



Centre for Integrative Physiology

Research Briefings

NMDA receptor control of neuronal survival and death

IN CENTRAL NEURONS, CA²⁺ ENTRY THROUGH THE NMDA-TYPE GLUTAMATE RECEPTOR (NMDAR) IS A MAJOR SOURCE OF SYNAPTICALLY-EVOKED CA²⁺ TRANSIENTS AND DIRECTLY AFFECTS NEURONAL SURVIVAL/DEATH: WHILE TOO MUCH NMDAR ACTIVITY IS HARMFUL, SO IS TOO LITTLE . UNDERSTANDING THE MECHANISMS BEHIND THIS DICHOTOMOUS SIGNALLING IS AN AREA OF MOLECULAR NEUROSCIENCE WITH DIRECT CLINICAL IMPLICATIONS. THE RESEARCH OF MY GROUP FOCUSES ON UNDERSTANDING THE SIGNALLING EVENTS THAT ARE TRIGGERED BY NMDAR ACTIVITY, AND THEIR IMPACT ON NEURONAL SURVIVAL AND DEATH.

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BACKGROUND

In the developing CNS, apoptosis is crucial for the elimination of unwanted or inappropriately connected neurons. However, pathological apoptosis can take place following trauma such as oxidative stress or hypoxia/ischemia. In the mature CNS neurons are less vulnerable to apoptosis, but the activation of apoptotic biochemical cascades (e.g. caspases) are associated with certain neurodegenerative diseases, such as Alzheimer's. Apoptosis is also a feature of acute trauma, including in the ischemic penumbra and following mechanical trauma. Given the relevance of apoptosis to CNS development and pathophysiology, it is important to understand endogenous signals that suppress apoptosis: this may lead to therapeutic targets and an understanding of pathological process.

Survival of many neuronal types rely on physiological electrical activity, as evidenced by the deleterious effects of blocking activity *in vivo* and *in vitro*. Activity-dependent intracellular Ca²⁺ transients are important mediators of this neuroprotection, and NMDARs are a key source of such transients. Blockade of synaptic NMDAR activity promotes neuronal apoptosis, indicating a pro-survival role for NMDARs. Neurons are particularly vulnerable to NMDAR blockade

during post-natal development, however, in the adult rat brain NMDAR antagonists can trigger neurodegeneration and exacerbate apoptosis and prevent survival of new neurons in the dentate gyrus.

As well as having a pro-survival role, the NMDAR has long been known to be able to promote neuronal death. During an ischemic episode, glutamate levels build up which induce excessive activation of NMDARs. Too much NMDAR activity may also contribute to neuronal loss in Alzheimer's and Huntington's disease.

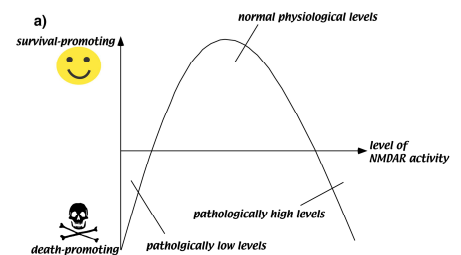


Fig. 1. Responses of neurons to NMDAR activity follow a bell-shaped curve: both too much and too little is potentially harmful. See TINS 26, 81-89

It would be desirable to be able to block pro-death NMDAR signaling in pathological conditions, without affecting pro-survival signaling or indeed synaptic plasticity, many forms of which are mediated by NMDARs. This requires a thorough knowledge of the signals which underlie both protective and destructive signaling by the NMDAR. Our work falls under three themes:

ANTI-APOPTOTIC SIGNALLING AFFORDED BY NMDAR ACTIVITY

Physiological patterns of synaptic NMDAR activity are strongly neuroprotective, the basis for which is unclear. Synaptic NMDAR activity induces signalling pathways which activate new gene expression as well as triggering the post-translational modification of existing proteins. We aim to understand the molecular events that underlie activity-dependent protection, including the role of gene expression changes. Our studies focus on key components of the intrinsic apoptosis machinery which are master regulators of neuronal apoptosis. An understanding of the brain's natural "neuroprotective" mechanisms is important, since malfunction of these may contribute to neurodegeneration in a variety of brain disorders (Alzheimer's, ALS, Huntington's), and also neurodevelopmental disorders associated with NMDAR inhibition (e.g. Foetal Alcohol Syndrome).

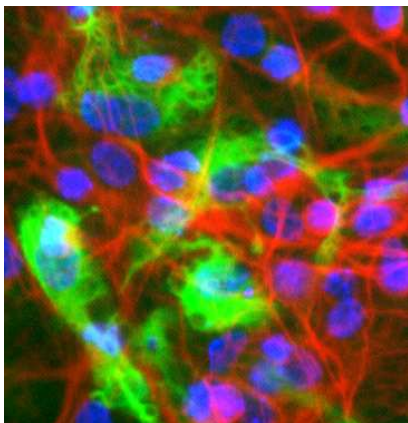


Fig. 2. A co-culture of mouse cortical neurons with astrocytes derived from human foetal stem cells designed to investigate protection of neurons by astrocytic signaling.

REGULATION OF ANTIOXIDANT DEFENCES BY ENDOGENOUS AND EXOGENOUS MECHANISMS

Intrinsic antioxidant defences are important for neuronal longevity. However, little is known about whether they are subject to dynamic regulation, or are a fixed function of neuronal type/age. This is an important question: any regulation could influence biological ageing, or progression of neurodegenerative disorders associated with oxidative damage. We are studying the influence of synaptic NMDAR activity on antioxidant enzymic systems and how it influences the vulnerability of neurons to oxidative insults. We are also investigating ways by which neuronal antioxidant defences can be artificially boosted by pharmacological compounds, including those which target astrocyte-neuronal signaling. Such interventions may delay progression of pathological conditions associated with oxidative damage, which include many neurodegenerative diseases.

DIFFERENCES BETWEEN PROTECTING AND TOXIC EPISODES OF NMDAR ACTIVITY

An important area of our work is aimed at understanding what parameters determine whether an episode of NMDAR activity promotes neuroprotection, or cell death, other than simply the magnitude of Ca^{2+} influx. One important determinant of the nature of NMDAR signaling is its location: we found that extrasynaptic NMDARs are coupled preferentially to death, while synaptic NMDARs promote survival. The basis for this is not clear and is under investigation. We are also examining the relative importance of NR2 subunit composition, since the C-termini of

major NR2 subunits NR2A and NR2B are very different and have the capacity to differentially associate with signaling molecules which may influence neuronal survival and death.

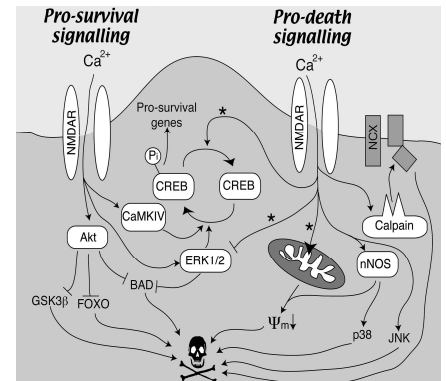


Fig. 3. A schematic illustrating the pro-survival and pro-death signaling cascades triggered by NMDA receptor activity.

Selected references:

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