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Cerebral Blood Flow and Metabolism in Dogs with Chronic Diabetes

Frederick E. Sieber, M.D., Phillip R. Brown, D.V.M.,† Ying Wu, B.S.,‡ Raymond C. Koehler, Ph.D.,* Richard J. Traystman, Ph.D.§*

Background: **Previously, the authors found that anesthetized diabetic dogs had increased cerebral blood flow (CBF) and oxygen consumption ($CMRO_2$). These results may have been influenced by anesthesia or surgery. The aim of this study was to determine whether CBF and $CMRO_2$ are increased in the awake or anesthetized state in the absence of acute surgical stress in diabetic dogs. A second aim was to determine whether increased CBF and $CMRO_2$ in diabetic dogs are mediated through β-adrenergic mechanisms.**

Methods: **Diabetic dogs (n = 8) underwent total surgical pancreatectomy followed by 4 months of insulin management (16 ± 0.4 units/day, mean ± SE) to maintain fasting and 3 PM blood glucose 10–17 mM. Control dogs (n = 8) underwent sham operation followed by a 4-month convalescence. Using previously inserted catheters, CBF (radiolabelled microspheres) and $CMRO_2$ (sagittal sinus sampling) were measured before and after propranolol (2 mg/kg) in both the awake and anesthetized states.**

Results: **During the 4 months before CBF studies, the fasting blood glucose was greater in diabetic group than in the control group (11.0 ± 0.3 *vs.* 4.0 ± 0.1 mM, respectively). No difference occurred between groups in CBF or $CMRO_2$. In the awake state, propranolol administration caused no CBF or $CMRO_2$ changes. However, during anesthesia with 50 μg/kg fentanyl plus 10 mg/kg pentobarbital, propranolol administration decreased CBF in control, but not in diabetic, dogs.**

Conclusions: **The authors' previous results showing increased CBF and $CMRO_2$ with diabetes may be secondary to a differential response to acute surgical stress, a factor that was eliminated in this study. These results indicate that diabetes is associated with changes in the β-adrenergic system that become evident under fentanyl/pentobarbital anesthesia. (Key words: Brain: cerebral blood flow. Diabetes: blood glucose. Surgery: stress. Sympathetic nervous system: β-adrenergic receptors.)**

THE effects of chronic hyperglycemia on cerebral blood flow (CBF) and metabolism are unclear. In humans, long-standing diabetes can alter CBF and metabolism.[1,2] However, the available human studies do not provide information concerning the degree of atherosclerosis or microangiopathy. Thus, it is difficult to assess the relative contributions of chronic hyperglycemia *versus* vascular disease in mediating these changes. Studies on animals indicate that chronic hyperglycemia alone alters CBF and metabolism.[3] In addition, other organ systems clearly show increases in regional blood flow during the early onset of diabetes.[4] These organ-specific increases in blood flow may subsequently lead to basement membrane damage and the development of microangiopathy. Microangiopathy can occur in the diabetic brain.[5] For these reasons, it is important to determine whether CBF increases occur in diabetes.

In a previous study, we found that chronic hyperglycemia associated with surgical pancreatectomy in dogs increased CBF and cerebral oxygen consumption ($CMRO_2$).[6] However, these measurements were obtained during anesthesia after surgery was performed for catheter placement. Thus, it is unclear whether the observed CBF and $CMRO_2$ changes were a response to anesthesia, surgery, or diabetes. The aim of this study was to determine whether CBF and $CMRO_2$ increase with diabetes in the absence of anesthesia and acute surgery. The hypothesis tested was that CBF and metabolism increase with diabetes.

During certain stresses, such as surgery, CBF and metabolism increases are partially mediated through β-

* Associate Professor, Department of Anesthesiology and Critical Care Medicine.

† Assistant Professor, Departments of Surgery and Comparative Medicine.

‡ Research Technician, Department of Anesthesiology and Critical Medicine.

§ Distinguished Research Professor, Department of Anesthesiology and Critical Care Medicine.

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Address reprint requests to Dr. Sieber: Division of Neuroanesthesia, Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Hospital, Meyer 8-134, 600 North Wolfe Street, Baltimore, Maryland 21287-7834.

adrenergic mechanisms.[7] Diabetes causes alterations in vascular responses to catecholamines and decreases in brain catecholamines.[8,9] These changes may influence CBF and metabolism during anesthesia. The second aim of this study was to determine whether increased CBF and $CMRO_2$ in diabetic dogs are mediated through β-adrenergic mechanisms. We tested the hypothesis that differences in CBF and $CMRO_2$ between nondiabetic and diabetic dogs are eliminated by propranolol in awake and anesthetized states.

Methods

Experimental Model

Conditioned, purebred, male beagle dogs were anesthetized with halothane. In sham-operated controls, a midline laparotomy was performed and the peritoneum was sutured closed. To produce diabetes, a total pancreatectomy was performed. Both groups received the antibiotic ampicillin (250 mg/day) for 1 week. Pancreatectomized dogs were allowed a 1-week convalescence period, during which Ultralente pork insulin was given. This was followed by a 4-month period of hyperglycemia managed by low-dose subcutaneous injections of Ultralente insulin. Daily blood samples were drawn from a foreleg vein at 8–9 AM (overnight fasting) and at 3 PM (after main feeding) for analysis of glucose. The dose of insulin was adjusted individually to maintain blood glucose between 10 and 17 mM throughout the day, and averaged $1.4\ U \cdot kg^{-1} \cdot day^{-1}$ (1 mM glucose = 18 mg/dl; thus, 10 mM glucose = 180 mg/dl glucose). Glucose concentrations greater than 17 mM caused the dogs to develop acidosis and excessive weight loss. Pancreatectomized dogs were provided with a fixed amount of food with water *ad lib,* and received pancreatic enzyme supplementation (Viokase (Aveco, Ft. Dodge, IA); 5 ml/day). Two groups of dogs were studied: a sham-operated, normoglycemic, nondiabetic control group (n = 8), and a chronically hyperglycemic (4 months) diabetic group (n = 8).

Four months after the initial surgery, and approximately 1.5 weeks before the awake blood flow studies, the dogs were anesthetized with halothane, and a thoracotomy was performed for placement of aortic and left atrial catheters. A left thoracotomy at the fifth intercostal space was performed, and aortic and left atrial Tygon catheters (Norton, Akron, OH) were placed. The catheters were routed subcutaneously to the back of the neck, heparinized, and protected underneath a jacket. A chest tube was placed during surgery and removed the next day. Following recovery from anesthesia, analgesia was provided with morphine (1 mg/kg intramuscularly) as needed. Dogs received amoxycillin (500 mg daily), and rectal temperature was monitored to assure that the dogs were afebrile. One week after placement of aortic and left atrial catheters, the dogs were anesthetized with halothane and a sagittal sinus catheter was placed under aseptic conditions, routed subcutaneously to the back of the neck, and protected in a manner similar to that of the other catheters. Sagittal sinus catheterization was performed 1 week after thoracotomy because of occasional difficulties in maintaining catheter patency for prolonged periods.

Measurements

Regional CBF was measured with radiolabelled microspheres $16 \pm 0.5\ \mu m$ in diameter, as previously described.[6] Brain regions studied included: cerebrum, cerebellum, medulla, diencephalon, caudate nucleus, and periventricular white matter (including corpus callosum). Arterial and sagittal sinus pressure were continuously recorded. Arterial and sagittal sinus blood samples were collected anaerobically and analyzed immediately for *p*H and partial pressure of carbon dioxide (P_{CO_2}) and oxygen (P_{O_2}) using a Radiometer analyzer and self-calibrating electrodes (model ABL 3; Copenhagen, Denmark). Oxygen saturation and hemoglobin concentration were measured using a Radiometer Hemoximeter OSM3. Blood glucose and lactate were measured with a Yellow Springs whole blood glucose analyzer (model 2300A; Yellow Springs, OH). Global $CMRO_2$, cerebral fractional oxygen extraction, cerebral glucose consumption (CMRglu), cerebral lactate consumption (CMRlact), cerebral perfusion pressure (CPP), and cerebral vascular resistance were calculated as previously described.[6]

Experimental Protocol

Over the 4-month period of convalescence, the dogs were trained to lie quietly for approximately 1 h on a large laboratory table. The experimental protocol occurred over 2 days. On both days of the experimental protocol, all diabetic dogs received their usual morning dose of insulin and food allotment. On the day after placement of the sagittal sinus catheter (day 1), three sets of measurements were performed with the dogs in the awake state: one awake control measurement; one

Table 1. Peripheral Versus Whole Blood Glucose Concentrations and Change in Weight during the 4 Months before Cerebral Blood Flow Studies

	Sham Control (n = 8)	Diabetes (n = 8)
Insulin dose (units/day)	—	16 ± 0.4
Preoperative body weight (kg)	14.4 ± 0.3	11.8 ± 0.7
Change in weight from preoperative state (kg)	0.4 ± 0.2	−0.7 ± 0.1*
Fasting AM glucose (mM)	4.0 ± 0.1	11.0 ± 0.3*
Daily coefficient of variation of AM glucose (%)	9	28
3 PM glucose (mM)	4.2 ± 0.1	13.8 ± 0.3*
Daily coefficient of variation of PM glucose (%)	11	23

Values are mean ± SE.

* $P < 0.05$ from control group.

awake measurement 10 min after propranolol (2 mg/kg intravenously; Sigma, St. Louis, MO); and one awake measurement 3.5 h after the propranolol injection. These measurements allowed us to assess CBF and $CMRO_2$, as well as the response to propranolol, in the unstressed, awake state. Previous studies in our laboratory have demonstrated that this dose of propranolol provides total peripheral β-adrenergic blockade, defined as no change in heart rate or mean arterial pressure after intravenous administration of 10 μg/kg isoproterenol.[10]

On day 2, a second set of three measurements was obtained. The first set was performed while the dogs were awake. The dog was then anesthetized with pentobarbital (10 mg/kg intravenously) plus fentanyl (50 μg/kg intravenously). This combination and dose of anesthetic agents is the same as that previously used when CBF and $CMRO_2$ were found to be increased in diabetes.[6] After administration of pancuronium bromide (0.1 mg/kg intravenously), the trachea of each dog was intubated and the lungs were mechanically ventilated. The second set of measurements was obtained 1 h after induction of anesthesia. Next, propranolol (2 mg/kg intravenously) was administered and the third set of measurements was obtained under anesthesia 10 min after propranolol injection. While awake and anesthetized, dogs were studied while in the right lateral recumbent position. While anesthetized, dogs were placed on a heating blanket and covered with a blanket to maintain rectal temperature at ~38 ± 0.5° C.

Data Analysis

Comparison of variables among groups was made by a two-way ANOVA using a between–within design. If the F value for between group effects was significant, or if the F value for group–time interaction was significant, then a *t* test with Bonferroni's correction was performed at each of the six time points to compare mean values between groups. If the F value for the within-group factor (time) was significant, then a one-way repeated-measures ANOVA was performed for each group, and mean values at different time points were compared by the Newman-Keuls test. Values are given as mean ± SE. In all tests, the significance level was $P < 0.05$.

Results

There was a 6% weight loss in the diabetic group over the 4-month period of insulin treatment, whereas there was no change in the nondiabetic group (table 1). Foreleg venous blood glucose during the 4-month period was elevated in the diabetic group. The coefficient of variation was calculated from the daily blood glucose individually in each dog. The coefficient of variation in the low-dose insulin group exceeded that in the sham group (table 1).

Arterial blood gases were similar in both groups, both awake and anesthetized (table 2) Hemoglobin levels were lower in the diabetic group. Arterial glucose was greater in the diabetic group, whereas lactate was greater in the diabetic group on day 1 of the experiment. β-Hydroxybutyrate levels were highly variable among the diabetic dogs, but not statistically increased in the group as a whole. Cerebral perfusion pressure was similar between groups.

In the awake state, regional CBF in all areas examined was similar between control and diabetic groups (table 3). In addition, there was little variability in regional CBF between awake baseline values on day 1 and day 2. There were no regional CBF changes in either group with propranolol administration in the awake state on day 1, and cerebrovascular resistance was unchanged. Regional CBF decreased in a similar manner in both groups after anesthetic induction in all regions (table 3). After administration of propranolol in the anesthetized state, CBF was lower in the control group than in the diabetic group in all areas examined. The response to propranolol is illustrated in figure 1, in which regional CBF after propranolol during anesthesia is ex-

Table 2. Arterial Blood Values

		Day 1			Day 2		
		Awake Baseline	10 min after Propranolol	3 h after Propranolol	Awake Baseline	1 hr after Anesthetic Induction	10 min after Propranolol Anesthesia
*p*H	Control	7.45 ± 0.01	7.43 ± 0.01	7.43 ± 0.01	7.43 ± 0.01	7.41 ± 0.01	7.41 ± 0.01
	Diabetic	7.42 ± 0.01	7.41 ± 0.02	7.42 ± 0.02	7.44 ± 0.02	7.43 ± 0.02	7.43 ± 0.02
Pa_{CO_2} (mmHg)	Control	33 ± 1	34 ± 1	34 ± 1	35 ± 1	38 ± 2	36 ± 2
	Diabetic	33 ± 1	35 ± 1	35 ± 2	36 ± 3	35 ± 2	35 ± 2
Pa_{O_2} (mmHg)	Control	95 ± 4	97 ± 3	97 ± 2	94 ± 3	94 ± 5	94 ± 2
	Diabetic	90 ± 2	92 ± 2	93 ± 3	89 ± 4	90 ± 6	91 ± 3
Hemoglobin (g)	Control	13.3 ± 0.6	12.6 ± 0.6	13.4 ± 0.5	13.9 ± 0.6	13.0 ± 1.0	13.4 ± 1.3
	Diabetic	11.4 ± 0.4*	11.4 ± 0.5	11.7 ± 0.4*	11.1 ± 0.2*	10.7 ± 0.4	11.2 ± 0.4
Glucose (mM)	Control	4.0 ± 0.1	4.2 ± 0.2	3.9 ± 0.1	3.8 ± 0.1	3.8 ± 0.2	4.1 ± 0.2
	Diabetic	13.3 ± 1.6*	13.5 ± 1.5*	11.7 ± 1.9*	11.3 ± 1.1*	10.2 ± 1.6*	9.3 ± 1.6*
Lactate (mM)	Control	0.6 ± 0.1	0.5 ± 0.1	0.4 ± 0.0	0.6 ± 0.0	0.8 ± 0.2	0.9 ± 0.1†
	Diabetic	1.1 ± 0.1*	1.1 ± 0.2*	1.0 ± 0.2*	1.0 ± 0.3	0.8 ± 0.2	0.8 ± 0.2
β-Hydroxybutyrate (μM)	Control	560 ± 70	660 ± 120	660 ± 90	550 ± 50	480 ± 40	700 ± 90
	Diabetic	1,160 ± 640	1,070 ± 630	1,450 ± 610	1,680 ± 1,150	1,210 ± 730	1,220 ± 670
Cerebral perfusion pressure (mmHg)	Control	104 ± 7	102 ± 8	98 ± 7	104 ± 7	91 ± 4	105 ± 18
	Diabetic	102 ± 3	100 ± 5	96 ± 2†	104 ± 4	105 ± 6	108 ± 6

Values are mean ± SE; n = 8 in each group for respective measurements.

* $P < 0.05$ from control group at respective time.

† $P < 0.05$ from daily baseline within respective group.

pressed as a percent of blood flow during anesthesia before propranolol. The percent responses to propranolol differed between groups by approximately 20% in most regions.

No differences occurred between groups in CMRglu (table 4). However, the variance of diabetic group data for blood glucose and CMRglu was greater than the control group. In the anesthetized state, CMRglu was decreased from the awake state in both groups. Although global cerebral lactate uptake was similar between groups, some animals had a negative cerebral lactate uptake indicating lactate production. Fractional oxygen extraction was increased in the awake diabetic group 3 h after the administration of propranolol. Fractional oxygen extraction did not change with anesthesia in either group. Cerebral oxygen uptake was similar in both groups, and decreased with induction of anesthesia. Propranolol administration did not significantly affect $CMRO_2$ in either the awake or anesthetized state in either group (table 4, fig. 1).

Discussion

We found that, in the absence of acute surgery, there is no difference in CBF or $CMRO_2$ between diabetic and nondiabetic dogs in the awake or anesthetized states. Therefore, we reject our hypothesis that 4 months of hyperglycemia increases CBF and $CMRO_2$. Propranolol administration in the awake state did not alter CBF or metabolism. In the anesthetized state, propranolol administration caused cerebral vasoconstriction in control dogs, but not in diabetic dogs. Thus, there appears to be an abnormality involving the β-adrenergic system in diabetic dogs, which is expressed during fentanyl/pentobarbital anesthesia.

In a previous study, we found that diabetic dogs had increased CBF and metabolism compared with sham-operated dogs.[6] However, these results were obtained under anesthesia after acute surgery. In the current study, we found no difference in CBF or metabolism between diabetic and nondiabetic animals, whether awake or during anesthesia without surgery. This result indicates that anesthesia *per se* does not account for our previous results. These previous data showing increased CBF and $CMRO_2$ with diabetes may have been secondary to metabolic changes occurring after acute surgery, a factor that has been eliminated in the current study. Thus, there may be a differential response to surgical stimulation with diabetes; however, the cur-

Table 3. Regional Cerebral Blood Flow

		Day 1			Day 2		
		Awake Baseline	10 min after Propranolol	3 h after Propranolol	Awake Baseline	1 h after Anesthetic Induction	10 min after Propranolol Anesthesia
Cerebrum (ml · 100 g^{-1} · min^{-1})	Control	61 ± 5	59 ± 8	48 ± 5	57 ± 5	38 ± 4*	33 ± 2*
	Diabetes	62 ± 3	60 ± 4	52 ± 1	62 ± 5	39 ± 3*	42 ± 3*†
Cerebral vascular resistance (mmHg · ml^{-1} · min^{-1} · 100 g^{-1})	Control	1.8 ± 0.1	1.8 ± 0.2	2.0 ± 0.2	1.9 ± 0.1	2.5 ± 0.4*	3.3 ± 0.5*
	Diabetes	1.7 ± 0.1	1.7 ± 0.1	1.9 ± 0.1	1.7 ± 0.1	2.7 ± 0.3*	2.6 ± 0.3*†
Periventricular white matter (ml · 100 g^{-1} · min^{-1})	Control	28 ± 2	29 ± 4	24 ± 2	28 ± 3	23 ± 3*	18 ± 2*
	Diabetes	29 ± 1	27 ± 3	25 ± 1	29 ± 2	24 ± 2*	24 ± 2*†
Caudate nucleus (ml · 100 g^{-1} · min^{-1})	Control	96 ± 10	100 ± 16	81 ± 8	95 ± 13	68 ± 6*	55 ± 4*
	Diabetes	99 ± 9	98 ± 9	89 ± 3	92 ± 4	79 ± 10*	82 ± 12*†
Diencephalon (ml · 100 g^{-1} · min^{-1})	Control	58 ± 6	58 ± 11	45 ± 4	55 ± 7	33 ± 4*	30 ± 3*
	Diabetes	58 ± 6	56 ± 5	51 ± 3	57 ± 6	37 ± 3*	41 ± 4*†
Cerebellum (ml · 100 g^{-1} · min^{-1})	Control	59 ± 4	58 ± 7	48 ± 5	56 ± 7	36 ± 3*	31 ± 1*
	Diabetes	59 ± 4	55 ± 5	56 ± 5	63 ± 9	39 ± 3*	41 ± 4*†
Medulla (ml · 100 g^{-1} · min^{-1})	Control	37 ± 3	35 ± 4	31 ± 3	38 ± 5	27 ± 4*	23 ± 2*
	Diabetes	40 ± 3	36 ± 4	36 ± 3	37 ± 4	28 ± 3*	28 ± 3*†

Values are mean ± SE; n = 8 for each group for respective measurements.

* $P < 0.05$ from daily awake baseline within respective group.

† $P < 0.05$ from control group.

rent study does not delineate the specific mechanism associated with surgery that would account for increased CBF and metabolism.

There are several methodologic factors that may influence the results of this study. First, microspheres may have dislodged between the first and second day of the study. Previous studies in heart preparations have shown that, if microspheres are of sufficient size (>10 μm), the amount of microspheres in tissue remain stable for several weeks.[11] Thus, dislodging is unlikely. Second, pancreatectomy decreases glucagon. However, the effects of glucagon, or its lack thereof, on the cerebral circulation are not well known. Third, the hemoglobin values were lower in the diabetic dogs. A reduction in hemoglobin would ordinarily be expected to increase CBF by about 20%. Thus, we cannot exclude the possibility that the smaller hemoglobin levels in the diabetic dogs may have masked a small reduction in CBF.

In the pancreatectomized dog model of diabetes, we are able to study the effects of chronic hyperglycemia on the cerebral vasculature without the confounding influence of diabetic microangiopathy. The pancreatectomized dog model of diabetes develops progressive diabetic end organ vascular disease. The spectrum of the effects of diabetes can be examined, from acute hyperglycemia (acute glucose bolus and infusions), to chronic hyperglycemia without histologically defined vascular disease, to diabetes with microangiopathy (histologically reproducible retinopathy and glomerulopathy, which begins to appear at 24–30 months in dogs).[12] In the current study, the anesthetic response was studied in diabetic animals without histologically defined microangiopathy. Thus, our study examined the effects of chronic diabetic hyperglycemia, expressed as increases in hemoglobin A_1C, and is not necessarily analogous to the state of diabetic encephalopathy.

The effects of chronic hyperglycemia on cerebral metabolism are unclear. Gutniak *et al.*,[1] using positron emission tomography, showed that, in tightly controlled diabetic subjects, the unidirectional flux of glucose from blood to brain is similar to that of nondiabetics. However, the calculated metabolism of glucose was greater in the whole brain in nondiabetic than in diabetic subjects. These data indicate that, although brain glucose uptake is normal in diabetes, some aspect of glucose metabolism is abnormal. Animal studies us-

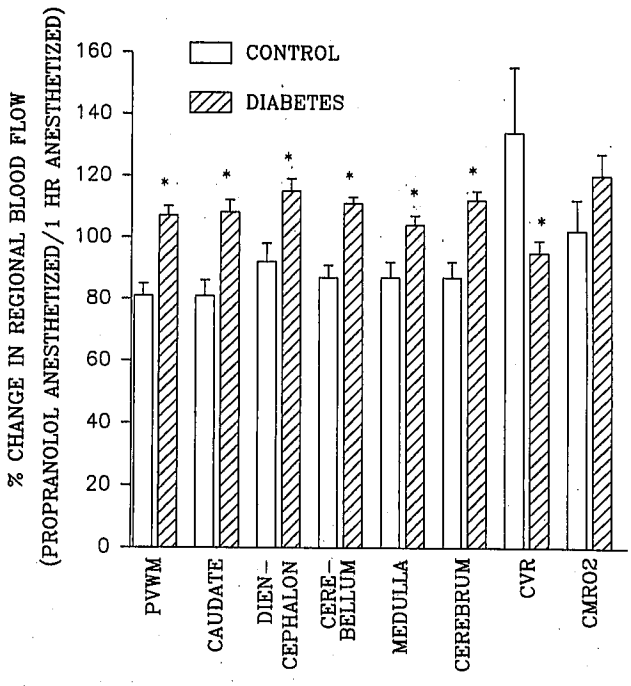

Fig. 1. Responses of regional blood flow, cerebral vascular resistance (CVR), and cerebral oxygen consumption ($CMRO_2$) in animals receiving 2 mg/kg intravenous propranolol while anesthetized, expressed as a percentage of values obtained 1 h after anesthetic induction (n = 8 in each group for respective measurements). PVWM = periventricular white matter. *$P < 0.05$ from control group.

ing different diabetic models failed to show consistent changes in brain metabolism with diabetes. Nedergaard *et al.*[13] reported that chronic diabetes in rats is associated with reductions in cerebral glucose utilization in conjunction with CBF reductions. In the same diabetic model, others have reported that cerebral glucose consumption and state 3 and 4 mitochondrial respiration is unaltered by chronic hyperglycemia.[14,15] There are also time-dependent effects in experimentally produced diabetes. Jacobsen *et al.*[16] found that diabetes produces a biphasic effect on brain metabolism. Two days after induction of diabetes, an increase in regional glucose uptake was observed in the neocortex and basal ganglia. However, at 4 months, regional cerebral glucose consumption was decreased in the basal ganglia and white matter. Mans *et al.*[17] similarly found that brain glucose use is increased by 20% 1 week after the induction of diabetes in rats; however, cerebral glucose consumption returned to normal by 4 weeks. This alteration in cerebral glucose consumption may be explained by increased brain oxidation of ketones occurring in these diabetic rats. Our diabetic animals did not show a consistent increase in blood ketones, and there was no change in cerebral metabolism. Thus, our data at 4 months of hyperglycemia would support human studies showing no change in global brain metabolism with diabetes, although selective regional alterations cannot be excluded.

Long-standing diabetes in humans is associated with a decrease in the cerebral artery blood flow,[2] attenuation of the cerebral vasodilator response to 5% CO_2,[18] and loss of global cerebral autoregulatory capacity.[19] Animal studies examining the effects of chronic hyperglycemia on CBF are conflicting. Several investigators using the diabetic rat model have reported regionally specific decreases in CBF.[3,12,20] However, other investigators using the same model have provided evidence that CBF increases.[21,22] The available data concerning the effects of diabetes on CBF is unclear. The discrepancy in results may be related to differences between human diabetes mellitus and the animal models studied. The effects of diabetes mellitus on the cerebral vasculature are complicated by a host of factors, including diabetic microangiopathy, atherosclerosis, hypertension, renal disease, and chronic hyperglycemia. It is likely that many of the reported abnormalities in CBF physiology are the result of diabetic vascular disease, rather than an effect of hyperglycemia. Nonetheless, it is important to assess what effects chronic hyperglycemia has on CBF. It is well documented that increases in regional blood flow occur in various organ systems, particularly the retina and glomerulus with chronic hyperglycemia. It is believed that surges in blood flow may lead to basement membrane damage, as well as increased capillary leakage in the diabetic.[23] It is unclear what mechanism causes the regional increases in blood flow with chronic hyperglycemia, although some investigators have postulated that changes in hemoglobin P50 (P_{O_2} at 50% oxyhemoglobin saturation) occur as hemoglobin glycosylation becomes predominant.[23] In the current study, we found no difference in P50 values (29.2 ± 3.3 *vs.* 29.8 ± 3.0 in diabetic and nondiabetic animals, respectively) or CBF with diabetes. In our animals, blood sugar levels were relatively stable and elevated throughout the day. This does not rule out the effects that acute elevations of blood glucose may have on CBF. In our previous study, acute elevations in blood sugar in nondiabetic dogs were associated with elevated

Table 4. Brain Metabolism

		Day 1			Day 2		
		Awake Baseline	10 min after Propranolol	3 h after Propranolol	Awake Baseline	1 h after Anesthetic Induction	10 min after Propranolol Anesthesia
Cerebral glucose uptake ($\mu M \cdot 100\ g^{-1} \cdot min^{-1}$)	Control	47 ± 6	35 ± 2	34 ± 4	42 ± 4	27 ± 2*	26 ± 2*
	Diabetic	52 ± 11	43 ± 5	61 ± 16	52 ± 8	31 ± 3*	31 ± 5*
Cerebral lactate uptake ($\mu M \cdot 100\ g^{-1} \cdot min^{-1}$)	Control	2.2 ± 2.7	0.1 ± 1.7	3.3 ± 1.5	2.3 ± 2.3	−0.9 ± 3.6	3.6 ± 0.3
	Diabetic	−4.0 ± 2.9	−6.0 ± 3.4	−15.5 ± 16.5	2.1 ± 2.1	−2.1 ± 2.9	−0.0 ± 0.8
Fractional O_2 extraction	Control	0.46 ± 0.02	0.46 ± 0.02	0.47 ± 0.03	0.41 ± 0.01	0.38 ± 0.05	0.42 ± 0.03
	Diabetes	0.48 ± 0.02	0.50 ± 0.02	0.55 ± 0.02*†	0.46 ± 0.01†	0.50 ± 0.03	0.50 ± 0.03
Cerebral oxygen uptake ($ml\ O_2 \cdot 100\ g^{-1} \cdot min^{-1}$)	Control	4.9 ± 0.5	4.2 ± 0.4	4.1 ± 0.6	4.3 ± 0.5	2.4 ± 0.1*	2.4 ± 0.2*
	Diabetic	4.6 ± 0.2	4.4 ± 0.2	4.4 ± 0.1	4.4 ± 0.4	2.6 ± 0.2*	3.1 ± 0.2*

Values are mean ± SE; n = 8 in each group for respective measurements.

* $P < 0.05$ from daily awake baseline within respective group.

† $P < 0.05$ from control at respective time.

CBF, but not with elevated $CMRO_2$. Thus, brittle diabetes may produce more CBF alterations than are produced in the poorly controlled diabetic with a chronically elevated blood sugar.

In nondiabetic animals, several studies have shown no effect of propranolol on cerebral metabolism.[24–26] However, with anesthesia, propranolol has a varied effect on CBF.[25,26] In baboons, propranolol causes cerebral vasoconstriction.[24] Rat cerebral microvessels contain both β-1- and β-2-adrenergic receptor subtypes, with a predominance of the β-2 type.[27] Similar findings have been reported in humans.[28] These β-adrenergic receptors mediate the adenylate cyclase response of the cerebral endothelium, thus lending support for the proposal that adrenergic receptors in the endothelium are involved in CBF regulation.[29,30] Brain microvessels of streptozotocin-induced diabetic rats have a decreased number of β-adrenergic receptors, but no alterations in receptor affinity.[31] These decreases are associated with attenuation of adenylate cyclase sensitivity to activation by norepinephrine.[32] These observations may explain the reported enhanced cerebral vasoconstriction by norepinephrine in diabetic animals as a secondary effect of reduced cerebral vascular β-adrenergic component.[9] However, other investigators have reported no differences in the contractile responses to norepinephrine in diabetic *versus* normal mice.[33] In addition to the specific receptor changes in brain microvessels, there are alterations in the turnover rate and steady state level of brain monoamines with diabetes.[8] These findings have been corroborated in human autopsy studies showing that these changes in brain monoamines are regionally specific.[34] However, it is unclear what effect changes in central catecholamine physiology have on the CBF changes observed in our study, and it is unclear what changes occur between the awake and anesthetized state such that the CBF effects of propranolol are more evident. Lass *et al.*[35] have shown an attenuation, in diabetic rats, of the CBF increase that normally accompanies administration of the β-agonist isoproterenol. In addition, human studies have demonstrated decreased β-adrenergic sensitivity in diabetic subjects.[36,37] Because propranolol failed to decrease CBF in anesthetized diabetic dogs, our results are consistent with previous work indicating that cerebral vessel β-adrenergic responses are attenuated with diabetes. The effects seen in our diabetic dog model are subtle, but still agree with those observed in experimental and human studies of diabetes. However, these effects may be specific for high-dose fentanyl/low-dose pentobarbital anesthetic regimens used in this study.

In summary, we have shown no difference in CBF or metabolism in the pancreatectomized dog model of chronic diabetes mellitus. Our previously recorded changes in CBF and $CMRO_2$ in the pancreatectomized dog model of chronic diabetes mellitus may have been surgically induced. In the awake state, propranolol ad-

ministration causes no change in CBF or metabolism. In control animals under fentanyl/pentobarbital anesthesia, propranolol is associated with vasoconstriction. However, this effect is not observed with diabetes. These results indicate that the chronic hyperglycemia of diabetes is associated with β-adrenergic changes in the cerebral vasculature and, possibly, in the central nervous system that is expressed under fentanyl/pentobarbital anesthesia. The CBF and $CMRO_2$ response of the brain to surgery may be altered with diabetes; however, the response to anesthesia is similar to that of the nondiabetic dog.

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