

**Olivier Baud : [Olivier.baud@rdb.aphp.fr](mailto:Olivier.baud@rdb.aphp.fr)**

**#7**

**Impact of inhaled nitric oxide on white matter development in rat pups.**

Olivier P, Loron G, Fontaine RH, Espagne S, Massonneau V, Mercier JC, Gressens P and Baud O.  
UMR 676 INSERM – Université Paris 7.

Inhaled nitric oxide (iNO) is one of the most controversial therapy used in preterm neonates. In addition to respiratory and vascular effects of iNO, only sparse data are available about the impact of iNO on cerebral white matter damage associated with premature neonates. A recent study suggest a beneficial effect of iNO on the neurodevelopmental outcome at 2 years of age. We asked the question whether inhaled NO could have a remote impact on immature rat brain and specifically developing white matter development.

Rat pups and their dams were placed in a chamber containing 20 ppm NO and < 1 ppm NO<sub>2</sub> for postnatal days (P) 0 to P7. NO and NO<sub>2</sub> were monitored using iNOvent (INOTherapeutics, Clinton, NJ). Control litters were submitted to normal room air condition. White matter development was evaluated at P1, P3, P7 and P14 using several immunohistochemical markers : Olig2 (total oligodendrocytes), APC (mature oligodendrocytes), MBP (myelinated axons), GFAP, S100b (astrocytes) and tomatolectin (microglia). Cell proliferation was assessed using nuclear marker Ki67.

No difference of microglial density and activation in the white matter was observed in NO-exposed pups compared to the controls. Conversely, NO-exposed animals exhibited an increased astrogliosis throughout the white matter and in the cortical plate compared to controls. In parallel, myelination of the corpus callosum was significantly improved in treated pups. This finding was associated with an increased mature oligodendrocytes (APC-positive) density in the corpus callosum in NO-exposed animals at P14. However, we did not observed any increased density of total oligodendrocytes (olig2-positive) nor cell proliferation in the white matter of both groups.

This study suggests that inhaled NO has a promyelinating effect on the developing white matter associated with an enhancement of oligodendroglial maturation. These results emphasize the need to further explore the impact of inhaled NO on the brain development.