P67

mGlu3 receptors in Parkinson's disease as a candidate target for neuroprotective therapy: evidence from preclinical studies to human genetic

Marika Alborghetti[1], L. Di Menna[2], V. Bruno[2,3], G. Battaglia[2,3], F.E. Pontieri[1], E. Bianchini[1], M. Simmaco[1], M. Borro[1], F. Nicoletti[2,3]

[1]Neuroscience, Mental Health and Sensory Organs (NESMOS), Rome, Italy
[2]Mol. Pathology, I.R.C.C.S. Neuromed, Pozzilli, Italy
[3]Physiol. and Pharmacol., Univ. Sapienza, Rome, Italy

Background: Type-3 metabotropic glutamate (mGlu3) receptors exert pleiotropic functions in the CNS [1]. Presynaptic mGlu3 receptors inhibit glutamate release, whereas postsynaptic mGlu3 receptors boost mGlu5 receptors signaling [2]. Activation of mGlu3 receptors in astrocytes stimulates the production of GDNF and TGF-β and drives microglia towards an anti-inflammatory phenotype [3,4].

Methods: WT and mGlu3-/- mice were chronically treated with MPTP (20 or 10 mg/kg, s.c., every other day). We analyzed dopamine (DA), DOPAC and HVA levels in the striatum at 10, 15 and 30 days through HPLC detection. We assessed nigro-striatal degeneration by immunohistochemical analysis of Tyrosine Hydroxylas in Substantia Nigra pars compacta (SNpc). We evaluated microglia phenotype in the striatum, the release of neutrophic factors and glial reaction. We are also examining the association between polymorphic variants of GRM3 (rs12704290, rs13242038, rs1468412, rs1527768, rs187993, rs1989796, rs2228595, rs2237562, rs2282966, rs2299225, rs274622, rs6465084, rs724226, rs802457, rs906415, and rs917071) or GRM5 (rs60954128 and rs3824927) and PD in a large cohort of patients.

Results: Chronic administration of MPTP in WT and mGlu3-/- mice caused a substantial drop in DA, DOPAC and HVA levels in the striatum. At 10 and 30 days, the DA loss was significantly greater in mGlu3-/- mice treated with 10 or 20 mg/kg respectively, as compared to their WT counterparts. mGlu3 receptor may have an anti-inflammatory activity, because of in mGlu3-/- mice microglia M2 is less represented. These mice also showed lower levels of neurotrophic factors and a greater glial reaction. Moreover, ad interim analysis suggests an association between the GRM3 and GRM5 variants, PD and dyskinesias.

Conclusion: These findings suggest that mGlu3 receptors might shape the balance between neurodegeneration and neuroprotection in PD and might be targeted by therapeutic intervention.

References:

[1] Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015 Aug 29;386(9996):896-912.
[2] Di Menna L, Joffe ME, Iacovelli L, Orlando R, Lindsley CW, Mairesse J, Gressèns P, Cannella M, Caraci F, Copani A, Bruno V, Battaglia G, Conn PJ, Nicoletti F. Functional partnership between mGlu3 and mGlu5 metabotropic glutamate receptors in the central nervous system. Neuropharmacology. 2018 Jan;128:301-313.
[3] Battaglia G, Molinaro G, Riozzi B, Storto M, Busceti CL, Spinsanti P, Bucci D, Di Liberto V, Mudò G, Corti C, Corsi M, Nicoletti F, Belluardo N, Bruno V. Activation of mGlu3 receptors stimulates the production of GDNF in striatal neurons. PLoS One. 2009 Aug 12;4(8):e6591.
[4] Zinni M, Mairesse J, Pansiot J, Fazio F, Iacovelli L, Antenucci N, Orlando R, Nicoletti F, Vaiman D, Baud O. mGlu3 receptor regulates microglial cell reactivity in neonatal rats. J Neuroinflammation. 2021 Jan 6;18(1):13.