

Dextromethorphan is protective against sensitized NMDAR – mediated excitotoxic brain damage in the developing mouse brain

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Introduction: Enhanced glutamate release and inflammation play an important role in the pathogenesis of developmental brain injury. We have shown in a previous study that the systemic injection of Dextromethorphan (DM), a low-affinity N-Methyl-D-Aspartat receptor (NMDAR) antagonist significantly reduced excitotoxic brain injury, without the associated stimulation of apoptotic degeneration. With regard to perinatal brain damage, DM has also documented anti-inflammatory properties. This is of particular importance, since the presence of inflammatory factors is associated with a higher risk of cerebral palsy and neurological injury in neonates (Dammann, 1998; Volpe, 2001).

Hypothesis: We hypothesized that DM, which combines NMDAR antagonism and anti-inflammatory properties, may be particularly effective in the treatment of inflammation-sensitized neonatal brain injury.

Methods: We used an established animal model of excitotoxic brain damage that mimics key characteristics of human periventricular leukomalacia. On postnatal day 5 animals were randomized into three pre-injury groups: i) vehicle intraperitoneal (i.p.), ii) IL1-beta (10ng in 20µl PBS) twice a day from P1 to P4 and iii) a single i.p. injection of LPS (1µg in 20µl) i.p. six hours before the excitotoxic insult (single intracranial ibotenate injection into the right hemisphere). After the insult animals were further randomized into two groups: i) DM i.p. (5µg/g bw) and ii) vehicle treated group i.p.. The selection of DM dosage and treatment regimen was based on the results of our previous trials. Brains were analyzed 24 hours after setting the lesion.

Results: Pre-treatment with IL-1β or LPS significantly enhanced NMDAR-mediated excitotoxic brain damage and significantly increased the amount of activated microglial cells in white matter and the cortical plate. The sensitizing effect was abolished by DM treatment since the effectiveness of DM in reducing lesion size and microglial cell activation was similar to PBS pre-treated controls.

Conclusion: Although functional parameters were not measured, our data corroborate reports that DM is neuroprotective and that DM may improve functional outcome following perinatal brain injury. Our study supports its putative neuroprotective role in neonatology.