. A. Safonov, *Byull. Eksp. Biol. Med.*, **115**, № 6, 583-587 (1993).
5. J. Champagnat, M. Denavit-Saubie, S. Moyanova, and C. Rondouin, *Brain Res.*, **237**, 351-365 (1982).
6. R. A. Mueller, D. B. A. Lundberg, and G. R. Breese, *Pharmacol. Rev.*, **34**, № 3, 255-285 (1982).