ASL-MRI Measurement of Cerebral Blood Flow following Experimental Traumatic Brain Injury and the Role of Human Aβ

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INTRODUCTION

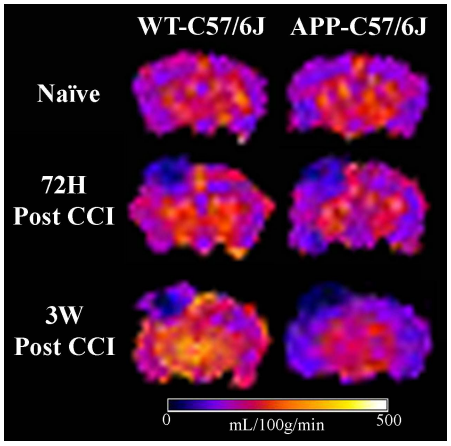
Traumatic brain injury (TBI) initiates inflammatory responses in the brain that cause rapid increases in pro-inflammatory cytokine production. Interleukins contribute to the secondary pathological mechanisms of brain injury, including brain hypoperfusion and ischemia. One of the mechanisms whereby the post-TBI inflammatory reaction can impair brain hemodynamics, involves increased expression and amyloidogenic metabolic processing of the amyloid-β (Aβ) precursor protein (APP), and increased brain concentrations of Aβ peptide. Aβ concentrations increase acutely after TBI and remain elevated for a prolonged period of time, thereby increasing the risk for human TBI patients to develop Alzheimer's disease (AD) later in life. The exact mechanism behind Aβ's contribution to post-injury changes in cerebral vasculature and cerebral blood flow (CBF) impairment after TBI is not known. Experiments in cultured cells and in *in vivo* models of AD demonstrated that Aβ has vasoactive effects [1] which are mediated by a pro-inflammatory pathway [1,2].

The main goal of this study was to investigate if increased brain concentrations of human Aβ in APPNLh/NLh mice predispose these animals to more profound changes in CBF after TBI using ASL-MRI.

MATERIALS AND METHODS

Male C57BL/6 wildtype (n=13) and $APP^{NLh/NLh}$/C57BL/6 (n=16) mice were anesthetized with isoflurane in N_2O:O_2 (1:1). The mouse controlled cortical impact (CCI) model was used as previously described [3] with minor modifications [4]. Animals were placed in a stereotaxic holder and a temperature probe was inserted through a burr hole into the left frontal cortex. The parietal bone was removed for trauma. Once brain temperature reached 37˚C and was maintained at this temperature for 5 minutes, a vertically directed CCI was delivered at 5.0m/sec with a depth of 1.0mm. The bone flap was replaced, sealed with dental cement and the incision closed. Animals were divided into one of three groups for MRI assessment, naïve, 72 hours or 3 weeks after trauma.

MR studies were performed on a 4.7-Tesla, 40 cm bore Bruker AVANCE AV1 system, equipped with a 12 cm diameter shielded gradient insert and a home-built RF coil. T_1 maps and perfusion images were generated using the following paramters (*TR* = 8000, 4300, 2300, 1200, 650, 350, 185, 100 msec, 2 averages, 128 x 70 matrix; and *TR*/*TE* = 2000/10, 20, 30, summation of 3 echoes, 2 averages, 128 x 70 matrix, with labeling applied ± 2 cm from the imaging plane). During each study, mice were intubated and mechanically ventilated; then femoral arterial and venous catheters were surgically placed. $PaCO_2$, PaO_2, MABP, HR and rectal temperature was recorded.



RESULTS AND DISCUSSION

Naïve (uninjured) $APP^{NLh/NLh}$/C57BL/6 mice had slightly lower basal CBF values than age-matched C57BL/6 wild types (Figure 1). Both at 72 hr and 3 weeks after CCI, CBF deficits were observed in the ipsilateral cortex regardless of genotype, however they were significantly greater in $APP^{NLh/NLh}$/C57BL/6 mice compared to C57BL/6 wild types. In contrast, C57BL/6 mice, but not $APP^{NLh/NLh}$/C57BL/6 mice showed increased CBF on the contralateral (non-injured) side at both time points after CCI injury. These results are consistent with previously reported vasoactive effects of Aβ and its potential contribution to chronic hypoperfusion in AD brains. Increased human Aβ concentrations may contribute to impaired cerebral hemodynamics and prolonged deficits in recovery of cerebral perfusion after brain injury, further supporting the idea that TBI is a risk factor for developing AD later in life.

Figure 1 Representative CBF maps of naïve wildtype C57BL/6 and $APP^{NLh/NLh}$/C57BL/6 mice at 72 hours and 3 weeks following CCI. Marked CBF reductions are obvious in the mutant strain vs wild type at both time points, supporting a role for Aβ in exacerbating the hypoperfusion that is observed after TBI .

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