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Curcumin mediates presenilin-1 activity to reduce β-amyloid production in a model of Alzheimer's disease

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Abstract:
Curcumin has been reported to inhibit the generation of Aβ, but the underlying mechanisms by which this occurs remain unknown. Aβ is thought to play an important role in the pathogenesis of Alzheimer's disease (AD). The amyloid hypothesis argues that aggregates of Aβ trigger a complex pathological cascade that leads to neurodegeneration. Aβ is generated by the processing of APP (amyloid precursor protein) by β- and γ-secretases. Presenilin 1 (PS1) is central to γ-secretase activity and is a substrate for GSK-3β, both of which are implicated in the pathogenesis of AD. The present study aimed to investigate the effects of curcumin on the generation of Aβ in cultured neuroblastoma cells and on the *in vitro* expression of PS1 and GSK-3β. To stimulate Aβ production, a plasmid expressing APP was transfected into human SH-SY5Y neuroblastoma cells. The transfected cells were then treated with curcumin at 0–20 μM for 24 h or with 5 μM curcumin for 0–48 h, and the extracellular levels of $A\beta_{40/42}$ were determined by ELISA. The levels of PS1 and GSK-3β mRNA were measured by RT-PCR, and the expression of the PS1 and GSK-3β proteins (including the phosphorylated form of GSK-3β, p-GSK-3β-Ser9) were evaluated by western blotting. Curcumin treatment was found to markedly reduce the production of $A\beta_{40/42}$. Treatment with curcumin also decreased both PS1 and GSK-3β mRNA and protein levels in a dose- and time-dependent manner. Furthermore, curcumin increased the inhibitory phosphorylation of GSK-3β protein at Ser9. Therefore, we propose that curcumin decreases Aβ production by inhibiting GSK-3β-mediated PS1 activation.

Key words:
Alzheimer's disease, β-amyloid, curcumin, GSK-3β, PS1