The University of Edinburgh

Mechanisms underlying the bell-shaped response of neurons to glutamate

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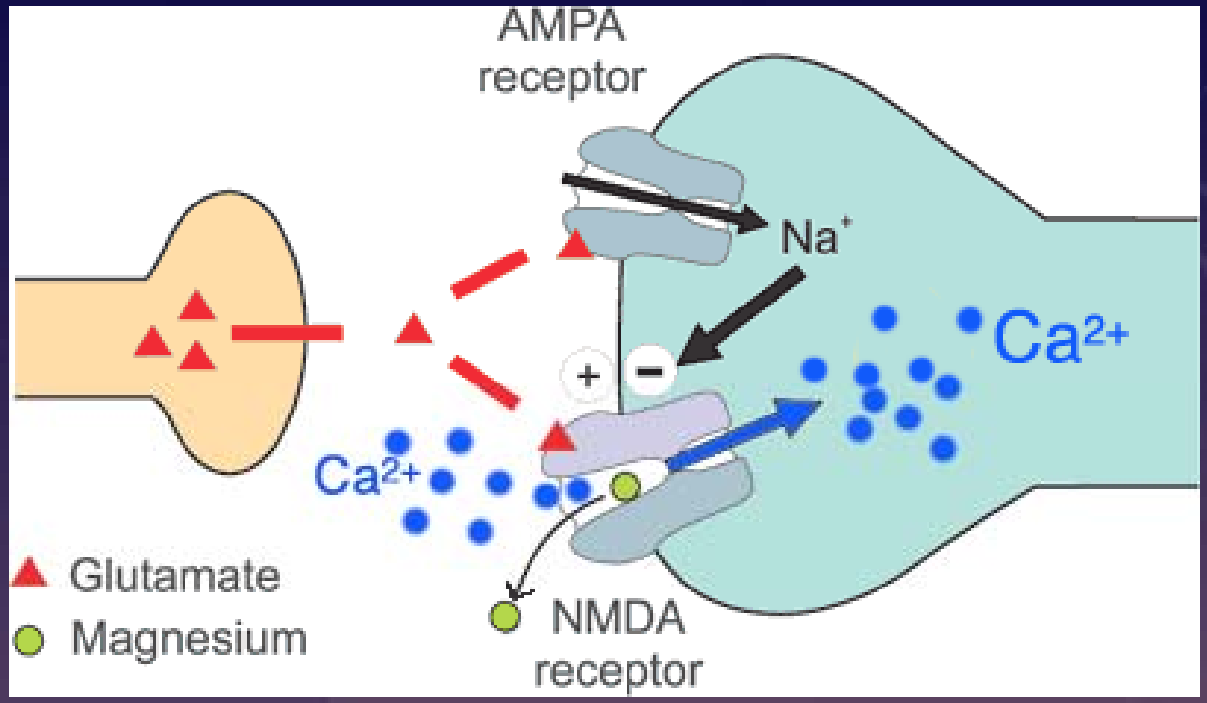
Centre for Neuroscience Research

Glutamate is the major excitatory neurotransmitter in the mammalian CNS



Glutamate activates 2 main types of ionotropic receptors:

-AMPA/Kainate receptors pass Na^+ to depolarize the neuron and make it fire an action potential

-NMDA receptors pass Ca^{2+} into the neuron to trigger functional changes such as synaptic plasticity. *All the glutamate induced processes described today are mediated by Ca2+ influx through the NMDA receptor.*

Glutamate can kill neurons at high doses, acting via the NMDA receptor

Olney JW. Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. Science. 1969 May 9;164(880):719-21.

Olney JW, Sharpe LG. Brain lesions in an infant rhesus monkey treated with monsodium glutamate. Science. 1969 Oct 17;166(903):386-8.

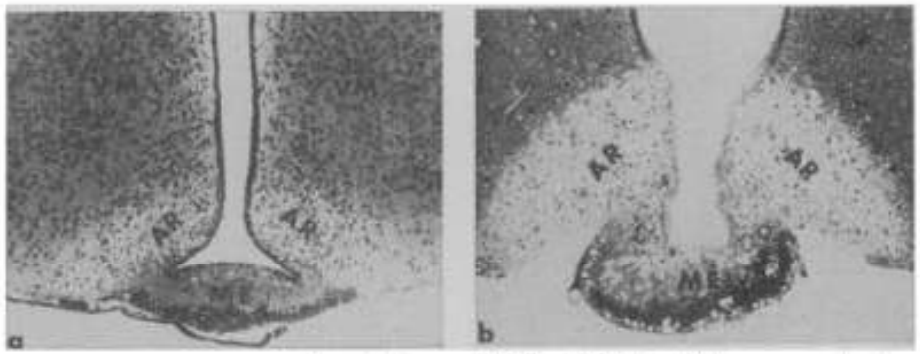


Fig. 1. (a) Section through hypothalamus of 5-day-old Swiss albino mouse showing lesion formation 3 hours after a subcutaneous dose of MSG (1 mg/g). Scattered neurons in the median eminence (*ME*) are necrotic with bloated cytoplasm and pyknotic nuclei. The majority of neurons in the arcuate nuclei (*AR*) are necrotic, but those of the ventromedial nuclei (*VM*) are unaffected (× 100). (b) Section through hypothalamus of adult C57BL/6 mouse 3 hours after a subcutaneous dose of MSG (6 mg/g). The arcuate nuclei (*AR*) are completely destroyed along with neuronal constituents in the median eminence (*ME*). Capillary lumina are empty and widely dilated because this animal was killed by perfusion of glutaraldehyde through the ascending aorta (× 115).

719

Too little NMDA receptor activity in can also kill neurons

In vivo blockade of NMDA receptors in the perinatal rat causes extensive apoptosis in many brain regions

Ikonomidou et al. Science 1999;283:70-4.

Blockade of NMDA Receptors and Apoptotic Neurodegeneration in the Developing Brain

Chrysanthy Ikonomidou,* Friederike Bosch, Michael Miksa, Petra Bittigau, Jessica Vöckler, Krikor Dikranian, Tanya I. Tenkova, Vanya Stefovska, Lechoslaw Turski, John W. Olney

Newborn neurons in the adult dentate gyrus have a requirement for NMDA receptor activity in order to survive

Tashiro et al. Nature 2006; 442, 929

Vol 442|24 August 2006|doi:10.1038/nature05028 nature

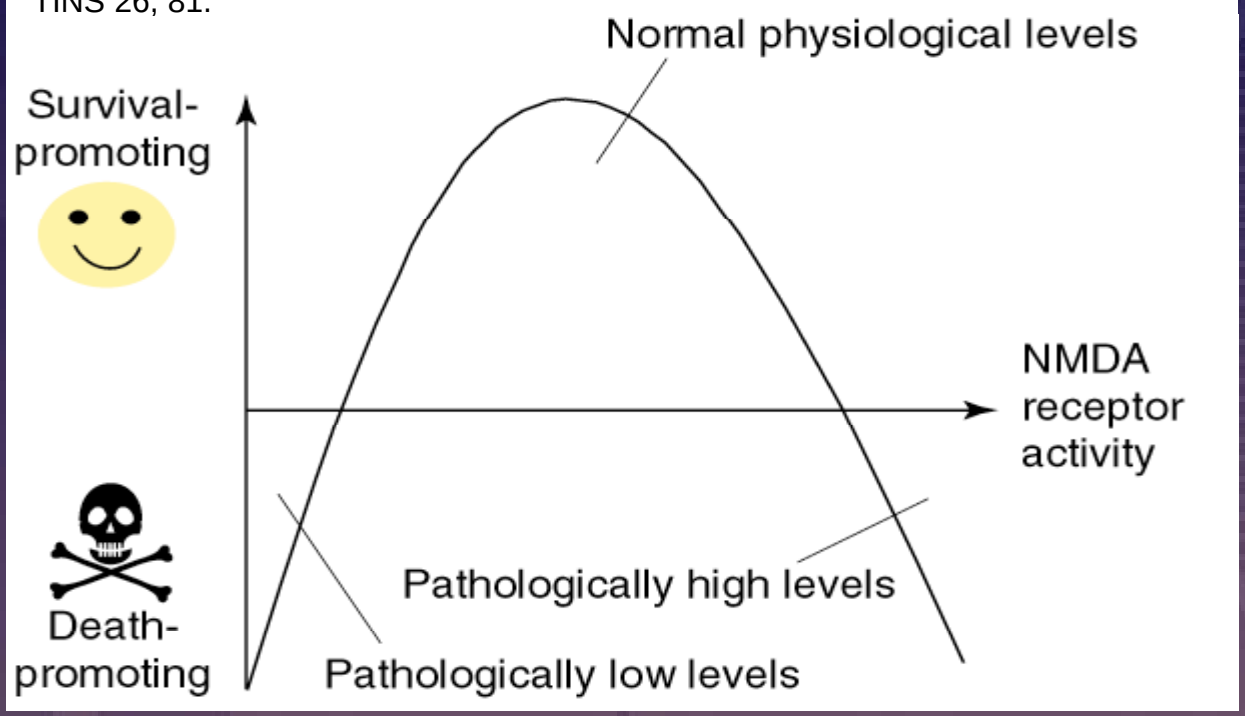
LETTERS

NMDA-receptor-mediated, cell-specific integration of new neurons in adult dentate gyrus

Ayumu Tashiro[1]†, Vladislav M. Sandler[1], Nicolas Toni[1], Chunmei Zhao[1] & Fred H. Gage[1]

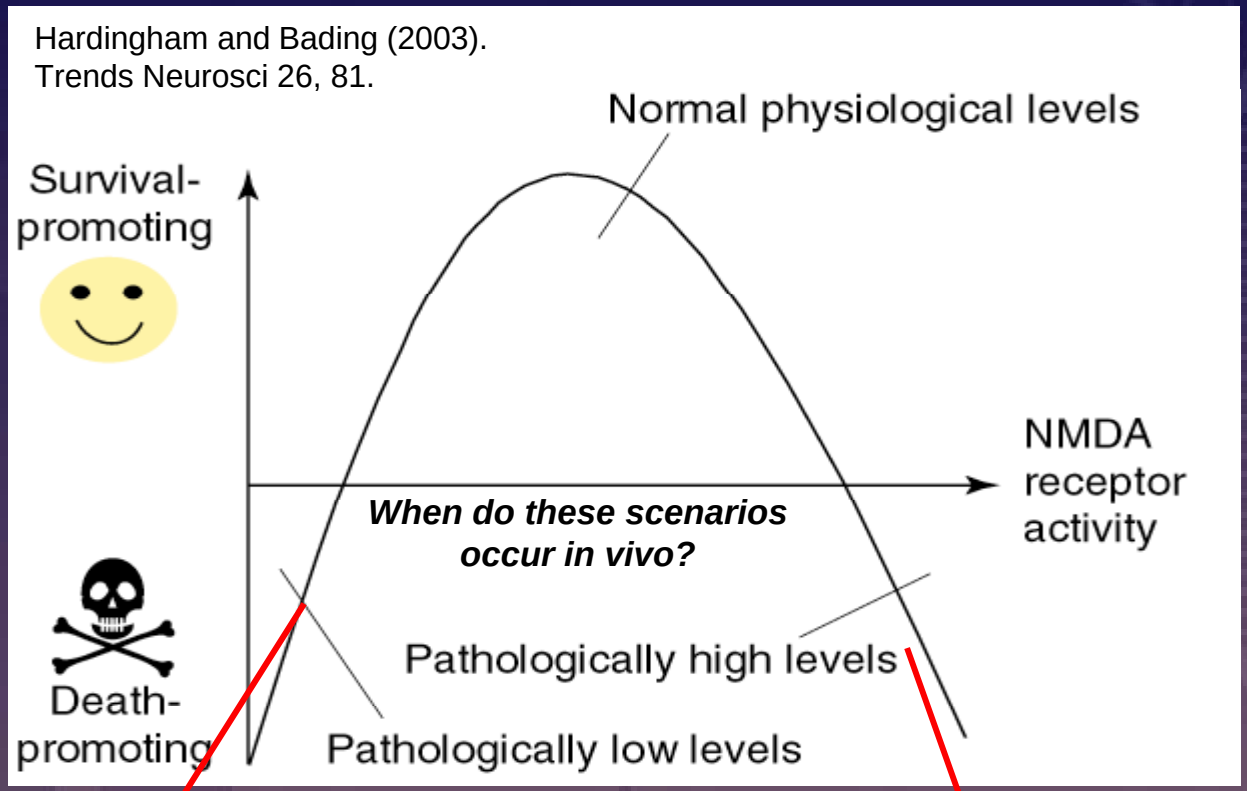
Neuronal fate as a function of [glutamate] exposure, mediated by NMDA receptor activation

Hardingham and Bading (2003).
TINS 26, 81.



High [glutamate] arises during excitotoxic trauma such as ischemia, due to reversal of glutamate uptake mechanism

NMDA receptor inhibition during synaptogenesis kills neurons, renders adult neurons vulnerable to trauma



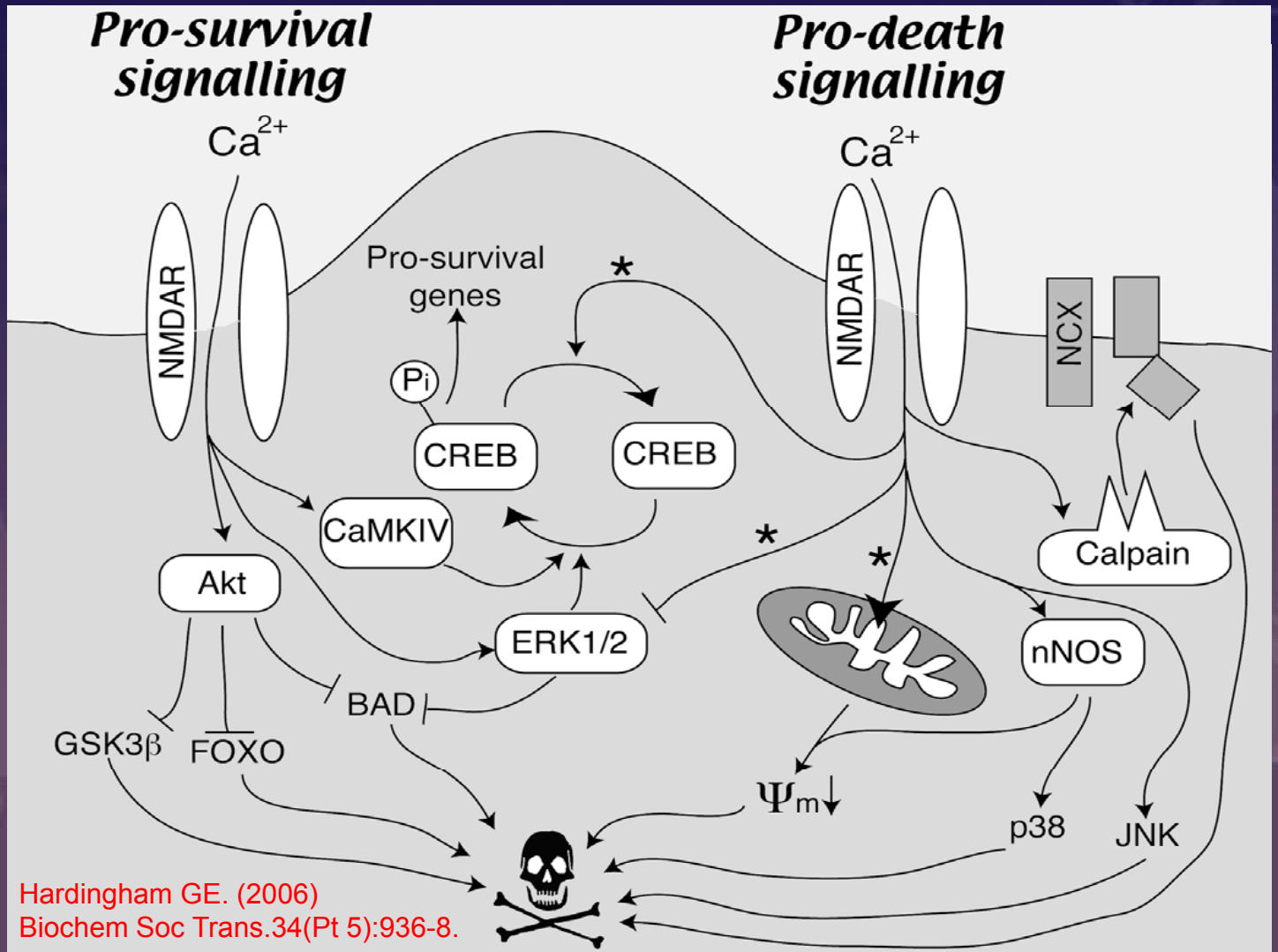
Alcohol
Angel dust (PCP)
Ketamine (Special K)

Anaesthetics
Anti-convulsants

Effects pronounced in utero & early post-natal

Stroke
Epileptic seizure
Mechanical trauma
Neurodegenerative diseases e.g. Alzheimers

Pro-survival and pro-death signalling from the NMDA receptor is extensively studied



Hardingham GE. (2006)
Biochem Soc Trans.34(Pt 5):936-8.

Pro-survival signalling from the NMDA receptor

Akt signalling is activated by NMDARs:

Zhang et al. (1998) JBC 273, 26596
Lafon Cazal et al. (2002) EJN 16, 575
Sutton & Chandler (2002) J. Neurochem 82, 1097

Gene expression mediated by CREB promotes survival:

Mantamadiotis et al. (2002). Nature Genetics 31, 47
Lonze et al. (2002). Neuron 34. 371

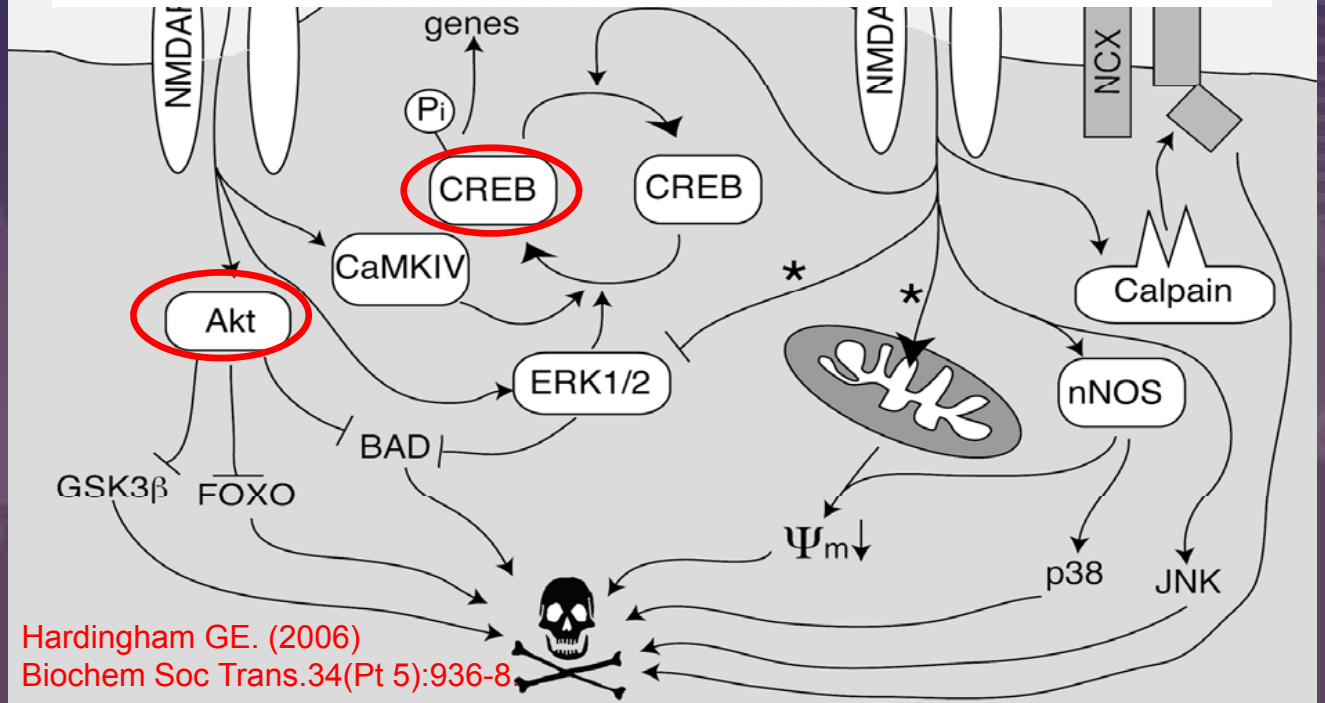
CREB is activated by synaptic NMDARs

Hardingham et al. Nat. Neuro 4, 565
Hardingham et al. Nat. Neuro 4, 261
Hardingham et al. Nat. Neuro 5, 405

The Journal of Neuroscience, April 27, 2005 • 25(17):4279–4287 • 4279

Nuclear Ca^{2+} and the cAMP Response Element-Binding Protein Family Mediate a Late Phase of Activity-Dependent Neuroprotection

Sofia Papadia,[1] Patrick Stevenson,[1] Neil R. Hardingham,[2] Hilmar Bading,[3] and Giles E. Hardingham[1]



Hardingham GE. (2006)
Biochem Soc Trans.34(Pt 5):936-8

Pro-death signalling from the NMDA receptor

ARTICLES nature medicine

A peptide inhibitor of c-Jun N-terminal kinase protects against excitotoxicity and cerebral ischemia

Tiziana Borsello[1], Peter G H Clarke[1], Lorenz Hirt[4], Alessandro Vercelli[2], Mariaelena Repici[2], Daniel F Schorderet[3], Julien Bogousslavsky[4] & Christophe Bonny[3]

Distinct Requirements for p38α and c-Jun N-terminal Kinase Stress-activated Protein Kinases in Different Forms of Apoptotic Neuronal Death*

Received for publication, March 2, 2004, and in revised form, May 24, 2004
Published, JBC Papers in Press, June 10, 2004, DOI 10.1074/jbc.M402353200

Jiong Cao‡, Maria M. Semenova‡, Victor T. Solovyan‡, Jiahuai Han§, Eleanor T. Coffey¶‖, and Michael J. Courtney‡**

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articles

Glutamate-induced neuron death requires mitochondrial calcium uptake

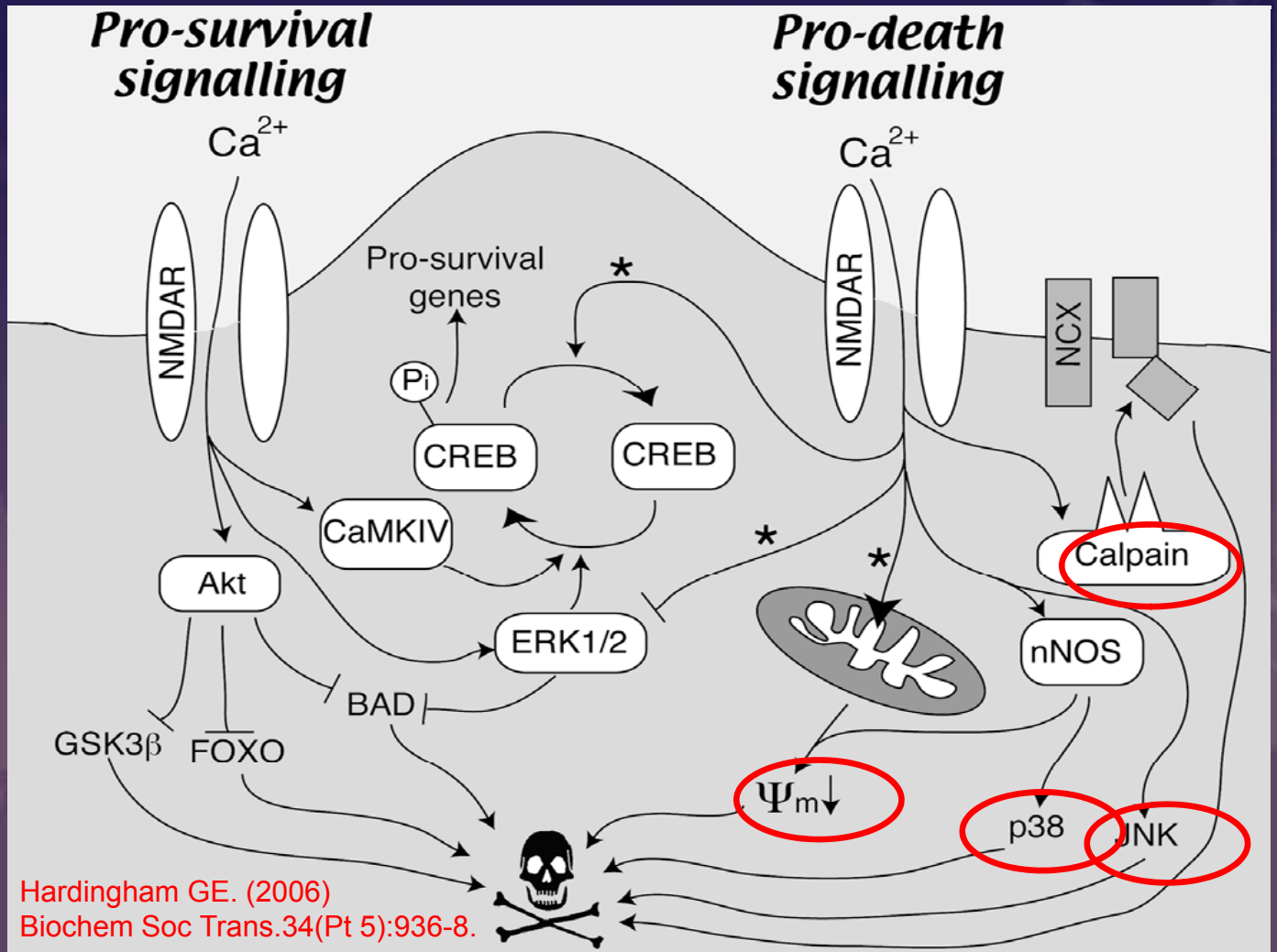
Amy K. Stout[1], Heather M. Raphael[1], Beatriz I. Kanterewicz[2], Eric Klann[2] and Ian J. Reynolds[1]

Cell, Vol. 120, 275–285, January 28, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.cell.2004.11.049

Cleavage of the Plasma Membrane Na^+/Ca^{2+} Exchanger in Excitotoxicity

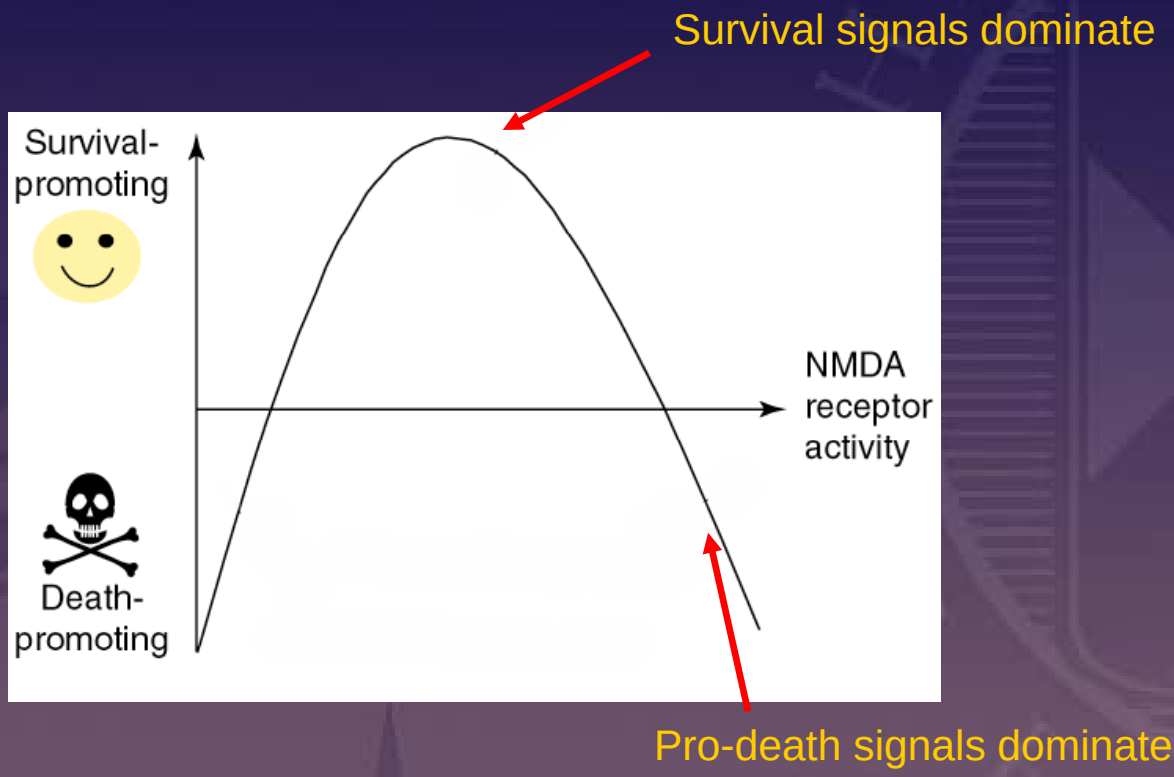
Daniele Bano,[1] Kenneth W. Young,[2] Christopher J. Guerin,[1] Ros LeFeuvre,[3] Nancy J. Rothwell,[3] Luigi Naldini,[4] Rosario Rizzuto,[5] Ernesto Carafoli,[6,7] and Pierluigi Nicotera[1,*]

cued neurons from excitotox
down-regulation of NCX by siR
ronal Ca^{2+} handling transform



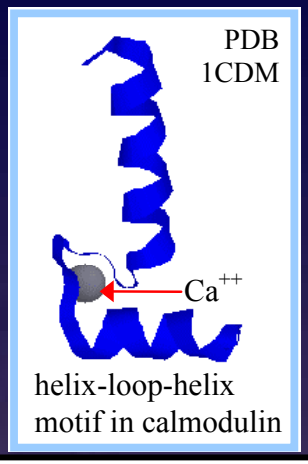
Hardingham GE. (2006)
Biochem Soc Trans.34(Pt 5):936-8.

Why do different signals dominate at different activity levels?



Pro-survival signaling may require lower [Ca^{2+}] than pro-death signals

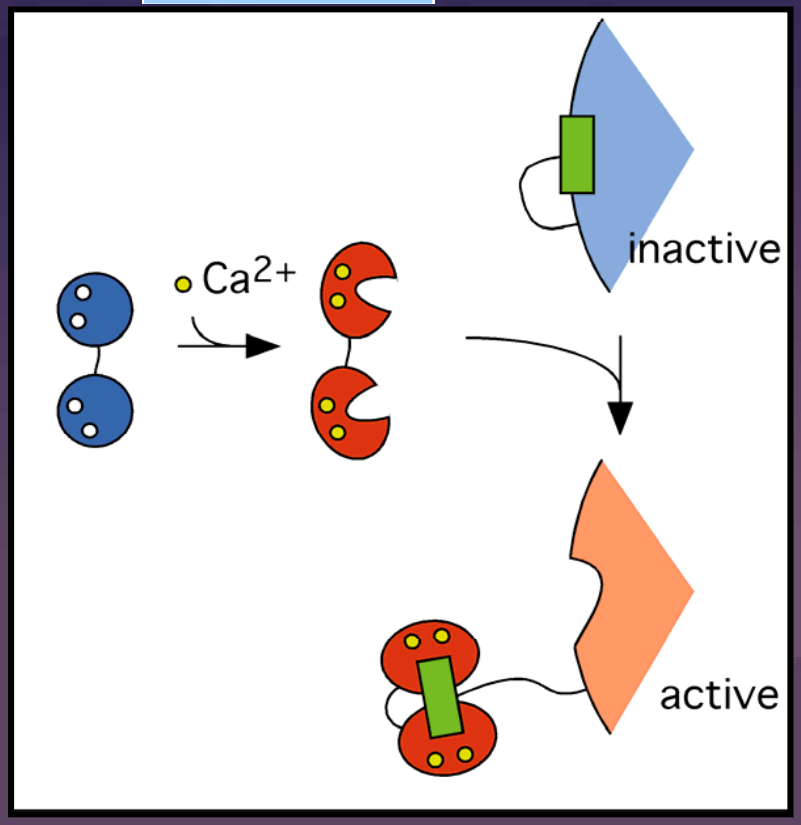
Effectors of survival are activated by Ca^{2+}/Calmodulin

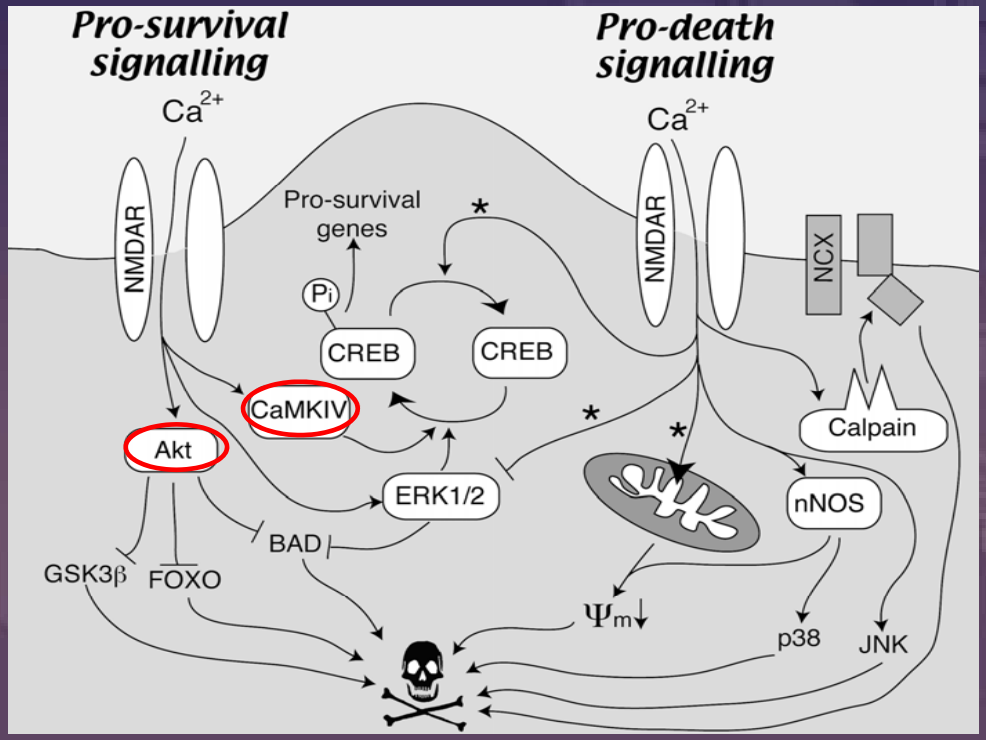


-Ca^{2+} binds to Calmodulin
-Ca^{2+}/Calmodulin then binds and activates target molecules

-Ca^{2+}/Calmodulin activates PI3K (upstream activator of Akt)
Joyal et al. (1998). JBC 272, 28183

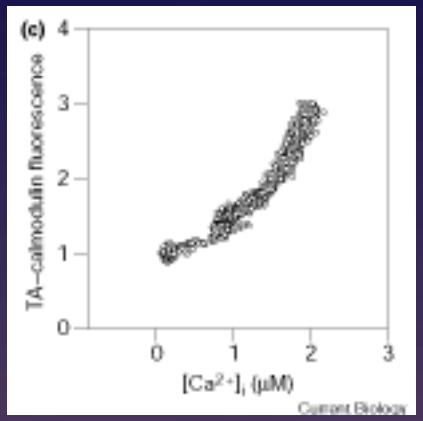
-Ca^{2+}/Calmodulin directly activates CaMKIV
(Tony Means and coworkers)





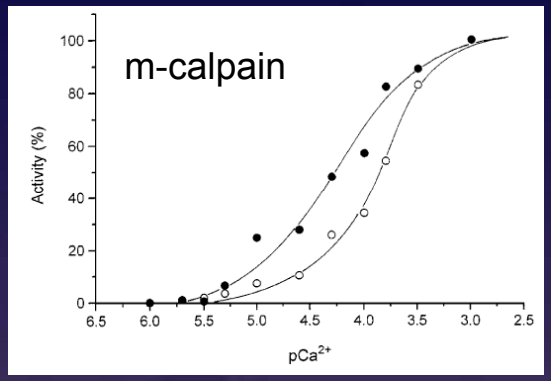
Ca^{2+} binds to Calmodulin appreciably at relatively low $[Ca^{2+}]$, particularly in the presence of target

Imaging calmodulin binding to Ca^{2+} in vivo

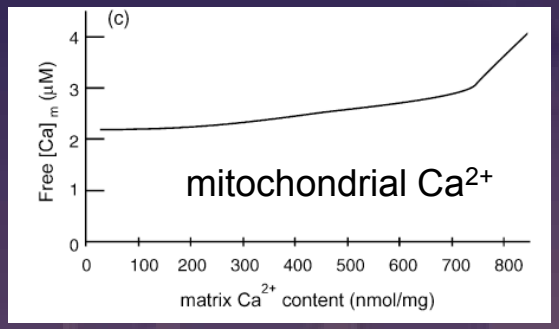


Torok et al. (1998). Current Biology 8, 692

Effectors of death are generally not activated by Ca^{2+}/Calmodulin, may require higher [Ca^{2+}]

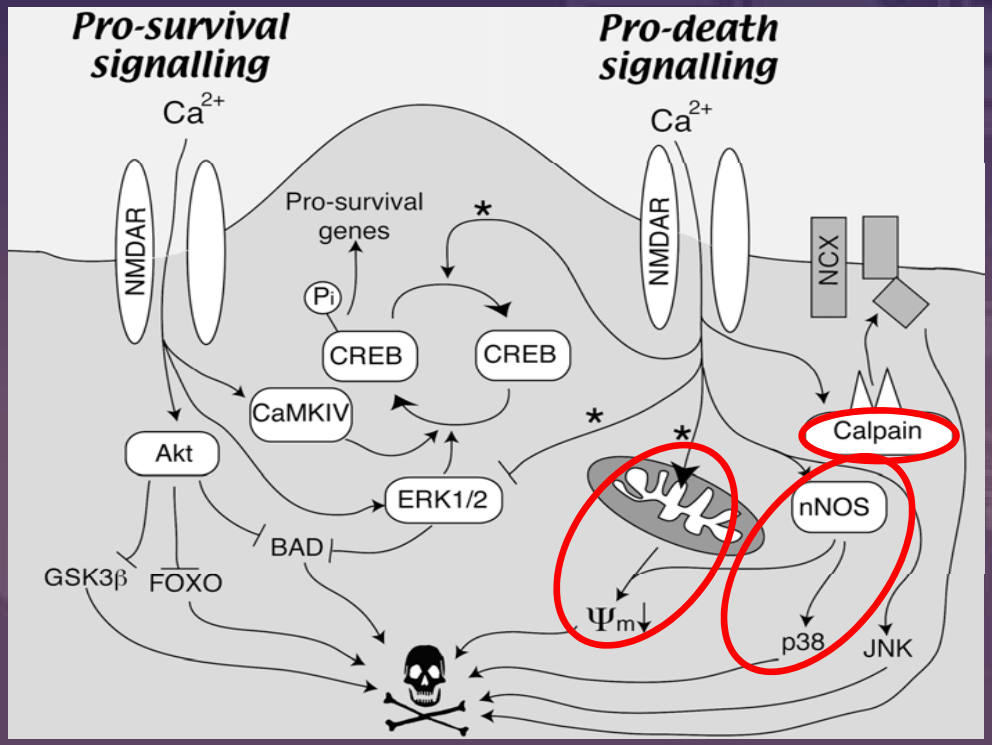


Tompa et al. (1996). JBC 271, 33161



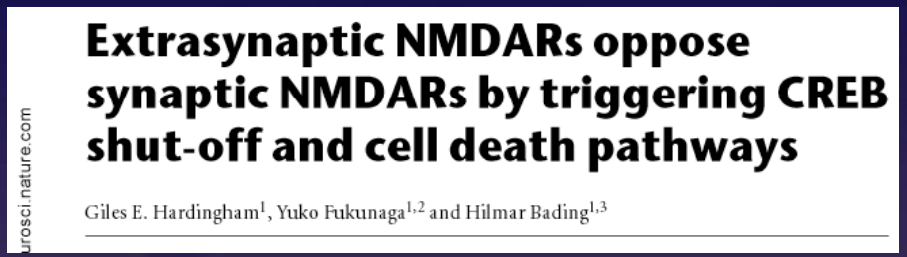
Nicholls (2005). Cell Calcium 38, 311

In the case of p38 activation, its upstream activator (nNOS) *is* Ca^{2+}/calmodulin dependent



Degree of NMDAR activation is not the only determinant of survival vs. death signaling…

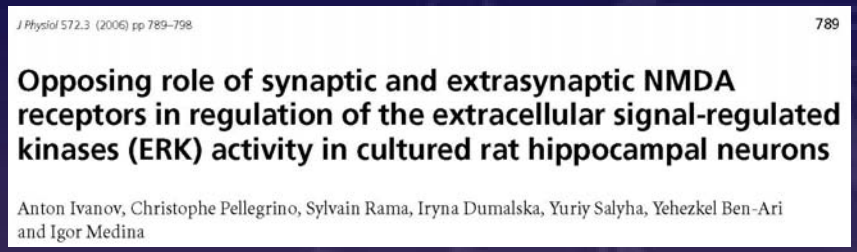
Synaptic NMDARs favour pro-survival signaling pathways
Extrasynaptic NMDARs favour pro-death signaling pathways



Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways

Giles E. Hardingham[1], Yuko Fukunaga[1,2] and Hilmar Bading[1,3]

Hardingham et al., (2002) Nature Neuroscience 5, 405

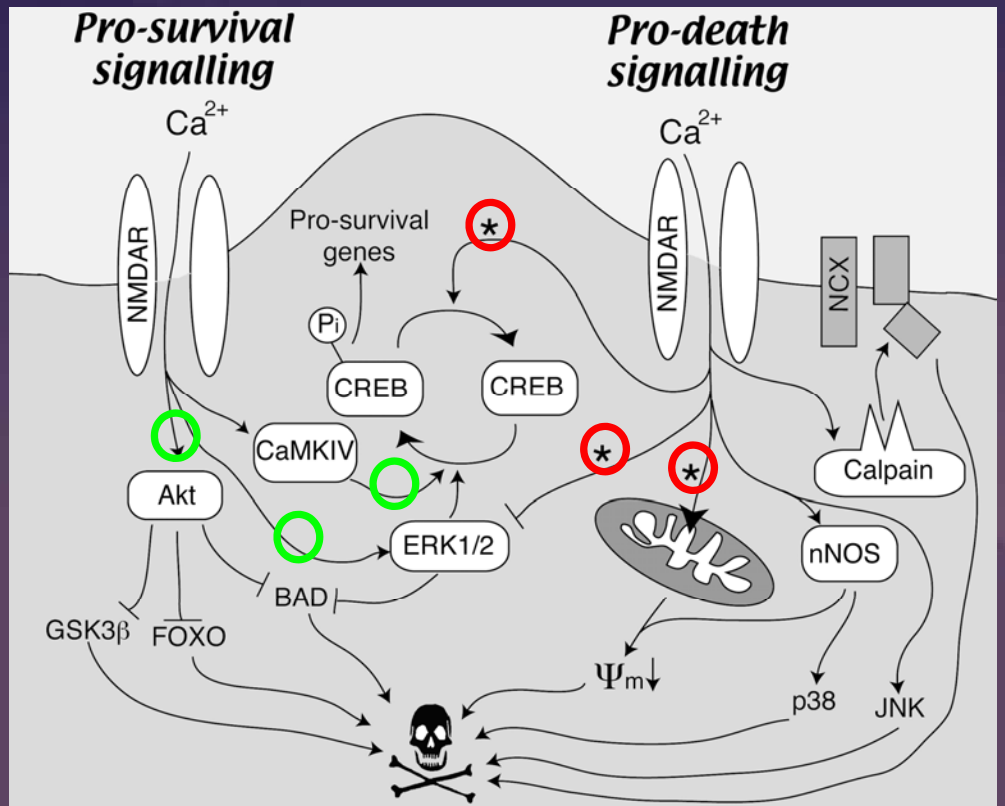


J Physiol 572.3 (2006) pp 789–798 789

Opposing role of synaptic and extrasynaptic NMDA receptors in regulation of the extracellular signal-regulated kinases (ERK) activity in cultured rat hippocampal neurons

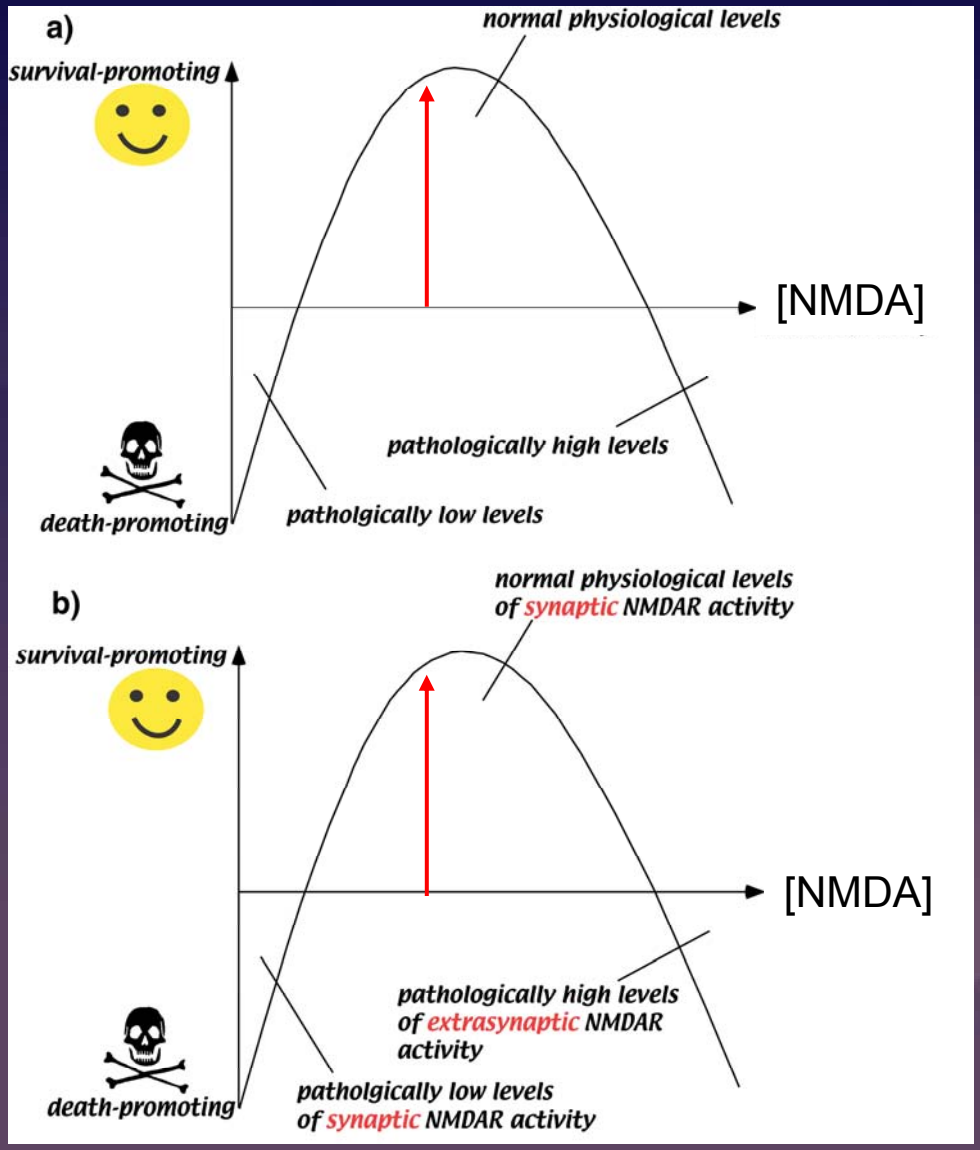
Anton Ivanov, Christophe Pellegrino, Sylvain Rama, Iryna Dumalska, Yuriy Salyha, Yehezkel Ben-Ari and Igor Medina

Ivanov et al., (2006) Journal of Physiology 572.3, 789



Extrasynaptic signaling dominates over synaptic signaling at high doses of NMDA

2 models-are they compatible?

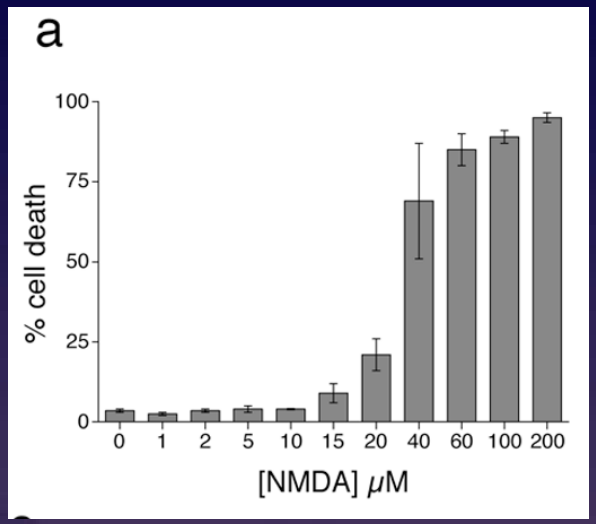


We know that dose of NMDA/glutamate matters, but so does receptor location…

How can pro-survival synaptic signaling dominate at low doses of NMDA?

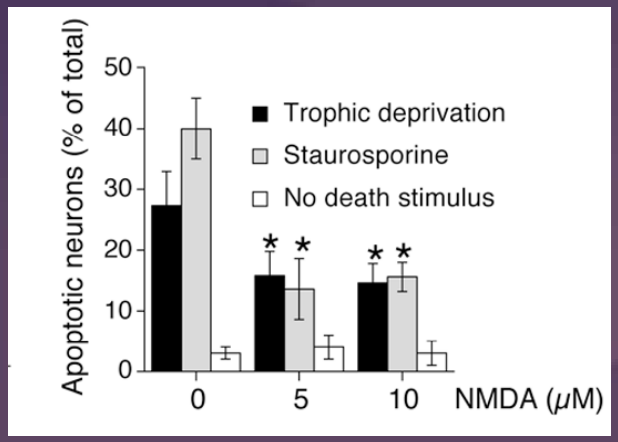
Strategy: analyse neuronal response to escalating doses of NMDA.

In DIV11 hippocampal neurons, 20 μM NMDA is at the threshold of toxicity

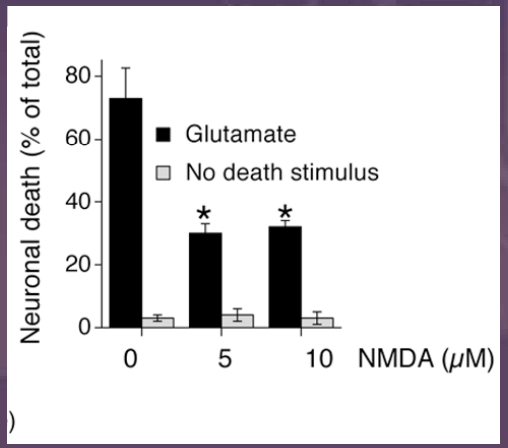


Tolerated doses of NMDA are neuroprotective:

Anti-apoptotic

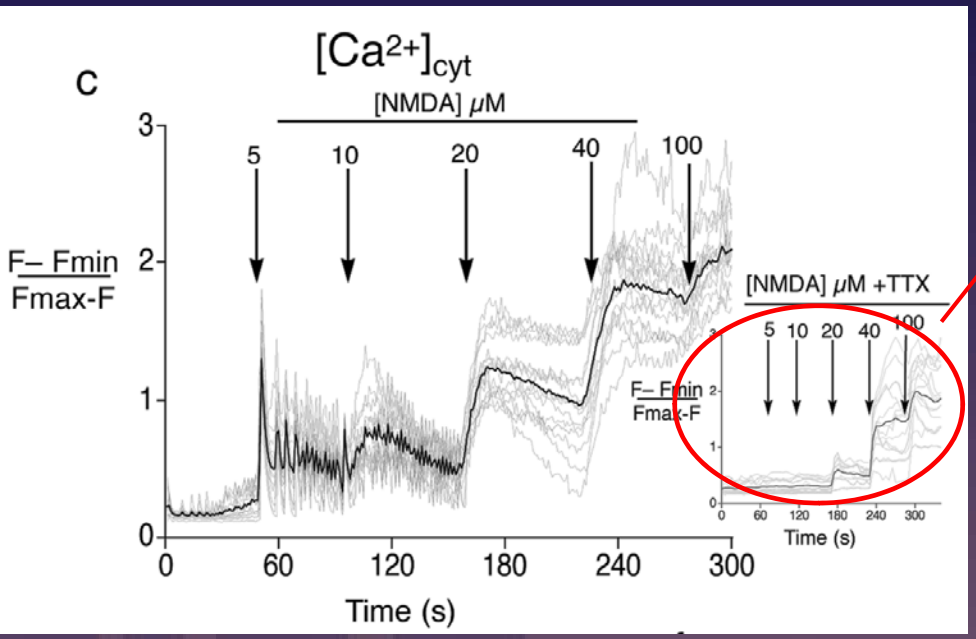


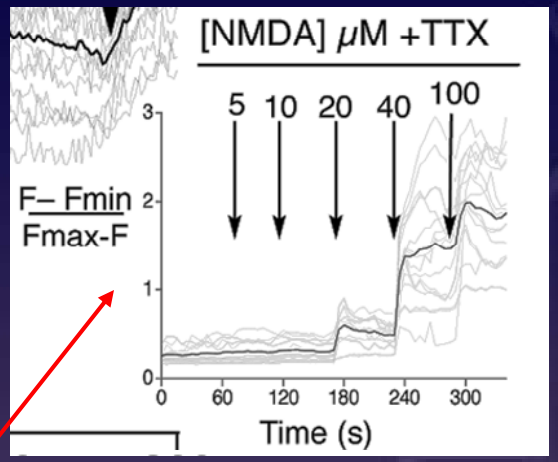
Anti-excitotoxic



Soriano et al. (2006). J. Neurosci 26, 4509

Qualitative differences in cytoplasmic Ca^{2+} transients as the toxicity threshold is crossed

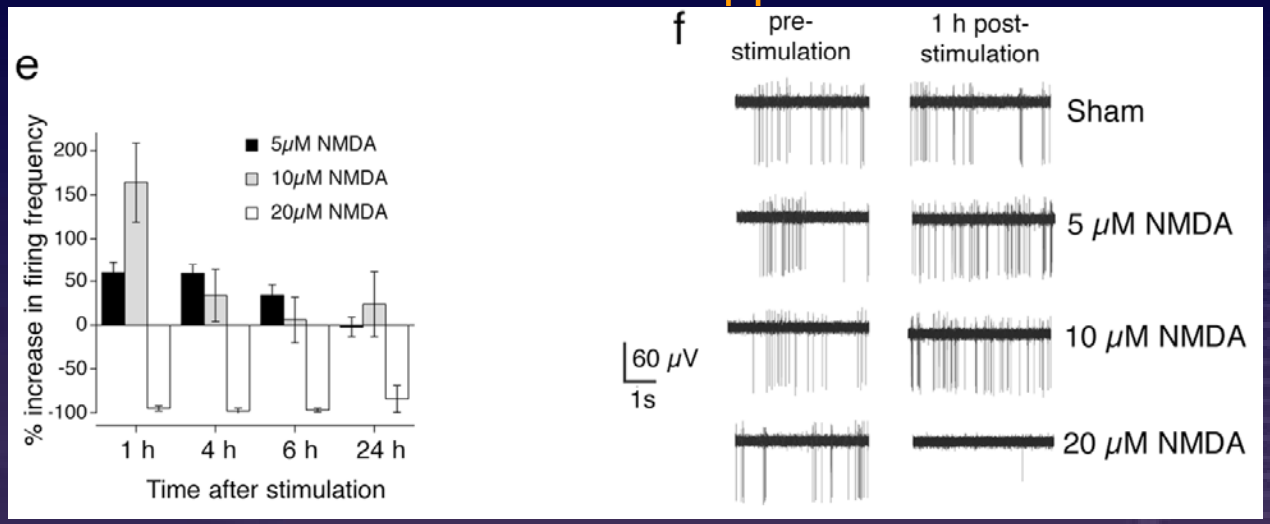




Ca^{2+} transients induced by protecting doses of NMDA are dependent on AP firing

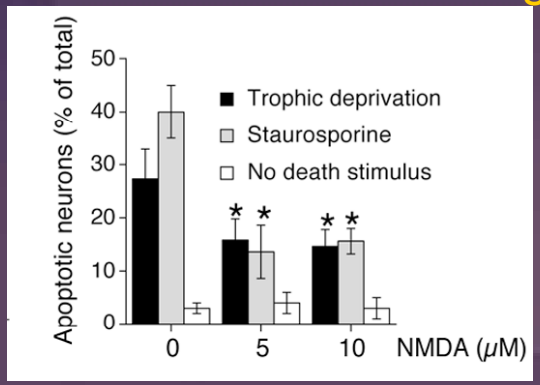
Soriano et al. (2006). J. Neurosci 26, 4509

Protecting doses of NMDA enhance firing activity, toxic doses suppress it

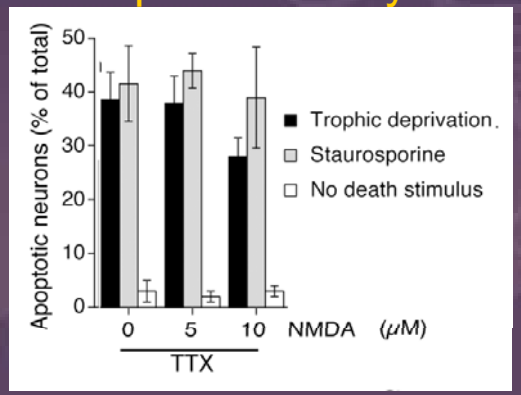


This firing results in preferential activation of synaptic NMDARs and is responsible for:

-signalling to Akt and CREB and the resulting neuroprotection by low NMDA

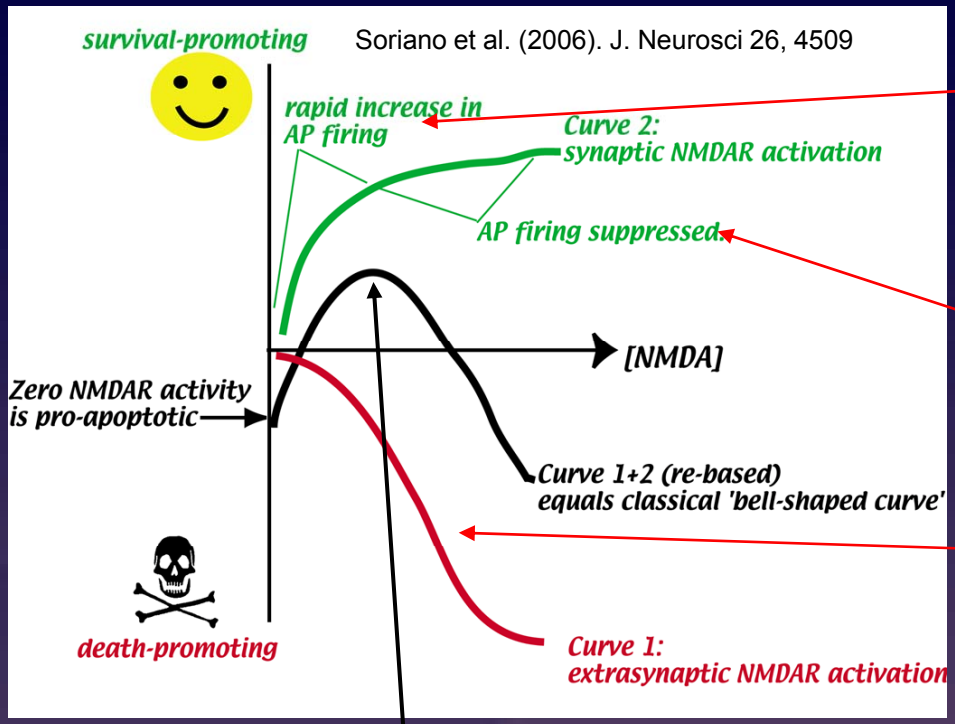


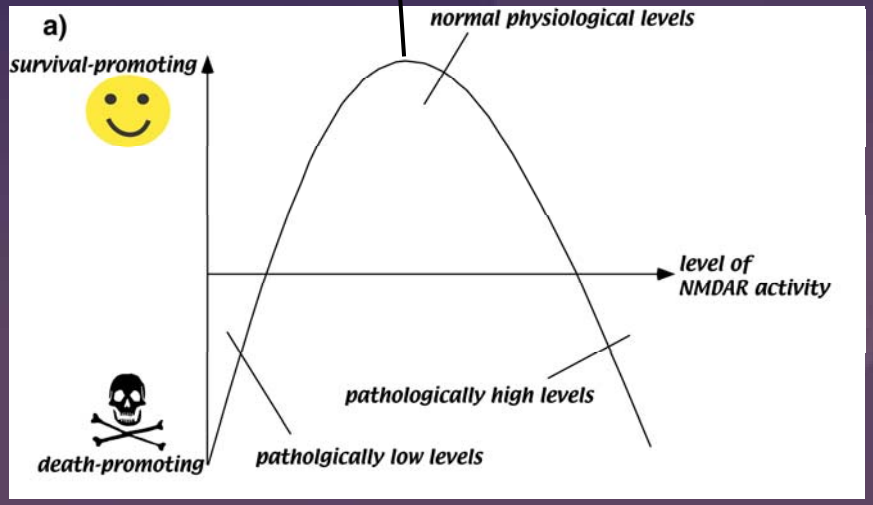
Firing allowed



Firing blocked

Soriano et al. (2006). J. Neurosci 26, 4509





-rapid initial enhancement of firing results in preferential activation of synaptic NMDARs

-as toxicity threshold is crossed AP firing stops, preferential trans-synaptic activation of synaptic NMDARs ceases

-extrasynaptic NMDAR signaling is able to dominate

-bell-shaped curve is the net effect of two antagonizing curves promoting survival and death respectively.

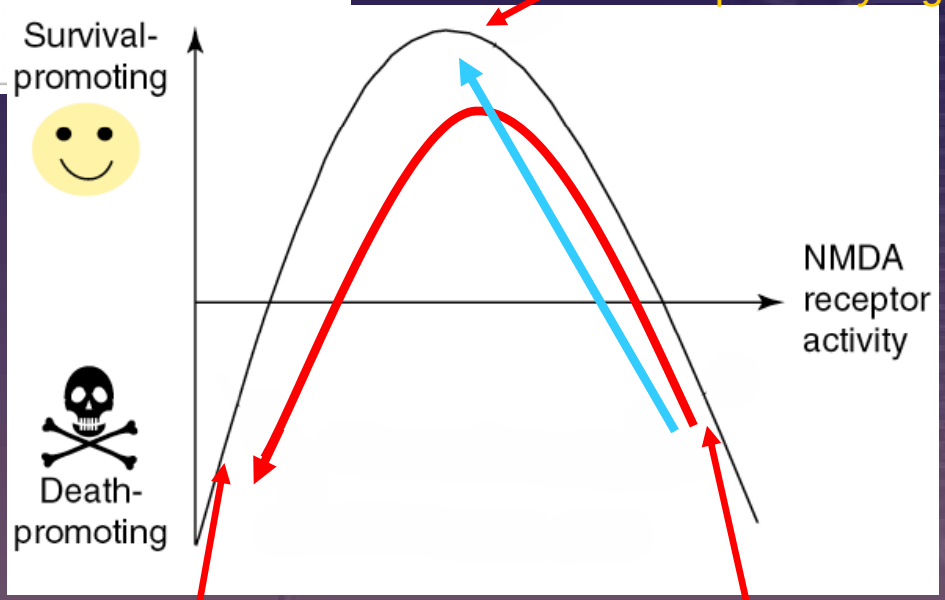
Clinical implications of the bell-shaped response

Why did NMDA receptor antagonists fail clinical trials for stroke and traumatic brain injury?

THE LANCET Neurology Vol 1 October 2002 http://neurology.thelancet.com

Chrysanthy Ikonomidou and Lechoslaw Turski

We ideally want to block pro-death signalling, while allowing survival signalling and normal NMDAR function



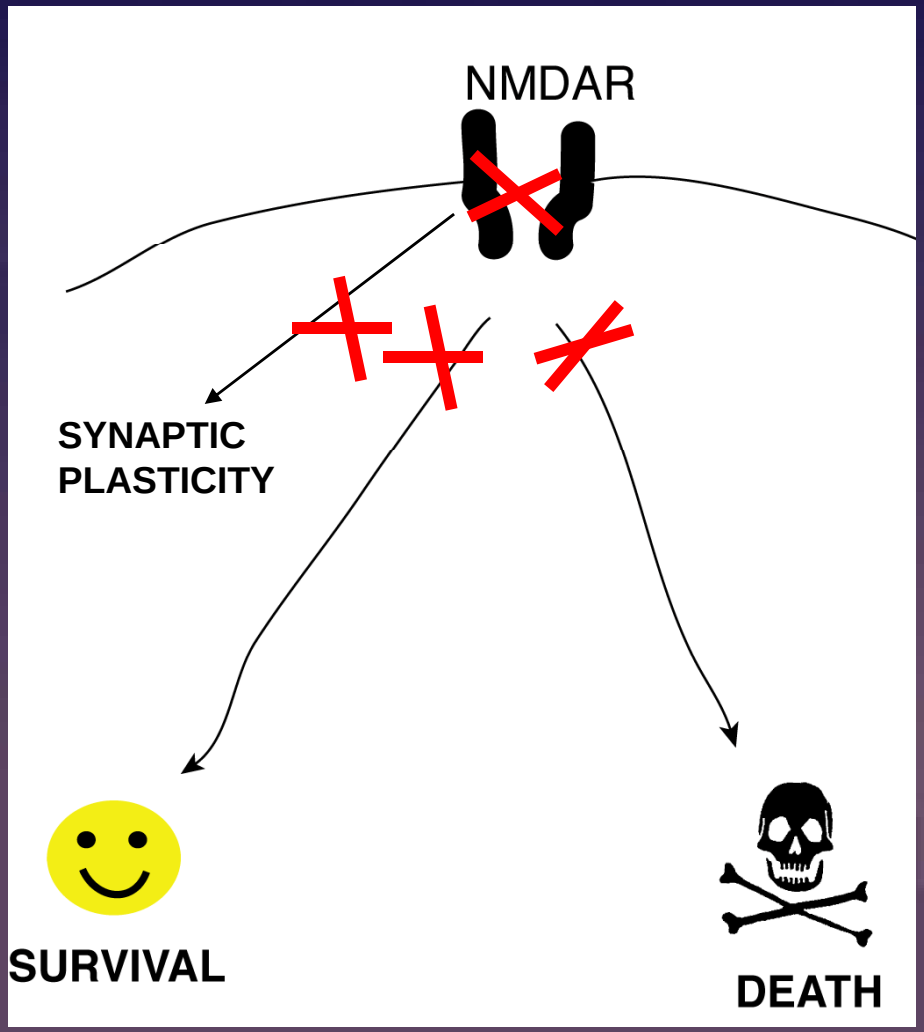
Synaptically evoked survival and plasticity signalling

Ischemia

Blockade of NMDARs

Hardingham and Bading (2003). TINS 26, 81.

Complete blockade of the NMDA receptor is not desirable- *can just pro-death signalling be inhibited?*



Pro-death signalling pathways downstream of the NMDA receptor should be targeted….