MECHANISM OF DILATATION OF THE LIMB VESSELS IN THE POSTHYPOXIC PERIOD

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Posthypoxic dilatation of the limb vessels persists in anesthetized animals after blocking of the carotid and aortic reflexogenic zones. Chronic experiments with intraarterial injection of atropine and bretylium bromide showed that dilatation of the limb vessels in the posthypoxic period is not due to activation of cholinergic vasodilators. This indicates that sympathetic adrenergic fibers in unanesthetized animals are the only conductors of both constrictor effects in hypoxia and vasodilator effects in the posthypoxic period.

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Vasoconstriction in the limbs, intestine, skin, and other regions in generalized hypoxia has been demonstrated experimentally [2, 5-7, 10, 11]. A distinguishing feature of the response of the limb vessels at the beginning of the posthypoxic period is a temporary but well-defined dilatation. The vascular tone in other regions, which was increased during hypoxia, returns to its prehypoxic level in the posthypoxic period.

Both vasoconstriction and vasodilatation are neurogenic in origin [2, 7, 8]. The principal afferent sources of vasoconstriction in hypoxia are the chemoreceptors of the carotid and aortic reflexogenic zones. Posthypoxic vasodilatation, according to some investigators [10, 11], also persists after blocking of these zones, while other workers [9] found that this is dependent on integrity of the peripheral chemoreceptors.

Doubts are still expressed regarding the participation of cholinergic vasodilators of skeletal muscles in the mechanism of dilatation of the limb vessels at the beginning of the posthypoxic period. Litwin and co-workers [10] found that injection of atropine into dogs anesthetized with chloralose sharply reduces the degrees of dilatation of the limb vessels in the posthypoxic period. Results obtained by the writers [2] in experiments on dogs under Nembutal anesthesia showed that atropinization of the animals does not produce significant changes in the reaction of the limb vessels either during hypoxia or in the posthypoxic period.

Because of the conflicting nature of views held regarding the mechanism of dilatation of the limb vessels in the posthypoxic period, the problem was investigated, and the results are described below.

EXPERIMENTAL METHOD

Acute experiments were carried out on 15 dogs anesthetized with Nembutal (40-45 mg/kg body weight intraperitoneally) and short-term chronic experiments on 8 dogs.

In the acute experiments the systemic arterial pressure was recorded in the femoral artery, the vascular tone in the lower limb was recorded by resistography [3], and respiration by a pneumographic method. These indices were determined by inhalation of gas mixtures containing 8-10 and 92-96% oxygen in nitrogen for 3-5 min, both for animals with intact peripheral chemoreceptors and after denervation of the aortic zones by vagotomy and by physiological blocking of the carotid chemoreceptors [12]. Blocking of the carotid chemoreceptors in hypoxia and in the posthypoxic period was carried out by isolated perfusion of the carotid zones with oxygenated blood from a thermostat. Humoral isolation of the carotid zones was carried out by ligation of the internal and external carotid arteries and all other arteries branching from

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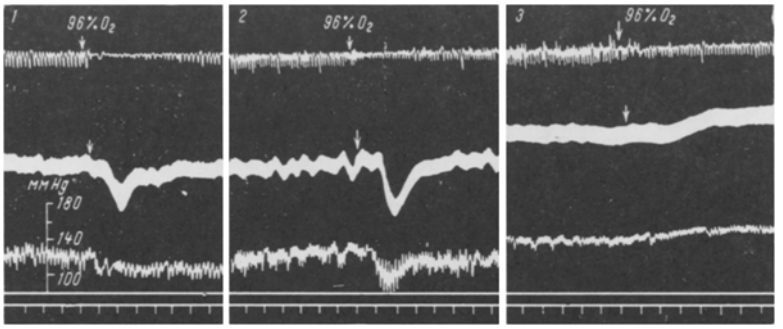

Fig. 1. Changes in circulation of an unanesthetized dog in the posthypoxic period. 1) Innervation intact; 2) after injection of atropine (1 mg/kg); 3) after injection of bretylium bromide (5 mg/kg). Legend on kymograms (from top to bottom): pneumogram, perfusion pressure in femoral artery, arterial pressure in common carotid artery, time marker (15 sec); arrows indicate beginning of inhalation of 96% oxygen following inhalation of 8% oxygen for 3 min.

them in the region of the bifurcation. These arteries were ligated as distally as possible from their origins in order to avoid damage to or disturbance of the blood supply to the carotid bodies. Integrity of the carotid bodies after humoral isolation of the carotid zones was shown by a well-marked respiratory response to blood with a reduced oxygen content.

Chronic experiments were carried out on unanesthetized animals subjected to a preliminary operation and habituated to the experimental conditions. Respiration, systemic arterial pressure, and tone of the limb vessels (by resistography) were recorded on a kymograph. To record the tone of the limb vessels and the arterial pressure, polyethylene catheters were implanted into the central end of the common carotid artery and into one branch of the femoral artery (usually the profunda femoris artery) of the anesthetized animals under sterile conditions. The catheters were filled with physiological saline containing heparin, closed with airtight stoppers, and their free ends were brought out onto the dorsal surface of the neck in the region of the 5th-6th cervical vertebrae and on the lateral surface of the thigh. A movable ligature was placed on the iliac artery. The animals were used in the experiments 5-6 days after operation. The catheters implanted into the vessels were irrigated with physiological saline and connected to a previously sterilized perfusion pump. Blood entered the perfusion system from the catheter in the common carotid artery and was pumped into the catheter introduced into the profunda femoris artery. Exclusion of the perfused region from fluctuations of the systemic arterial pressure was achieved by tightening the movable ligature on the iliac artery. This exclusion was satisfactory if, after tightening the movable ligature, stopping the pumping of blood caused the pressure in the femoral artery to fall to 15-30 mm Hg.

The catheters were left in the vessels for 8-20 days, so that the vascular tone of the limb could be investigated repeatedly in the same animal during hypoxia and in the posthypoxic period. Heparin was injected into all the animals during the experiments (1000 units/kg). Inhalation of the same gas mixtures as in the acute experiments was carried out through a mask with valves. The vascular tone was recorded in intact animals and after blocking of the cholinergic fibers by intraarterial injection of atropine (0.1-1 mg/kg) in doses completely abolishing the vasodilator effect of test doses of acetylcholine.

The effect of bretylium bromide (5-8 mg/kg), which has marked antiadrenergic properties [1], on the posthypoxic vasodilatation was studied in 7 animals in chronic experiments.

EXPERIMENTAL RESULTS

In agreement with earlier findings [2], in the acute experiments on animals with intact peripheral chemoreceptors the tone of the limb vessels was increased by 3-30% in the initial period of hypoxia, after which in most experiments it fell to its initial level or slightly below it. At the beginning of the posthypoxic period (when the hypoxic mixtures breathed by the animal were replaced by hyperoxic), in every case a decrease in perfusion pressure was observed in the femoral artery (by 25-45 mm Hg). The decrease in vascular tone in the femoral arterial system in all experiments coincided with a sharp decrease in

pulmonary ventilation, and in 90% of cases was accompanied by lowering of the systemic arterial pressure (by 6-28 mm Hg).

After blocking of the carotid and aortic zones, the dilator response of the limb vessels in the posthypoxic period persisted in 11 of the 15 experiments. The dilator reaction was unchanged in 5 dogs with denervated carotid bodies, and in 6 animals it was reduced by 10-30%. The pulmonary ventilation in the posthypoxic period was reduced in all these animals regardless of the response of the vascular tone of the limbs. The systemic arterial pressure gradually increased in all cases.

Reoxygenation of the blood in the posthypoxic period in the chronic experiments constantly evoked a marked decrease in tone of the limb vessels by a varied degree (by 15-38% of the prehypoxic level) in all the animals. Meanwhile, in all experiments the pulmonary ventilation was reduced. A systemic depressor response in the posthypoxic period appeared in 85% of the cases.

Atropinization of the animals caused no significant changes in the response of tone of the limb vessels, the systemic arterial pressure, or respiration when the hyperoxic gas mixtures were replaced by hypoxic (Fig. 1). Meanwhile, after injection of bretylium bromide, the phase of vasodilatation in the limb constantly disappeared at the beginning of the posthypoxic period. The decrease in pulmonary ventilation in the posthypoxic period also persisted after administration of bretylium bromide. The systemic arterial pressure usually rose under these conditions.

The results of this investigation thus confirm those obtained by other workers [8, 10, 11], and they show that posthypoxic vasodilatation of the limb vessels persists in anesthetized animals and after blocking of the carotid and aortic chemoreceptors. Experiments in which atropine and bretylium bromide were injected showed that dilatation of the limb vessels in unanesthetized animals in the posthypoxic period is not connected with activation of cholinergic vasodilators, but is dependent on post-stimulation depression of activity of the vasomotor center.

The results of this investigation show that in both anesthetized [2] and unanesthetized animals, sympathetic adrenergic fibers are the only conductors of vasoconstrictor effects during hypoxia and vasodilator effects in the posthypoxic period.

Dilatation of the limb vessels in the posthypoxic period is entirely dependent on responses of vessels of the skeletal muscles [11]. These changes in tone of vessels of skeletal muscles in the posthypoxic period must be regarded as a special case of the general rule for responses of skeletal muscle vessels to any sufficiently sharp decrease in impulse frequency in constrictor fibers [4].

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