NEUROPHYSIOLOGY

Via ferrata — the iron way

Overactivation of NMDA (*N*-methyl-D-aspartate) receptors causes neurotoxicity, with calcium dysregulation and oxidative stress being proposed as possible downstream mechanisms. Now, a newly identified signalling pathway links NMDA receptor activation to the uptake of iron — which is required for numerous physiological processes but is toxic in excess — suggesting that disruption of iron homeostasis might also contribute to NMDA-mediated neurotoxicity.

Following NMDA receptor activation, the resulting influx of calcium stimulates the formation of a protein complex containing neuronal nitric oxide synthase (nNOS), the adaptor protein CAPON and the GTPase DEXRAS1. The close proximity of nNOS and DEXRAS1 leads to *S*-nitrosylation and activation of DEXRAS1 by nitric oxide (NO). However, the physiological function of active DEXRAS1 has remained unknown.

To elucidate the downstream targets of DEXRAS1, Cheah and colleagues performed yeast two-hybrid experiments using full-length DEXRAS1 as bait. They identified the peripheral benzodiazepine receptor-associated protein (PAP7), which interacts with the divalent metal transporter (DMT1), as a potential interactor of DEXRAS1. Co-immunoprecipitation experiments using antibodies to the three proteins confirmed these interactions and revealed the existence of a ternary complex containing all three.

Because of the known role of DMT1 in iron uptake, the authors investigated the possibility that DEXRAS1 and PAP7 might be involved in iron homeostasis. Co-expression of both proteins in HEK cells (which express endogenous DMT1) led to an enhancement of iron uptake that was considerably greater than the modest enhancement seen when DEXRAS1 alone was overexpressed.

Having identified a physiological role for DEXRAS1 and PAP7 in iron uptake, the authors went on to determine whether NO/nNOS and NMDA receptors act upstream of DEXRAS1 in the same pathway. In PC12 cells (which express DEXRAS1, PAP7 and DMT1 endogenously), the application of NO donors led to an increase in iron uptake, an effect that was abolished by RNA interference-mediated depletion of DEXRAS1 or mutation of the nitrosylation site. Furthermore, NMDA treatment of mouse primary cortical neurons increased iron uptake in a concentration-dependent manner, an effect that was blocked by the NMDA receptor antagonist MK801 and in neurons from mice lacking nNOS.

Because iron is toxic in excess, this raised the interesting possibility that a build up of intracellular iron might be involved in the neurotoxicity associated with overactivation of NMDA receptors. Supporting this, a dose of NMDA that killed more than 90% of primary cortical neurons in an untreated culture had virtually no effect when cells were pretreated with a selective iron chelator.

These findings reveal a novel signalling pathway that connects neurotransmission with iron uptake, and that seems to be operative in the pathophysiological actions of glutamate. Because a number of neurodegenerative diseases are associated with both iron accumulation and excessive NMDA receptor activation, it is tempting to speculate that members of this pathway represent viable targets for the treatment of those diseases.

Daniel McGowan

ORIGINAL RESEARCH PAPER Cheah, J. H. *et al.* NMDA receptor-nitric oxide transmission mediates neuronal iron homeostasis via the GTPase Dexras1. *Neuron* **51**, 431–440 (2006)