Increased Cerebrovascular Complications of Diabetic Mice-A Magnetic Resonance Imaging Study

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INTRODUCTION

Diabetes mellitus currently affects more than 150 million adults worldwide. Cardiovascular or cerebrovascular complications are the major cause of death in patients with diabetes mellitus (1). Diminished basal cerebral blood flow (CBF) and impaired cerebral vasodilatory response are two possible cerebrovascular complications. However, the effect that diabetes has on basal CBF is controversial. Dandona et al. reported similar basal CBF and rate of CBF decline with age in control and diabetic patients (2), while Duckrow et al. reported significant CBF decrease in multiple brain regions during chronic and acute hyperglycemia (3). Dandona et al. (2) and Kadoi et al. (4) reported diabetic patients showed impaired cerebral vasodilatory response to 5% hypercapnic challenge, which was related to the severity of diabetes mellitus (4). Ins2Akita mice have an autosomal dominant mutation in the insulin 2 gene which results in hyperglycemia, detectable after 4 weeks of age (5). Akita mice have been used as an animal model of type 1 diabetes. In this study, we investigated the effects of diabetes on basal CBF and cerebral vasodilatory response to hypercapnia in hyperglycemic Akita mice with MRI.

METHODS

C57BL/6 mice (control) (N = 4 at 3-months, N = 4 at 9-months) and Akita mice (diabetic) on a C57BL/6 background (N = 4 at 3-months, N = 3 at 9-months) mice were anesthetized with ~1.0% isoflurane in 30% O_2 and 70% N_2 without mechanical ventilation. Body temperature, respiration rate, and SpO_2 were continuously monitored and maintained within normal ranges.

MRI experiments were performed on a 7-T/30-cm magnet and a 150-G/cm BGA6S gradient insert. A surface coil (1.0-cm ID) was used for brain imaging. A circular labeling coil (0.8-cm ID) was placed at the heart position for a cardiac spin labeling technique as described previously (6). The two coils were separated by 2 cm from center to center and actively decoupled. Quantitative CBF and apparent diffusion coefficient (ADC) were measured using continuous arterial spin labeling (cASL) gradient-echo EPI and diffusion weighted spin-echo EPI. Hypercapnic challenge was performed on 9-month mice using cASL with 5% CO_2 and 30% O_2 gas balanced with N_2. MRI parameters were: single shot, matrix = 64x64, FOV = 12.8mm x 12.8mm, nine 1.0mm thick slices, TR=3s, TE=7.8ms for CBF and 28ms for ADC, and 90 degree flip angle. $P<0.05$ (equal variance t-test) was considered to be statistically significant.

RESULTS

Fig. 1 shows CBF maps of representative 9-month control and diabetic mice using the same display range. Group-averaged CBF values of 3-month and 9-month groups are shown in **Fig. 2**. Three-month old diabetic mice showed slightly, but not significantly, lower CBF. Nine-month diabetic mice showed significantly (P=0.01) lower CBF than age-matched controls.

The absolute CBF change due to hypercapnic challenge for the 9-month control group was significantly higher (P=0.02, ~100% higher) than that of the 9-month diabetic group (**Fig. 3**). However, the CBF percent changes of these two groups were not significantly different since basal CBF of the diabetic group was lower.

One 9-month diabetic mouse showed further regional CBF deficits in some cortical regions (**Fig. 4**). No ADC reduction or apparent anatomical lesions were observed (data not shown).

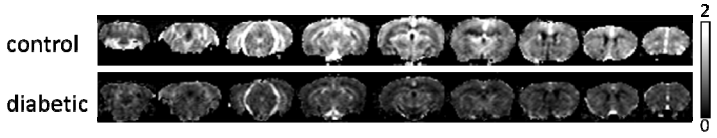

Fig. 1 CBF (ml/g/min) maps of representative 9-month control and diabetic mice

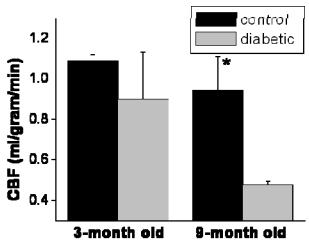

Fig. 2 Group-averaged CBF values (mean±SD)

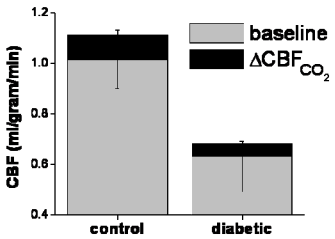

Fig. 3 Group-averaged CBF change of CO_2 challenge (9-month) (mean±SD)

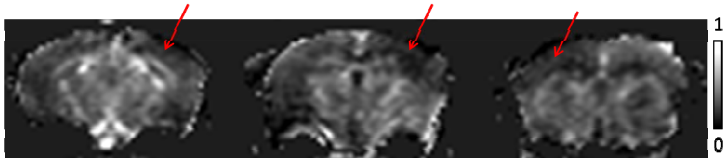

Fig. 4 Reduced CBF (ml/g/min) in some regions of a diabetic mouse

DISCUSSION AND CONCLUSION

This study investigated the effect of diabetes on basal CBF and cerebral vasodilatory response to hypercapnia. The main findings are: 1) Global basal CBF decreased in diabetic mice. 2) Regional reduction in CBF was observed in one diabetic mouse, although ADC, which is an important marker for ischemic injury, was unchanged. The reduced CBF was likely still above critical viability threshold to prevent tissue damage and ADC changes (7). 3) Diabetic mice showed attenuated vasodilatory response to hypercapnic challenge, suggesting that Akita mice have compromised CBF autoregulation. In conclusion, diabetic mice showed impaired basal CBF and vasodilatory response to hypercapnia. CBF MRI and CBF fMRI could offer a means to study neurological effects of diabetic complications in the brain before anatomical changes can be detected. Future studies will expand to include addition time points in the disease spectrum (4) and evoked changes (BOLD and CBF) by functional stimulations.

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