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Amyloid and tau accumulation precede CSF production decline in normal aging

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Background

It has been shown that there is an age-related decrease in CSF production in the Fischer rat brain, and that this decrease follows the CNS deposition of amyloid rather than preceding it [1]. We have postulated that amyloid and Tau accumulation in normal aging is multi-factorial, combining early defects in the blood-brain barrier (BBB) efflux transport of amyloid beta-peptide (A-beta) with later changes in CSF production and turnover, as well as up-regulation of A-beta influx transport.

Materials and methods

Brown-Norway/Fischer (B-N/F) rats between three and 36 months were studied. CSF production rates were measured by the ventriculo-cisternal perfusion of blue dextran mock CSF. Whole brain A-beta and hyperphosphorylated Tau (hpTau pT231 and AT-100) were measured by ELISA and western blotting (WB). The expression of the BBB A-beta transport proteins LRP-1, P-gp and RAGE were measured by quantitative immunostaining, qPCR and WB.

Results

A-beta 40 and 42 ELISA showed a significant increase over the course of normal aging, beginning at 12 mos, but with a different temporal profile for each. A-beta 40 increased from 1.64 ± 1.09 pg/mg total protein at three mo to 6.62 ± 2.72 pg/mg at 12 months ($p = 0.01$) and then plateaued. A-beta 42 showed a continuous rise from 0.07 ± 0.06 pg/mg at three months to 13.37 ± 1.85 pg/mg at 30 months ($p = 0.005$). HpTAU pT231 and AT-100 also increased with aging by WB measurement: pT231 increasing nearly fourfold by age 36 mos and AT-100 doubling. LRP-1 and P-gp began to decrease between nine and 12 months whereas RAGE increased significantly much later in life. CSF production increased from three to 12 mos and then decreased. Mean CSF production rates were 1.8 ± 0.1 μl/min at three mos, rising to 2.5 ± 0.2 μl/min at 12 mos ($p = 0.05$), then falling to 2.0 ± 0.3 μl/min at 30 mos ($p = 0.06$).

Conclusion

Significant A-beta accumulation in normal aging in the B-N/F rat begins at 12 mos and appears to correlate initially with BBB efflux transport decrease due to reduced expression of LRP-1 and P-gp. Later increases in A-beta appear to be related to decreasing CSF clearance and increased expression of the A-beta influx transport receptor RAGE. [Supported by NIH R01 AG027910, and grants from the Richter and Saunders Foundations].

References

1. Preston JE: **Ageing choroid plexus-cerebrospinal system.** *Microsc Res Tech* 2001, **52:**31-37.