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EXPERIMENTAL MODEL OF APNEUSIS AND PERIODIC BREATHING

I. A. Tarakanov, V. A. Safonov, G. A. Semkina, and E. A. Golovatyuk

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Pathological breathing develops in terminal states in the form of Cheyne-Stokes', Biot's, and Kussmaul's breathing, apneusis, or gasping. Many clinical and experimental cases of pathological types of breathing have been described [1, 2, 7]: deep hypoxia of varied origin, intoxication, head injuries, shock, asphyxia neonatorum, deep anesthesia, extensive blood loss, and division and cooling of the brain stem [3, 8, 9]. A common component of the different causes of pathological types of breathing is a disturbance of the central component of regulation of breathing, namely rhythmogenesis [5, 6]. The study of the mechanisms of pathological types of breathing have aroused the interest of experimenters (chiefly as a method of studying the causes of rhythmogenesis and the principles governing regulation of breathing) and clinicians (mainly concerned with a search for their effective treatment). However, the experimental study of this problem is difficult because of the lack of simple, reliable, and readily reproducible experimental models of pathological types of breathing. The known methods are as a rule laborious and very traumatic: surgical division and cooling of the brain stem and vagus nerves, arterial bloodletting of up to 50% of the total circulating blood volume [11-14]. There have been only sporadic studies in which several pathological types of breathing have been reproduced experimentally by administration of various drugs (pentobarbital, cyanides) [4, 10].

The aim of this investigation was to develop an experimental model of apneusis and periodic breathing by injecting hydroxybutyrate (HB) into cats.

EXPERIMENTAL METHOD

Experiments were carried out on 19 noninbred cats, male and female, weighing from 2 to 4 kg, anesthetized with pentobarbital (40 mg/kg, intraperitoneally). The rectal temperature was measured and maintained by means of an electric heater with an accuracy of 0.5% within the range from 37.5 to 38.5°C. Tracheotomy was performed at the level of the upper third of the trachea. A cannula connected to transducers for recording the parameters of respiration (respiration rate – RR, pneumotachogram) was introduced into the trachea. To record the intraesophageal pressure (IEP) a sterile catheter was introduced into the esophagus, with an elastic balloon filled with liquid, and joined to a venous pressure transducer, fitted on its tip. The arterial blood pressure (BP) was recorded by means of

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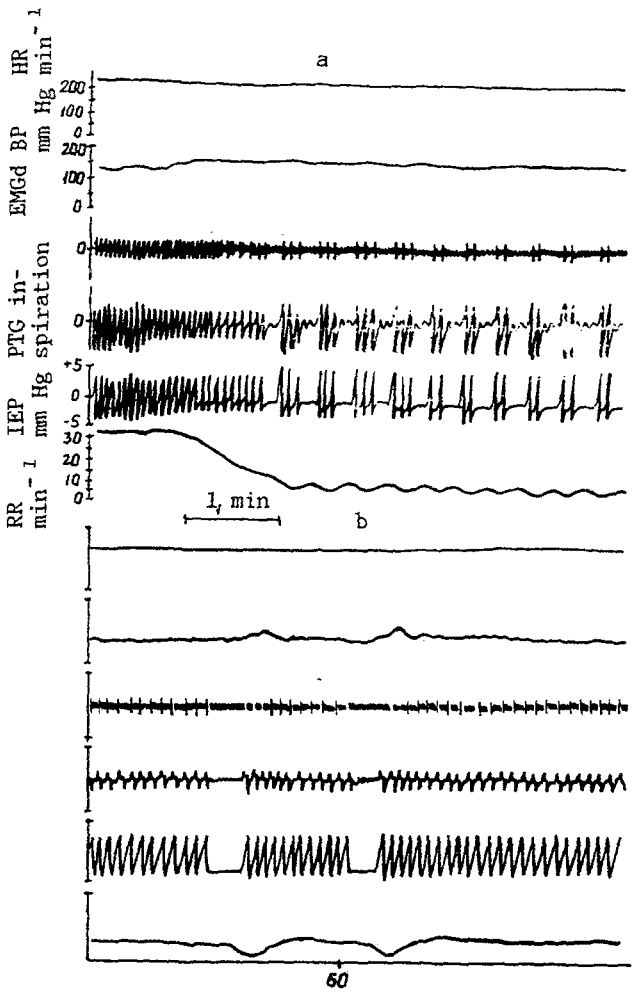

Fig. 1. Dynamics of principal parameters of respiration and the circulation in anesthetized cats after intravenous injection of sodium hydroxybutyrate (200 mg/kg). a) initial value (arrow indicates time of injection); b) 60 min after injection (beginning of recovery of regular breathing). From top to bottom, on each trace: heart rate (HR, beats/min), mean systemic arterial pressure (BP, mm Hg), electromyogram of diaphragm (EMGd), pneomotachogram (PTG) (inspiration downward), intraesophageal pressure (IEP, mm Hg), respiration rate (RR, cycles/min). Time marker 1 min.

a catheter introduced through the femoral artery, and the same catheter was used for sampling blood in order to measure pH and partial pressures of blood gases. Values of pH and partial pressures of blood gases were measured on an ABL-330 instrument ("Radiometer International"). The EMG of the diaphragm was recorded by means of bipolar electrodes of hook type and an M-42 electromyograph (Hungary). The various preparations were injected through the catheter into the femoral vein. Parameters of respiration, heart rate (HR), RR, BP, and IEP were recorded by means of an MKh-01 surgical monitor of USSR origin. Lithium (Li HB)and sodium (Na HB) hydroxybutyrates were used in the experiments and injected in doses of 200 mg/kg to 400 mg/kg in the course of 1 min. In the instructions for the use of Na HB it is stated that although this compound has low toxicity, if the method of injection is not followed it may cause periodic breathing or even respiratory arrest. In our experiments on anesthetized animals, even injection of the appropriate dose of NA HB led to side effects. Observations continued for 1.5-2 h. The results were subjected to statistical analysis, using Student's test at the $p \leq 0.05$ level.

TABLE 1. Partial pressure of Gases and pH of Arterial Blood in Anesthetized Cats after Intravenous Injection of Hydroxybutyrate (200 mg/kg, M ± m, n = 6)

Experimental condition	pH	pCO_2, mm Hg	pO_2, mm Hg	S_aO_2, %
Background	7,424±0,021	23,3±0;9	89,2±2,8	96,8±0,4
Li HB	7,394±0,032	29,3±2,4	74,6±4,6	93,4±1,8
		<0,05	<0,05	

EXPERIMENTAL RESULTS

The experimental results showed that hydroxybutyrate, irrespective of its counter ion – sodium or lithium – is an effective agent for slowing breathing through lengthening of inspiration. Since sodium and lithium hydroxybutyrates, as has been found, have a similar effect on the mechanism of formation of the respiratory rhythm, the results of the two series of experiments are combined into one group.

Slow breathing with a marked increase in the duration of inspiration (breathing of apneustic type) always develops 3-5 min after intravenous injection of hydroxybutyrate, and in about 80% of cases (15 of 19) this changed into periodic breathing. Characteristically, in the intervals between groups of respiratory movements a negative pressure typical of the phase of inspiration was preserved in the chest, and maintained by continuous activity of the inspiratory muscles, especially the diaphragm (Fig. 1). The fact will be noted that during this pause breathing, judging by the IEP curve, was stimulated (paradoxical stimulation of inspiration during the inspiration phase), although under these conditions a switch of the phases of respiration evidently ought to have been taking place. These facts point to a disturbance of activity of the mechanism of "blocking" inspiration, taking place under the influence of hydroxybutyrate.

The periodic breathing which developed continued steadily for 30-90 min, so that during this time the functions of the different elements of the respiratory system and/or the circulation could be studied under different conditions. Later the periodic breathing usually changed again into slow but regular breathing of apneustic type. This possibility of interchanges between periodic and apneustic breathing suggests that they share similar mechanisms of formation, which are evidently located in the system for switching from inspiration to expiration. The mutual transition between these two types of breathing was observed previously by other workers both clinically and experimentally [1-4, 8, 9].

A characteristic feature of the experimental model we are demonstrating is that in our experiments respiration usually regarded as pathological did not, on the one hand, lead to, nor, on the other hand, was is the result of any significant changes in the blood gas composition. Judging from the data in Table 1, during periodic breathing significant changes were observed toward an increase in p_aCO_2 and a decrease in p_aO_2, and acidification and hypoxemia were absent (present only as tendencies). However, even the most marked decrease in p_aO_2 observed during periodic breathing after injection of hydroxybutyrate could not explain its appearance, for the more severe hypoxia leading to a reduction of p_aO_2 by two or more times, did not cause the appearance of a similar type of breathing, apneustic or periodic, in the experimental animals under anesthesia. An even more important state of affairs, in our opinion, is that despite marked changes in the character of external respiration (judging from the blood gas composition), it was sufficiently effective for keeping the animal alive, i.e., by itself it is not critical for life. There is no doubt that periodic breathing is a sign but not the cause of the onset of critical states.

As additional characteristics of the state of the animal during periodic breathing, we can turn to accompanying changes in the central hemodynamics, the main parameters of which are given in Table 2. Comparison of these parameters of respiration and the circulation, given in Table 2, shows that disturbances of the respiratory rhythm take place against a background of virtually unchanged blood pressure. Under these conditions a gradual decrease was observed in the heart rate, and at the 15th minute after injection of hydroxybutyrate the decrease became statistically significant. The decrease in this parameters was caused both by a true reduction in the frequency of the cardiac contractions and also by the appearance of periods of cardiac arrhythmia, observed in about 30% of cases.

TABLE 2. Parameters of Respiration and Central Hemodynamics in Anesthestized Cats after Intravenous Injection of Hydroxybutyrate (200 mg/kg, M ± m, n = 9)

Parameter	Time, min							
	0	1	3	5	10	15	20	30
HR, min^{-1}	223,2±6,6	217,0±6,9	204,4±14,8	206,2±15,3	186,3±17,0	174,3±15,1	178,9±15,3	154,0±21,6
						<0,01	<0,02	<0,01
Mean BP, mm Hg	133,9±11,0	134,6±11,7	137,9±7,4	139,0±8,2	141,2±9,7	139,0±11,5	138,1±12,3	125,3±7,1
RR, min^{-1}	33,2±2,8	30,6±2,4	21,4±4,1	16,3±2,3	12,9±2,2	7,7±1,1	7,3±0,9	8,7±2,5
			<0,05	<0,001	<0,001	<0,001	<0,001	<0,001

In our experiments arrhythmia appeared more often under the influence of lithium than of sodium hydroxybutyrate. The fact will be noted that the decrease in respiration rate took place significantly before the decrease in heart rate taking place under the influence of hydroxybutyrate.

To conclude, we may state once again that the proposed model of reproduction of apneustic and periodic respiration with the aid of hydroxybutyrate is sufficiently simple, reliable, and easily reproducible. It can therefore be used with success for the experimental study of the mechanisms of pathological respiration, both in cats and in rats, which, as our preliminary studies showed, respond similarly to injection of hydroxybutyrate.

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