day (P 7). Both groups received iNO (5 ppm) or air from E21 to F7. Animals were evaluated at F3, F10 and F21 using immunohistochemistry, cognitive functions and mass spectrometry imaging.

iNO significantly attenuated the severity of hyperoxia-induced WMD induced in neonatal rats. Specifically, iNO decreased white matter inflammation, cell death, and enhanced the density of developing oligodendrocytes and oligodendrogial maturation. Furthermore, iNO triggered an early upregulation of P27k1p and brain-derived growth factor (BDNF). Whereas hyperoxia disrupted early associative abilities, iNO treatment maintained learning scores to a level similar to that of control pups. In contrast to its marked neuroprotective effects, iNO induced only small and transient improvements of CLD. These findings suggest that iNO exposure at low doses is specifically neuroprotective in an animal model combining simultaneously injuries of the developing lung and brain that mimicked CLD and WMD in preterm infants.

THE SIGMA-1 RECEPTOR AGONIST PRE-084 ATTENUATES INFLAMMATION-SENSITIZED NMDAR-MEDIATED EXCITOTOXIC BRAIN INJURY IN NEWBORN MICE

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Excitotoxicity and inflammation play crucial roles in the etiopathogenesis of perinatal brain injury. We have shown that the sigma-1 receptor agonist 2-(4-morpholinethyl) 1-phenylcyclohexanecarboxylate (PRE-084) protects against N-methyl-d-aspartate (NMDA) receptor-mediated excitotoxic brain injury. In models of adult central nervous system pathology, PRE-084 has demonstrated potent anti-inflammatory properties, which makes it a promising candidate for countering inflammation-enhanced perinatal brain injury.

In the present study we evaluated the effect of PRE-084 in a neonatal mouse model of inflammation-sensitized excitotoxic brain injury.

From postnatal days 1 to 4, pups were pre-sensitized by intraperitoneal injections of IL-1beta (10ng). Two hours after the last IL-1beta dose, pups received an intracranial ibotenate injection, 1 hour after the insult they were randomly treated with i) 0.1 µg/g bodyweight PRE-084 or ii) vehicle.

Administration of PRE-084 resulted in a significant decrease in cortical grey (mean length of the lesion: vehicle 780.00µm ± 495.35 vs. PRE-084 433.33µm±116.51; n=8–9; p<0.05) and adjacent white matter damage (mean length of the lesion: vehicle 767.50µm ± 489.07 vs. PRE-084 391.11µm±126.14; n=8–9; p<0.05). No sex-specific differences in lesion size were detected (n=5–6; p>0.05). PRE-084 treatment significantly reduced the number of isolecitin B4-positive activated microglial cells in perilesional white matter (mean number of isolecitin B4-positive activated microglia vehicle 36.40±6.96 vs. PRE-084 19.93±11.99; n=5; p<0.05).

We are the first to report that PRE-084 reduces inflammation-sensitized NMDAR-mediated excitotoxic perinatal brain damage. Since sigma-1 receptor agonists are investigated in clinical trials in adult neurological diseases, they might be considered a promising therapeutic option also in perinatal brain injury.
10 Mtor Activates Hypoxia-Inducible Factor-1α and Inhibits Neuronal Apoptosis in the Developing Rat Brain During the Early Phase After Hypoxia-Ischemia

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