ROLE OF ENDOGENOUS PROSTAGLANDINS IN MECHANISMS OF ACTION OF CO_2 AND O_2 ON MORPHOLOGY AND FUNCTION OF THE CEREBRAL CORTICAL CAPILLARY SYSTEM IN CATS

É. S. Gabrielyan, É. A. Amroyan, and R. Sh. Matevosyan

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KEY WORDS: cerebral capillaries; hypocapnia; hypercapnia; hypoxia; indomethacin.

In previous investigations a combined study was made of the cerebrovascular resistance, local cerbral blood flow, inflow of blood into the brain, and concentrations of vasoactive prostaglandins (PG) under conditions of hypo- and hypercapnia and hypoxia, and also during inhibition of PG biosynthesis [1, 3, 8]. The next stage of these investigations was to study the state of the cerebral microcirculation under the above conditions.

EXPERIMENTAL METHOD

Experiments were carried out on 39 cats anesthetized with pentobarbital and artificially ventilated (nitrous oxide with oxygen). The acid–base balance (ABB) of the arterial blood was monitored by means of a blood microsystem (Radiometer, Denmark). Hypocapnia was induced by hyperventilation and hypercapnia by the addtion of 5% CO_2 to the inspired mixture; hypoxia was induced by inhalation of 5% O_2 with nitrogen. Each of the above states lasted 5 min. A solution of indomethacin (2 mg/ml/min, from Polfa, Poland) was injected by intravenous infusion over a period of 30-40 min to inhibit PG biosynthesis. Material for investigations was obtained through a burr-hole in the frontal part of the skull. Pieces of brain measuring 1 mm^3, fixed in 5% formalin, were subsequently treated by the new noninvasive method of demonstrating the microcirculatory system of an organ [7], based on direct staining of the blood vessel walls. The diameter of functioning (over 4 μ) capillaries was measured by means of an ocular micrometer in microscopic preparations and the number of highly constricted capillaries (under 4 μ) was counted in 100 fields of vision. The significance of differences between data for the experimental and control groups was evaluated by the Fisher–Student test.

TABLE 1. Changes in Morphology and Function of Cerebral Cortical Capillary System in Cats during Hypo- and Hypercapnia, Hypoxia, and Inhibition of PG Biosynthesis by Indomethacin

Experimental conditions	Mean diameter of capillaries, μ	Number of highly constricted capillaries (mean per 100 fields of vision)	pH	p_aCO_2, mm Hg	p_aO_2, mm Hg
Intact cats (n = 6)	6,60±0,05	12	7,30±0,01	28,5±0,9	98,2±1,5
Hypocapnia (n = 5)	6,08±0,08†	28†	7,57±0,01†	12,1±0,9†	98,8±5,2
Hypocapnia + indomethacin (n = 4)	6,02±0,19*	28†	7,43±0,01	13,3±1,1†	100,8±2,5
Hypercapnia (n = 5)	8,55±0,10†	0*	7,09±0,02	69,9±1,3†	116,2±4,7
Hypercapnia + indomethacin (n = 5)	6,40±0,33	0*	6,99±0,01†	71,9±2,1 †	120,4±3,8
Hypoxia (n = 5)	7,15±0,16*	13	7,35±0,02*	35,5±0,9	45,2±0,6†
Hypoxia + indomethacin (n = 5)	6,57±0,16	13	7,40±0,02	30,9±0,8	50,2±0,9†
Indomethacin (n = 4)	6,54±0,33	12	7,47±0,02	25,2±1,1	110,0±2,5

Legend. *P < 0.05, †P < 0.001

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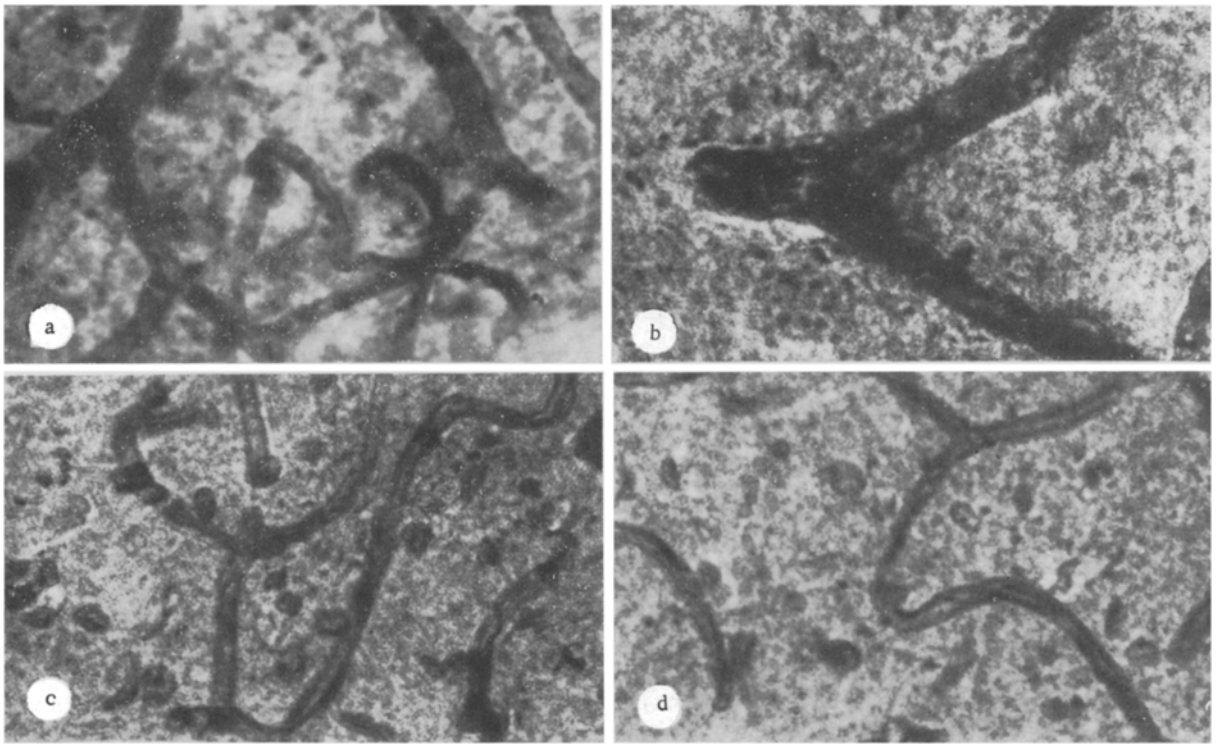

Fig. 1. Capillaries in cat cerebral cortex. Calcium-ATP method. a) Control; b) hypercapnia; c) indomethacin; d) hypercapnia + indomethacin. Ocular 10, objective 40.

EXPERIMENTAL RESULTS

In the experiments of series I the diameter of the cerebral cortical capillaries was determined and the number of highly constricted capillaries counted in intact animals with near-normal values of the blood ABB for cats (Table 1).

In series II the effect of hypocapnia on the diameter of the capillaries and the number of nonfunctioning capillaries (by 2.3 times) and to a decrease in capillary diameter by 7.88%. Inhibition of PG biosynthesis by indomethacin affected the changes in the cerebral cortical microcirculation caused by hypocapnia.

In series III the response of the cerebral cortical capillary system to CO_2 was studied. An increase in p_aCO_2 by 2.4 times compared with the control increased the mean capillary diameter by 29.5% and opened all the nonfunctioning capillaries. Indomethacin prevented this effect of CO_2; all the capillaries observed were functioning, just as before infusion of indomethacin (Fig. 1).

In series IV the experiments were carried out under hypoxic conditions. In response to a fall in p_aCO_2 by 53.9% the capillary diameter increased by 8.3% and the number of highly constricted capillaries remained at the control level. Injection of indomethacin prevented the dilating effect of hypoxia on the cerebral cortical capillary system without changing the number of highly constricted capillaries. As Table 1 shows, indomethacin itself caused no significant changes in the state of the capillary system of the cerebral cortex compared with the control.

Capillaries from 1 to 4 μ in diameter are known to be permeable only for blood plasma, and no blood cells can circulate along them [4]. In control animals, among capillaries of this kind vessels 3-4 μ in diameter were most frequently observed, vessels 2 μ in diameter were rare, and capillaries 1 μ in diameter or completely closed were absent, in agreement with the results of investigations by other workers [4]. Besides reducing the mean capillary diameter, hypocapnia also caused a significant increase in the number of nonfunctioning capillaries. Reduction of the blood flow in the cortex at the microcirculatory level in response to hypocapnia takes place more through an increase in the number of nonfunctioning microvessels than through a decrease in capillary diameter.

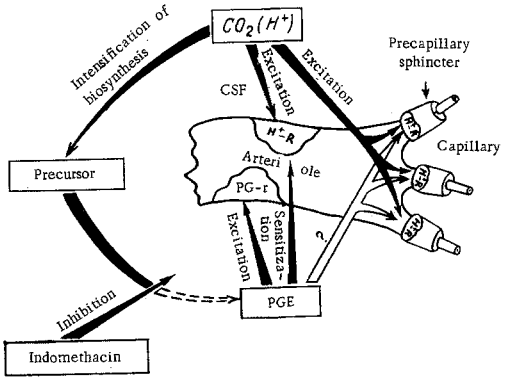

Fig. 2. Diagram of hypothetical effect of hypercapnia on cerebral cortical microcirculation in cats.

Inhibition of PG biosynthesis by indomethacin did not abolish the effect of hypocapnia, in agreement with the results of previous investigations including a quantitative study of the local cerebral blood flow [8], and also with the observations of Viahov [10]. Hence it follows that the effect of hypocapnia is not mediated through PG.

Data obtained by the present writers and others in previous studies of the effect of hypercapnia on the cerebral circulation demonstrated that inhibition of PG biosynthesis prevented the response of the cerebral vessels to CO_2 [1, 9]. The results of a study of the microcirculation showed that elevation of p_aCO_2 increases the capillary diameter and, at the same time, opens all the reserve microvessels. Injection of indomethacin inhibits the action of CO_2 on the capillary diameter but does not affect the number of nonfunctioning capillaries. The number of open capillaries is known to determine the functional capacity of the capillary system, and it depends on activity of the precapillary sphincters [6]. The latter, which are highly sensitive to humoral factors, change their tone and, consequently, the number of nonfunctioning capillaries is highly dynamic depending on the energy needs of the organ and local vasodilator metabolites [5]. The blood supply to regions of the brain and also the hydrostatic pressure and, consequently, the capillary diameter, depend mainly on changes in the diameter of the precapillary resistive vessels, which are characterized by a high degree of basal tone, which is modified under the influence of both local physical and chemical factors and nervous factors.

The following hypothetical mechanism of the action of CO_2 in the cerebral cortical microcirculation can thus be submitted. Carbon dioxide, a dilator of the cerebral vessels, relaxes the muscle cells of the precapillary restrictive vessels and the precapillary sphincters. As a result of dilatation of the precapillary arterioles the inflow of blood increases, leading to an increase in capillary diameter. Meanwhile, as a result of relaxation of the precapillary sphincters, the number of functioning capillaries and the functional capacity of the capillary system increase. Besides their direct dilator effect on arterioles, PG also evidently prepare the appropriate receptors to respond to CO_2, for inhibition of PG biosynthesis by indomethacin leads to loss of the ability of CO_2 to increase the capillary diameter. It can be tentatively suggested that the absence of an increase in the cerebral blood flow observed previously in response to an increase in the partial pressure of CO when PG biosynthesis is inhibited by indomethacin is the result of inhibition of the response of the smooth-muscle cells of the arterioles to CO_2. So far as the precapillary sphincters are concerned, the prostaglandin mechanism either does not play an essential role in this sphere or that role is manifested only weakly. Hence it can be concluded that the receptor formations of the smooth-muscle structures of the walls of the arterioles and precapillary sphincters, responding to CO_2, are heterogeneous.

This conclusion confirms results obtained during hypoxia, when both the O_2 deficiency and the blocking of PG biosynthesis acted only on capillaries of medium diameter and did not affect the number of nonfunctioning vessels. It can be concluded from a comparison of these data with results obtained previously indicating an increase in the cerebral blood flow and biosynthesis of PGE under hypoxic conditions, which was inhibited by indomethacin, that PG play an important role in the mechanism of the hypoxic increase in cerebral blood flow through their action in the region of the precapillary resistive vessels, without affecting the precapillary sphincters.

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EFFECT OF THE ANTIOXIDANT IONOL ON FORMATION AND PERSISTENCE OF A DEFENSIVE CONDITIONED REFLEX DURING PEAK EXERCISE

F. Z. Meerson, V. M. Boev, and R. I. Kruglikov

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During exposure to extremal environmental factors, including peak exercise, changes take place in the formation, fixation, and recall of temporary connections in untrained animals [1]. It has also been shown that exposure to stress and unusually heavy exercise cause activation of lipid peroxidation (LPO) [3], especially in the brain [2]. It can accordingly be postulated that activation of LPO in the brain is one cause of the disturbance of higher nervous activity during peak exercise and that, correspondingly, administration of inhibitors of LPO (antioxidants) before loading might prevent these disturbances.

To test this hypothesis, the effect of preliminary injection of the LPO inhibitor ionol on the disturbance of formation and preservation of conditioned bilateral avoidance reflexes (BCAR), which usually appear under the influence of peak loading (up to the limit), was studied in the investigation described below.

EXPERIMENTAL METHOD

Experiments were carried out on 120 male Wistar rats weighing about 200 g. In the experiments of series I the animals were divided into four groups: 1) control, 2) daily intraperitoneal injection of ionol in a dose of 20 mg/kg for 3 days, 3) a single session of peak exercise consisting of running on a treadmill at a speed of 16 m/min "to the limit," 4) administration of ionol in the dose indicated above, followed by the same exercise. A defensive BCAR was formed in all the animals in a shuttle box. The conditioned stimulus consisted of a flashing light and after it had acted for 5 min an electric current was applied through the floor of the box. The intervals between combinations measured 0.5-1.5 min. In the first and second training sessions, the interval between which was 7 days, the animals were given

Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. Orenburg Medical Institute. Institute of Higher Nervous Activity and Neurophysiology, Academy of Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR P. D. Gorizontov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 96, No. 9, pp. 70-71, September, 1983. Original article submitted December 22, 1982.

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