Repurposing renin-angiotensin system-targeting medications for the prevention of cerebral amyloid angiopathy and associated cognitive-behavioral deficits in Tg-SwDI mice

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Background: Cerebral amyloid angiopathy (CAA), the accumulation of beta-amyloid around the cerebral vasculature, can cause vascular cognitive impairment and dementia (VCID) and stroke, and is highly comorbid with Alzheimer's disease (AD). No currently available drugs can prevent, nor effectively treat, VCID or CAA. Epidemiological studies suggest that certain renin-angiotensin system (RAS)-targeting anti-hypertensive medications decrease the risk of dementia. This study assesses whether FDA-approved RAS-targeting anti-hypertensive drugs can be repurposed to mitigate CAA, associated neuropathologies, and cognitive decline in a transgenic mouse disease model (Tg-SwDI), in a sex-specific manner. Two RAS-blocking drugs that we hypothesize to be protective in Tg-SwDI mouse are being assessed: telmisartan (a moderately brain-penetrant angiotensin receptor blocker (ARB)), and lisinopril (a brain-penetrant angiotensin-converting enzyme (ACE) inhibitor).

Methods: At 3 months of age, prior to onset of significant CAA pathology, Tg-SwDI mice undergo a 5-month treatment period, with either telmisartan (1 mg/kg/day) or lisinopril (15 mg/kg/day) dissolved in their drinking water. Tg-SwDI vehicle-treated controls and C57BL/6J wild-type (WT) controls receive plain drinking water. At approximately 7 months of age, when cognitive impairment is evident in untreated Tg-SwDI mice, animals undergo cognitive-behavioral testing (open field, novel object recognition, Barnes maze, and object placement tests). At approximately 8 months of age, when significant CAA pathology is evident in this model, animals are euthanized. Post-mortem analyses include cardiometabolic outcomes, brain RAS activity, CAA pathology, neuroinflammation, and vascular integrity.

Results: Voluntary oral drug consumption delivered doses similar to the target dose for both drugs. Telmisartan and lisinopril treatment did not significantly reduce blood pressure in Tg-SwDI mice. As expected, cognitive-behavioral testing revealed significant deficits in untreated Tg-SwDI mice of both sexes compared to WT controls. Open field testing uncovered attenuated exploratory behavior in Tg-SwDI mice, with trends of increased anxiety-like behavior in Tg-SwDI females. Interestingly, chronic drug treatment improved cognitive performance in Tg-SwDI mice; a finding particularly striking for lisinopril-treated females, whose cognitive-behavioral function was normalized to near equivalence with WT mice.

Conclusions: RAS-targeting drugs at non-hypotensive doses may hold therapeutic potential against CAA-induced cognitive impairment, with benefits potentially varying based upon biological sex and specific drug class.