Pro-survival signalling from the NMDA receptor

Published in final edited form as:
Biochem Soc Trans. 2006 November ; 34(Pt 5): 936–938. doi:10.1042/BST0340936.

Pro-survival signalling from the NMDA receptor

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Abstract

Ca^{2+} influx through the NMDA subtype of ionotropic glutamate receptors plays a Jekyll and Hyde role in the mammalian central nervous system. While it mediates excitotoxic death triggered by stroke and other acute trauma, there is growing evidence that physiological levels of NMDA receptor activity promote survival. Understanding the mechanisms that underlie these opposing effects may lead to strategies to selectively block pro-death signalling, which could have considerable clinical benefits.

Keywords

Excitotoxicity; neuroprotection; apoptosis; CREB; Extrasynaptic; Calcium signalling

Introduction

N-Methyl-D-Aspartate receptors (NMDARs) are cation channels, gated by glutamate, the main excitatory neurotransmitter in the mammalian central nervous system (CNS). As well as passing Na^{+}, NMDARs also pass Ca^{2+}, which mediates most of the physiological consequences of NMDAR activity. NMDARs are found at the synapse, but also at extrasynaptic locations, where their physiological role is ill-defined. NMDARs are essential mediators of synaptic plasticity, as well as mediating aspects of development and synaptic transmission. However, NMDARs cause cell death in many neuropathological scenarios when excessively activated. Disturbance of extracellular glutamate levels, acting on NMDARs, is a primary cause of neuronal death following acute trauma such as stroke, mechanical trauma, and seizure [1].

NMDAR-dependent survival signalling

In contrast to the deleterious effects of *excessive* NMDAR activity, physiological patterns of synaptic NMDAR activity actually promote neuronal survival. Elimination of NMDAR activity *in vivo* causes widespread apoptosis in the developing CNS, exacerbates ongoing neurodegeneration [2], and blocks ischemic preconditioning. The pro-survival effects of NMDAR activity have been recapitulated in neuronal cultures as well [3, 4], enabling scientists to study the signalling events responsible. Key among them is the PI3K-Akt cascade, strongly activated by NMDARs in many, but not all neuronal types [4]. The PI3K-Akt pathway can evoke neuroprotection via several routes, including phosphorylating/inactivating both glycogen synthase kinase-3β, and the pro-apoptotic bcl-2 family member BAD [5]. Akt also phosphorylates and triggers nuclear export of the FOXO subfamily of forkhead transcription factors, which control the expression of pro-death genes such as *FasL*, and *Bim* [5]. Stimulation of NMDAR signalling promotes PI3K-dependent FOXO export and GSK3-beta phosphorylation, while GSK3-beta inhibitors can mimic the

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neuroprotective effect of low levels of NMDA [6]. Synaptic NMDAR signalling also activates the Ras-ERK1/2 cascade [7] , with pro-survival consequences which including CREB activation [7], BAD inactivation, and antagonizing GSK3β-induced apoptosis [4].

Synaptic NMDAR-dependent Ca^{2+} transients trigger a number of transcriptional changes which mediates long-lasting neuroprotection [10]. An important mediator of activity-dependent gene expression is the transcription factor, cAMP response element (CRE) binding protein (CREB) [8]. Synaptic NMDAR activity induces CRE-dependent gene expression [9] by a mechanism discussed elsewhere [3], and is causally linked to the long-lasting phase of activity-dependent neuroprotection [10]. Induction of this long-lasting phase requires Ca^{2+} transients to invade the nucleus, consistent with the known role for nuclear Ca^{2+} in CREB activation via CaM Kinase IV [3]. The identity of the CREB-regulated gene(s) responsible for long-lasting protection against apoptosis is currently not well understood. The large number of known CRE-containing genes make it unlikely that a single gene is responsible. The upregulation of CREB targets involved in responses to oxidative stress (e.g. *Sod2*) or in inhibiting apoptosis (e.g. *Bcl2*) are implicated, although the pro-survival neurotrophin *Bdnf* is supported by the most evidence [4].

NMDAR-dependent cell death

Pathological activation of NMDARs, with consequent intracellular Ca^{2+} deregulation, is the primary cause of neuronal death following acute excitotoxic trauma such as ischemia [1]. In cultures, neurons respond to high levels of NMDAR activity by undergoing delayed Ca^{2+} deregulation which precedes and predicts excitotoxic cell death. There are several fundamental mechanisms implicated in NMDAR-dependent cell death, including cleavage of the the plasma membrane Na+/Ca^{2+} exchanger (NCX) by the Ca^{2+}-dependent protease calpain [11], and mitochondrial dysfunction brought about by excessive Ca^{2+} uptake through the uniporter [12]. Furthermore, overactivation of the Ca^{2+}-dependent nNOS by NMDAR activity has toxic downstream effects, including p38 map kinase signalling, mitochondrial dysfunction and TRPM channel activation [1].

What determines whether an episode of NMDAR activity is neuroprotective or excitotoxic?

The simplest answer is the magnitude of activation (intensity or duration). Response of neurons to NMDA or glutamate dose follows a bell-shaped curve ([3] and references therein): while low levels are protective, higher levels are toxic. This fact implies that the Ca^{2+} effectors of survival have considerably lower requirements for Ca^{2+} than the death effectors. Thus, the [Ca^{2+}] threshold for activating pro-survival signalling by PI3K, ERK1/2 and CaMKIV-CREB must be lower than that which triggers toxic levels of calpain activation, mitochondrial uptake or NO production. This idea sits well with the known low Ca^{2+} affinity of certain potential death effectors, such as m-calpain and the mitochondrial uniporter. Indeed, when exposing cortical neurons to escalating levels of NMDA, only toxic doses evoke sustained increases in mitochondrial Ca^{2+} and loss of mitochondrial membrane potential [6].

In addition to stimulus intensity, receptor location may play a role. We showed that extrasynaptic NMDAR activity promotes inactivation of CREB and early excitotoxic events such as mitochondrial depolarisation [9]. In contrast, similar Ca^{2+} loads evoked via synaptic NMDARs strongly activate CREB, do not disturb mitochondrial function, and are neuroprotective [9]. Interestingly, extrasynaptic NMDARs are also coupled to inactivation of the ERK1/2 pathway, antagonizing the activation mediated by synaptic NMDARs [13].

Fig. 1 shows an overview of the various NMDAR-induced pro-death and pro-survival signalling events.

CREB dephosphorylation by extrasynaptic NMDAR activity is generally dominant over CREB activating signals [9], possibly by activating a CREB phosphatase such as PP1. However, in neurons exposed to low, protecting doses of NMDA, synaptic NMDARs are preferentially activated due to the NMDA causing a dramatic increase in action potential firing [6]. This enhanced firing mediates the NMDA-induced pro-survival signalling to Akt, ERK1/2 and CREB [6]. In contrast, higher, toxic doses of NMDA do not favour synaptic NMDAR activation because they strongly suppress firing rates [6], due presumably to chronic depolarisation. While chronic exposure of neurons to glutamate and activation of extrasynaptic NMDARs is unlikely to occur under normal physiological conditions, it will occur under pathological conditions such as brain injury, or during hypoxic/ischemic insults where glutamate transporters operate in reverse]. Consistent with this, CREB dephosphorylation has been observed in *in vivo* stroke [3].

Clinical implications and concluding remarks

The pro-survival role of physiological synaptic NMDAR signalling, particularly prominent during CNS development, points to the dangers of NMDAR antagonism during this period in humans, which extends to several years post-natal [2]. Many paediatric/obstetric anaesthetics and anticonvulsants (in)directly reduce NMDAR activity, while the dangers of *in utero* exposure to NMDAR-antagonistic recreational drugs such as ketamine, phencyclidine and ethanol cannot be overstated [2].

In treating excitotoxic trauma such as stroke, trials of NMDAR antagonists have failed due to poor tolerance and efficacy [14], likely due to inhibition of physiological NMDAR-mediated processes such as plasticity and pro-survival signalling. It is becoming clear that the optimal therapeutic strategy should be to block the excitotoxic consequences of NMDAR activation, while sparing pro-survival signals. Thus, targeting of calpains or nNOS, or specific uncoupling of the NMDAR from pro-death signalling cascades may prove more effective than global antagonists [1, 15].

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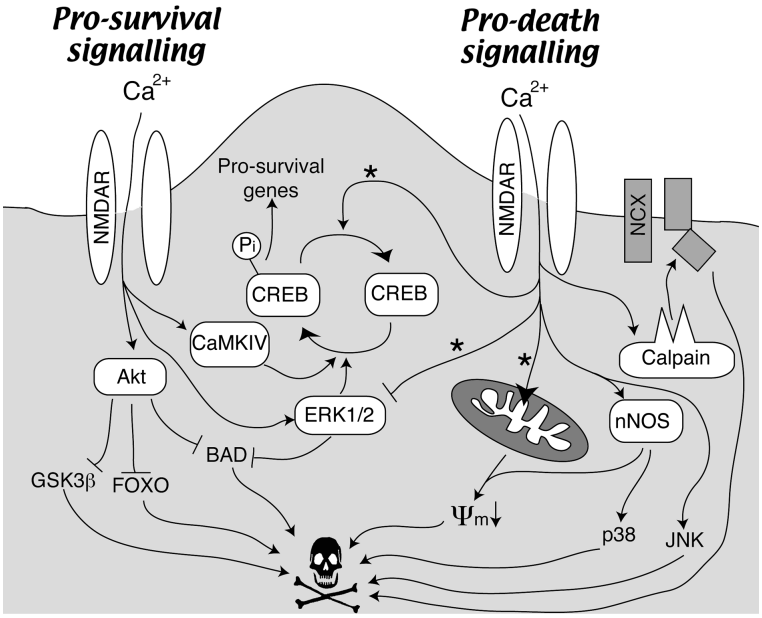

Fig. 1. Pro-survival and-death signaling from the NMDA receptor (see text for details)

Note that pro-death signaling generally requires more intense activation of NMDARs than pro-survival signalling. Also, the pathways marked with a * are favoured by extrasynaptic NMDAR activation [3, 9]. Ψm denotes mitochondrial membrane potential.