PRO-SURVIVAL AND PRO-DEATH MOLECULAR EVENTS DOWNSTREAM OF NMDA RECEPTOR ACTIVITY

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Research Abstract

NMDA receptors are a subtype of ionotropic glutamate receptor with an important role in the physiology and pathophysiology of central neurons. Inappropriate levels of Ca\(^{2+}\) influx through the NMDA receptor can contribute to neuronal loss in acute trauma such as ischemia and traumatic brain injury, as well as certain neurodegenerative diseases such as Huntington’s. However, normal physiological patterns of NMDA receptor activity can promote neuroprotection against both apoptotic, oxidative and excitotoxic insults. As a result, NMDA receptor blockade can promote neuronal death outright or render them vulnerable to secondary trauma.

There is a growing knowledge of the molecular mechanisms underlying both the neuroprotective and neurodestructive effects of NMDA receptor activity, as well as the factors that determine whether an episode of NMDA receptor activity is harmful or beneficial. The coordinated transcriptional changes that underlie NMDAR-dependent neuroprotective effects will be discussed, both in terms of the molecular mechanisms by which they are initiated, as well as the basis for their effect. Furthermore, we will discuss the factors that determine whether an episode of NMDA receptor activity is toxic to neurons, including synaptic vs. extrasynaptic localization, and subunit-specific signalling by the NR2 C-terminus. Increased understanding in these areas of NMDAR signalling is leading to new potential therapeutic targets and strategies for excitotoxic disorders, as well as a growing appreciation of the harmful consequences of NMDA receptor blockade.

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