NEUROBIOLOGY UNIT
IIBB/CSIC/IDIBAPS
CIBERNED

LA PENTRAXINA NEURONAL 1:

dinàmica mitocondrial i neurodegeneració

Neurodegeneration

Neurodegeneration refers to the process of progressive worsening of structure and function of neurons

Neurodegenerative disorder corresponds to any pathological condition primarily affecting structure and function of neurons.

Neurodegenerative diseases include a large group of neurological disorders with heterogeneous clinical and pathological expressions affecting specific subsets of neurons in specific brain areas.

Diseases of the nervous system that primarily implicate cells other than neurons are not considered neurodegenerative disorders: Neoplasm, edema, brain trauma, ischemia, multiple sclerosis, etc…

Classification of neurodegenerative diseases

ANATOMOPATHOLOGICAL AND CLINICAL CRITERIA

DISEASES OF THE CEREBRAL CORTEX **(presence-absence of dementia)**

Alzheimer's disease ("senile dementia")

Fontotemporal Dementias, **Pick's disease**

Creutzfeld-Jakob disease (subacute spongyform encephalopathy)

DISEASES PREDOMINANTLY INVOLVING BASAL GANGLIA **(Abnormal movements)**

(Hypokinetic) Parkinson disease and Parkinsonism

(Hyperkinetic) **Huntington's Chorea**

DISEASES OF THE CEREBELLUM AND ITS CONNECTIONS

Friedreich's ataxia (Spinal degeneration, inability to co-ordinate voluntary movements)

Olivo-ponto-cerebellar atrophy

DISEASES PREDOMINANTLY AFFECTING SPINAL CORD

Amyotrophic lateral sclerosis (ALS) - affects selectively the motor neuron system

Nature 8 December 2011

IN FOCUS NEWS

PHARMACEUTICALS

Novartis to shut brain research facility

Drug giant redirects psychiatric efforts to genetics.

"Developing drugs for the brain has become high-risk, with most candidates failing."

It follows similar moves by GlaxoSmith-Kline and AstraZeneca, both based in the United Kingdom, which last year announced the closure of all their neuroscience research divisions globally. US-based companies Pfizer and Merck, as well as the French company Sanofi, have also pulled back on research into brain disorders. Rather than abandon neuro-

We need more basic research to uncover mechanisms of brain function

HYPOTHESIS

Neurodegenerative diseases are caused by unregulated expression lethal proteins of the mitochondrial program of cell death in mature neurons

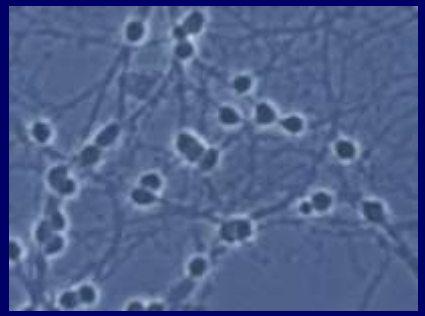
Programmed cell death is an intrinsic sequence of biochemical events that involves the new synthesis of lethal proteins (Thanatins) that lead to cell destruction

OBJECTIVE

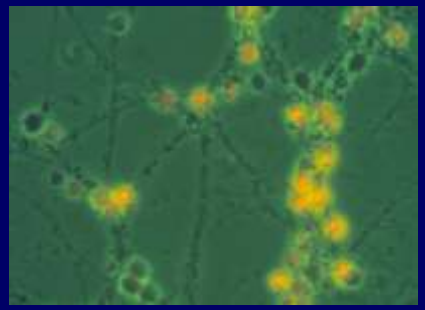
Identify and characterize the lethal proteins (Thanatins) that are synthesized within the initial period of neurodegeneration triggered by reduction of neuronal activity in mature and differentiated neurons

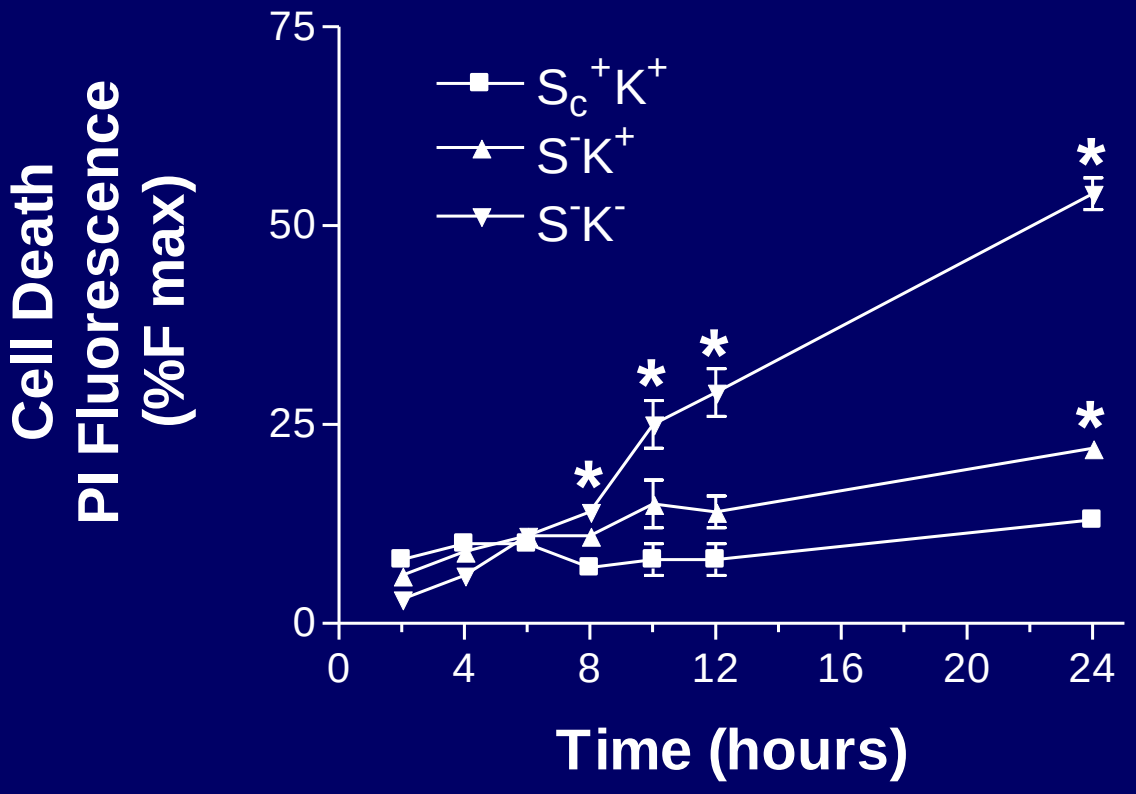
Reduction of Neuronal activity by low K^+ induces Programmed cell death in cerebellar granule cells

Phase Contrast
$S^+_cK^+$

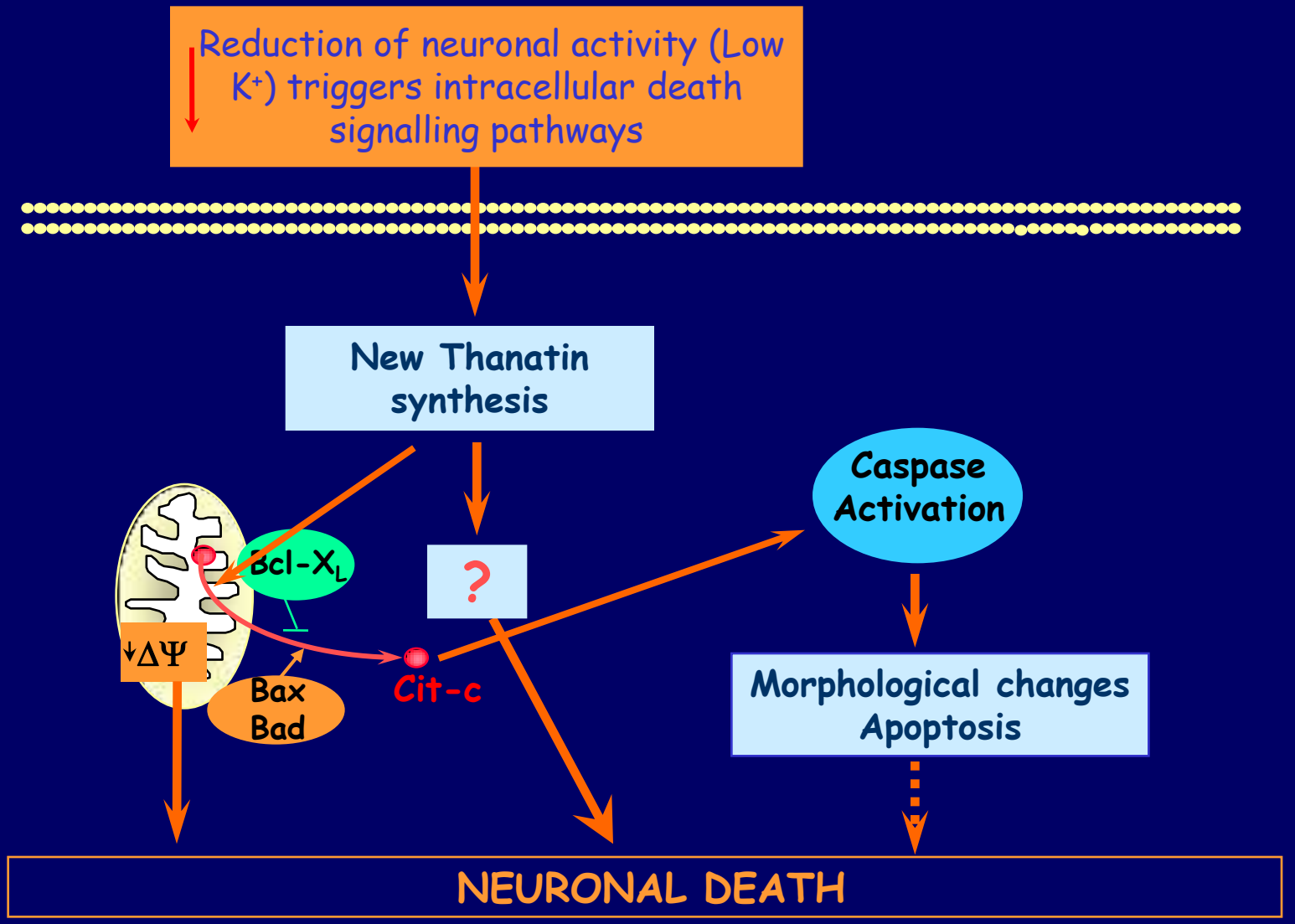


Fluorescence/Phase Contrast
Propidium Iodide, S^-K^-

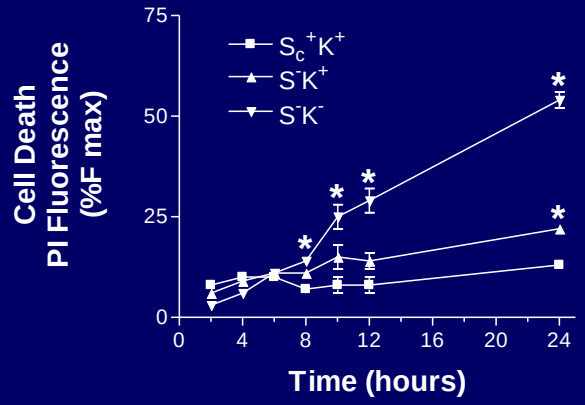


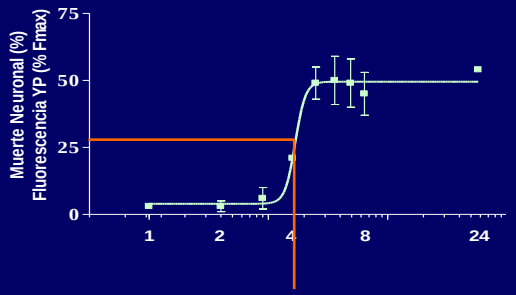


Reduction of Neuronal activity causes cell death by inducing the new synthesis of thanatins and not by reduccion of survival proteins.



Programmed Cell Death by reduction of Neuronal Activity: Overexpression of Neuronal Pentraxin 1 (NP1) before reaching commitment to die





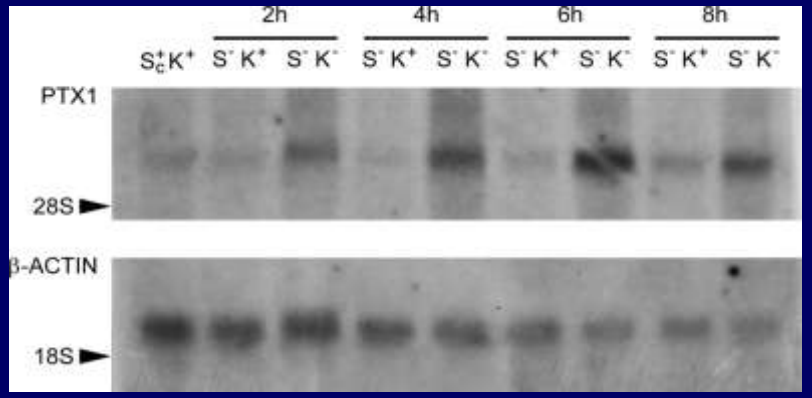
Commitment point> 4 H

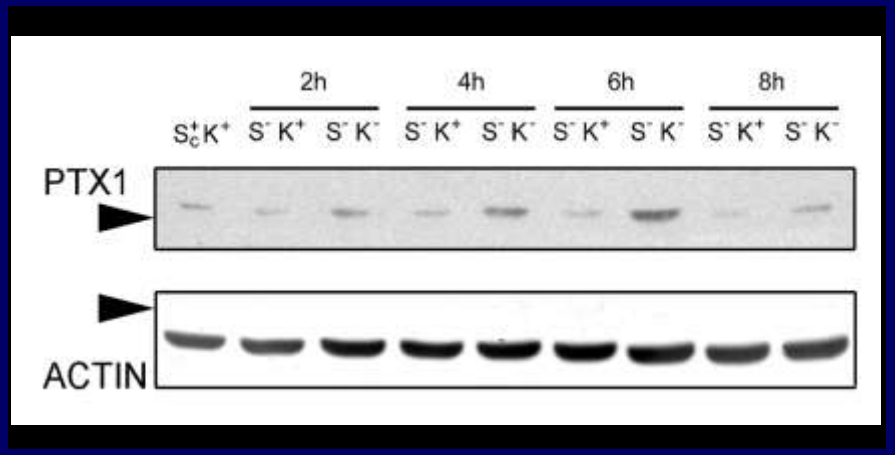
- Neuronal Pentraxin 1 is part of the mitochondrial program of apoptotic neuronal death.
- It is only expressed in the nervous system
- Protein encoded by only one gene

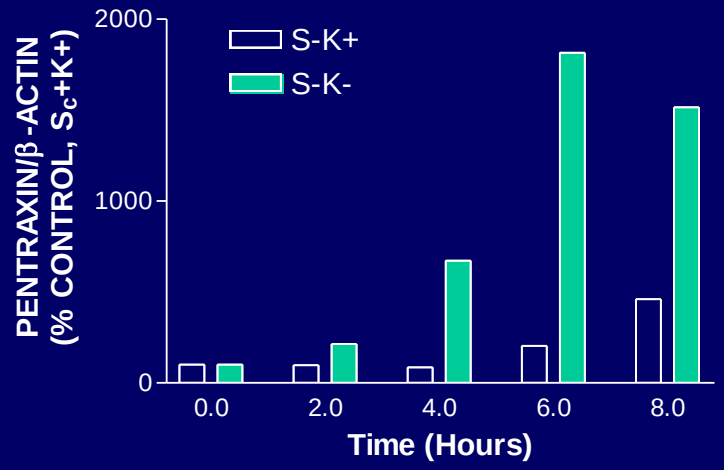
DeGregorio et al.(2001). JBC 276:796-803

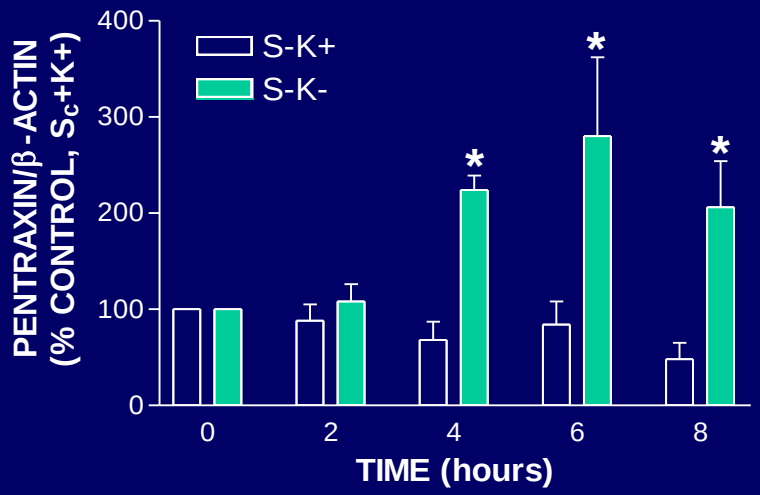
Enguita et al.(2005). Mol. Pharm 67:1237

Time course of NP1 mRNA and protein expression evoked by Low K^+ in CGNs



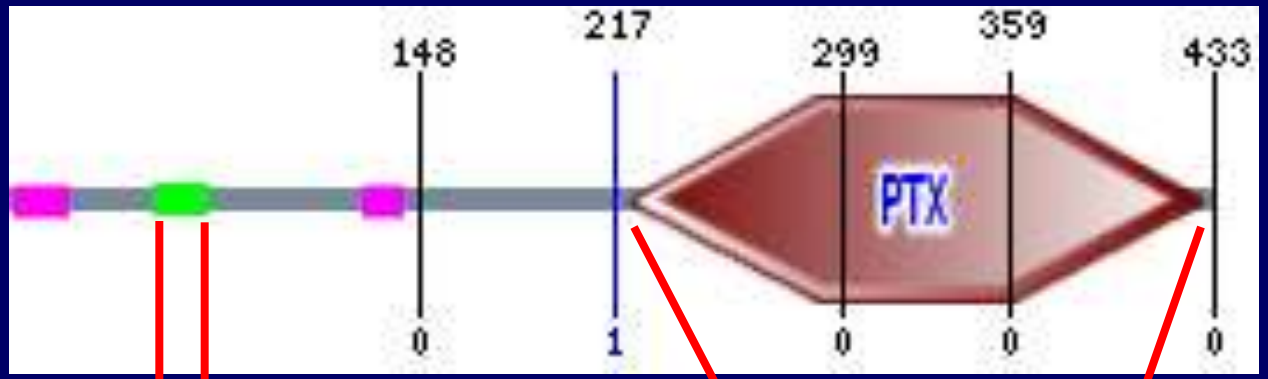


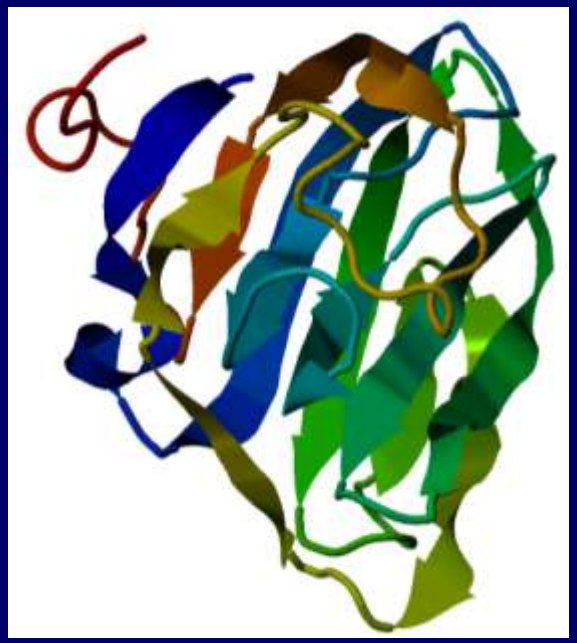




DeGregorio et al.(2001). JBC 276:796-803

Neuronal Pentraxin 1

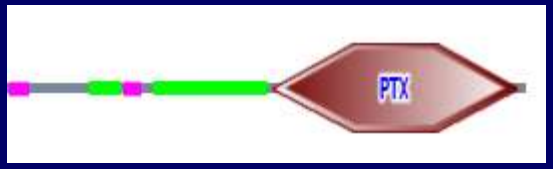




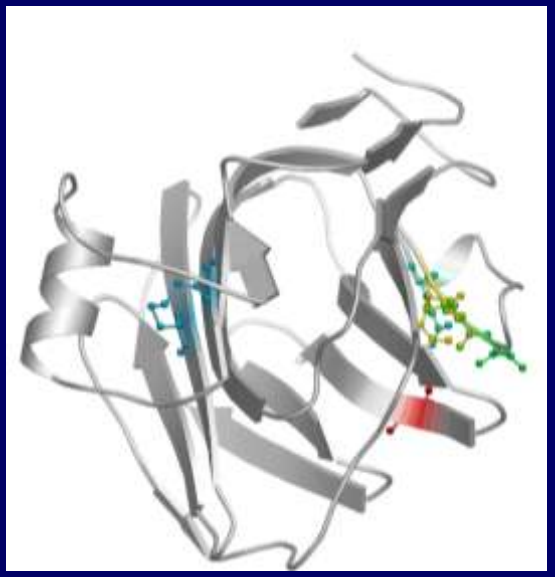
52-72
Coiled-Coil Region

228-248
Pentaxin Domain
Calcium Dependent Binding

Low-Complexity Regions



Neuronal Pentraxin 2



Signal transduction pathways involved in neurodegeneration

Which signal transduction pathway regulates NP1 expression?

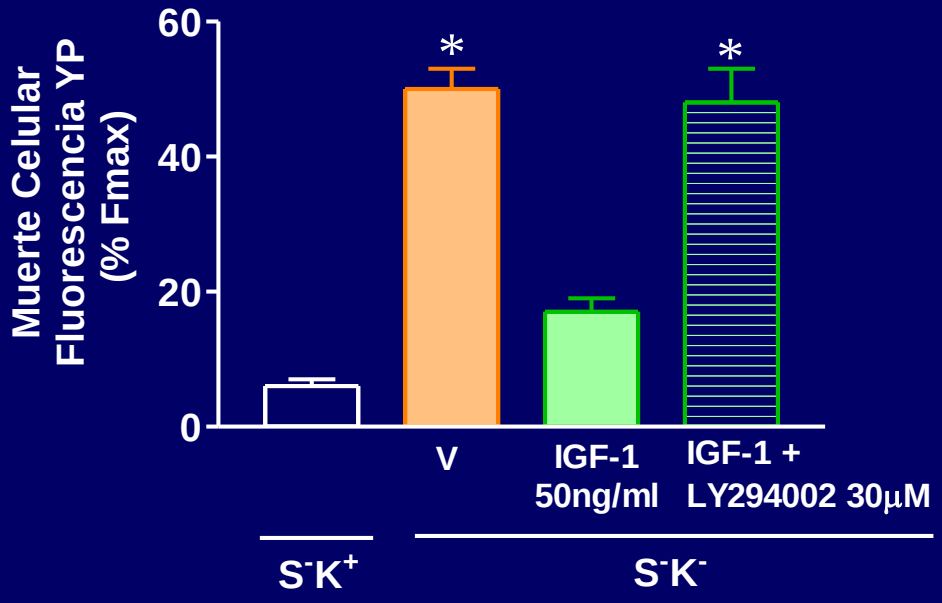
Signal transduction pathways involved in neurodegeneration

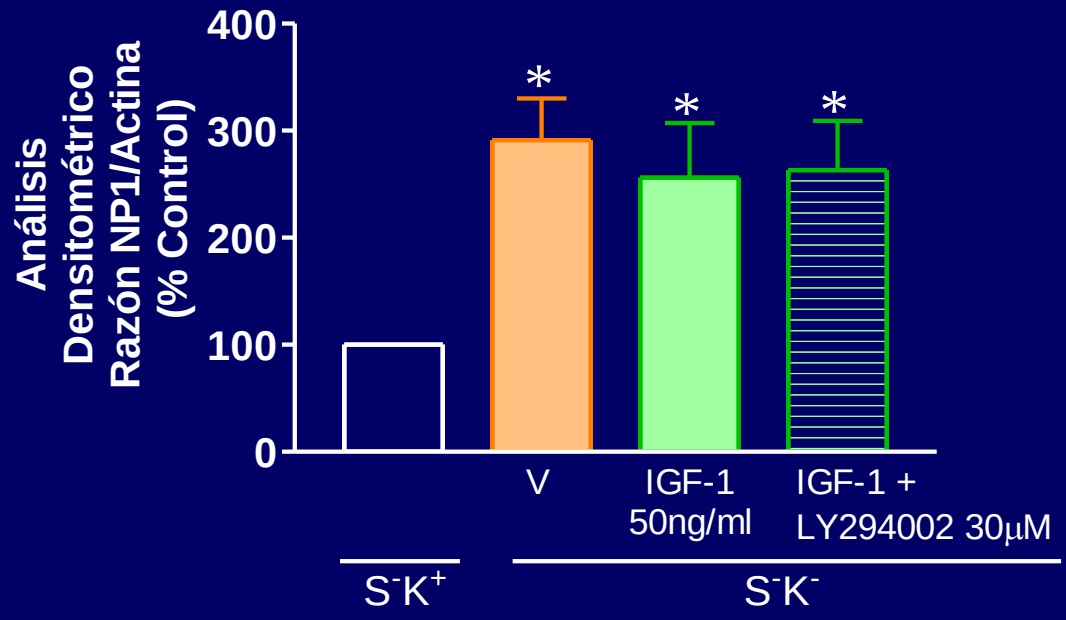
Presumably, neuronal death may be blocked through two different antagonistic strategies :

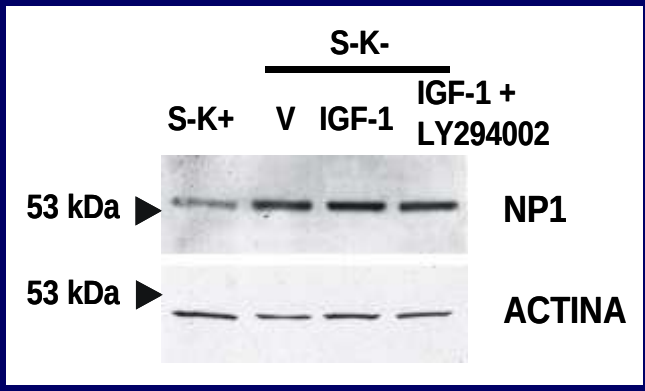
- Activating neurotrophic signaling pathways.
- Blocking cell death signaling pathways.

Life signaling pathways: PI3K-AKT, MAPK
Death signaling pathways : p38MAPK, JNK

PI3K-AKT PATHWAY
IGF-1 is neuroprotective but does not block NP1 overexpression evoked by low K^+

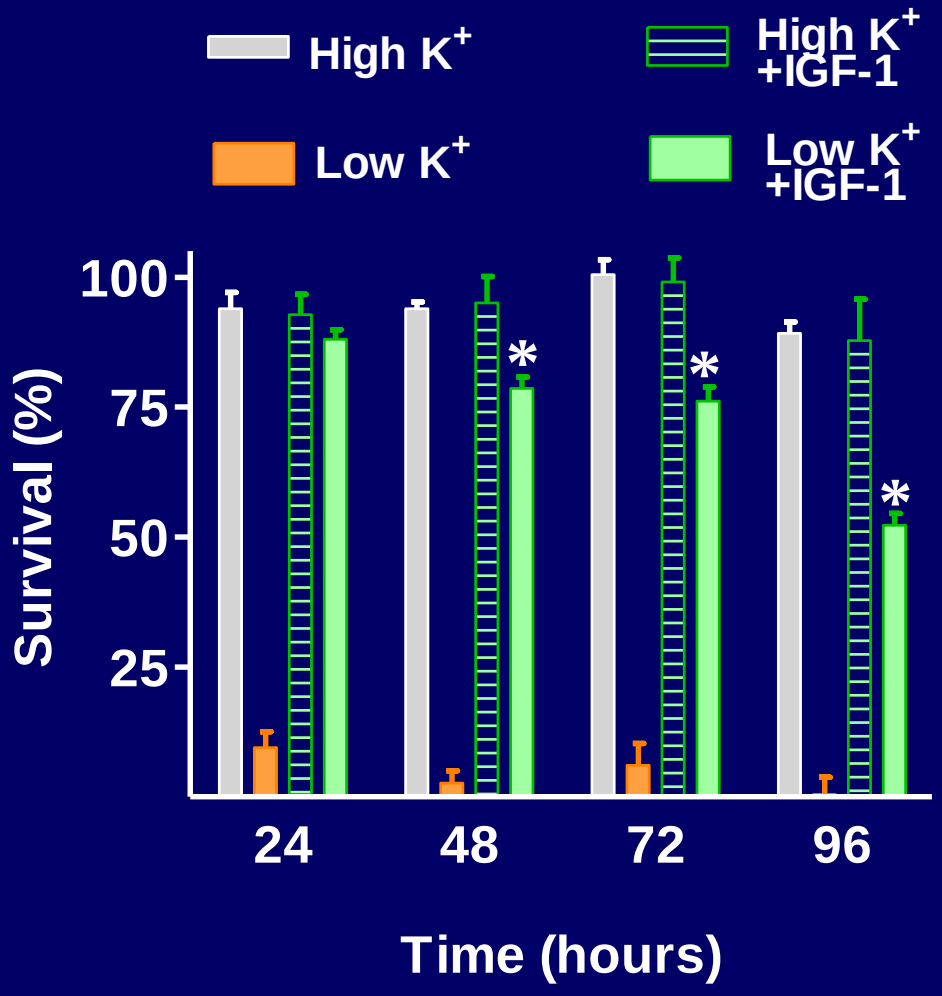






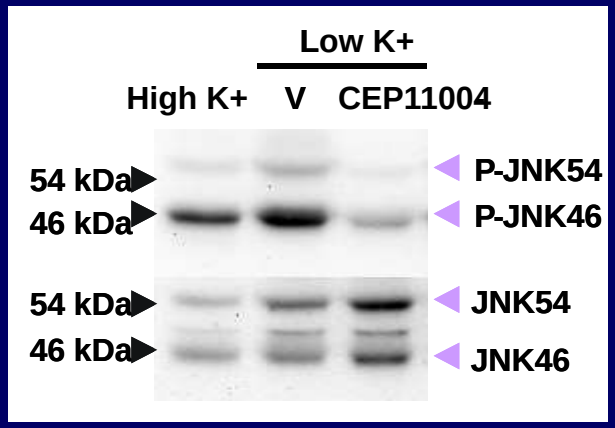
Enguita et al.(2005). Mol. Pharm 67:1237

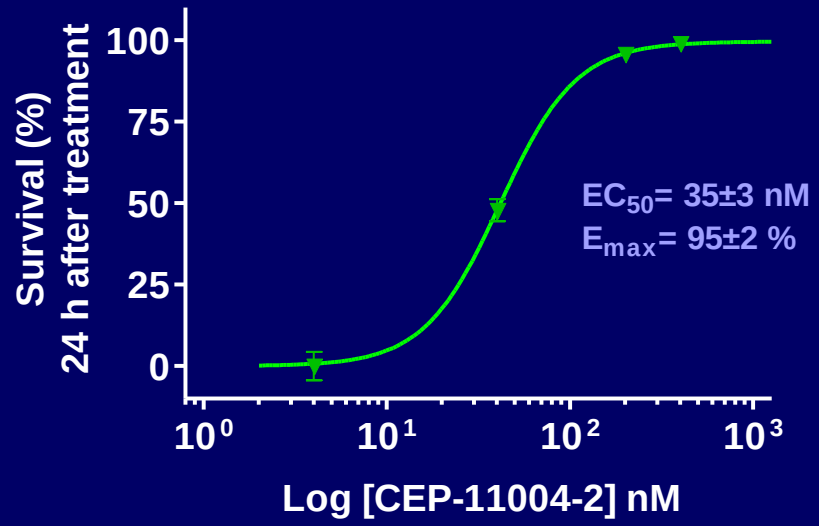
IGF-1 neuroprotection is transient

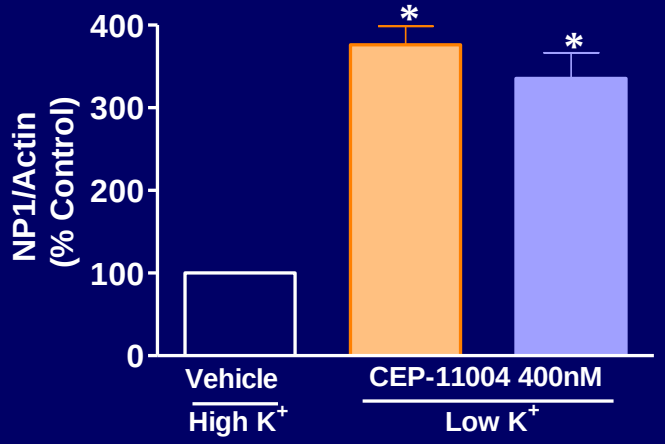


Enguita et al.(2005). Mol. Pharm 67:1237

CEP-11004-2 blocks JNK phosphorylation and cell death evoked by low K+ but does not modify NP1 overexpression

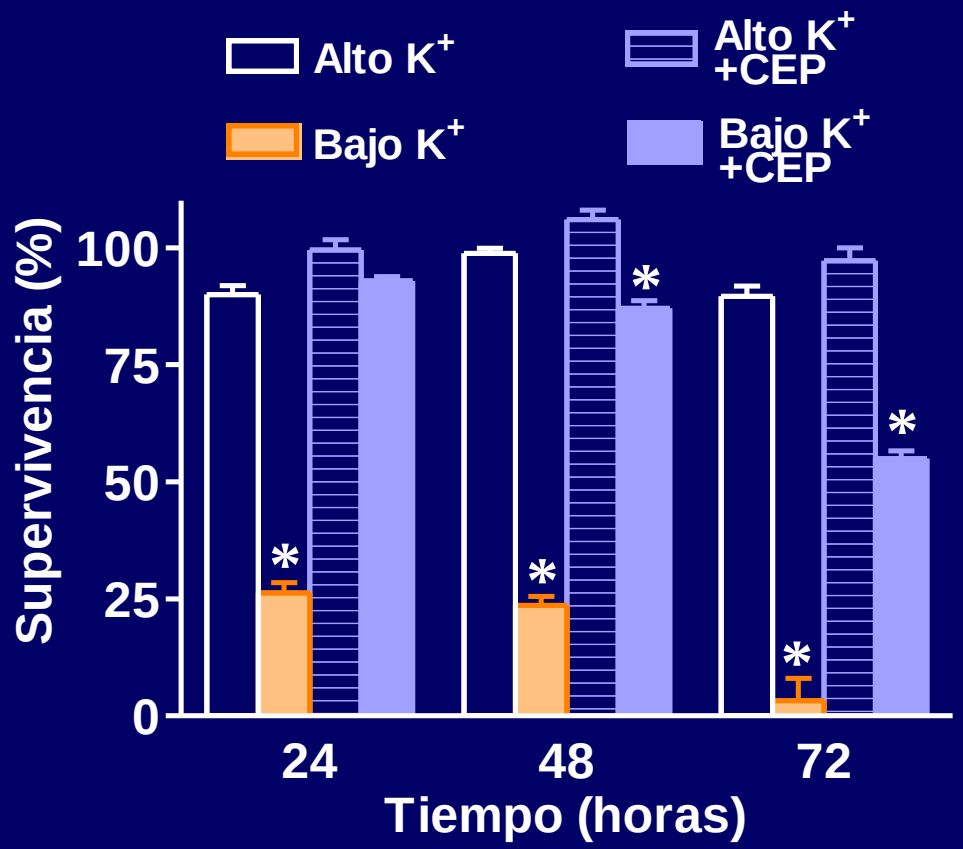






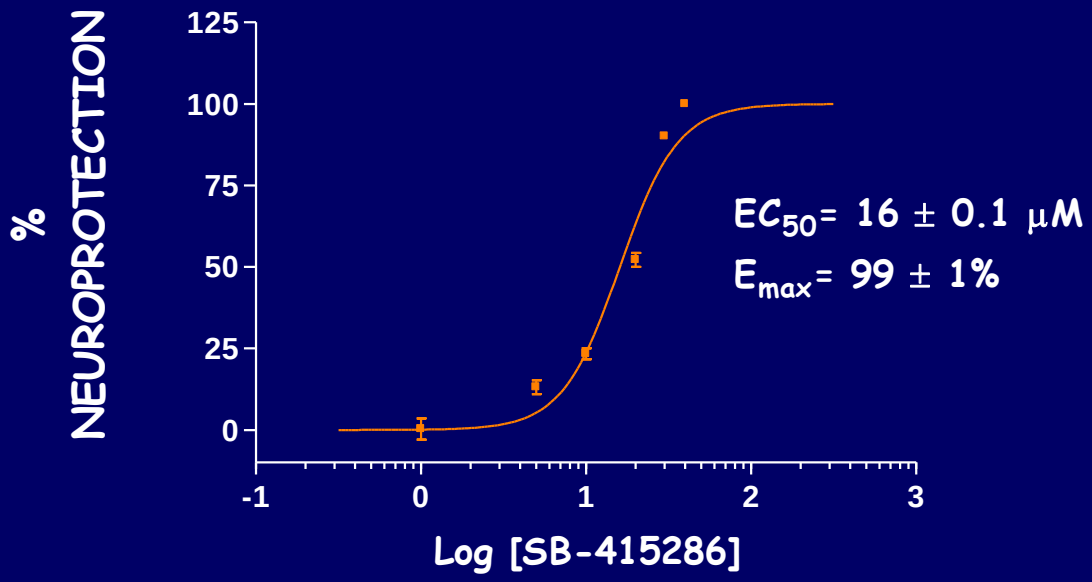
Enguita et al.(2005). Mol. Pharm 67:1237

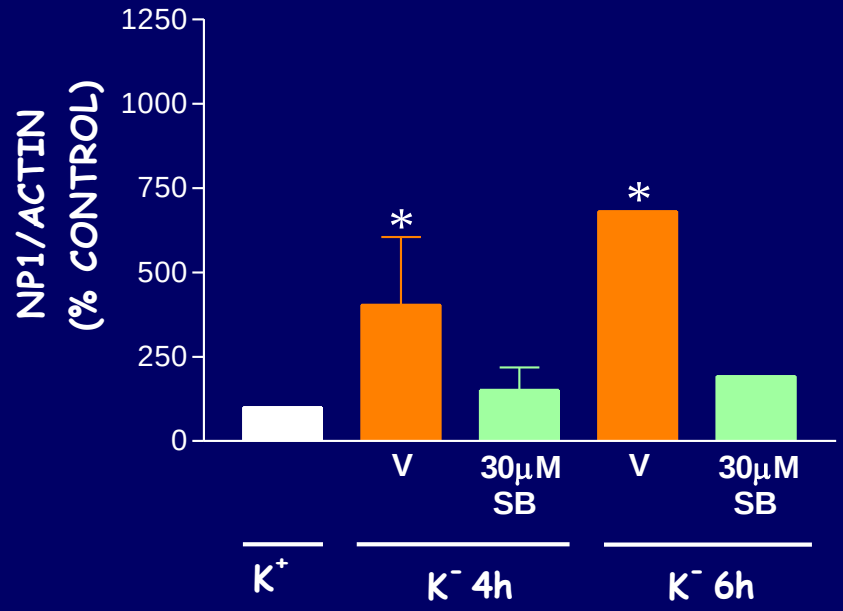
Inhibition of JNK by CEP-11004-2 provides full, but transient neuroprotection

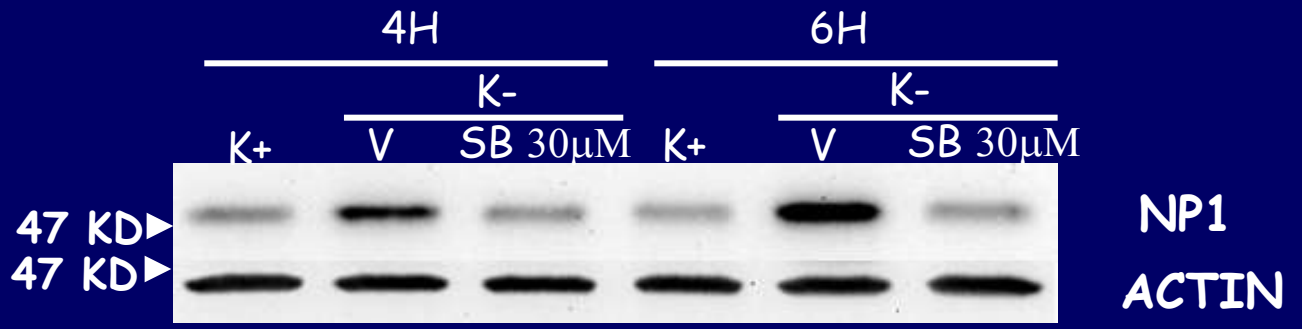


Enguita et al.(2005). Mol. Pharm 67:1237

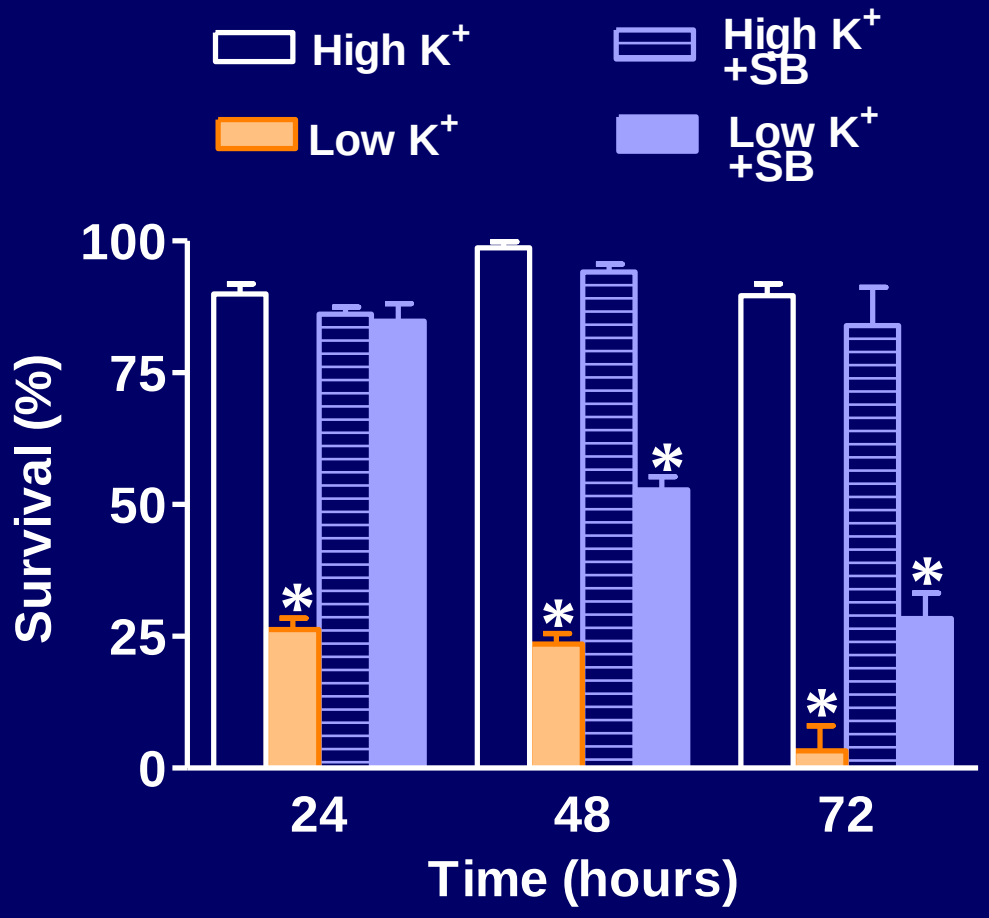
SB-415286, a GSK3β inhibitor blocks NP1 overexpression and prevents neuronal death by Low K^+





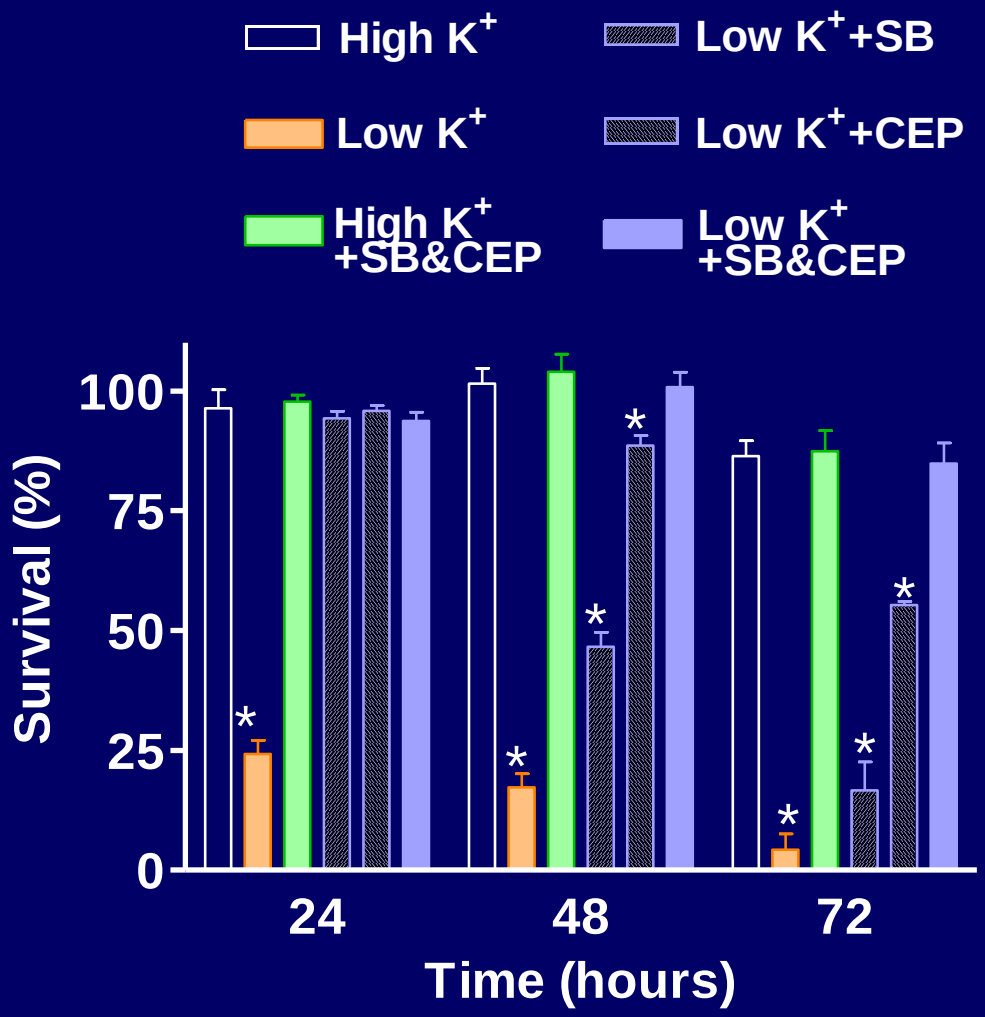


Inhibition of GSK-3 provides full, but transient neuroprotection



Enguita et al.(2005). Mol. Pharm 67:1237

Simultaneous combined inhibition of GSK-3 and JNK signaling pathways provides long-term neuroprotection



Enguita et al.(2005). Mol. Pharm 67:1237

CONCLUSIONS

1. NP1 is part of the intrinsic program of apoptotic neuronal death
2. GSK3, but not p38MAPK, JNK, or PI3K, regulates NP1 expression
3. Both JNK and GSK3 signaling pathways are the main routes by which low neuronal activity triggers apoptotic neurodegeneration
4. Simultaneous pharmacological blockage of both JNK and GSK3 activities provides long-term protection against cell death.

Neurology. 2008, 71:462-3.

MIXED LINEAGE KINASE INHIBITOR CEP-1347 FAILS TO DELAY DISABILITY IN EARLY PARKINSON DISEASE

PI3-kinase. The addition of GSK-3 inhibitors to MLK inhibitor-maintained CGNs is able to sustain long-term neuronal survival.[4] Perhaps with the potential availability of GSK-3 inhibitors, this is a worthy and testable hypothesis for dopaminergic and possibly other neurons.

Leo H. Wang, Eugene M. Johnson, Jr., St. Louis, MO

Conclusions

Neuronal Pentraxin 1 contributes to the synapse loss, neurite damage and apoptotic neuronal death evoked by beta-amyloid.

Neuronal Pentraxin 1 regulates the number of excitatory synapses

Neuronal Pentraxin 1 acts as a limiting factor in the regulation of synaptic excitability and knockdown of NP1 increases long term potentiation

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