TITLE: CEREBROVASCULAR REACTIVITY IN THE DIABETIC RAT

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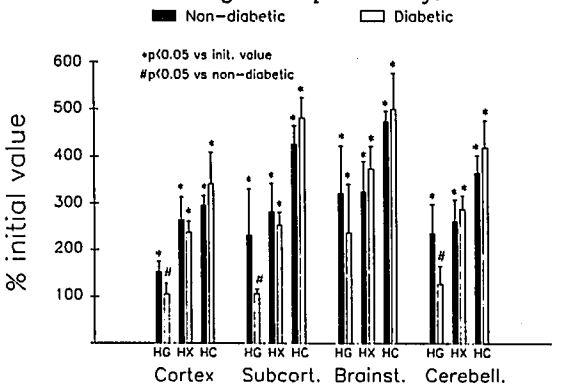
Introduction. In humans and rats with diabetes mellitus (DM), a cerebral microangiopathy has been reported to be present, as well as indications of sympathetic neuropathy. Adrenergic influences have been reported to play a role in the cerebral hyperemic responses to hypoglycemia (HG), hypoxia (HX), and hypercarbia (HC). The possibility therefore exists that the cerebral vasodilatory reserve may be diminished in DM. To investigate this, we measured, in the chronically hyperglycemic diabetic rat, the regional cerebral blood flow (rCBF) changes accompanying HG, HX, or HC.
Methods. The study was IACUC approved. Male SD rats with DM (n=13) were studied at ~6 months post-streptozotocin (60 mg/kg i.p.) and compared to age-matched, non-diabetic (ND) controls (n=13). Catheters were inserted into both femoral arteries and veins and into the left ventricle (via the rt. carotid) while the rats were maintained on 0.7% halothane/70% N_2O/30% O_2, paralysis, and artificial ventilation. The halothane was then discontinued and wound sites infiltrated with bupivacaine. rCBF was measured with radiolabeled microspheres in the following regions: cortex (CX), subcortex (SC), brainstem (BS), and cerebellum (CE). Initial rCBF determinations in DM and ND rats (>1 hr. post-halothane) were made with P_aCO_2=35-40 mmHg, P_aO_2>90 mmHg, MAP=100-125 mmHg, and rectal temperature (T)=37°C. For HG evaluations, rCBF was measured prior to i.v. insulin and at a plasma glucose (G_p)=1.7-1.8 mM (P_aCO_2, P_aO_2, MAP, T maintained at initial values). For HX studies, rCBF was determined with P_aO_2>90 mmHg and at a P_aO_2=30-40 mmHg (P_aCO_2,MAP,and T normal). For HC experiments, rCBF was measured at P_aCO_2 values of 35-40 mmHg and 70-80 mmHg (P_aO_2,MAP,and T at initial values). rCBF results were analyzed using a multivariate statistical procedure.
Results. The rCBF results, expressed as a percent of the initial value, are summarized in the figure below. In diabetic rats, the cerebral hyperemic response to HG was lost in 3 of the 4 regions assessed (CX,SC,CE). On the other hand, no changes in the hyperemic responses to HX or HC were seen in association with DM.
Discussion. In contrast to previous speculation, a general loss of the cerebral vasodilatory reserve does not appear to accompany chronic hyperglycemic DM. Earlier work (Patel DG. Diabetes 32:55, 1983) and our own preliminary findings (Pelligrino DA et al. J Neurosurg Anesth 2:S7, 1990) indicate a blunted sympathetic response to HG in rats with DM. It remains for future studies to determine if this occurs in diabetic rats only in response to HG and not HX or HC and whether such a condition specific effect can account for the CBF findings of the present study.



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TITLE: ALTERED HORMONE-SENSITIVE LIPASE (HSL) ACTIVITY AS THE DEFECT IN MALIGNANT HYPERTHERMIA (MH)

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Free fatty acids (FFAs) are produced to a greater extent in MH muscle once it is homogenized.[1] While phospholipids were originally proposed as the source of these FFAs, more recent evidence suggests that the FFAs may be derived from triglycerides (TGs).[2] However, the enzymatic activities of the major fatty acid generating enzymes in skeletal muscle have not been directly examined. Using radiolabeled phospholipid and TG substrates, we directly examined two of the three major fatty acid generating enzymes [phospholipase A_2 (PLA_2) and the TG lipase *not* under hormonal regulation]. Both enzyme activities were normal in MH susceptible swine (Table 1). By the process of elimination, these results suggest that HSL, the third major source of FFAs, is overactive in MH muscle homogenates. The HSL is activated by ß-adrenergic receptor stimulation through a cAMP-dependent protein kinase. To test if ß-adrenergic stimulation would make normal muscle respond as if MH susceptible, we examined the interaction between isoproterenol (ISO) and halothane in the *in vitro* preparation used for MH diagnostic testing. Muscle strips were exposed to ISO (10 µM) for 10 min before adding halothane (3%). Muscle strips from normal patients demonstrated significantly increased contractures to halothane (Table 2). Muscle from three of these normal patients exhibited greatly increased responses to halothane that would be regarded as MH susceptible (0.7-1.5 g) if they had occurred in the absence of ISO. The MH defect in humans has been localized to chromosome 19 (q13.1), as determined by linkage analysis with the glucose phosphate isomerase and the ryanodine receptor genes.[3] The gene coding for HSL is also located on chromosome 19 (q13.1).[4] Therefore, HSL is a candidate for the MH defect, as supported by biochemical, physiological and genetic approaches.

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References.
1 Biochim biophys Acta 638 40 1981; Br J Anaesth 58 1433 1986
2 Eur J Anaesth 6 355 1989
3 Nature 343 562 1990; Nature 343 559 1990
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Table 1. PLA_2 and TG lipase activities in whole *longissimus dorsi* from six MH- and six MH+ pigs.

	Lipolytic Activities (mean±SEM)	
	PLA_2	TG Lipase
Susceptibility	(pmol FA/mg/min)	(pmol FA/mg/hr)
MH-	2.7±0.5	6.4±0.7
MH+	2.6±0.5	6.2±0.9

Table 2. Effects of ISO on halothane contractures in muscle from five normal patients.

	Contracture (g)	t-test
No ISO	0.13±0.06	
ISO (10 µM)	0.70±0.27	P<.05