GLIA

NMDA receptors on oligodendrocytes

The prevailing view that white matter oligodendrocytes lack NMDA (*N*-methyl-D-aspartate)-type glutamate receptors seems to have been wrong, according to three papers published recently in *Nature*. The reports provide compelling evidence for the involvement of oligodendrocyte NMDA receptors in glutamate-mediated damage to these cells in injury and disease.

Damage to oligodendrocyte processes — the structures responsible for myelination — leads to functional impairments in a wide range of conditions, including cerebral palsy, spinal cord injury, multiple sclerosis and stroke. Unlike neurons, which are susceptible to NMDA receptor-mediated damage, white matter oligodendrocytes were previously thought to be damaged by glutamate acting on AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and kainate receptors alone. Three groups now challenge this view by showing that a distinct form of NMDA receptor is present on the processes of oligodendrocytes.

Káradóttir *et al.* recorded from rat precursor, immature and mature oligodendrocytes in the white matter of the cerebellum and the corpus callosum. These cells showed glutamate- and NMDA-evoked inward currents that were inhibited by NMDA receptor antagonists. Oligodendrocyte NMDA receptors were less susceptible to Mg^{2+} block than neuronal receptors, allowing significant current to be generated even at the cell resting potential. Simulating ischaemia generated inward currents that were mediated, in part, by an action of glutamate at oligodendrocyte NMDA receptors.

Salter and Fern looked at developing oligodendrocytes in the mouse optic nerve by specifically expressing green fluorescent protein (GFP) in these cells. Oxygen and glucose deprivation led to a rapid Ca^{2+}-dependent loss of oligodendrocyte processes. Blocking AMPA and kainate receptors prevented the loss of cell bodies, but had no effect on the detachment and disintegration of oligodendrocyte processes, whereas a selective NMDA receptor antagonist largely prevented injury to processes.

Micu *et al.* measured changes in the concentration of Ca^{2+} in the cytoplasm of compact myelin in the adult rat optic nerve. Shortly after the onset of chemical ischaemia, the fluorescence of a Ca^{2+} indicator rose in myelin regions and in the cell bodies of oligodendrocytes. The researchers showed that whereas blocking AMPA and kainate receptors could prevent the Ca^{2+} rise at the cell body, NMDA receptors were responsible for ischaemic Ca^{2+} influx in the myelin sheath: NMDA receptor antagonists blocked the rise in cytosolic Ca^{2+} and subsequent damage to myelin.

All three research groups confirmed the presence of NR1, NR2 and NR3 NMDA receptor subunits — including NR1, NR2A, NR2B, NR2C, NR2D and NR3A — in developing oligodendrocyte processes or adult myelin, where the small intracellular space could allow large, toxic increases in intracellular ion concentrations.

These studies highlight NMDA receptors of unusual subunit composition as a potential therapeutic target for preventing white matter damage in a range of conditions, and suggest a new mechanism of signalling from axon to myelin under physiological conditions.

Rebecca Craven

ORIGINAL RESEARCH PAPER Káradóttir, R. *et al.* NMDA receptors are expressed in oligodendrocytes and activated in ischaemia. *Nature* **438**, 1162–1166 (2005) | Salter, M. G. & Fern, R. NMDA receptors are expressed in developing oligodendrocyte processes and mediate injury. *Nature* **438**, 1167–1171 (2005) | Micu, I. *et al.* NMDA receptors mediate calcium accumulation in myelin during chemical ischaemia. *Nature* 21 December 2005 (doi:10.1038/nature04474)