THE NEUROTOXIC AND NEUROINFLAMMATORY EFFECTS OF METHAMPHETAMINE IN THE STRIATUM ARE EXACERBATED IN NRF2 NULL MICE

N. Granado1,2, S. Ares1,3, I. Lastres-Becker3,4, A. Cuadrado3,4, R. Moratalla1,3

1Instituto Cajal (CSIC), 2Universidad Complutense de Madrid, 3CIBERNED (Spain), 4Dpto. de Bioquímica, Instituto de Investigaciones Biomédicas “Alberto Sols” UAM-CSIC, Madrid, Spain

Introduction: Methamphetamine (METH) is a psychostimulant drug known to be neurotoxic. A hallmark of METH toxicity is the generation of oxidative stress that correlates with damage to the nigrostriatal dopaminergic neurons and reactive gliosis in the basal ganglia. The transcription factor Nrf2 (Nuclear factor-erythroid 2-related factor 2) is the guardian of redox homeostasis and regulates the expression of a group of genes that are cytoprotective against oxidative and inflammatory stress in the brain.

Aims: To study the potential protective role of Nrf2 in METH-induced neurotoxicity

Methods: Nrf2-/- and WT mice received METH (4 mg/kg, x 3, 3h) or saline. Hyperthermia, dopaminergic, proinflammatory and oxidative stress markers and glial response were measured.

Results: We found that Nrf2-deficiency exacerbates the damage of METH to dopamine neurons, shown by an increase loss of tyrosine hydroxylase (TH)- and dopamine transporter (DAT)-containing fibers in striatum. In agreement with these effects, of Nrf2 deficiency potentiated glial activation, as determined with markers for microglia (Mac-1 and Iba-1) and astroglia (GFAP) in the striatum, one day after METH administration. At the same time, lack of Nrf2 dramatically potentiated the increase in TNFα mRNA as well as IL-15 protein expression in the striatum. Interestingly, IL-15 increased expression occurred in GFAP+ cells. In sharp contrast to striatal damage, deficiency of Nrf2 did not alter METH-induced dopaminergic neuron death nor did significantly change glial markers or pro-inflammatory molecules in the SN.

Conclusion: Nrf2 plays an important protective role against dopaminergic neurotoxicity by modulating the inflammation and oxidative stress induced by METH.