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INTERACTION OF TRKA WITH APP IN NGF-TARGET NEURONS IS MODULATED DURING CELL DEATH

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Aims

The amyloid precursor protein (APP) interacts with the tropomyosin receptor kinase A (TrkA) in normal but not in Alzheimer's disease (AD) brain tissue. It has not been reported whether the two proteins interact directly, and if so, which domains are involved. Clarifying these points will increase our understanding of the role and regulation of the TrkA/APP interaction in normal brain functioning as well as in AD

Method

HEK293 cells expressing full length and mutant constructs of APP and TrkA were assessed for mapping the domains involved in TrkA/APP association by co-immunoprecipitation and Western blot analysis. Bimolecular fluorescence complementation was used for direct visualization of APP/TrkA complex and for evaluating the involvement of shared partners in favoring APP/TrkA complex. Proximity ligation assay was used to detect the complex and its modulation by several agents in primary septal neurons

Results

Exogenously expressed APP and TrkA associate through their juxtamembrane/transmembrane domains to form a complex, insensitive to cation chelation, that localizes to the plasma membrane, endoplasmic reticulum (ER) and Golgi. Formation of the complex does not require p75NTR, ShcC or Mint-2. The association between endogenous APP and TrkA in primary septal neurons was modified by NGF, by drugs that either inhibit ER-to-Golgi transport or perturb microtubules and microfilaments. Interestingly, several agents that induce cell death albeit via different mechanisms, all caused dissociation of APP/TrkA complexes, formation of p75NTR/APP complex and increased production of β-CTF APP fragment

Conclusion

Our findings open new perspectives for investigating the interplay between APP and TrkA during neurodegeneration and AD