Interleukin-1 mediated exacerbation of excitotoxic brain injury in the rat depends upon signalling via a sphingomyelinase-dependent pathway

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It is now well established that neuroinflammation contributes to many neurodegenerative diseases. In particular, the pro-inflammatory cytokine interleukin-1 (IL-1) is recognised as a key mediator of neuronal death, especially in acute injury, as observed after stroke and head injury. We have previously shown that IL-1 markedly exacerbates excitotoxic cell death in the rat brain, induced by intrastriatal injection of the glutamate agonist AMPA. IL-1 mediated exacerbation of AMPA injury is dependent on seizure activity and cortical NMDA receptor activation. Recently, a rapid non-transcriptional IL-1 signalling mechanism has been shown to mediate effects of IL-1 on kainate-induced seizure in the hippocampus. This signalling pathway is sphingomyelinase and Src-family of kinase dependent and results in phosphorylation of the NR2B subunit of the NMDA receptor.

Therefore we set out in this study to test the hypothesis that IL-1-mediated exacerbation of excitotoxic cell death was dependent on signalling via this newly described pathway. To achieve this male Sprague-Dawley rats received, under isofluorane anaesthesia, local striatal injections of AMPA (5 nmol) and recombinant IL-1 (7.5 ng), immediately followed by direct cortical injection of the neutral sphingomyelinase inhibitor spiroepoxide (40 ng; n=9) or vehicle (n=8). Neuronal injury was assessed 24 h post-injection by cresyl violet staining of coronal cryostat brain sections.

As previously demonstrated co-injection of AMPA+IL-1 resulted in widespread cortical injury, in addition to local striatal cell death. Direct injection of spiroepoxide significantly reduced both the cortical (vehicle 156.5 $\pm$ 60.7 mm^3; spiroepoxide 74.8 $\pm$ 71.1 mm^3, $P<0.05$) and total (vehicle 197.1 $\pm$ 60.8 mm^3; spiroepoxide 110.4 $\pm$ 69.7 mm^3, $P<0.05$) lesion volume, while having no effect on local striatal cell death (vehicle 40.6 $\pm$ 22.8 mm^3; spiroepoxide 39.9 $\pm$ 17.0 mm^3).

These data suggest that co-injection of IL-1 with AMPA in the rat striatum results in distant IL-1 signalling in the ipsilateral cortex via a non-transcriptional sphingomyelinase-dependent pathway that enhances NMDA receptor activation, resulting in increased seizure activity and neuronal cell death.