RESPONSES OF THE CEREBRAL BLOOD FLOW TO HYPO- AND HYPERCAPNIA AFTER INHIBITION OF PROSTAGLANDIN BIOSYNTHESIS BY INDOMETHACIN

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Quantitative investigation of the local cerebral blood flow by the hydrogen clearance method and of the blood flow into the brain by means of an electromagnetic flowmeter showed that inhibition of prostaglandin biosynthesis by indomethacin inhibits the response of the cerebral vessels to hypercapnia, whereas the effects of hypocapnia are not only preserved but are actually enhanced. This difference in the response of the brain vessels to hypo- and hypercapnia during inhibition of prostaglandin biosynthesis suggests that effects of hyper- and hypocapnia are produced by different mechanisms. It is postulated that a decrease in the prostaglandin concentration reduces the sensitivity of the brain vessels to hypercapnia and increases their sensitivity to hypocapnia.

KEY WORDS: cerebral circulation; hypocapnia; hypercapnia; indomethacin; prostaglandins.

Brain tissue produces large quantities of prostaglandins (PG) of the $F_{2\alpha}$ and E_2 types. The high physiological activity of the various PG in relation to the cerebral vessels has been described by many workers following their systemic and local application [13]. Much less has been published on the role of PG in the regulation of the cerebral circulation.

The object of this investigation was to study quantitative changes in the cerebral blood flow during certain typical vascular responses of the brain (to hyperventilation and inhalation of CO_2) in intact animals and after inhibition of PG biosynthesis by indomethacin.

EXPERIMENTAL METHOD

Cats and dogs were anesthetized with pentobarbital (0.25 mg/kg) and their lungs artificially ventilated with a mixture (4 : 1) of nitrous oxide and oxygen; the muscle relaxant listhenon was injected in a dose of 5-10 mg/kg intravenously every 30 min. The animal's body temperature was maintained at not more than 36-38°C by means of a heating lamp.

Changes in the local cerebral blood flow were recorded by a modified Aukland's hydrogen clearance method [2, 5]. In some experiments the inflow of blood into the brain was measured in dogs by means of an electromagnetic blood flowmeter (from Hugo Sachs Elektronik). The detector unit of the flowmeter was applied to the common carotid artery and branches of the external carotid artery were ligated. In all experiments the blood pressure was recorded synchronously through a catheter introduced into the femoral artery and connected to the EMT-35 detector and EMT-31 amplifier (from Elema-Schönander). These parameters were recorded on a four-channel automatic writer (Watanabe-Multicorder). Synchronous measurements were made of pH and pCO_2 of the arterial blood, and in one series, of pH and pCO_2 of the cerebrospinal fluid (CSF) and pH, pCO_2, and pO_2 of the arterial blood by means of a Radiometer system. A solution of indomethacin, pH 8.0, made up by the method of Palmer et al. [7], was injected by means of a peristaltic pump toward the brain through the linguofacial branch of the carotid artery after ligation of branches of the external carotid artery. The dose of indomethacin ($0.2\ mg \cdot kg^{-1} \cdot min^{-1}$) was chosen on the basis of the fact that the dose of indomethacin required to inhibit PG biosynthesis is $1\ \mu g \cdot ml^{-1}$, and the ratio of brain indomethacin : plasma indomethacin is 0.02 [8].

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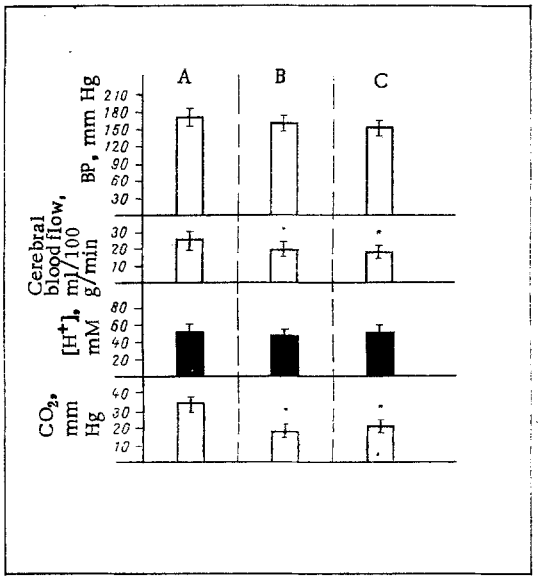

Fig. 1. Effect of hypocapnia on changes in local cerebral blood flow following intracarotid infusion of indomethacin (0.2 mg·kg^{-1}·min^{-1}; pooled data). A) Control, B) hypocapnia, C) hypocapnia + indomethacin; *) statistically significant difference from control ($P < 0.05$).

CSF samples were obtained by puncture of the cisterna magna and blood samples from the femoral arteries. Hyperventilation and inhalation of CO_2 (5%) were carried out for 5 min [6]. The significance of differences between the data for the experimental and control groups was evaluated by the Fisher–Student criterion.

EXPERIMENTAL RESULTS AND DISCUSSION

Changes in the cerebral blood flow in response to hypocapnia during inhibition of PG biosynthesis were studied in the experiments of series I (19 cats). As Fig. 1 shows, a decrease in arterial pCO_2 by 48.1% led to a decrease of 26.4% in the cerebral blood flow compared with the control (intact cats). During perfusion of indomethacin hypocapnia caused a more marked decrease in the cerebral blood flow than previously, despite the comparatively smaller decrease in arterial pCO_2 (p_aCO_2). A decrease in p_aCO_2 by 41% of the control value led to a reduction of 31.2% in the local cerebral blood flow.

In the experiments of series II (14 cats) changes in the cerebral blood flow in response to inhalation of CO_2 were studied after inhibition of PG biosynthesis. The pooled data, given in Fig. 2, show that inhalation of CO_2, leading to elevation of p_aCO_2, increased the cerebral blood flow by 75.2%. Meanwhile the blood pressure rose by 24.3%. Infusion of indomethacin, as is clear from Fig. 2, by contrast with the experiments with hypocapnia, almost completely inhibited the effects of CO_2 on the cerebral blood flow.

In the experiments of series III (ten dogs) changes in the inflow of blood into the brain under the influence of CO_2 before and during infusion of indomethacin were studied by means of an electromagnetic blood flowmeter. The pooled results of these experiments are given in Table 1. They show that, just as in series II, inhalation of CO_2 caused an increase in the blood supply to the brain. The inflow of blood into the brain was increased by 90.9% with an increase in p_aCO_2 of 72.8%. Infusion of indomethacin reduced the blood flow somewhat. Addition of CO_2 to the anesthetic mixture, increasing p_aCO_2 by 84%, 20-30 min after the beginning of intracarotid infusion of indomethacin had hardly any effect on the volume of blood flowing into the brain (comparison with control).

In the experiments of series IV (eight cats) the effect of indomethacin was studied on some indices of the acid-base balance of the CSF and arterial blood in response to inhalation of CO_2. As Table 2 shows, addition of CO_2 to the inhaled mixture increased pCO_2 in the arterial blood by 150.9% and in the CSF by 37.4%. There was a corresponding decrease in pH in both the blood and the CSF. To prevent hypoxia, the partial pressure of oxygen in the blood was maintained above the 100 mm Hg level. Infusion of indomethacin caused an increase in

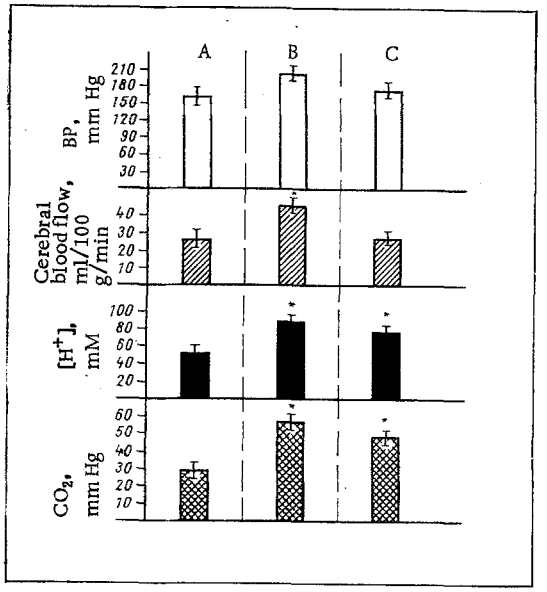

Fig. 2. Effect of hypercapnia on changes in local cerebral blood flow following intracarotid infusion of indomethacin (pooled data). A) Control; B) hypercapnia; C) hypercapnia + indomethacin. Remainder of legend as in Fig. 1.

TABLE 1. Effect of Inhalation of CO_2 on Inflow of Blood into Brain before and during Inhibition of PG Biosynthesis by Indomethacin

Index	Control	Inhalation of CO_2 for 5 min	Control	Intracarotid injection of indomethacin, 0.2 mg·kg^{-1}·min^{-1}	Inhalation of CO_2 for 5 min + indomethacin
CBF	26,60±5,40	50,80±7,90*	23,16±4,95	17,00±3,45	22,00±5.36
BP	206±14,28	248±19,19	224±12,85	212±7,99	222±22.7
pH	7,25±0,01	7,05±0,03*	7,14±0,02	7,22±0,01*	6,99±0.04*
$PaCO_2$	37,50±2,64	64,83±7,43*	34,50±2,27	34,66±3,47	63,50±6,30*
PaO_2	129±16,07	126,6±19,59	129,8±15,13	140±13,03	139±13.61

Legend: CBF) inflow of blood into brain in ml/100 g/min; BP) systemic arterial pressure in mm Hg; p_aCO_2 and p_aO_2 in mm Hg; *) difference statistically significant from control ($P < 0.05$) (here and in Table 2)

TABLE 2. Effect of Inhalation of CO_2 on Indices of Acid–Base Balance of CSF and Arterial Blood before and during Inhibition of PG Biosynthesis by Indomethacin

Procedure	CSF		Blood		
	pH	PCO_2	pH	PCO_2	PO_2
Control	7,40±0,01	20,42±2,34	7,32±0,02	28,40±0,82	191,2±4,10
Inhalation of CO_2 for 5 min	7,29±0,02*	28,07±2,53	7,10±0,02*	71,28±5,94*	182,0±10,49
Intracarotid injection of indomethacin	7,42±0,01	24,42±2,72	7,33±0,01	29,42±2,62	202,0±11,87
Inhalation of CO_2 for 5 min + indomethacin	7,26±0,03*	33,08±2,35*	7,09±0,01*	84,75±11,34*	183,6±9,77

pCO_2 and pH of the CSF compared with the control. Inhalation of CO_2 caused an increase of pCO_2 in the CSF by 35.4% and a decrease in pH during infusion of indomethacin. Similar but more marked disturbances were found in the arterial blood.

The fact that inhibition of PG biosynthesis had no effect on the reduction in the cerebral blood flow caused by hypocapnia, discovered in these experiments, is in agreement with Vlahov's observations [10, 11]. Marked hypocapnia resulting from cerebral vasoconstriction is known to lead to hypoxia, which increases PG biosynthesis [4]. The present writers' previous investigations [1] showed that hypocapnia inhibits the pressor action of noradrenalin on the brain vessels whereas indomethacin abolishes this effect. Hence it was suggested that hypocapnia increases PG biosynthesis. It is difficult at present to say whether this increase is the result of the direct action of hypocapnia or whether it is due to the action of hypoxia, but it can be tentatively suggested that the increase in the concentration of PG of the E series during hypocapnia [3] is a factor which limits any further constriction of the cerebral vessels. Evidence in support of this assumption is the fact that indomethacin leads to a more marked decrease in the cerebral blood flow in response to hypocapnia (31.2%) than in control experiments (26.4%).

Comparison of the results of experiments undertaken under the conditions of hypercapnia and with or without inhibition of PG biosynthesis reveals that PG deficiency contributes to the reduction in the response of the brain vessels to CO_2, in agreement with the findings of Pickard et al. [9]. Experimental investigations have shown that an increase in the cerebral blood flow in response to hypercapnia is due to an increase in the H^+ concentration in the interstitial fluid of the brain. The pial arteries are very sensitive to local changes in H^+ concentration, dilating when it rises and constricting when it falls [12]. Hence, it can be suggested that indomethacin either disturbs H^+ formation or inhibits sensitivity of the cerebrovascular receptors to it. As the study of the acid–base balance of the CSF and arterial blood in response to inhalation of 5% showed, H^+ formation in the CSF and blood under conditions of indomethacin infusion is not disturbed. Consequently, inhibition of PG biosynthesis is most likely to depress the sensitivity of the vascular receptors to H^+, as a result of which the brain vessels no longer respond to CO_2. The difference between the response of the cerebral vessels to hypo- and hypercapnia when indomethacin is given suggests that the effect of hypo- and hypercapnia are realized by different mechanisms. It can tentatively be suggested that an increase in the PG concentration increases the reactivity of the brain vessels to hypercapnia and reduces their reactivity to hypocapnia, whereas a decrease in the PG concentration had the opposite effect. This hypothesis requires further additional experimental verification.

LITERATURE CITED

1. É. S. Gabrielyan and É. A. Amroyan, Byull. Éksp. Biol. Med., No. 6, 643 (1976).
2. É. S. Gabrielyan, É. A. Amroyan, and E. S. Oganesyan, Krovoobrashchenie, No. 2, 9 (1976).
3. É. S. Gabrielyan, É. A. Amroyan, and A. G. Aivazyan, in: Prostaglandins in Experimental and Clinical Practice. Abstracts of Proceedings of the First All-Union Conference [in Russian], Moscow (1978).
4. S. Afonso, G. Bandow, and G. Rowe, J. Physiol. (London), 241, 299 (1974).
5. K. Aukland, B. F. Bower, and R. W. Berliner, Circulat. Res., 14, 164 (1964).
6. A. M. Harper and H. I. Glass, J. Neurol. Neurosurg. Psychiat., 28, 449 (1965).
7. M. A. Palmer, P. J. Piper, and J. R. Vane, Br. J. Pharmacol., 49, 226 (1973).
8. J. D. Pickard and E. T. MacKenzie, Nature New Biol., 245, 187 (1973).
9. J. D. Pickard, F. A. Simeone, and P. Vinall, in: Ionic Action on Vascular Smooth Muscle (E. Betz, ed.), Berlin (1976), p. 101.
10. V. Vlahov, Agressologie, 16, 31 (1975).
11. V. Vlahov, in: The Cerebral Vessel Wall (J. Cervos-Navarro et al., eds.), New York (1976), p. 143.
12. M. Wahl, P. Deetjen, K. Thurau, et al., Pflüg. Arch. Ges. Physiol., 316, 152 (1970).
13. K. M. Welch, L. Knowles, and P. Spira, Eur. J. Pharmacol., 25, 155 (1974).