Changes in Hemodynamics and Respiration in Rats with Different Resistance to Acute Hypoxia

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Effects of acute hypoxia on hemodynamics and respiration were studied in acute experiments on narcotized rats. The animals were divided into groups characterized by high, low-, and medium- resistance to hypoxia by the time of respiration arrest during inhalation of gas mixture containing 3% O_2. Hemodynamic parameters of highly resistant animals were higher than in low-resistant rats throughout the entire hypoxic period. The development of a rare (with prolonged inspiratory phase) respiratory rhythm in highly resistant rats is an adaptive reaction, which allows them longer tolerate hypoxia compared to low-resistant animals.

Key Words: *acute hypoxia; hemodynamics; respiration; rats; individual resistance to hypoxia*

Animals of the same species are characterized by different individual resistance to acute hypoxia [1-3,5,7]. Biochemical studies showed that animals highly resistant (HR), low-resistant (LR), and medium-resistant (MR) to hypoxia differ by characteristics of energy, lipid, and carbohydrate metabolism [2,5]. There are data on different reactions of cerebral neurons to acute hypoxia in animals with different individual sensitivity to oxygen deficiency [3]. It was previously shown that the main hemodynamic parameters in HR cats remain high during the entire period of hypoxic exposure, while in LR animals these parameters decrease at the beginning of this exposure [7].

The reaction to acute systemic hypoxia depends on many factors, including secondary hyperventilation, direct effect on the heart [8,9] and CNS [11]. The relative significance of these factors varies for different levels of hypoxia in the same animal species and between the species [9,10]. No comprehensive studies of hemodynamics in rats exposed to severe hypoxia were undertaken.

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We studied the effects of acute hypoxic hypoxia on the hemodynamics and respiration in rats with different resistance to hypoxia.

MATERIALS AND METHODS

Seventy-six acute experiments on random-bred male rats (350-400 g) were carried out under Nembutal narcosis (40 mg/kg intraperitoneally). Blood pressure (BP) was monitored throughout the experiment with a micromanometer in the femoral artery. Blood flow velocity in the ascending portion of the aortic arch was measured with a miniature ultrasonic transducer fixed at the tip of 0.6-mm catheter. The transducer worked at a frequency of 27 mHz [6]. It was introduced into the aorta through the right carotid artery. The data on the blood flow velocity in the ascending aorta and BP were transferred into an analog-computing device for estimation of the total peripheral vascular resistance (TVR; mm Hg/cm/sec). The dynamics of the stroke volume and cardiac output (CO) was evaluated using an electron device. Heart rate was recorded with a cardiotachometer triggered by the pulse wave in the aorta. The respiratory excursions were recorded with a tensiometric transducer. In 16 experiments the linear and volume blood flow velocities in the carotid and

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femoral arteries were measured using ultrasonic pickups with inner diameters of 0.7 and 0.5 mm. Electrical activity of the diaphragm (EMG) was studied using bipolar nichrome electrodes (0.3 mm) fixed on the diaphragmatic cupola on the abdominal side. The amplitude of the diaphragmatic discharge and the duration of respiratory phases were evaluated.

Individual resistance to hypoxia was evaluated during inhalations of gas mixture containing 3% O_2 in nitrogen by the time from the start of inhalation until apnea, after which the delivery of gas mixture was discontinued and the animals were allowed 1-1.5 min for respiration recovery. If the respiration did not resume spontaneously, jet ventilation was started. The apparatus was switched off after appearance of the first spontaneous inspirations.

Inhalation of a gas mixture containing 3% O_2 is incompatible with life [4]. However, the time of survival (resistance to severe hypoxia) differed in different animals: in our experiments respiration arrest was observed after 1 to 30 min in different animals. Animals in which apnea developed after 1-4 min were referred to LR group, 9 min and longer were considered as HR, and those tolerating 5-8 min were referred to the MR group [2]. In order to confirm animal appurtenance to this or that group, 32 rats were exposed to inhalations of the same gas mixture 30-40 min after the first hypoxic exposure.

RESULTS

Of the 76 animals examined, 31 (40.7%) were HR, 20 (26.3%) MR, and 25 (32.6%) LR to hypoxia.

In contrast to cats, rats always demonstrated BP drop during acute hypoxia (both LR and HR animals), but the degree of this decrease varied: in HR animals with the mean initial BP of 110-120 mm Hg it decreased to 50-60 mm Hg, while in LR animals it decreased below 30 mm Hg ($p<0.05$; Fig. 1; 2, *a*). This BP drop in rats during hypoxia is determined by vasodilatation in the majority of systemic tissues, including the kidneys, splanchnic organs, skeletal muscles, and brain vessels [9,10]. This is confirmed by our data indicating that TPR in rats appreciably decreased during hypoxia (by 50% in HR and by 70% in LR rats).

In our experiments with severe hypoxia we observed no initial tachicardia described by scientists studying moderate hypoxia (6-15% O_2) [9,10]. A decrease in heart rate was observed in all experiments: by 10-20 bpm in HR rats and by more than 40-50 bpm (sometimes beyond the scale) in LR animals. In HR and LR rats heart rate started to decrease 50-60 and 10-20 sec after the beginning of gas mixture inhalation, respectively. Extrasystoles were observed in some experiments. Bradycardia was presumably caused by the direct effect of hypoxia on cardiac pacemaker, because the sympathetic and parasympathetic influences on the heart were weak under conditions of severe hypoxia [8-10].

Cardiac output increased by 30-50% or did not change in HR animals exposed to severe hypoxia and did not change or slightly decreased in LR animals. Together with decreased heart rate (less pronounced in HR animals and more so in LR ones) this attests to an increase in stroke volume (which is also seen from

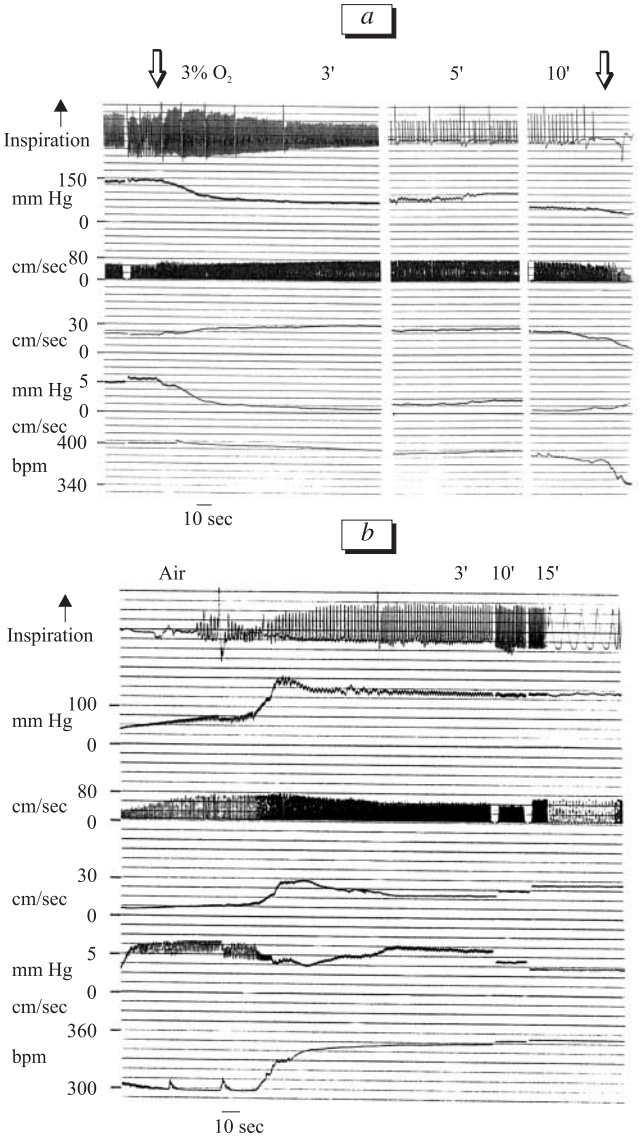

Fig. 1. Hemodynamic and respiratory parameters in animals with high resistance to hypoxia during inhalation of gas mixture (*a*) and during recovery (*b*). Curves here and in Fig. 2 present (from top to bottom): respiration (arrow directed upward shows inspiration); blood pressure; linear blood flow velocity in the ascending aortic arch; cardiac output; total peripheral resistance; heart rate. Here and in Figs. 2, 3: lines under each curve show zero levels. Arrows show the start and end of hypoxic gas mixture inhalation. Figures in the horizontal row: time from the start of exposure and during recovery, min. Time scale 1 and 10 sec.

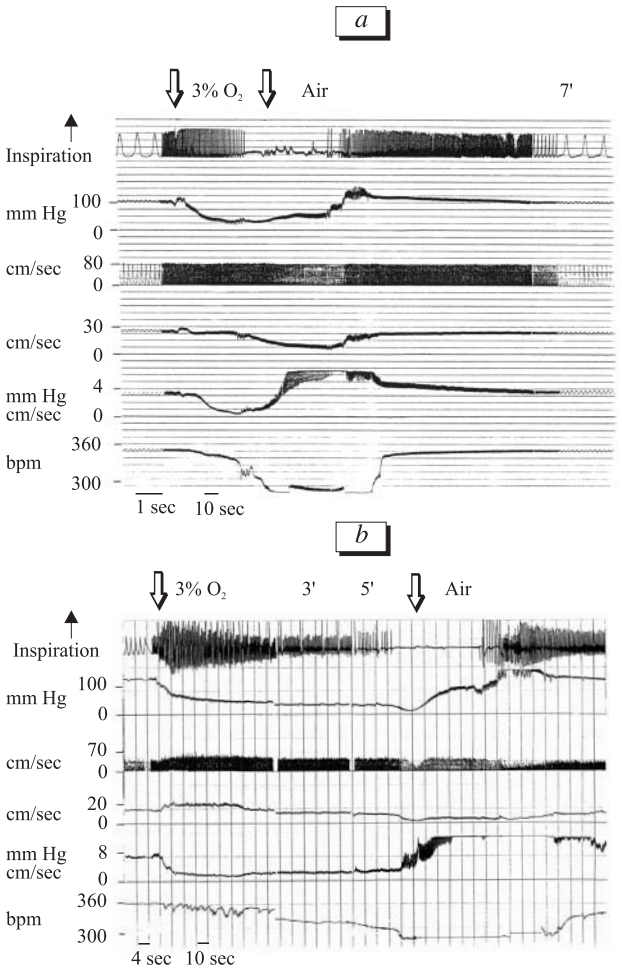

Fig. 2. Parameters of hemodynamics and respiration in rats with low (*a*) and medium (*b*) resistance to hypoxia.

direct stroke volume recording in some experiments), that is, the myocardial contractile function remains sufficiently high in all animals until apnea.

The respiratory system exhibits a characteristic biphasic response during acute hypoxia: initial hyperventilation is followed after several minutes of hypoxia by a decrease in ventilation below the initial peak, remaining above the baseline (before hypoxia) level ("roll off" phenomenon [12,13]). The mechanisms underlying this biphasic response remain unclear.

The biphasic reaction was clearly seen in our experiments under conditions of severe hypoxia: phase I (more frequent respiratory movements with greater amplitude) lasted for 1-2 min in HR rats (Fig. 1, *a*) and was followed by phase II (lower amplitude of respiratory movements at the same respiration rate). After 5-6 min respiratory movements of another type were observed (we can tentatively call them phase III): rare respiratory movements with greater amplitude. The respiration rate decreased 2-fold in comparison with the initial level in some experiments. This was paralleled by stabilization or even elevation of previously decreased BP. HR animals breathed in this rhythm for a long time (for 9-30 min) until apnea. In some experiments apnea was irreversible after long (25-30 min) inhalations of 3% gas mixture. In order to save the animals for further experiments, we switched HR rats to air respiration after 15-min inhalation of gas mixture.

In LR rats phase I lasted for 30-60 sec and was followed by short phase II (several rare inspirations) eventuating in apnea (Fig. 2, *a*).

In MR rats changes in hemodynamics and respiration during hypoxia were close to those observed in HR rats, but apnea developed after 5-8 min (Fig. 2, *b*).

Analysis of diaphragmatic EMG showed that the amplitude of the inspiratory (diaphragmatic) discharge increased by 80% in HR and LR rats exposed to hypoxia, but in HR animals this increase was stable and paralleled by prolongation of the inspiratory phase, while in LR animals the initial increase in the amplitude was transient and in some cases the amplitude decreased before apnea. Moreover, the duration of the inspiratory discharge also decreased in some LR rats, which was followed by apnea. It seems that inhibition of respiration and prolongation of the inspiration phase in HR animals exposed to acute hypoxia is an adaptive reaction which helps the animals maintain blood gas balance under conditions of hypoxia and sustain the hypoxic exposure during a longer time in comparison with LR animals. The mechanism of this reaction is not quite clear.

In 32 animals the hemodynamic and respiratory parameters were also recorded after repeated (30-40 min after the first exposure) inhalation of gas mixture. Of these, 11 were HR, 13 LR, and 8 MR rats. In HR rats, in whom apnea during the first exposure to hypoxia developed after 9-12 min (7 rats), this parameter during repeated procedure increased by 1-2 min (in 2 rats even by 1.5 and 2 times) and hypoxic exposure in this case was better tolerated (no extrasystole, less pronounced BP drop).

Hence, in some animals subjected to hypoxia adaptive processes developed even under conditions of acute experiment under narcosis. HR animals in which apnea developed after 15-20-min hypoxia during the first exposure were transferred into MR group during repeated exposure; it seems that their compensatory potential was exhausted during the first long-term exposure to severe hypoxia.

LR animals in which apnea developed after 1.5-2 min during the first hypoxic exposure (8 rats) developed it even sooner (after less than 1 min) during repeated exposure. LR animals in which apnea developed within 3-3.5 min during the first exposure (close to the MR group) were also transferred into MR group

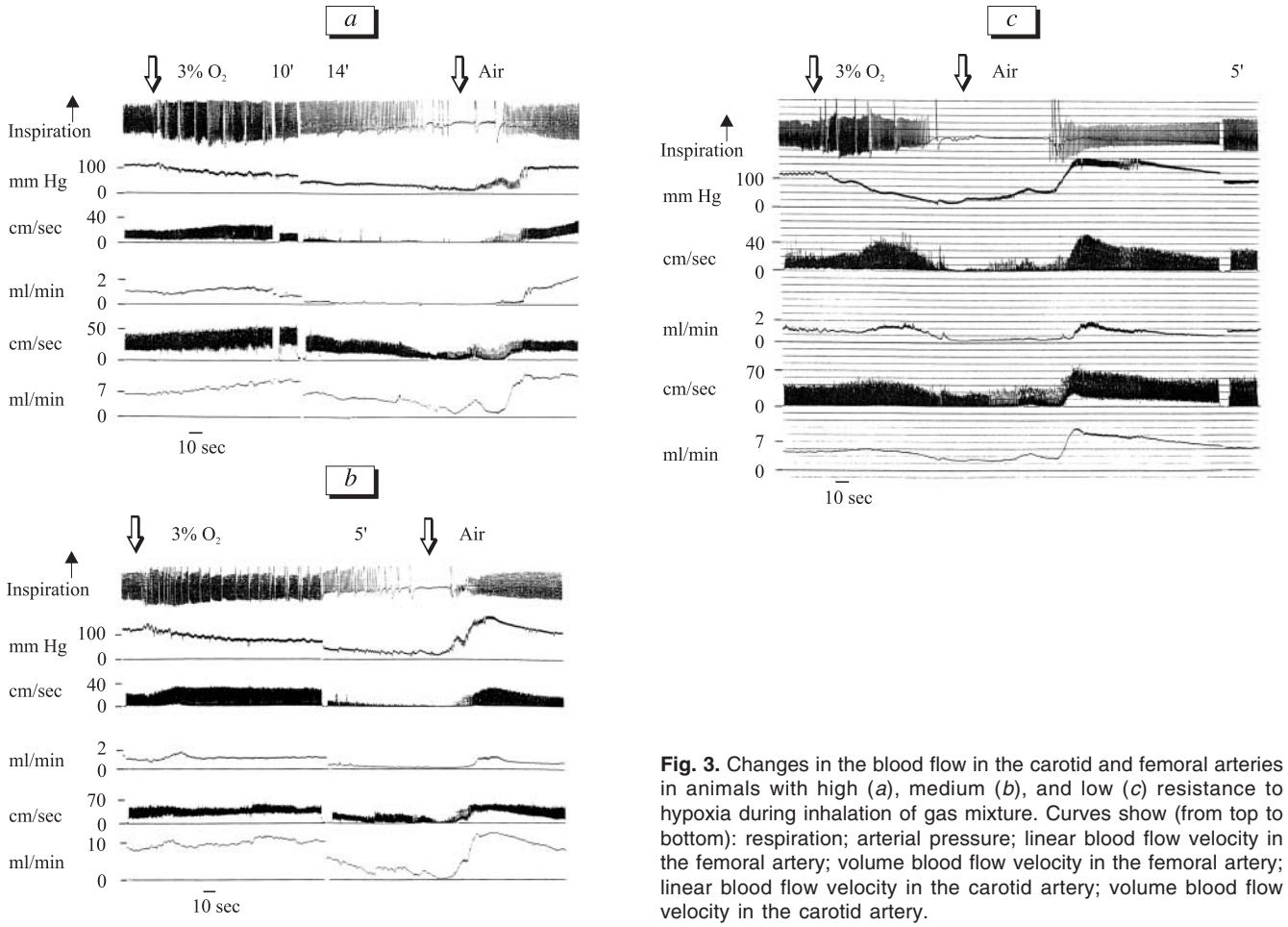

Fig. 3. Changes in the blood flow in the carotid and femoral arteries in animals with high (*a*), medium (*b*), and low (*c*) resistance to hypoxia during inhalation of gas mixture. Curves show (from top to bottom): respiration; arterial pressure; linear blood flow velocity in the femoral artery; volume blood flow velocity in the femoral artery; linear blood flow velocity in the carotid artery; volume blood flow velocity in the carotid artery.

after repeated exposure. HR animals were not transferred into LR group and vice versa, LR rats were not transferred into HR group. Experiments on non-narcotized animals also showed that an appreciable part of HR and LR animals were transferred into MR group after repeated exposure to hypoxia [2].

MR animals remained in this group during repeated exposure to hypoxia: the difference in the time of apnea development during the first and repeated hypoxic exposure was ±1 min.

It is known that acute hypoxia is associated with blood redistribution in the body: blood supply to vital organs (brain, heart, respiratory muscles) increases at the expense of limited blood supply to less important organs [4]. Similarly as in cats, in rats exposed to severe hypoxia blood supply to the brain and skeletal muscles changed individually because of variable changes in cardiac output, systemic BP, and individual reactivity of regional vessels in animals with different resistance to hypoxia.

Blood flow in the carotid and femoral arteries was studied in 16 animals (6 HR, 4 MR, and 6 LR). In HR animals blood flow in the carotid artery increased by 50-70% of the initial level, but dropped to the initial level and lower (in parallel with BP decrease) before apnea (Fig. 3, *a*). During apnea it decreased to 25-30% of the initial level and after respiration recovery it increased above the initial level. In MR animals the carotid arterial blood flow increased by 20-30% of the initial level during the first minutes of hypoxic exposure and then decreased below the initial level (Fig. 3, *b*). During apnea the blood flow dropped almost to zero. In LR animals the blood flow in the carotid artery did not change during hypoxia or increased by 10-15%; during apnea it dropped almost to zero level, and after recovery of respiration it increased above the initial level (Fig. 3, *c*).

The blood flow in the femoral artery increased in all animals during the first 1-2 min of hypoxic exposure, then it gradually decreased to zero. The data on increase of the blood flow in the femoral artery coincide with the data on dilatation of skeletal muscle vessels in rats exposed to hypoxia [9,10]. This reaction does not seem to be physiological, as it "steals" the vital organs.

The less pronounced decrease in systemic BP, heart rate, increased or stable cardiac output, decelerated respiratory rhythm with prolongation of inspira-

tion phase, increase in blood supply to the brain create more favorable oxygen status and prerequisites for longer survival under conditions of severe hypoxia in HR animals in comparison with LR rats.

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