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Evidence of TAU pathology in kaolin-induced hydrocephalus model of the aged rat

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Background

Accumulation of A-beta peptides and hyperphosphorylated Tau (hpTAU) has been observed in immunohistochemical (IHC) studies of kaolin-induced hydrocephalus in the aged rat. Defective clearance via CSF and altered transport via blood brain barrier receptor expressions was suggested to be causal [1]. The present study reports further evidence to the significance of A-beta and TAU pathology as disease mechanisms in hydrocephalus using quantitative A-beta and hpTAU ELISA in addition to IHC studies of the lipid oxygenase 12/15 enzyme (LOX12/15), a marker of the cytokine-induced inflammation in Alzheimer disease (AD).

Materials and methods

In nine 12 month-old Sprague-Dawley (SD) rats with kaolin-induced hydrocephalus, A-beta 40 and 42 and hpTau pT231 ELISA was performed at 2, 6 and 10 weeks post induction (3 age-matched controls) in cortical plus subcortical tissue homogenates. Specific LOX12/15 (1:1000, BIOZOL/CAYMAN) IHC was performed in another 20 animals (5 controls) at the same time points including double-label fluorescent IHC using CY2 and CY3 conjugated secondary antibodies for co-localizations of A-beta 42, LOX12/15, hpTau pT231 and hpTau AT100.

Results

A-beta 42 and 40 ELISA shows a significant increase over the course of hydrocephalus at 6 and 10 weeks post-induction when compared to the controls, e.g., A-beta 40 (pg/mg): 9.7 ± 1.3 and 9.5 ± 0.5 (6,10 wk) vs. 3.2 ± 1.2 (controls); $p < 0.01$ (ANOVA). HpTAU pT231 ELISA increased at 10 wk post-induction to 56.4 ± 17.3 from 28.5 ± 17.2 pg/mg in controls ($p < 0.01$). In hydrocephalus, LOX12/15 positive staining appeared in both cortical and hippocampal neurons, in glial processes (near vessels) and in hippocampal microglia-type cells. Image analysis (CellF©, OLYMPUS) revealed an increased number of LOX12/15 positive particles in the cortex of the hydrocephalic animals compared to controls ($p < 0.05$, unpaired t-test). Extracellular AT100 was clearly co-localized with the A-beta 42 around hippocampal vessels, while hpTAU pT312 IHC showed intraneuronal co-localisation at areas with "condensed excess" Tau. Intraneuronal A-beta 42 as well as pT231 was further co-localized with LOX12/15 in some cortical regions.

Conclusion

The findings of a 3–4 fold increase in A-beta is consistent with the amyloid burden in patients with early AD (Braak I). The increase in the amount of hpTAU at 10 wk as well as the co-localization pattern of the hpTAU markers with the A-beta supports that A-beta accumulation induces TAU pathology. LOX12/15 findings add further evidence

that the aged hydrocephalic rats might be a valid model for investigating the NPH/AD pathophysiological continuum.

References

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