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THE SELECTIVE SIGMA-1 RECEPTOR AGONIST PRE-084 REDUCES NDMAR-MEDIATED EXCITOTOXIC BRAIN INJURY IN NEWBORN MICE

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Background and aims: We have recently shown that Dextromethorphan is neuroprotective against excitotoxic and hyperoxic-induced brain injury. Beside its antagonistic effect on the NMDA [N-methyl-D-aspartate] receptor, DM also acts on sigma (σ) receptors. Sigma agonists have been shown to be neuroprotective in several adult animal models of brain injury. Neuroprotection by sigma agonists is accomplished by a variety of mechanisms like inhibition of presynaptic glutamate release and attenuation of postsynaptic glutamate-evoked Ca2+ influx. The selective σ1 receptor agonist Pre-084 [2-(4-Morpholinethyl) 1-phenylcyclohexanecarboxylate hydrochloride] has been shown to be neuroprotective in in-vitro and in-vivo studies of adult brain injury. The aim of this study was to evaluate the effect of Pre-084 in NMDAR-mediated excitotoxic brain injury in newborn mice.

Methods: 5-day-old mice pups were injected intracranially with ibotenate, a glutamate analogon. 1 hour after injury pups were randomly injected intraperitoneally (i.p.) with i) 0.1µg/g body weight (bw) ii) 10µg/g bw iii) PBS as control. Enpoints were set at postnatal day 6 and 10 and processed for histological analysis.

Results: Pre-084 reduced NMDAR-mediated excitotoxic brain injury in grey matter if administered 1 hour after injury. The low dose of 0.1µg/g body weight was as effective as the high dose of 10µg/g bw compared to PBS injected control animals.

Conclusion: We show for the fist time a protective effect of the selective σ1 receptor agonist Pre-084 in an animal model of neonatal excitotoxic brain injury. Sigma agonists show a great protective potential and further analysis on the underlying mechanisms are ongoing.

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WIDESPREAD WHITE MATTER DAMAGE IS SEEN ON DTI IN YOUNG ADULTS BORN PRETERM WITH VERY LOW BIRTH WEIGHT (VLBW)

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Background and aims: Perinatal brain injury in very low birth weight (VLBW) preterms is associated with permanent changes in white matter integrity and connectivity, and to neurodevelopmental problems including cognitive deficits.

The aim of study was to investigate whether being born with VLBW leads to white matter damage that persist into adulthood, and to examine the relationship between white matter integrity and perinatal data and IQ in the VLBW group.

Methods: Forty-nine VLBW young adults and 59 term controls were scanned at 1.5 T at ages 18-22 with DTI. Voxelwise maps of fractional anisotropy (FA) were calculated and Tract-Based Spatial Statistics was carried out to test for voxelwise differences between groups. Cognitive function was assessed with WAIS-III. The relationships between FA and total IQ and perinatal variables were explored.

Results: In VLBW adults all major central and posterior white matter tracts had reduced FA, mainly caused by an increase in the two lowest eigenvalues. FA correlated positively with birth weight and negatively with number of days on mechanical ventilator and in NICU. More than half of the VLBW subjects obtained a subnormal IQ score. The FA-IQ correlation analyses demonstrated positive correlations between FA and IQ in regions including corpus callosum and long and short association tracts.

Conclusions: Preterm birth with VLBW results in long-term irreversible changes in white matter