Old Elastin Haploinsufficient Mice Have Impaired Memory, Motor Coordination, and Endothelial Function

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Introduction

As we age, our large, elastic arteries get stiffer due to increased collagen and elastin fragmentation. Stiff large arteries are not as compliant, which causes increased pulse pressure in smaller vessels, such as the arteries of the brain. Young mice with large artery stiffness have been shown to have cerebrovascular endothelial dysfunction. Large artery stiffness is also correlated with cognitive decline. However, the direct effect of large artery stiffness with age on cognitive and cerebrovascular function is not understood.

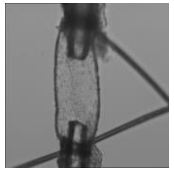
Hypothesis

Old mice with large artery stiffness will have decreased cognitive and cerebrovascular function as compared to old wildtype mice. Old wildtype mice will have decreased cognitive and cerebrovascular function compared to young wildtype mice.

Methods

•Old elastin haploinsufficient mice with large artery stiffness (Old Eln+/-, n = 8, 25 mo) and old wildtype mice (Old Eln+/+, n = 8, 25 mo) were studied. These groups were compared to young wildtype control mice (Young Eln+/+, n = 9, 7 mo).
•Motor coordination was assessed through an accelerating Rotarod test. Rod speed increased from 4 RPM to 40 RPM over 5 minutes. 3 trials/animal were conducted.
•Spatial memory was assessed through a Morris Water Maze probe trial, which occurred after 3 days of training.
•Cerebral artery endothelial function was studied through ex vivo pressurized posterior cerebral arteries.
•To measure endothelium-dependent dilation, increasing doses of acetylcholine (ACh) was added to a pre-constricted artery. To measure the contribution of nitric oxide (NO) to endothelium-dependent dilation, L-NAME, a nitric oxide synthase inhibitor, was added.
•To measure endothelium-independent dilation, increasing doses of sodium nitroprusside (SNP) were added to a pre-constricted artery.
•Coronal brain sections were embedded in paraffin and stained for Iba1, a marker of microglia, to study levels of neuroinflammation





Results

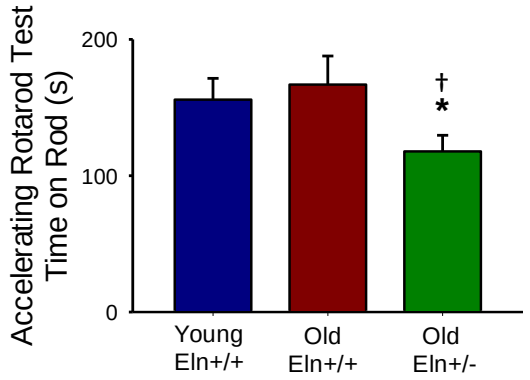


Figure 1. Old Eln+/- mice have impaired motor coordination. In the accelerating rotarod test, Old Eln+/- mice spend significantly less time on the rod, indicating poorer motor coordination when compared with both Young Eln+/+ mice and Old Eln+/+ mice. Old Eln+/+ mice did not have impaired motor coordination when compared to Young Eln+/+ mice. n = 8-9/group. Data is presented as mean ± SEM. * = p < 0.05 vs. Young Eln+/+. † = p < 0.05 vs Old Eln+/+

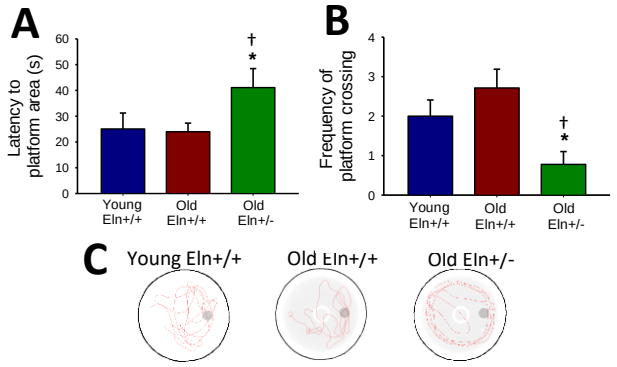


Figure 3. Old Eln+/- mice have impaired spatial memory. Results of the Morris Water Maze test. **A)** Old Eln+/- mice had a significantly higher latency to platform area compared to Young Eln+/+ and Old Eln+/+ mice. **B)** Old Eln+/- mice had significantly lower frequency of platform area crossing compared to Young Eln+/+ and Old Eln+/+ mice. No differences were seen between Young Eln+/+ mice and Old Eln+/+ mice. **C)** Example track path images for Young Eln+/+, Old Eln+/+, and Old Eln+/- mice. n = 8-9/group. Data is presented as mean ± SEM. * = p <0 .05 vs. Young Eln+/+. † = p < 0.05 vs Old Eln+/+

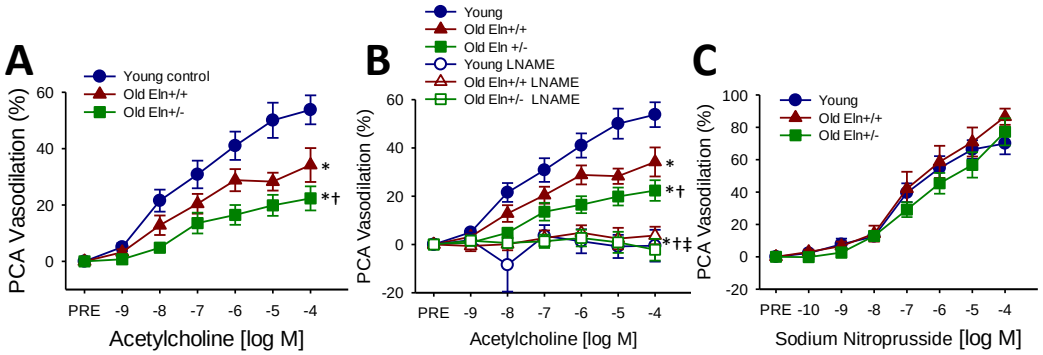
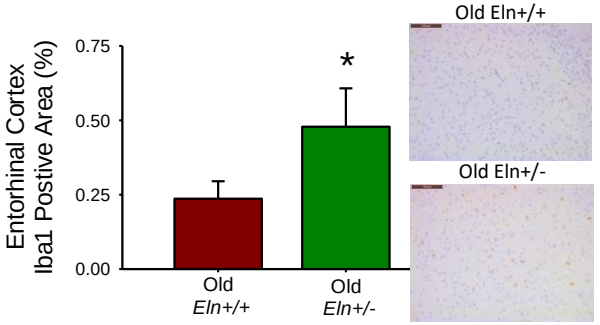


Figure 2. Old Eln+/- mice have impaired endothelial-dependent dilation due to decreased nitric oxide bioavailability. Endothelial function was measured through vasodilation caused by acetylcholine (ACh) and sodium nitroprusside (SNP). **A)** Old Eln+/- mice have significantly lower maximal vasodilation compared to Old Eln+/+ mice, who in turn have significantly lower maximal vasodilation compared to Young Eln+/+ mice. **B)** Incubation with LNAME, a nitric oxide synthase inhibitor, reduced dilation to ACh in all groups ($p < 0.05$) to values that were similar across all groups ($p > 0.05$). **C)** SNP vasodilation responses were similar in all groups ($p > 0.05$). Data is presented as mean ± SEM. n = 8-9/group. * = $p < 0.05$ vs. Young Eln+/+. † = $p < 0.05$ vs. Old Eln+/+. ‡ = $p < 0.05$ vs. Old Eln+/-.

Figure 4. Old Eln+/- mice have increased % area taken up by microglia in the entorhinal cortex. Iba1 is a marker of microglia, immune cells in the brain that cause inflammation. % area positive for Iba1 shown for Old Eln+/- mice (n = 8, 15 mo) and Old Eln+/+ mice (n = 10, 15 mo). Old Eln+/- mice have a significantly higher percentage of the entorhinal cortex taken up by microglia compared to Old Eln+/+ mice. Representative images showing Iba1 in the entorhinal cortex are shown for each group. n = 8-10/group. Data is represented as mean ± SEM; *p < 0.05 vs. Old Eln+/+.



Discussion

Old elastin haploinsufficent mice have impairments in spatial memory and motor coordination. Old Eln+/- mice also have impaired cerebral artery endothelial function, as well as due to reduced nitric oxide bioavailability, and have increased levels of neuroinflammation. In conclusion, the combination of age and large artery stiffness leads to reduced cognitive and cerebrovascular function, which points to the impact of the aging vascular system on other organs in the body.

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