Conditional loss of AMPK in neurons of APPswe/PS1ΔE9 mouse model reduces in amyloid related pathology.

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A mild inhibition of mitochondrial complex 1 by CP2 attenuates AD-like pathology in the APP/PS1 transgenic model, via the activation of AMPK due to an increase in AMP/ATP ratio. Here, we determined if the complete loss of AMPK function in neurons impacts AD pathology in the APPswe/PS1ΔE9 (APP/PS1) mouse model of AD. APP/PS1 mice were crossed to harbor AMPKα1$^{flox/flox}$:AMPKα2$^{flox/flox}$ in presence/absence of SLICK-H, a Cre-driver that expresses CreERT in neurons. Resulting APP/PS1:AMPKα1/α2$^{flox/flox}$: SLICK-H or WT mice were treated with tamoxifen at 6 months of age to induce deletion of AMPKα1/α2. The mice were evaluated at 10 months of age for Aβ pathology and neuroinflammation markers using quantitative immunohistochemistry. We observe that APP/PS1:AMPK^{cKO} exhibit reduced Aβ pathology and reduced glial activation compared to APP/PS1:AMPK^{WT} mice. The findings suggest that neuronal loss of AMPK function attenuates Abeta deposition and neuroinflammation in vivo, challenging the initial hypothesis. Thus, we treated mice with CP2 to test whether AMPK activity was required for anti-amyloid effects of CP2. In APP/PS1:AMPK^{WT} mice, CP2 treatment reduces amyloid pathology. However, CP2 did not affect amyloid pathology in the APP/PS1:AMPK^{cKO} mice. While CP2 treatment minimally impacts glial activation, CP2 treatment led to a significant increase in GFAP staining in the APP/PS1:AMPK^{cKO} mice. Thus, APP/PS1:AMPK^{cKO} neurons may be more sensitive to mild mitochondrial stress induced by CP2 treatment. Despite the paradoxical effects seen with APP/PS1:AMPK^{cKO} mice, our results show that normal neuroprotective effects of CP2 in AD mouse models require AMPK function.