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The amyloid precursor protein potentiates CHOP induction and cell death in response to ER Ca2+ depletion

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Here we investigated the role of the amyloid precursor protein (APP) in regulation of Ca2+ store depletion-induced neural cell death. Ca2+ store depletion from the endoplasmic reticulum (ER) was induced by the SERCA (Sarco/Endoplasmic Reticulum Calcium ATPase) inhibitor thapsigargin which led to a rapid induction of the unfolded protein response (UPR) and a delayed activation of executioner caspases in the cultures. Overexpression of APP potently enhanced cytosolic Ca2+ levels and cell death after ER Ca2+ store depletion in comparison to vector-transfected controls. GeneChipR and RT-PCR analysis revealed that the expression of classical UPR chaperone genes was not altered by overexpression of APP.Interestingly, the induction of the ER stress-responsive pro-apoptotic transcription factor CHOP was significantly upregulated in APP-overexpressing cells in comparison to vectortransfected controls. Chelation of intracellular Ca2+ with BAPTA-AM revealed that enhanced CHOP expression after store depletion occured in a Ca2+-dependent manner in APPoverexpressing cells. Prevention of CHOP induction by BAPTA-AM and by RNA interference was also able to abrogate the potentiating effect of APP on thapsigargin-induced apoptosis. Application of the store-operated channel (SOC)-inhibitors SK F96365 and 2-APB downmodulated APP-triggered potentiation of cytosolic Ca2+ levels and apoptosis after treatment with thapsigargin. Our data demonstrate that APP-mediated regulation of ER Ca2+ homeostasis significantly modulates Ca2+ store depletion-induced cell death in a SOC- and CHOP-dependent manner, but independent of the UPR.