

# Abstract

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## Intracellular Copper Deficiency Increases Amyloid-beta Secretion by Diverse Mechanisms.

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**BACKGROUND:** In Alzheimer's disease there is abnormal brain copper distribution, with accumulation of copper in amyloid plaques and a deficiency of copper in neighbouring cells. Excess copper inhibits Abeta production, but the effects of deficiency have not yet been determined.

**OBJECTIVE:** We therefore studied the effects of modulating intracellular copper levels upon the processing of the amyloid precursor protein and the production of Abeta.

**RESULTS:** Human fibroblasts genetically disposed to copper accumulation secreted higher levels of sAPPalpha into their medium, while fibroblasts genetically manipulated to be profoundly copper deficient secreted predominantly sAPPbeta and produced more amyloidogenic C-termini (C99). The level of amyloid-beta secreted from copper deficient fibroblasts was however regulated and limited by alpha-secretase cleavage. APP can be processed by both alpha and beta-secretase, as copper deficient fibroblasts secreted sAPPbeta exclusively but produced primarily alpha-cleaved C83. Copper deficiency also markedly reduced the steady-state level of APP mRNA while APP protein level remained constant; indicating that copper deficiency may accelerate APP translation. Copper deficiency in human neuroblastoma cells significantly increased the level of Abeta secretion, but did not affect the cleavage of the amyloid precursor protein

**CONCLUSION:** Therefore, copper deficiency markedly alters APP metabolism and can elevate Abeta secretion by either influencing amyloid precursor protein cleavage or by inhibiting its degradation, with the mechanism dependent on cell type. Overall our data suggests that correcting brain copper imbalance represents a relevant therapeutic target for Alzheimer's disease.

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