DOPAMINE D2-RECEPTOR KNOCKOUT MICE ARE PROTECTED AGAINST DOPAMINERGIC NEUROTOXICITY INDUCED BY METHAMPHETAMINE OR MDMA

S. Ares\textsuperscript{1,2}, N. Granado\textsuperscript{1,3}, I. Oliva\textsuperscript{4}, E. O'Shea\textsuperscript{3}, E.D. Martin\textsuperscript{4}, M.I. Colado\textsuperscript{3}, R. Moratalla\textsuperscript{1,2}

\textsuperscript{1}Instituto Cajal (CSIC), \textsuperscript{2}CIBERNED, \textsuperscript{3}Universidad Complutense de Madrid, Madrid, \textsuperscript{4}Laboratorio de Neurofisiología y Plasticidad Sínaptica. Instituto de Investigación en Discapacidades Neurológicas (IDINE), Universidad de Castilla-La Mancha, Albacete, Spain

Introduction: Methamphetamine (METH) and 3,4-methylenedioxymethamphetamine (MDMA) are psychostimulants that produce neurotoxic effects in the brain, inducing loss of dopamine fibres. Although dopamine is implicated in this neurotoxicity by increasing oxidative stress and free radical formation, it has not been established whether dopamine D2R mediate these effects. D2R are widely expressed in the striatum and regulate dopamine release and uptake due to its presynaptic localization and interaction with DAT.

Aims: To study the role of D2R in the neurotoxicity induced by METH and MDMA.

Methods: We used D2R\textsuperscript{-/-} and WT mice. We evaluated hyperthermia, dopaminergic markers and glial response and dopamine overflow by fast scan cyclic voltammetry in striatum and SN.

Results: In WT animals, both drugs induced marked hyperthermia, decreased striatal dopamine content and TH- and DAT-ir and increased GFAP and Mac-1 expression as well as iNOS and IL-15, 1 and 7 days after drug. These drugs also caused dopaminergic cell loss in the SNpc. By contrast, in D2R\textsuperscript{-/-} mice, METH or MDMA blocked hyperthermia and the loss of TH- and DAT-ir as well as the increase in GFAP and Mac-1. The increase of iNOS and IL-15 expression in the striatum were severely attenuated. Remarkably, inactivation of D2R prevented the loss of dopaminergic neurons in the SNpc caused by METH. In addition, striatal dopamine overflow, in the presence of METH was significantly reduced in D2R\textsuperscript{-/-} mice.

Conclusion: Our results suggest that D2R mediate dopaminergic neurotoxicity and inflammatory processes, as well as SNpc cell loss and hyperthermia induced by amphetamine derivatives.