Canonical activity of Apaf1 and Caspase-3 in mitochondria-dependent cell death

THE PRIMER: mitochondrion

THE RELAY: Apaf1 and the apoptosome

THE EFFECTOR: Active casp-3

Active casp-3

Procasp-3

Casp-9

Apoptosome

CELL DEATH
Caspase-3 triggers early synaptic dysfunction in a mouse model of Alzheimer’s disease

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Synaptic loss is the best pathological correlate of the cognitive decline in Alzheimer’s disease; however, the molecular mechanisms underlying synaptic failure are unknown. We found a non-apoptotic baseline caspase-3 activity in hippocampal dendritic spines and an enhancement of this activity at the onset of memory decline in the Tg2576-APPsw mouse model of Alzheimer’s disease. In spines, caspase-3 activated calcineurin, which in turn triggered dephosphorylation and removal of the GluR1 subunit of AMPA-type receptor from postsynaptic sites. These molecular modifications led to alterations of glutamatergic synaptic transmission and plasticity and correlated with spine degeneration and a deficit in hippocampal-dependent memory. Notably, pharmacological inhibition of caspase-3 activity in Tg2576 mice rescued the observed Alzheimer-like phenotypes. Our results identify a previously unknown caspase-3-dependent mechanism that drives synaptic failure and contributes to cognitive dysfunction in Alzheimer’s disease. These findings indicate that caspase-3 is a potential target for pharmacological therapy during early disease stages.

Review

Neuronal caspase-3 signaling: not only cell death

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Caspases are a family of cysteiny1 aspartate-specific proteases that are highly conserved in multicellular organisms and function as central regulators of apoptosis. A member of this family, caspase-3, has been identified as a key mediator of apoptosis in neuronal cells. Recent studies in snail, fly and rat suggest that caspase-3 also functions as a regulatory molecule in neurogenesis and synaptic activity. In this study, in addition to providing an overview of the mechanism of caspase-3 activation, we review genetic and pharmacological studies of apoptotic and nonapoptotic functions of caspase-3 and discuss the regulatory mechanism of caspase-3 for executing nonapoptotic functions in the central nervous system. Knowledge of biochemical pathway(s) for nonapoptotic activation and modulation of caspase-3 has potential implications for the understanding of synaptic failure in the pathophysiology of neurological disorders. Fine-tuning of caspase-3 lays down a new challenge in identifying pharmacological avenues for treatment of many neurological disorders.

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Detection of early synaptic alterations

Hippocampal post-synaptic density (PSD)

- kDa  WT  Tg
  - 106  GluR1
  - 100  GluR1pSer845
  - 106  GluR1pSer831
  - 108  GluR2/3
  - 115  NMDA1
  - 177  NMDA1
  - 180  NMDA2
  - 132  mGluR5
  - 100  PSD-95
  - 83  NSF
  - 54  αCaMKII

Hippocampal total extract

- kDa  WT  Tg
  - 106  GluR1
  - 100  GluR1pSer845
  - 55  Tubulin

Hippocampal synaptic fractionation

- kDa  WT  Tg
  - 106  GluR1
  - 132  mGluR5
  - 100  PSD-95
  - 83  NSF
  - 54  αCaMKII

Basic glutamatergic transmission

- WT
  - +20 mV
  - -65 mV
- Tg
  - 100 ms
  - 30 pA

Protein expression (% control)

- GluR1
- GluR1pSer845

GuoR1 (% control)

- TxP
- P3
Active caspase-3 localizes in post-synaptic compartment
Caspase-3 inhibition in vivo influences GluR1 distribution and rescues spine head size and memory performance.
Model of caspase-3 role in dendritic spine degeneration

- AMPA Receptor
- GluR1
- S845
- OH

- AMPA Receptor
- GluR1
- S845
- OH

- Active calcineurin

- Procasp-3
- Casp-9
- Apoptosome

- Aβ-mediated stress

- NMDA Receptor
An alternative role for **THE EFFECTOR**: Caspase-3 in mitochondria-dependent nonapoptotic cleavage of a synaptic substrate

**Diagram:**
- Aβ-mediated stress
- ProCasp-3
- Active casp-3
- Casp-9
- Apoptosome
- Specific target activation
- Cell death

**Diagram Details:**
- ProCasp-3 activates Active casp-3.
- Active casp-3 is involved in specific target activation.
- Aβ-mediated stress leads to cell death through the apoptosome pathway.