In vivo blood-brain barrier permeability assessment with Mn-enhanced MRI (MEMRI).

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Introduction

MRI is well suited to effectively measure the permeability of the blood-brain barrier (BBB), specifically *in vivo*. In the present study we utilized manganese-enhanced MRI (MEMRI) to evaluate changes in BBB functional integrity over time in hexB-/- mice. The ability for manganese ion (Mn^{2+}) to cross the BBB when injected intraperitoneally (IP) increases under influence of certain diseases. In a healthy state, Mn^{2+} does not readily cross the BBB unless the BBB becomes "leaky" due to a variety of factors such as disease. However, it should be noted that Dan Turnbull's group has elegantly demonstrated that although the kinetics across the BBB are not rapid, activation maps (e.g. in the auditory system) can still be generated many hours post Mn^{2+} and stimulus administration.

Since Mn^{2+} also can be used as a paramagnetic contrast agent, the ion can be identified in tissue as producing higher signal intensity in T_1-weighted MRI images. Since previous studies have shown the presence of antibodies in hexB-/- mice brains, it is possible that this may be due to a leaky BBB. Thus we hypothesized higher signal intensity due to increased Mn^{2+} accessing the brain, would be detectable after IP injections of a fixed manganese chloride ($MnCl_2$) concentration in the hexB-/- brain when compared to age-matched controls.

Methods

100 mM $MnCl_2$ was administered intraperitoneally (IP), amounts according to body weight, to five young (6-8 weeks) and five old (15-19 weeks) hexB-/- mice as well as age-matched controls. Spin echo images were acquired of the mouse brain 15 minutes post administration on a 9.4T, Bruker Avance, 21 cm bore horizontal scanner. The imaging parameters were as follows: TR = 500 ms; TE = 4 ms; FOV = 3.0cm; matrix = 128 x 128; number of slices = 6; number of averages = 1. Normalized signal intensity values between hexB-/- mice and controls were subsequently compared using Paravision 3.0.2 software.

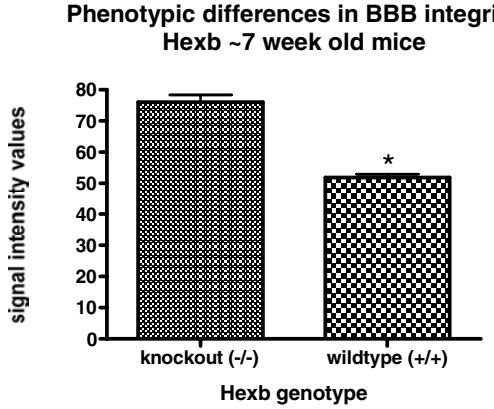
Results

Young hexB-/- mice displayed a statistically significant higher normalized signal intensity indicating a higher presence of Mn^{2+} ($p < 0.0001$) in the brain when compared to age-matched controls. Old hexB-/- mice also displayed a statistically significant higher normalized signal intensity ($p = 0.0021$) in the brain when compared to age-matched controls. Furthermore, BBB integrity appeared to worsen over time in hexB-/- mice at a statistically significant higher rate ($p = 0.0493$). A nonparametric two-tailed test with 95% confidence was used to determine the data's statistical significance.

Discussion and Conclusion

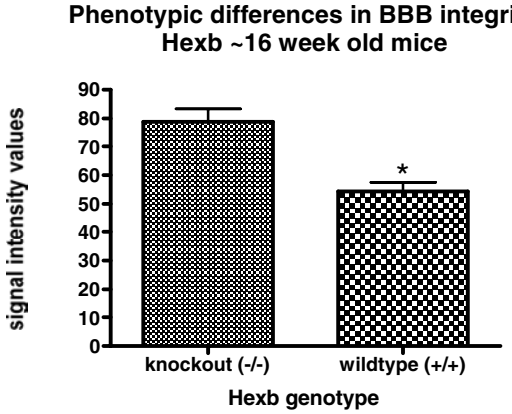
Sandhoff's-diseased (hexB-/-) mice display a leakier BBB when compared to WT mice, and their BBB integrity worsens over time. This BBB assessment can be performed quickly and effectively in vivo using MEMRI. We are currently assessing the coincidence of behavioral symptoms of Sandhoff's disease in the hexB-/- mice with the worsening of the BBB integrity.

Figure 1



p-value < 0.0001
n= 10

Figure 2:



p-value: 0.0021
n= 10