MOLECULAR NEURODEGENERATION

POSTER PRESENTATION Open Access

Cytoprotective functions of amyloid precursor protein family members in stress signaling and aging

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From Molecular Neurodegeneration: Basic biology and disease pathways
Cannes, France. 10-12 September 2013

Background

The amyloid precursor protein (APP) is processed via two different metabolic pathways: the amyloidogenic and the non-amyloidogenic pathway, the latter of which leading to generation of the secreted N-terminal APP fragment sAPPα [1]. Previous studies from our group suggest that sAPPα exerts potent neuroprotective effects and inhibits stress-triggered cell death via modulation of gene expression, as well as by antagonizing different types of neurotoxic stress [2]. It was also observed that the biochemical processing of APP is downregulated during aging which in turn reduced the secretion of sAPPα [3]. Based on these observations, we have studied the potential physiological function of sAPPα/APP and APLPs (APP like proteins) on the regulation of age-associated, stress induced signaling pathways, apoptosis and senescence.

Materials and methods

SH-SY5Y, PC12, IMR90 cells were used as cellular models. Depletion of APP, APLP1 (APP like protein 1) and APLP2 (APP like protein 2) in SH-SY5Y cells was achieved by stable lentiviral knockdown. To analyze the protective function of sAPPα, we have used conditioned supernatants of wild type APP overexpressing HEK cells and recombinant His-tagged sAPPα purified from yeast. The cells were treated with sAPPα prior to the addition of different stress stimuli (MG132, epoxomicin, UV, H_2O_2) after which cell death, gene expression and senescence were analyzed by MTT assays, caspase activity assays, Western blots and X-Gal staining respectively.

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Results

Our data show that sAPPα can antagonize premature senescence induced by repetitive short term induction of proteasomal stress in IMR-90 cells and apoptosis triggered by prolonged proteasomal stress and other death stimuli in PC12, SH-SY5Y and IMR90 cells which was accompanied by a sAPPα-dependent inhibition of the JNK stress signaling pathway. In contrast, no significant changes in cell viability and apoptosis were observed when APP knockdown cells were pretreated with sAPPα.

Conclusions

Our observations suggest that sAPPα can antagonize both apoptosis and cellular senescence and requires expression of holo-APP to mediate its cytoprotective effects. They also support the notion that the physiological function of APP is linked to modulation of neuronal and brain aging.

Acknowledgements

This study is supported by the German Research Foundation (DFG, FOR1332: Physiological functions of the APP Gene Family in the Central Nervous System)

Published: 13 September 2013

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doi:10.1186/1750-1326-8-S1-P26
Cite this article as: Kundu *et al.*: Cytoprotective functions of amyloid precursor protein family members in stress signaling and aging. *Molecular Neurodegeneration* 2013 **8**(Suppl 1):P26.