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REGIONAL CHANGES IN CEREBRAL ENDOTHELIUM DEPENDENT VASCULAR RELAXATION IN THE DIABETIC RAT.

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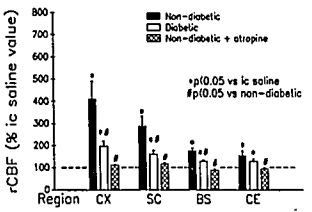
Microangiopathies can accompany diabetes and chronic hyperglycemia and are often manifested as a diminished capacity for endothelium-dependent vascular relaxation (EDVR) (1). However, relatively few reports have addressed the issue of possible cerebrovascular alterations in the diabetic. Findings regarding cerebral EDVR changes in the diabetic are few in number and are conflicting, indicating an impairment in pial arterioles of diabetic rats (2), but not mice (3). Furthermore, no studies have investigated whether an obtunded EDVR capacity exists in vivo beyond the pial circulation in the brain. In the present study (following IACUC approval), we investigated, in streptozotocin (STZ)-treated, chronically hyperglycemic rats the possible presence of a diminished EDVR in a number of brain regions. The BBB-permeant muscarinic (M)-agonist oxotremorine (OXO) was employed as the EDVR-inducing agent and introduced via intracarotid (ic) infusion. Regional CBF (rCBF) responses were then compared in diabetic (D) (n=6) vs age-matched non-diabetic (ND) (n=11) rats. The anesthesia during surgical preparation of the paralyzed, mechanically ventilated rats was 0.7% halothane/70%N_2O/30% O_2. Catheters were inserted into both femoral arteries and veins, into the left external carotid artery and into the left ventricle via the right brachial artery (used for microsphere injections). In 4 of the ND rats, atropine was co-infused with OXO in order to establish that the CBF response was M-receptor mediated (and a function of EDVR). In 1 ND rat, a sagittal venous catheter was placed to permit measurement of cortical $CMRO_2$. For study, the rats were maintained on fentanyl (25 µg/kg/h)/ 70% N_2O/ 30% O_2. rCBF was measured using radiolabeled microspheres. Values were obtained at 15 min of ic saline infusion (at 0.05 ml/min), and at 5, 15, and 30 min of ic OXO infusion (3.5 µg/kg/min). Arterial PCO_2 (35-40 mmHg), PO_2 (>90 mmHg), and mean pressure (110-140 mmHg) and rectal temperature (37°C) remained constant throughout. The rCBF results for the cortex (CX), subcortex (SC), brainstem (BS) and cerebellum (CE) are summarized in the figure below (% control ± S.E.). The data represents peak responses. The normal cerebral hyperemic response to OXO was attenuated in the D vs ND rats in all regions, with statistical significance ($p<0.05$) being achieved in the CX, SC, and BS. There was a trend toward a greater degree of attenuation in forebrain vs hindbrain structures. In the 1 ND rat where $CMRO_2$ was assessed, no OXO-associated changes in $CMRO_2$ were found (indicates that the hyperemia was not related to metabolic stimulation). Furthermore, the OXO-induced CBF increases were exclusively a result of M-receptor stimulation, as evidenced by a complete inhibition of this response in the presence of atropine co-infusion. Results of preliminary experiments essentially have eliminated the possibility that the above is a result of insufficient delivery of OXO to hindbrain regions. The D vs ND findings are a likely result of vascular specific alterations rather than a primary change in M-receptor function. Thus, previous work has indicated normal or near normal cerebral M-receptor mediated responses (unrelated to EDVR mechanisms) in D rats (4). The regional pattern of the D vs ND results suggests that forebrain structures may be particularly susceptible to diabetes-related vascular endothelial damage.



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TITLE: HYPOCAPNIA-INDUCED CONTRACTION OF ISOLATED DOG CEREBRAL ARTERY IS MORE SUSCEPTIBLE TO HALOTHANE THAN PENTOBARBITAL

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Introduction: CO_2 is considered to be a major metabolic factor to regulate cerebral blood flow (CBF). Halothane (H) and barbiturates reduce $CMRO_2$, resulting in a reduction in CO_2 production, which would be expected to constrict cerebral arteries. However, H increases CBF while barbiturates decrease it (1,2). The purpose of this study is to compare the direct effects of H and pentobarbital (P) on the contraction of cerebral artery induced by hypocapnia in vitro.

Methods: Helical strips of dog cerebral (basilar and middle cerebral) arteries were suspended under a resting tension of 1.5 g in Krebs-bicarbonate solution aerated with a gas mixture of 5%CO_2 and 95%O_2 (pH, 7.44±0.01; PCO_2, 35.7±0.6 mmHg; PO_2, 615.0±13.2 mmHg; n=14). Hypocapnia was induced by aerating with a gas mixture of 2.5%CO_2 and 97.5%O_2 (pH, 7.69±0.01; PCO_2, 21.4±0.3 mmHg; PO_2, 624.6±12.2 mmHg, n=16), and each strip was exposed to hypocapnia three times. Contractile response to second exposure to hypocapnia was compared in the absence (control) or presence of H and P. Data were mean ± SEM and were analyzed by ANOVA with Newman-Keuls test; ** =P<.01 vs controls.

Results indicate that: Exposure of cerebral arterial strips to hypocapnia produced a sustained contraction which was significantly inhibited by H at 0.4, 0.7, 1.5% and by P only at high concentration ($3x10^{-4}$ M) (Fig. 1).

Discussion: Since the plasma concentration of P has been estimated to be in a range of 10^{-5} to 10^{-4} M (3), these results indicate that hypocapnia-induced cerebral vasoconstriction is more susceptible to H than to P at clinical relevant concentrations. It is suggested that the metabolically mediated contraction of cerebral artery is offset during H anesthesia, but is preserved during P anesthesia.

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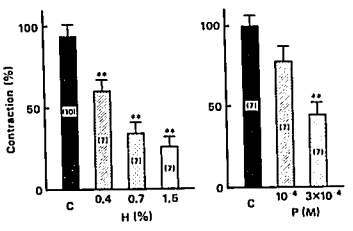

Fig. 1. Contractile response to the first exposure to hypocapnia was taken as 100%. C, control (without anesthetics).