0031-3998/88/2401-0041$02.00/0
PEDIATRIC RESEARCH

Vol. 24, No. 1, 1988
Printed in U.S.A.

Autoradiographic Determination of Regional Cerebral Blood Flow during Hypoglycemia in Newborn Dogs

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ABSTRACT. To ascertain the regional cerebral blood flow (CBF) responses to hypoglycemia, nine newborn dogs were treated with insulin to blood glucose concentrations ranging from 1 to 35 mg/dl (mean 22 mg/dl). Systemic physiologic monitoring revealed no differences in mean arterial blood pressure, heart rate, paO_2, $paCO_2$, pHa, or blood lactate in the hypoglycemis animals and five normoglycemic controls. Significant increases in CBF occurred in 17 of 20 analyzed structures of brain in the hypoglycemic puppies, ranging from 158 to 446% of the normoglycemic values. The percent increases in CBF were greatest in brainstem structures compared to other major regions of brain. A positive correlation existed between mean arterial blood pressure and cerebral cortical blood flow, suggesting a loss of CBF autoregulation during hypoglycemia. The pathophysiologic mechanism for the elevations in regional CBF might relate to stimulation of β-adrenergic receptors in brain, as has been shown in adults. (*Pediatr Res* 24: 41–45, 1988)

Abbreviations

CBF, cerebral blood flow
rCBF, regional CBF
MABP, mean arterial blood pressure
PCA, perchloric acid

Hypoglycemia, defined as a blood glucose concentration of <30 mg/dl in full-term infants and <20 mg/dl in premature infants, is a common clinical problem in high risk newborn infants (1–5). Asymptomatic hypoglycemia has not been associated with adverse neurologic sequelae, whereas up to 60% of infants exhibiting symptomatic hypoglycemia suffer permanent brain damage (6–8). Premature and small for gestational age infants are especially vulnerable to hypoglycemic brain injury (2, 9, 10). However, offspring of diabetic mothers appear to be at less risk for symptomatic hypoglycemia and ultimate brain injury (4, 6–8).

The underlying pathophysiologic mechanism(s) producing brain dysfunction and clinical symptoms in hypoglycemic newborn infants is not entirely known. Hypoglycemic brain damage presumably results from inadequate mobilization and utilization of alternate cerebral metabolic fuels; specifically ketone bodies, lactic acid, and amino acids; or from an accumulation of one or more toxic metabolites in brain when these alternate fuels are consumed. Investigations have shown that whereas glucose consumption is reduced during hypoglycemia, oxygen consumption is essentially unchanged (11–14); indicating that alternate fuels are being used for energy production. In this regard, Geiger (15) has shown that the perfused adult cat brain is capable of functioning for more than 1 h without exogenous glucose so long as a high perfusion rate is maintained. This finding suggests that while the brain is able to use endogenous noncarbohydrate substrates for energy production, hypoglycemic symptoms and ultimate brain injury are, at least in part, due to the local accumulation of toxic breakdown products of these substrates. Thus, changes in CBF adversely affecting any region of the brain would allow the local accumulation of toxic metabolites, resulting in brain injury.

We previously have determined the blood flow responses of newborn dog cerebral cortex to insulin-induced hypoglycemia using an arteriovenous technique with ^{133}Xenon as the diffusible indicator (14). In that study, no differences in CBF were observed in normoglycemia and hypoglycemic animals. Now that techniques are available to measure rCBF, we decided to study the regional distribution of blood flow in the brain during hypoglycemia in newborn dogs in an attempt to ascertain the vulnerability of specific structures to hypoglycemic brain damage.

MATERIALS AND METHODS

Newborn Beagle dogs of 2 to 5 days postnatal age initially were anesthetized with halothane (4% induction; 1% maintenance), tracheostomized, and paralyzed with pancuronium bromide 1.0 mg/kg body weight subcutaneously. The puppies then were artificially ventilated with a gas mixture of 70% nitrous oxide-30% oxygen by means of a small animal respirator (Harvard Apparatus Co., Inc., S. Natick, MA). A femoral artery was catheterized under local anesthesia (procaine HCl 1%) for the continuous recording of systemic blood pressure via a Statham transducer connected to a dynographic recorder (Beckman Instruments Inc., Fullerton, CA). The arterial catheter also allowed for intermittent collection of blood (~0.2 ml) for measurement of paO_2, $paCO_2$, and pHa on a microelectrode system (Corning Medical, Medford, MA). Additional blood specimens (0.02 ml) were obtained and immediately diluted 1:10 in 0.5 M perchloric acid for later determination of glucose and lactate concentrations by standard enzymatic techniques (16, 17). The total volume of blood removed was similar in all animals and amounted to no more than 1.5 ml, which is less than 5% of the circulating blood volume of the newborn dog. Rectal temperature was maintained at 37 ± 0.5° C by means of a thermister controlled heating lamp.

Received November 12, 1987; accepted February 29, 1988.
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Supported in part by Grant 15738 from The National Institute of Child Health and Human Development and by a Grant from The American Diabetes Association, New York affiliate.

When the newborn dogs had achieved normal arterial oxygen and acid-base balance (paO_2 70–110 mm Hg; $paCO_2$ 35–45 mm Hg; pHa 7.35–7.45), hypoglycemia was induced by the intravenous injection of regular insulin USP 0.2 U/g body weight; control animals received an equivalent volume of N NaCl. Hypoglycemia, with final blood glucose concentrations at or below 35 mg/dl, was achieved within 90–120 min.

rCBF was measured by the indicator-fractionation method as originally described by Van Uitert and Levy (18) and applied to the newborn dog by Cavazzuti and Duffy (19). The radioisotope 4-iodo-[^{14}C]-antipyrine (59 mCi/mM: New England Nuclear, Boston, MA) was used as the diffusible indicator, and the quantity of the indicator accumulated in brain was assessed by ^{14}C autoradiography. This technique is based on the Fick equation:

$$CBF = \frac{Q(t)}{\int_0^t (Ca - Cv)dt \times 100}$$

where CBF is in ml/100 g/min; Q(t) is the amount of indicator accumulated in brain during time (t); and (Ca − CV)dt is the integrated difference between amount of indicator in arterial and venous blood.

If a freely diffusible indicator is used and the time from bolus injection to animal death is relatively brief (s) so that venous outflow is negligible, then the integrated arterial concentration can be used as an approximation of the integrated arteriovenous difference (18). Furthermore, if the integrated arterial indicator concentration is the same for two organs and the time from bolus injection to termination of organ blood flow is also the same, then the ratio of the indicator to blood flow will be the same for the two organs. Thus,

$$\frac{Q_i(t)}{CBF_i} = \int_o^t Ca_i dt = \int_0^t Ca_{ii} dt = \frac{Q_{ii}(t)}{CBF_{ii}}$$

An artificial organ was produced by withdrawing blood into a syringe at a specified constant rate. Thus,

$$CBF = \frac{\text{brain counts (dpm)}}{\text{brain mass (g)}} \times \frac{\text{arterial flow (ml/min)}}{\text{arterial counts (dpm)}}$$

Cavazzuti and Duffy (19) have shown that the optimal circulation time for ^{14}C-iodoantipyrine is 9 s. At 9 s the intregral of venous radioactivity in newborn dogs is <5% of the integral of the arterial radioactivity, thus satisfying the requirement of negligible venous outflow at the time of the animal's death.

For measurement of rCBF in the newborn dog, the femoral artery catheter was connected via polyethylene tubing (5–7 cm in length) to a syringe set in a Harvard infusion/withdrawal pump calibrated to withdraw blood at a constant rate of 1.57 ml/min. At 0 time, 50 μCi of ^{14}C-iodoantipyrine dissolved in 0.5 ml of 0.9% NaCl were injected rapidly through the venous catheter and the withdrawal pumps started. At 9 s the animal was decapitated with a small animal guillotine and the arterial catheter rapidly disconnected. The brain was quickly removed from its skull and frozen in freon 12 chilled to −65° C. The blood collected in the syringe was expelled into a tube containing 1.0 ml of water. An aliquot of the mixture then was solubilized in 0.5 ml of Protosol (New England Nuclear) and later diluted in 10 ml of Omnifluor-Toluene scintillation cockatail (New England Nuclear). The mixture then was counted in a scintillation spectrometer (Beckman) with appropriate standards and blanks.

Coronal sections of the frozen brain were cut at 20-μ thickness in a cryostat (American Optical, Buffalo, NY) at −15° C. The sections were mounted on glass coverslips, dried at 55° C, and subjected to quantitative ^{14}C-autoradiography along with calibrated ^{14}C-methylmethacrylate standards. Comparison of the optical densities of 1–2 mm diameter portions of the autoradiograms corresponding to specific brain regions with the optical densities of the ^{14}C standards yielded the concentration (nCi/g) of ^{14}C-iodoantipyrine in each brain region. rCBF was calculated according to the following equation:

$$rCBF\ (ml/100\ g/min) = \frac{(nCi\ in\ brain/g)}{\frac{(2.22 \times 10\ dpm/nCi)(1.57\ ml/min) \times 100}{Total\ dpm\ in\ syringe\ blood}}$$

Statistical analysis of the data was carried out using the two-tailed Student's t test and linear regression analysis.

Table 1. *Systemic physiologic variables during normoglycemia and hypoglycemia in newborn dogs**

Variable	Normoglycemia (6)	Hypoglycemia (9)
MABP (mm Hg)	72 ± 3	70 ± 4
Heart rate (/min)	222 ± 7	248 ± 7
PaO_2 (mm Hg)	106 ± 6	95 ± 6
$PaCO_2$ (mm Hg)	37 ± 1	34 ± 4
pHa	7.38 ± 0.02	7.34 ± 0.05
Blood glucose (mg/dl)	122 ± 6.3	22 ± 3.2†
Blood lactate (mmol/liter)	1.1 ± 0.2	1.2 ± 0.2

* Values represent means ± SEM for the number of animals in parentheses.

† $p < 0.001$.

RESULTS

Systemic physiologic data on five normoglycemic and nine hypoglycemic newborn dogs at the time of the CBF measurements are shown in Table 1. The two groups were comparable with regard to MABP, heart rate, paO_2, $paCO_2$, pHa, and blood lactate. As expected, blood glucose concentrations in the hypoglycemic animals were significantly lower than those of the control animals. Blood glucose concentrations in the former group ranged from 1 to 35 mg/dl.

Blood flow to 20 selected regions of newborn dog brain during normoglycemia and hypoglycemia are shown in Figure 1. Significant increases in blood flow, ranging from 158 to 446% of control, occurred in 17 of the 20 analyzed structures. In no structure was blood flow decreased. Linear regression analysis of each individual structure failed to reveal a progressive increase in CBF with decreasing blood glucose concentrations of less than 35 mg/dl. Grouping the percent increases in CBF according to major regions of brain[1] indicated a relative preferential perfusion of the brainstem compared to cerebral cortex, hippocampus, diencephalic gray matter nuclei, cerebellum, and white matter ($p < 0.01$). Visual inspection of the autoradiograms also suggested relatively greater increases in blood flow to brainstem rather than to forebrain or cerebellar structures (Fig. 2).

DISCUSSION

The present investigation indicates that hypoglycemia is associated with essentially global increases in perinatal CBF as has been shown to occur in mature animals, including man (12, 20, 21). Thus, hypoglycemia joins hypoxia, hypercapnic acidosis, and seizures as the major metabolic stresses known to produce substantial vasodilation of the cerebral circulation (22–24). Indeed, the CBF responses of the newborn dog brain to hypoglycemia appear to be as great as those observed during other insults

[1] Cerebral cortex: frontal cortex, parietal cortex, occipital cortex; hippocampus; diencephalon: caudate nucleus, globus pallidus, thalamus, hypothalamus; brainstem: lateral geniculate body, red nucleus, superior colliculus, inferior colliculus, basis pontis, vestibular nucleus, superior olivary nucleus, medulla; cerebellum: cerebellar hemisphere, cerebellar vermis; white matter: corpus callosum, subcortical white matter.

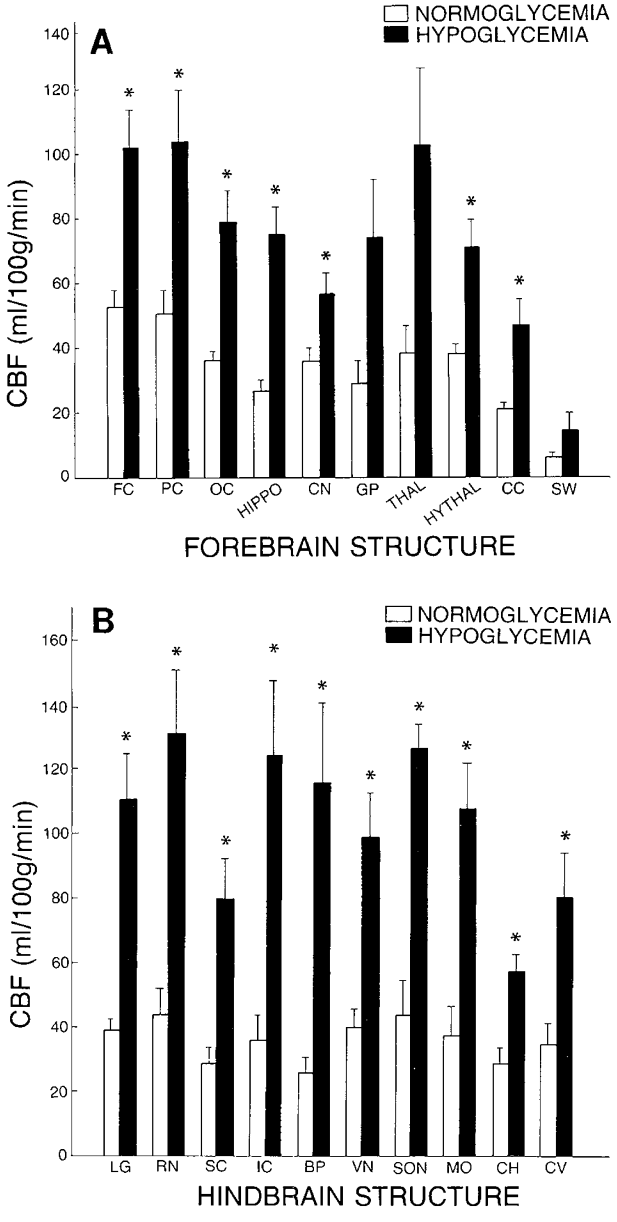

Fig. 1. rCBF in normoglycemic and hypoglycemic newborn dogs. *Vertical bars* represent means ± 1 SE of five normoglycemic and nine hypoglycemic puppies. * $P < 0.05$. *FC*, frontal cortex; *PC*, parietal cortex; *OC*, occipital cortex; *HIPPO*, hippocampus; *CN*, caudate nucleus; *GP*, globus pallidus; *THAL*, thalamus; *HYTHAL*, hypothalamus; *CC*, corpus callosum; *SW*, subcortical white matter; *LG*, lateral geniculate body; *RN*, red nucleus; *SC*, superior colliculus; *IC*, inferior colliculus; *BP*, basis pontis; *VN*, vestibular nucleus; *SON*, superior olivary nucleus; *MO*, medulla oblongata; *CH*, cerebellar hemisphere; *CV*, cerebellar vermis.

to brain, although regional variations do exist. During normotensive hypoxia ($paO_2 \simeq 15$ mm Hg), 1- to 2-fold increases in CBF occur but with a substantial preferential perfusion of the lower brainstem and with a blunted response of white matter structures (19, 25). A similar hierarchy of blood flow responses to hypercapnia has been described, with those brain structures possessing the highest basal flows exhibiting the greatest elevations during acidosis (19, 26). Convulsive-induced increases in rCBF of newborn dog brain are relatively uniform in nature (27) and, therefore, mimic most closely the present findings of hypoglycemia-induced hyperemia. Indeed, seizures may have contributed to the increases in CBF, although convulsive activity has not been observed in newborn dogs until blood glucose levels fall below 12 mg/dl (a single animal in our study) (28). Possibly, the underlying pathophysiologic mechanisms producing increased rCBF during hypoglycemia and seizures are similar but differ from that of hypoxia/hypercapnia (see below).

In a previous communication from our laboratory, Hernandez *et al.* (14) measured CBF in newborn dogs during insulin-induced hypoglycemia. In that study, cerebral cortical blood flow was determined using a modification of the original Kety-Schmidt technique (29), using ^{133}Xenon as the diffusible indicator. In that study and unlike the present findings, CBF was unchanged from control in eight hypoglycemic puppies in which blood glucose concentrations averaged 9 mg/dl (range 4–13 mg/dl). An explanation for the discrepant results of the two studies is the fact that in the former investigation all of the hypoglycemic animals exhibited significant lactacidemia and an associated systemic hypotension with MABP ranging from 22 to 50 mm Hg (mean 30 mm Hg). In the present study, systemic physiologic homeostasis was more stable with MABP in the hypoglycemic puppies near identical to those of the normoglycemic animals (Table 1). This observation prompted us to correlate the alterations in MABP and in CBF obtained in the two investigations (Fig. 3), inasmuch as lactacidemia per se does not influence rCBF (30). The data show a positive correlation between systemic blood pressure and cerebral cortical blood flow, suggesting that CBF autoregulation is abolished during hypoglycemia (see also Refs. 31 and 32). Thus, as in hypoxia, hypercapnia, and seizures, hypoglycemia appears to render the perinatal brain passive to fluctuations in systemic blood pressure (22, 24). If substantiated by further experiments, the finding would have relevance to newborn human infants, in whom systemic hypotension superimposed on hypoglycemia might influence the presence of clinical manifestations as well as ultimate brain damage.

It is reasonable to assume that the elevations in rCBF during hypoglycemia promote optimal substrate delivery to the perinatal brain during systemic glucose deficiency. Indeed, the enhanced glucose delivery provides adequate glucose equivalents for energy production via oxidation until blood glucose concentrations decline below 10 mg/dl, at which point alternate exogenous and endogenous fuels are required for cerebral metabolism (14, 28). In a more recent investigation from our laboratory, Mujsce *et al.* (33) measured regional cerebral glucose utilization by the 2-deoxyglucose technique of Sokoloff *et al.* (34) in newborn dogs subjected to hypoglycemia with a mean blood glucose concentration of 17 mg/dl. Hypoglycemia was associated with no or relatively minor decreases in glucose consumption in 13 of 16 analyzed structures of brain, indicating that the compensatory increases in blood flow to these regions were sufficient to maintain physiologic glucose metabolism. Brainstem regions exhibited the smallest reductions in glucose utilization, owing to maximal increases in CBF and glucose delivery, as in our study. In contrast, subcortical white matter showed the poorest blood flow response with resultant greatest decline in glucose utilization. The findings target white matter as that region of brain most vulnerable to the damaging effect of perinatal hypoglycemia.

Richardson *et al.* (35) have published the only other investigation pertaining to rCBF responses of the perinatal brain to hypoglycemia. Fetal lambs near term received a constant intravenous infusion of insulin over 4 h, during which blood glucose decreased from a control level of 17 to 12 mg/dl (−30%). Blood flow to five major regions of brain was measured with radioactive microspheres. No major alterations in systemic physiologic or acid-base homeostasis occurred during the infusion (paO_2 decreased slightly). In contrast to the present findings in newborn dogs, CBF actually declined in cerebral cortex and diencephalon, whereas flows to pons, medulla, and cerebellum were unchanged from control. Thus, blood flows were better preserved in hindbrain than in forebrain structures (see above). The absence of a hyperemic response to insulin infusion may have related to the physiologic low blood glucose levels (<20 mg/dl) and to the dilated cerebrovascular bed produced by the relatively hypoxic environment both of which characterize the sheep fetus.

The physiochemical mechanisms responsible for the increases

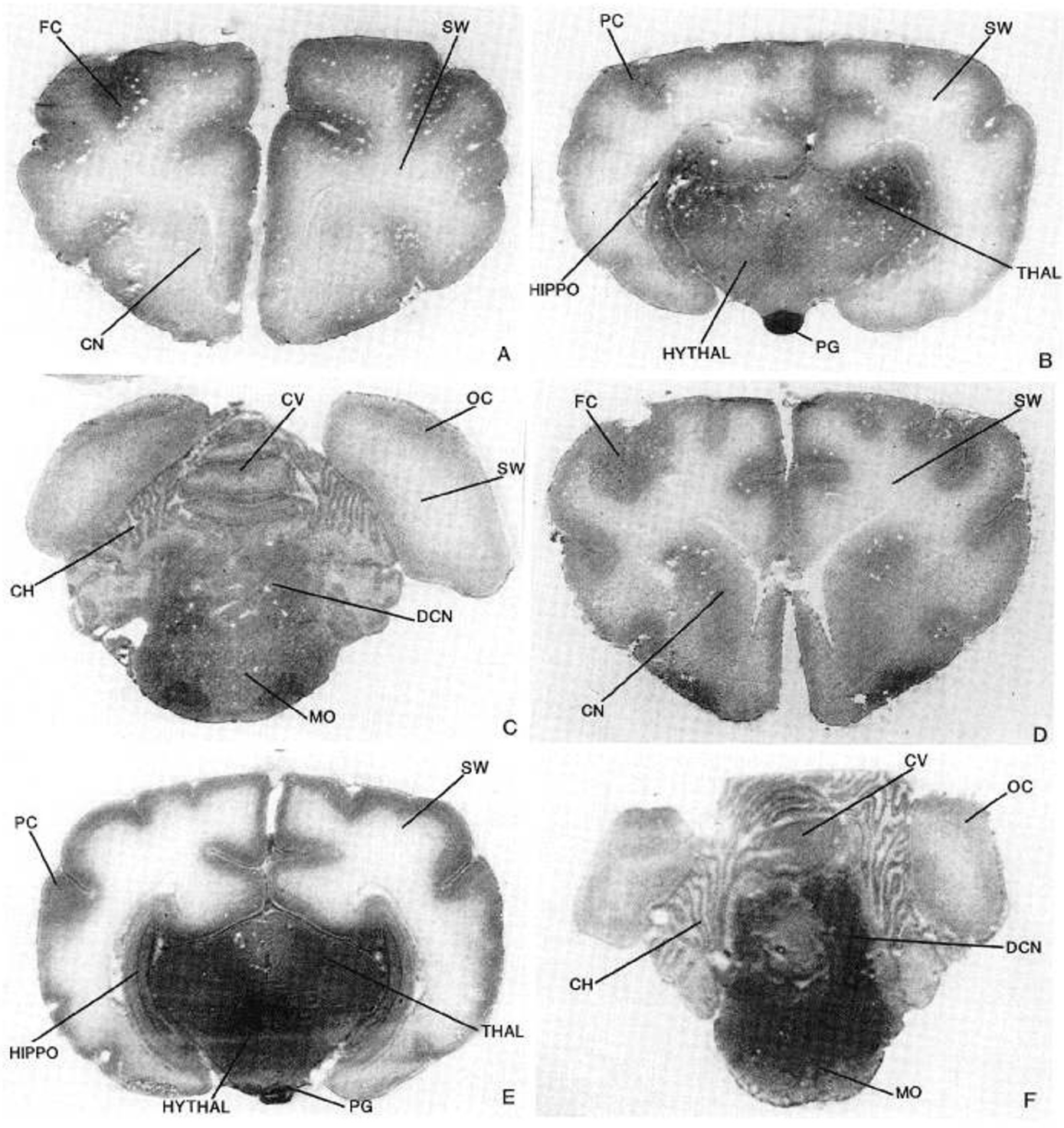

Fig. 2. Representative CBF autoradiograms during normoglycemia and hypoglycemia. Shown are coronal sections of a brain from a normoglycemic (*A, B, C*) and a hypoglycemic (*D, E, F*) newborn dog. *Darker areas* represent regions of increased CBF. *FC*, frontal cortex; *PC*, parietal cortex; *OC*, occipital cortex; *HIPPO*, hippocampus; *THAL*, thalamus (pulvinar); *HYTHAL*, hypothalamus; *CN*, caudate nucleus; *SW*, subcortical white matter; *PG*, pituitary gland; *MO*, medulla oblong ata; *CV*, cerebellar vermis; *CH*, cerebellar hemisphere; *DCN*, deep cerebellar nuclei.

in rCBF during hypoglycemia presently are not entirely clear. The vasodilatory response of cerebral blood vessels to systemic hypoxia and hypercapnia presumably results from increased H^+ ion concentrations in the resistance vessels (arterioles) of the brain (22, 24). This mechanism readily explains why those brain regions with the greatest intrinsic metabolic activity (*e.g.* brainstem) exhibit the greatest increases in blood flow under these conditions. However, during hypoglycemia in adult animals; brain tissue, if anything, is more oxidized than during normoglycemia (22, 36, 37), and studies in newborn dogs suggest an undisturbed cerebral redox state even at blood glucose concentrations as low as 5 mg/dl (28). Adenosine accumulation in brain as a cause of cerebral vasodilation (38, 39) also cannot explain the hyperemic response to hypoglycemia, inasmuch as the ade-

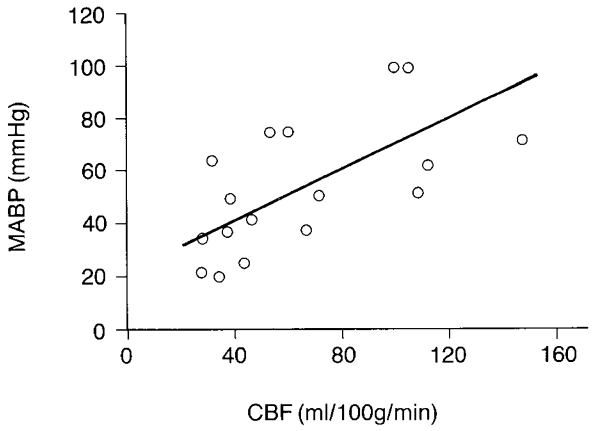

Fig. 3. Relationship between MABP and CBF during hypoglycemia. Values include those of the present study and of normalized values from Hernandez *et al.* (14). Linear regression analysis: $r = 0.71$; $p < 0.01$.

nine nucleotides, the major source of adenosine, are well preserved in newborn dog brain even at the extremes of hypoglycemia (28).

Bryan *et al.* (21) recently demonstrated a close correlation between increases in rCBF and elevated plasma concentrations of epinephrine and norepinephrine during hypoglycemia in adult rats. The investigators speculated that adrenergic stimulation of β-receptors in brain might cause or contribute to the global alterations in CBF. Confirmation of their proposal was provided by Hollinger and Bryan (40), who were able to partially or completely abolish the regional hyperemic responses to hypoglycemia by pretreating adult rats with the β-receptor blocker, propranolol. Presumably, a similar mechanism underlies the cerebrovascular response of newborn dogs to hypoglycemia.

Acknowledgments. The authors thank Francesca Vasta for her expert technical assistance and Thomas Hegyi, I. Mark Hiatt, and Anne Koons for their helpful suggestions and support.

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