Cerebral blood flow deficits in the Tc1 mouse model of Down's syndrome

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Introduction

Down's syndrome (DS), or trisomy 21, is a genetic disorder caused by the presence of an extra copy of chromosome 21. Interestingly, individuals with DS have a greater predisposition to Alzheimer's disease (AD), thought to be due to the extra dosage of the amyloid precursor protein (APP) gene, which is an established risk factor for AD [1]. Studying mouse models of DS have led to a greater understanding of the significance of trisomy 21 and its relationship with AD [2]. The Tc1 DS mouse carries an almost-complete copy of human chromosome 21 but is not functionally trisomic for APP, a gene important in the development of AD. The unique genetics of the Tc1 allow the study of the DS phenotype without the effects of APP pathology. Several of the key features seen in the human DS condition are recapitulated in this mouse model, including altered heart development and behavioural changes [3]. While initial characterisation of the Tc1 showed abnormalities in cerebellar neuronal density and skull morphology, there has since been no further investigation into additional cerebral defects in this mouse model. Cerebral blood flow is a key biomarker of tissue vitality and function, and regional hypoperfusion has been observed in AD patients (4). In this work, we have used arterial spin labelling (ASL) to image cerebral blood flow in the Tc1 mouse to investigate the specific effects of chromosome 21 on brain function, without the confounding effects of the APP gene.

Methods

Animals Tc1 mice and wild-type (WT) littermates were bred as published previously [3]. 5 Tc1 and 6 WT litter matched control mice (15 -16 months) were imaged *in vivo*. Prior to imaging, mice were secured in a cradle under anaesthesia with 1-2% isofluorine in 100% oxygen using a custom-built head holder to reduce motion. Body temperature was maintained at 36 – 37.5 ^{o}C using a water-heating system and warm air fan. Core body temperature and respiratory rate were monitored using a temperature probe and pressure pad (SA Instruments, NY) *Image acquisition* All scans were performed on an Agilent 9.4 T VNMRS 20 cm horizontal-bore system (Agilent Inc. Palo Alto, CA, USA). A 72 mm birdcage radiofrequency (RF) coil was used for RF transmission and a quadrature mouse brain surface coil (RAPID, Germany) was used for signal detection. A flow-sensitive alternating inversion recovery (FAIR) sequence with a 4-shot segmented spin-echo EPI readout was implemented with parameters: 5 slices, slice thickness = 1 mm, FOV = 20 x 20 mm, slice selective inversion pulse width = 12 mm, inflow time = 1.5 s. T1 maps were also acquired using an inversion recovery SE-EPI sequence for CBF quantification. CBF was quantified according to the model proposed by Buxton et al [5].

Results

Figure 1 shows the mean CBF for the Tc1 and control mice within the cortex (A) and hippocampus (B). The Tc1 animals demonstrated a significant decreased in CBF ($p<0.05$) relative to the control group in both regions. These results may arise for a number of reasons, including the possibility that a neurodegenerative process is occurring.

Conclusion

We report a reduction in cerebral blood flow in the cortex and hippocampus of the Tc1 mouse. Blood flow deficits have previously been reported in clinical DS studies [6], and attributed to the AD neuropathology seen universally in individuals with DS. In the absence of the APP gene, our results suggest that other genes on chromosome 21 may be contributing to the AD-like patterns of hypoperfusion in the Tc1 mouse. A longitudinal study is required to investigate the possibility that this is a progressive reduction in blood flow, and we wish to investigate it in other DS lines.

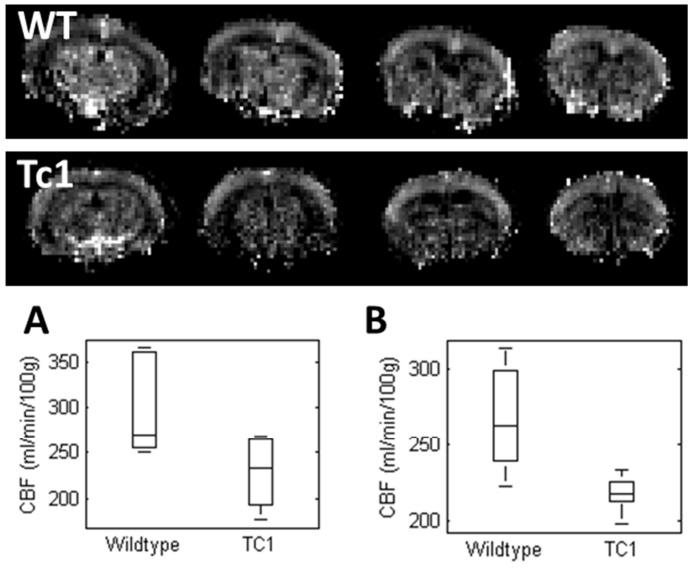

Figure 1 CBF maps for WT and Tc1 mice. Mean CBF within an ROI in the cortex (A) and hippocampus (B) of the Tc1 (n=5) and WT (n=6) mice.

References

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