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Effects of Indomethacin upon Cerebral Hemodynamics of Newborn Pigs

CHARLES W. LEFFLER, DAVID W. BUSIJA, ANTHONY M. FLETCHER, DONATHAN G. BEASLEY, JACK R. HESSLER, AND ROBERT S. GREEN

Department of Physiology and Biophysics [CWL, DWB, AMF, DGB, JRH, RSG] and the Department of Pediatrics, Section of Neonatology [RSG], University of Tennessee Center for the Health Sciences, Memphis, Tennessee 38163

ABSTRACT. Treatment of unanesthetized newborn pigs with indomethacin trihydrate (5 ± 1 mg/kg, intravenous) decreased cerebral blood flow uniformly throughout the brain by 18–28% without changing cardiac output, arterial pressure, or arterial blood gases and pH. Breathing 10% O_2, 9% CO_2 with the balance N_2 (hypoxia/hypercapnia) caused cerebral blood flow to increase from 102 ± 12 to 218 ± 19 ml/100 g·min. Intravenous administration of indomethacin during hypoxia/hypercapnia caused a uniform decrease in cerebral flow throughout the brain to levels (94 ± 5 ml/100 g·min) indistinguishable from those when the piglet was breathing ambient air. Further, 2.5 h later, the cerebral hyperemia caused by hypoxia/hypercapnia was attenuated markedly (129 ± 19 ml/100 g·min). Vehicle treatment did not alter resting cerebral blood flow or cerebral hyperemia in response to hypoxia/hypercapnia. Measurements of 6-keto-prostaglandin $F_{1\alpha}$, thromboxane B_2, and prostaglandin E_2 demonstrated that intravenously administered indomethacin crossed the blood-brain barrier of newborn pigs in sufficient quantity to inhibit prostanoid release into the cerebrospinal fluid passing over the surface of the brain. The mechanism by which indomethacin reduces cerebral blood flow and attenuates cerebral hyperemia cannot be determined from the present experiments. We conclude that intravenous administration of indomethacin decreases cerebral blood flow and attenuates cerebral hyperemia induced by severe, combined hypoxia/hypercapnia in newborn pigs. (*Pediatr Res* 19: 1160–1164, 1985)

Abbreviations

CSF, cerebrospinal fluid
6-keto-$PGF_{1\alpha}$, 6-keto-prostaglandin $F_{1\alpha}$
PGE_2, prostaglandin E_2
TXB_2, thromboxane B_2

Reports of the effect of systemic treatment with indomethacin on cereral hemodynamics in adult animals have been conflicting. Several investigators working with adult baboons, rats, and gerbils have presented evidence that indomethacin reduces cerebral blood flow during normocapnia, and virtually abolishes the increase in cerebral blood flow during hypercapnia (1–3). In contrast, others have found that indomethacin does not affect cerebral blood flow, pial arterial diameter, or responses of cerebral arteries to hypercapnia, hypocapnia, or hypoxia in adult cats, rabbits, or dogs (4–7). These divergent results in adult animals may represent species differences or differences in experimental procedure and conditions.

Since prostanoids are important in perinatal circulatory control (*e.g.* 8–15) and treatment with very low doses of indomethacin can affect neonatal renal function and close the ductus arteriosus (16–18), treatment with indomethacin might alter cerebral hemodynamics in the newborn animal more consistantly and to a greater extent than in the adult.

The present investigation in unanesthetized newborn pigs was designed to determine if treatment with indomethacin 1) alters resting cerebral blood flow and/or 2) alters cerebral hyperemia in response to severe blood gas stress.

METHODS

Animal preparations. Newborn pigs (0.9–1.5 kg) were instrumented prior to 48 h of age. Surgery was performed under aseptic conditions. Piglets were anesthetized with a mixture of halothane, nitrous oxide, and oxygen. Polyurethane catheters (Braintree Scientific, Inc., Braintree, MA) were placed in the descending aorta (via an umbilical artery) for blood sampling and reference withdrawal in microsphere experiments and in the left ventricle via the right carotid artery for microsphere injections. In piglets, ligation of one carotid artery has no detectable effect on cerebral blood flow. During control conditions, and during hypercapnia, hypoxia, and hypertension, we have found that blood flow to the side of the brain ipsilateral to the ligation was not different from the side with the patent carotid artery. From 19 control measurements in 14 piglets with ligated right carotid arteries, the flow to the left hemisphere was 76 ± 7 (SEM) ml/100 g·min and the flow to the right hemisphere was 77 ± 7 ml/100 g·min. No disproportionate distribution to the two hemispheres was seen during hypercapnia, hypoxia, or hemorrhage. For example, during increased blood flow caused by hypoxia and/or hypercapnia, flow to the left hemisphere was 134 ± 14 and to the right was 132 ± 14 ml/100 g·min (n = 15). Similarly, Laptook *et al.* (19) found that unilateral ligation of the carotid artery did not affect cerebral blood flow in piglets even when cerebral flood flow values were greater than 100 ml/100 g·min. We have seen no disproportionate distribution even at flows greater than 200 ml/100 g·min. Unlike most animals, ligation of a femoral or brachial artery in a piglet results in a dysfunction of the dependent limb.

Following surgery, the piglets were given benzathene penicillin and placed in cages warmed by overhead lamps. They were provided a continual supply of pig milk substitute (Nursing Melk, Cadco Inc., Des Moines, IA) and water. Experimentation was

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Correspondence may be addressed to Dr. Charles W. Leffler, University of Tennessee Center for the Health Sciences, Department of Physiology and Biophysics, 894 Union Avenue (NA 426), Memphis, TN 38163.
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performed on the 3rd postoperative day, with the unanesthetized piglet resting in a comfortable cloth sling which did not interfere with breathing movements. The breathing mixture was controlled by placing the pig's head in a bag through which was passed either air or 10% O_2, 9% CO_2, with the balance N_2 (hypoxia/hypercapnia; to simulate effects of severe respiratory distress). Radioactive microsphere determinations of cerebral blood flow were made at the end of 30 min of breathing air, 30 min of breathing hypoxic/hypercapnic gas mixture, and 15 min after intravenous administration of indomethacin trihydrate (Merck, Sharp and Dohme Research Laboratories, Rahway, NJ) (5 ± 1 mg/kg) during breathing of hypoxic/hypercapnic mixture. Following indomethacin administration, the piglet was returned to its cage for 2 h and then the cerebral blood flow determinations were repeated while breathing air and hypoxic/hypercapnic gas mixture. Separate time-vehicle control animals received saline injections instead of saline that contained indomethacin trihydrate.

In seven additional piglets, anesthetized with ketamine (7 mg/kg, intramuscular) and maintained on α chloralose (70 mg/kg initially, plus 15 mg/kg·h), a stainless steel and glass cranial window was implanted in the skull over the parietal region. The space under the window was filled with artificial CSP through needles incorporated into the sides of the window. CSF from under the window was collected by injecting 300 μl of artificial CSF into one port on the window, while sampling from the opposite port. To determine if indomethacin crossed the blood-brain barrier in sufficient quantity to inhibit prostanoid production, prostanoid concentration in the CSF was determined prior to and 45 min following intravenous administration of indomethacin trihydrate.

Radioactive microsphere determination of cerebral blood flow. A known amount of radioactivity in 15 μm microspheres (New England Nuclear, Boston, MA) (minimum 500,000 microspheres) was injected into the left ventricle and the injection line flushed with 1 ml saline. Withdrawal of reference blood samples (R = 1.03 ml/min from the descending aorta) was begun 15 s prior to microsphere injections and continued for 2 min after the injection. Withdrawn blood was replaced with blood from a baby pig donor. Following each experiment, the piglet was killed and the brain removed. The brain was subdivided into major regions. Samples were counted in a 2 inch well-type γ counter. The energy from each nuclide was separated by differential spectroscopy. Aliquots of the actual microsphere solutions injected were used for overlap calculations. The lungs were counted to detect extensive arteriovenous shunting of microspheres. "Lung blood flow" (comprised of bronchial flow and whole body arteriovenous shunting flow) averaged 2% of cardiac output, indicating that no extraordinary shunting of microspheres occurred. Cardiac output was calculated as:

$$\text{CO (ml/kg·min)} = \text{R (ml/kg·min)} \cdot \text{inj counts} \cdot \text{CR}^{-1}$$

where CR = total counts in reference withdrawal sample and CO = cardiac output. Blood flow to each brain region at the time the microspheres were injected was calculated by using the formula:

$$Q = C \times R \times CR^{-1}$$

where Q = organ blood flow in ml/min·100 g, C = counts per 100 g of tissue, R = rate of withdrawal of reference blood sample in ml/min, and CR = total counts in reference withdrawal blood sample. A sufficient number of microspheres was injected to insure that all brain regions contained at least 400 microspheres. For example, the smallest region (caudate nucleus, about 300 mg) contained about 1200 microspheres during untreated hypoxia/hypercapnia (highest flow) and about 450 microspheres following indomethacin treatment while breathing air (lowest flow).

Prostanoid analysis. Prostanoids in plasma were determined by radioimmunoassay following liquid chromatographic preparation as described previously (12, 20), or by direct radioimmunoassay. When direct radioimmunoasay was used, all tubes contained an identical amount of pig plasma. The standard curves, knowns, blanks, and makeup for greater dilutions used plasma from the same piglet as the unknowns, following dialysis of the plasma against 4 liters of Krebs bicarbonate buffer. Since the results from extracted plasma and unextracted plasma against a dialyzed plasma matrix were not significantly different when extracted samples were corrected for recovery, results from the two methods were combined. CSF samples were analyzed by direct radioimmunoassay against an artificial CSF matrix. Plasma samples were assayed for radioimmunoassayable 6-keto-$PGF_{1\alpha}$ and TXB_2. CSF samples were assayed for radioimmunoassayable 6-keto-$PGF_{1\alpha}$, TXB_2, and PGE_2. Plasma samples were not assayed for PGE_2 because the levels consistently were nondetectable (<13 pg/ml of blood).

Antisera used were produced in rabbits immunized with prostanoids (standards from Upjohn, Kalamazoo, MI) coupled to thyroglobulin using the mixed anhydride method. Cross-reactivities of our antibodies with other known biologically relevant prostanoids tested were all below 1%. The assays were performed in gelatin tris buffer using the appropriate tritiated prostanoid (New England Nuclear, Boston, MA). Following 24 h incubation at 4° C, the free fraction was separated from the fraction bound to antibody by precipitating the rabbit antibodies with antirabbit γ globulin and 60% saturated ammonium sulfate. Data were handled by computer, with determination of second order regression of free-tracer over tracer-bound-to-antibody against unlabelled prostanoid by the method of least squares. All unknowns were assayed at three dilutions with parallelism between the unknown dilution curve and the standard curve required before using the results.

Statistical analysis. All values are presented as means ± SEM. Comparisons between two values were made using t tests (for paired or unpaired observations as appropriate), and comparisons among three or more values were made using analysis of variance (followed by pairwise tests, when appropriate). Significance at the 5% level was required for inference that populations were different.

RESULTS

The effect of indomethacin treatment (5 ± 1 mg/kg, intravenous) on the arterial plasma prostanoid concentrations of piglets is show in Table 1. The predominant prostanoid detected in the arterial plasma of the unanesthetized newborn pigs was 6-keto-$PGF_{1\alpha}$, although low but detectable levels of TXB_2 were observed as well. The extent to which the thromboxane level was due to activation of platelets during passage through the catheter is not known. The concentrations of both 6-keto-$PGF_{1\alpha}$ and TXB_2 decreased to nondetectable levels by 2.5 h after indomethacin administration. In contrast to arterial plasma, the CSF passing under the cranial window contained relatively high concentrations of all three prostanoids examined (Table 1). Forty-five min after systemic administration of indomethacin, the concentrations of 6-keto-$PGF_{1\alpha}$, TXB_2, and PGE_2 in the CSF passing under the cranial window were reduced markedly (Table 1), indicating that systemic indomethacin crosses the blood-brain barrier in sufficient amounts to decrease cerebral prostanoid production.

Table 2 shows, in separate animals, the effects of vehicle treatment and of intravenous administration of indomethacin between the morning (control) and afternoon (vehicle or indomethacin) experimental sessions on resting cerebral blood flow. Treatment with the vehicle (saline) had no significant effect on total cerebral blood flow or on regional cerebral blood flow; although flows to all brain regions tended to increase in the afternoon compared to the morning. In contrast, systemic treatment with indomethacin decreased cerebral blood flow uni-

Table 1. *Prostanoid concentration in aortic plasma (n = 7) and CSF passing over the cerebral surface (n = 7) in piglets prior to and 150 min (aorta) or 45 min (CSF) following treatment with indomethacin (5 ± 1 mg/kg, intravenous) (means ± SEM)*

	Prostanoid concentration (pg/ml)				
	6-keto-$PGF_{1\alpha}$		TxB_2		PGE_2
	Aorta	CSF	Aorta	CSF	CSF
Control	103 ± 32	575 ± 69	41 ± 19	289 ± 77	3330 ± 1207
Indomethacin	<13*	<13*	<13	<13*	394 ± 130*

* $p < 0.05$ compared to preindomethacin value. (Not detectable was treated as 13 pg/ml to allow statistical analyses to be performed.)

Table 2. *Effects of vehicle (n = 7) and indomethacin (5 ± 1 mg/kg, intravenous; n = 8) on cerebral blood flow and its distribution and upon cardiac output, arterial pressure, and blood chemistry of unanesthetized piglets (means ± SEM; % change was calculated only when the groups were different significantly); indomethacin was administered 2 h 45 min prior to the blood flow determination; control determinations were made in the morning and vehicle or indomethacin determinations were made in the afternoon*

	Flow (ml/100 g·min)				
	Vehicle		Indomethacin		
	Control	Vehicle	Control	Indomethacin	% Change
Total brain	69 ± 12	84 ± 12	78 ± 12	58 ± 6*	−21 ± 7
Cerebrum	69 ± 13	84 ± 12	77 ± 12	57 ± 6*	−22 ± 7
Mesen-Dien	69 ± 12	88 ± 12	84 ± 12	60 ± 7*	−23 ± 9
Cerebellum	61 ± 11	84 ± 14	78 ± 12	61 ± 8*	−19 ± 8
Pons	83 ± 16	99 ± 13	74 ± 9	52 ± 6*	−23 ± 9
Medulla	57 ± 7	67 ± 10	68 ± 11	49 ± 7*	−23 ± 7
Caudate n.	99 ± 23	120 ± 22	96 ± 17	73 ± 9*	−18 ± 8
Gray	107 ± 26	124 ± 22	126 ± 21	82 ± 7*	−28 ± 8
White	50 ± 10	58 ± 7	50 ± 9	38 ± 5*	−20 ± 7
Cardiac output (ml/kg·min)	322 ± 55	287 ± 30	279 ± 43	271 ± 17	
Arterial pressure (mm Hg)	68 ± 4	71 ± 3	66 ± 2	65 ± 2	
pH	7.45 ± 0.02	7.43 ± 0.02	7.46 ± 0.02	7.45 ± 0.01	
Pa_{O_2}	76 ± 4	71 ± 4	72 ± 3	77 ± 4	
Pa_{CO_2}	37 ± 2	39 ± 3	37 ± 1	38 ± 2	

* $p < 0.05$ from control.

Table 3. *Cardiac output, mean arterial pressure, and arterial blood gases and pH during normoxia/normocapnia and hypoxia/hypercapnia (10% O_2, 9% CO_2, balance N_2) in the indomethacin-treated piglets (n = 5) (means ± SEM)*

			Indomethacin		
			15 min*	165 min*	195 min*
	Normoxia/ normocapnia	Hypoxia/ hypercapnia	Hypoxia/ hypercapnia	Normoxia/ normocapnia	Hypoxia/ hypercapnia
Cardiac output (kg·min)	365 ± 51	482 ± 58	451 ± 54	354 ± 48	508 ± 115
Mean arterial pressure (mm Hg)	66 ± 5	76 ± 4	79 ± 7	67 ± 6	81 ± 5
Arterial pH	7.50 ± 0.06	7.25 ± 0.08		7.49 ± 0.03	7.19 ± 0.05
Pa_{O_2} (mm Hg)	70 ± 3	42 ± 1		75 ± 5	41 ± 4
Pa_{CO_2} (mm Hg)	36 ± 2	66 ± 2		38 ± 2	65 ± 2

* Time after indomethacin administration.

formly throughout the brain by 18–28% (Table 2). There were no changes in cardiac output, arterial pressure, or blood gases and pH that would account for this decrease (Table 2).

The effect of breathing 10% O_2, 9% CO_2 with the balance N_2 (hypoxia/hypercapnia) on cardiac output, arterial pressure, and arterial blood gases and pH are shown in Table 3. This degree of hypoxia/hypercapnia caused total cerebral blood flow to increase from 102 ± 12 to 218 ± 19 ml/100 g·min (Fig. 1). The regional increases were greatest in the medulla (95 ± 8 to 392 ± 58 ml/100 g·min) and least in the cerebrum (101 ± 12 to 189 ± 12 ml/100 g·min). Intravenous administration of indomethacin during hypoxia/hypercapnia caused, within 15 min, a uniform decrease in cerebral blood flow throughout the brain to levels indistinguishable from those obtained when the piglet was breathing air (Fig. 1). Further, 3.25 h later, the cerebral hyperemia caused by hypoxia/hypercapnia was attenuated markedly. In contrast, vehicle control animals had a similar hyperemia during hypoxia/hypercapnia during the morning and afternoon sessions. Thus, in the four vehicle control animals, cerebral blood flow increased from 73 ± 25 to 211 ± 25 ml/100 g·min during

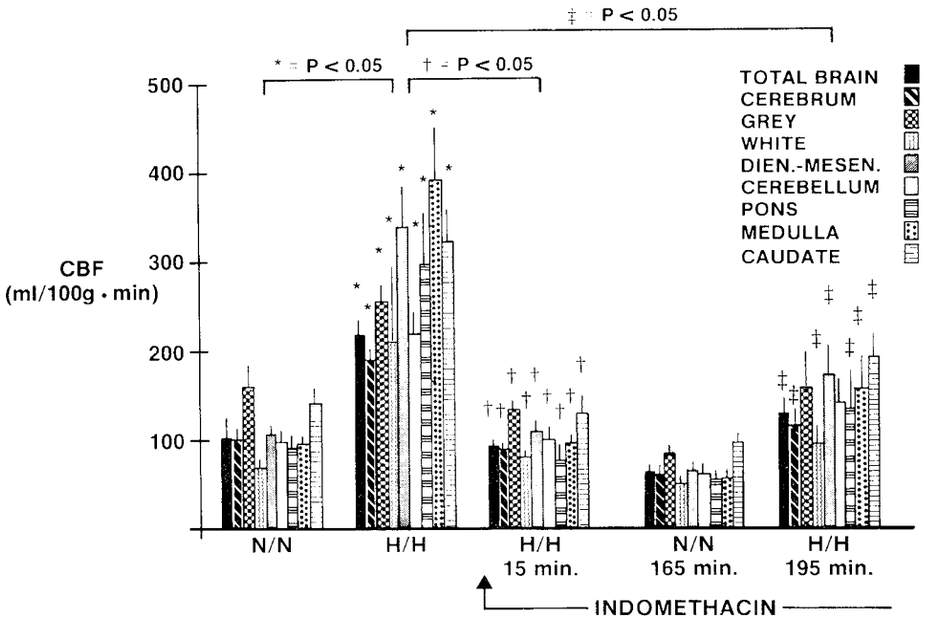

Fig. 1. Effect of indomethacin (5 ± 1 mg/kg, intravenous) on total and regional cerebral blood flow of piglets (n = 5) during normocapnia/normoxia (N/N) and hypoxia/hypercapnia (H/H) (10% O_2, 9% CO_2, balance N_2) (means ± SEM). Indomethacin was administered after 30 min of breathing hypoxic/hypercapnic mixture and the next cerebral blood flow determination was made 15 min later. The piglet then breathed ambient air for 150 min before the next normoxic/normocapnic flow determination was made. Arterial blood gases and pH, arterial pressures, and cardiac outputs are shown in Table 3. See text for vehicle-time control data.

hypoxia/hypercapnia in the morning and from 104 ± 17 to 242 ± 15 ml/100 g·min during the afternoon of the same day.

DISCUSSION

The present study demonstrates that 1) indomethacin crosses the blood brain barrier of newborn pigs in sufficient quantity to inhibit prostanoid release into the CSF passing over the surface of the brain, and 2) intravenous administration of indomethacin decreases cerebral blood flow and attenuates the cerebral hyperemia induced by combined severe hypoxia/hypercapnia in newborn pigs.

Our results in newborn pigs are similar to those of others studying adult baboons, rats, and gerbils who found that indomethacin reduced cerebral blood flow during normocapnia and virtually abolished the increase in cerebral blood flow during hypercapnia (1–3). On the other hand, we and others found that indomethacin, at doses that block vasodilatory responses of pial vessels to exogenous arachidonic acid, did not affect cerebral blood flow, pial artery diameter, or responses of cerebral arteries to hypercapnia in adult cats, rabbits, or dogs (4–7). These differences in adults could involve species differences. In adult animals, the cerebral vasodilator response to arterial hypoxia consistently was not altered by intravenous administration of indomethacin (3, 7).

Reported effects of cyclooxygenase inhibitors on cerebral blood flow of perinatal animals have been more consistent than findings in adult animals. Bedard *et al.* (21) reported that although cerebral blood flow was not altered significantly by indomethacin in pentobarbital-anesthetized puppies 3–27 days old, indomethacin appeared (not significant with small sample size) to reduce cerebral blood flow in puppies less than 3 days old. Further, Ment *et al.* (22, 23) found, using carbon-14 autoradiography, that indomethacin and ethamsylate decreased cerebral blood flow of newborn puppies. Heymann and Rudolph (10) found that aspirin treatment of fetal lambs *in utero* decreased cerebral blood flow.

The mechanism by which indomethacin reduces cerebral blood flow and attenuates cerebral hyperemia in response to blood gas stress in newborn pigs cannot be determined from the present experiments. One possibility is that cerebral prostanoids represent an important dilator component in the regulation of cerebral blood flow in the neonatal animal and that indomethacin causes cerebral vasoconstriction and reduced dilator responses by inhibiting prostanoid synthesis. Consistent with this possibility is the data presented herein that intravenous indomethacin greatly reduces the concentration of prostanoids in cerebrospinal fluid on the surface of the brain.

Several lines of evidence suggest that the prostanoid system is an integral component of circulatory control in the perinatal animal. First, we and others have found that the concentration of the prostacyclin hydrolysis product, 6-keto-$PGF_{1\alpha}$, in neonatal arterial plasma, although less than fetal, is far higher than that found in the adult (12, 20, 24). Similarly, the concentration of 6-keto-$PGF_{1\alpha}$ in neonatal urine is more than 10 times the concentration in adult urine (25). Second, treatment of the fetus or neonate with cyclooxygenase inhibitors causes closure of the ductus arteriosus, suggesting that prostanoids are important in maintenance of patency of the ductus arteriosus in the fetus (8, 10, 11). Third, data from our laboratory support the hypothesis that pulmonary prostacyclin production contributes to the decline in pulmonary vascular resistance with the onset of ventilation at birth (12, 13, 26–28). Fourth, in contrast to the negligible effects of cyclooxygenase inhibition in adults, treatment with cyclooxygenase inhibitors to close the patent ductus arteriosus in the neonate often produces a transient decline in renal function (16, 17), suggesting a role for prostanoids in the function of this organ. Further, although inhibition of prostanoid synthesis may (10, 14) or may not (29) affect renal blood flow in unstressed fetal lambs, prostanoids appear to help maintain renal blood flow during hypoxia (15, 30). Thus, it would not be surprising to find that prostanoids play a more important role in maintenance of cerebral blood flow in the neonatal than in the adult animal. If prostanoids were important in regulation of cerebral hemodynamics in the neonatal animal, their effects could be by a variety of actions including direct effects on the vascular smooth

muscle, inhibition of sympathetic nervous activity and effect (31–34), or mediation of vasoactive intestinal peptide-induced vasodilation (35).

Conversely, indomethacin may decrease cerebral blood flow and attenuate cerebral hyperemia by a mechanism which is independent of prostanoids. For example, indomethacin may function as a free radical scavenger (36), and free radicals have been shown to be potent vasodilators of pial vessels (37). Indomethacin may also inhibit active calcium transport processes (38, 39) and affect responses by this mechanism. Probably via effects on calcium, indomethacin can inhibit phospholipase (40–42), thereby reducing not only the production of prostanoids but of products of alternative pathways of arachidonic acid metabolism such as the products of the cytochrome P450 pathway. Indomethacin may inhibit phosphorylation, thereby functioning as a cyclic-AMP antagonist (43). Also, indomethacin could have a direct vasoconstrictor effect on the cerebral vasculature of newborn pigs. Additional studies will be necessary to delineate the mechanism by which indomethacin reduces resting cerebral blood flow and attenuates the cerebral hyperemia in response to combined hypercapnia and hypoxia in newborn pigs.

The dose of indomethacin in the present experiments was selected because it is highly efffective in inhibiting prostanoid synthesis throughout the body. Whether the very low doses of indomethacin used to close the patent ductus arteriosus in the premature newborn infant can affect cerebral blood flow and/or the cerebral hyperemic response to asphyxia is unknown.

In summary, indomethacin treatment of unanesthetized newborn pigs causes a decrease in resting cerebral blood flow and attenuates the hyperemia induced by severe combined hypoxia/hyercapnia.

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