Mild traumatic brain injury causes persistent disruption of the blood-brain barrier with cognitive consequences in rats with chronic arterial hypertension


POSTER Nr: 2275
Introduction

- Traumatic brain injury (TBI) induces blood-brain barrier (BBB) disruption, which contributes to secondary injury of brain tissue and development of chronic cognitive decline. However, single mild (m)TBI, the most frequent form of brain trauma disrupts the BBB only transiently.

- We hypothesized, that co-morbid conditions exacerbate persistent BBB disruption after mTBI leading to long term cognitive dysfunction.
Method(s)

• Since hypertension is the most important cerebrovascular risk factor in populations prone to mild brain trauma, we induced mTBI in normotensive and spontaneously hypertensive rats (SHR) and two weeks after trauma we assessed BBB permeability, extravasation of blood-borne substances, neuroinflammation and cognitive function of the animals.

• The open field test (OFT) was carried out in normotensive Wistar rats and SHRs (n = 15) before and two weeks after mTBI. Declarative memory performance of the animals was assessed by the novel object recognition test (NOR).

• Blood-brain barrier permeability was assessed by the Evans blue extravasation method.

• Western Blot analysis was carried out on cortical samples
Results

• We found that in SHRs mTBI induced a significant BBB disruption two weeks after trauma, which was associated with a significant accumulation of fibrin in the cortex and hippocampus and increased neuronal expression of inflammatory cytokines TNF, IL-1 and IL-6 compared to normotensive wistar rats. SHRs two weeks after mild TBI showed impaired learning and memory, whereas cognitive function of normotensive wistar rats remained intact.
Figure 1. Mild traumatic brain injury (TBI) induces persistent disruption of the blood brain barrier and extravasation of blood borne substances in hypertensive rats. (A) shows blood pressure of Wistar rats and spontaneously hypertensive rats (SHR) with and without mild traumatic brain injury (mTBI) measured by the tail-cuff method. Data are means ± S.E.M. (n = 6 in each group) * p < 0.05 vs. Wistar, & p < 0.05 vs. Wistar + mTBI. (B) Summary data show blood brain barrier permeability indicated by extravasated Evans blue content of cerebral tissue (depicted as fold change compared to control) in sham operated Wistar rats and SHRs, and in rats two weeks after mTBI. Data are means ± S.E.M. (n = 6 in each group) * p < 0.05 vs. Wistar, & p < 0.05 vs. Wistar + mTBI, $ p < 0.05 vs. SHR. (C) One representative Western blot presents fibrin level in perfused cerebral tissue from Wistar and spontaneously hypertensive rats (SHR) with and without mild traumatic brain injury (mTBI) (showing two in each group) two weeks after trauma. (D) Summary data depicts cerebral fibrin protein level in cortical tissue of the above groups of animals. Data are means ± S.E.M. (n = 6 in each group) * p < 0.05 vs. Wistar, & p < 0.05 vs. Wistar + mTBI.
Figure 2. Mild TBI induces persistent neuroinflammation and cognitive decline in hypertensive rats. (A,B) mRNA expression of inflammatory cytokines IL1β, IL6 and TNFα in cortical (A) and hippocampal (B) tissue of sham operated normotensive Wistar rats and SHRs, and of animals two weeks after mild TBI, expressed as fold change compared to control. Data are means ± S.E.M. (n = 8 in each group) * p < 0.05 vs. Wistar, & p < 0.05 vs. Wistar + mTBI, $ p < 0.05 vs. SHR. (C) In a standard open field test normotensive Wistar animals showed attenuated exploratory activity (number of crossings) two weeks after mTBI (Wistar + mTBI) indicating habituation to the environment and intact locational memory function. In contrast, SHRs did not show habituation to the environment in the repeated open field test (OFT) session two weeks after mTBI (SHRmTBI), indicating impaired locational memory. Data are means ± S.E.M. (n = 15 in each group) * p < 0.05 vs. Wistar. (D) Intermediate-term declarative memory was tested two weeks after mTBI by the novel object recognition test. Discrimination index was not changed in normotensive Wistar rats two weeks after mTBI, but it was significantly decreased in SHRs, indicating impaired declarative memory of the
Conclusions

• Future studies should establish the mechanisms through which hypertension and mild TBI interact to promote persistent BBB disruption, neuroinflammation and cognitive decline, in order to restore BBB function after mTBI to exert neuroprotection and improve cognitive function in patients.