Inflammatory transcription factors in glial cells: inhibition effects in a neuroexcitotoxic model

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The glial and inflammatory response to injury plays a key role in most types of neural damage, determining survival or death of neuronal cells. Regarding the importance of the glial response in lesion outcome, the characterisation of possible glial inducing factors and secretory products may give some insights into the mechanisms of neuronal cell death and allow, in a future, to interact therapeutically with glial cell metabolism, in order to modulate glial cells' activity in pathological situations. In this sense, in the last few years we have focused on the study of neuronal affectation and the glial and inflammatory response to an excitotoxic lesion induced by the injection of N-methyl-D-aspartate (NMDA) in the postnatal rat cortex.

NMDA injection causes primary neuronal degeneration accompanied by an important glial response and blood-brain barrier disruption. The neuronal response to the excitotoxic process is characterised, during the first hours post-injection, by overactivation of the transcription Factor Nuclear factor kappa B (NF-κB), expression of the enzyme cycloxygenase-2 (COX-2), the cytokine interleukin-6 (IL-6) and c-fos and c-jun stress genes. All these metabolic changes precede massive neuronal death observed at 24 hours post-lesion. Parallely, in these areas of neuronal degeneration, microglial cells suffer rapid morphological changes to pseudopodic/ameboid shapes that precede the expression of major histocompatibility complexes I and II (MHC I-II) as well as the expression of cytokine IL-1ß and the enzyme COX-2. In contrast, astroglial response is characterised by very early changes in gene expression, including activation of the inflammatory-related transcription factors NF-κB and the signal transducer and activator of transcription-3 (STAT-3). Subsequently, there is a marked astroglial hypertrophy, overexpression of glial fibrillary acidic protein (GFAP) and de novo expression of the cytoskeletal protein vimentin, antioxidant protein metallothionein I-II, the enzyme inducible nitric oxide synthase (iNOS) and the cytokines IL-6, IL-1ß and tumour necrosis factor alpha (TNF-α).

In regards to the important role of inflammatory transcription factors and their target genes in the evolution of the glial response, we have evaluated the capacity of Triflusal (2-acetoxy-4-trifluoromethyl-benzoic acid) to downregulate the inflammatory and glial response and ameliorate lesion outcome. Triflusal is a compound structurally related to the salicylates that downregulates activation of the transcription factor NF-κB. When triflusal is administered orally (30mg/kg) eight hours after the NMDA-induced excitotoxic lesion, treated animals present significative inhibition of glial NF-κB, accompanied by a downregulation of the glial response: reactive microglial cells are mainly pseudopodic/ramified and reactive astrocytes show decreased GFAP labelling and hypertrophy. Triflusal administration also induces a decrease in the glial expression of IL-1ß, TNFα, COX-2 and iNOS. Downregulation of the glial response and inflammatory molecules correlates with a strong reduction in the lesion volume (49% decrease). Our studies suggest that inflammatory and glial responses play an important role in excitotoxic lesion outcome in the postnatal brain and indicate that Triflusal administration may be a therapeutic strategy in neuropathological conditions where these responses have a relevant role.