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Brain amyloid accumulation in senescent rats with kaolin-induced hydrocephalus

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Background

NPH patients have a high rate of Alzheimer's disease (AD) on cortical biopsy. 30–50% of shunted NPH patients show amyloid (Aβ)plaques and neurofibrillary tangles. It is postulated that Aβ accumulates in AD and NPH due to decreased Aβ clearance via CSF and blood-brain barrier (BBB). The present study investigates Aβ accumulation and Aβ transport in aged hydrocephalic rat brains.

Materials and methods

Kaolin-hydrocephalus was induced in senescent (12 months) SD-rats. Untreated age- matched rats served as controls. Aβ accumulation was investigated by specific Aβ(1–40) and Aβ(1–42)antibody immunohistochemistry performed 2 weeks (short-term), 6 and 10 weeks (long-term) after hydrocephalus induction. Each group consisted of five animals. Also, specific BBB Aβ receptors were labelled: LRP-1, which transports Aβ from the interstitial fluid (ISF) into the plasma, and RAGE, which transports Aβ from the plasma into the ISF. Both receptors are located on the capillary endothelium.

Results

After 2 weeks of hydrocephalus, both Aβ 42 and Aβ 40 showed increased staining of the arachnoid and ependyma compared to controls. Cortical and hippocampal CA3 pyramidal neurons displayed Aβ 42 cytoplasmic staining in some animals. At 6 weeks, cortical and hippocampal endothelial and perivascular Aβ 42 and 40 accumulations were observed, most prominently with Aβ 42. Importantly, interstitial Aβ 42 and Aβ 40 accumulations were observed, and periventricular plaque-like formations were found in all animals. At 10 weeks, the observed plaque-like formations were increased, whereas cortical perivascular accumulations varied and were either increased or identical to the 6 weeks animals. LRP-receptor staining was decreased in cortical and subcortical vessels at two weeks. However, the decrease was most prominent after 6 weeks. After 10 weeks, LRP-1 receptor staining was restricted to large dilated capillary vessels. RAGE receptor staining showed diametrically opposite changes to those seen for the LRP-1 receptor.

Conclusion

In a rat model of chronic hydrocephalus, perivascular, interstitial and periventricular accumulations of Aβ42 and 40, both of which play a major role in AD-plaque formation, are observed, with Aβ staining increasing the longer hydrocephalus exists. BBB receptor staining indicates impaired Aβ clearance from the ISF into the plasma. These preliminary studies indicate that Aβ accumulation in hydrocephalus is, in part, due to a failure of brain amyloid clearance as it is in AD. Reduced CSF turnover seen in AD, NPH and rat kaolin-hydrocephalus, and reduced Aβ net transport at the BBB appear to be involved. Perivascular Aβ accumulation, known to be a potent vasoconstrictor, may also play a role in the white-matter ischaemia seen in both human NPH and in rat chronic hydrocephalus.