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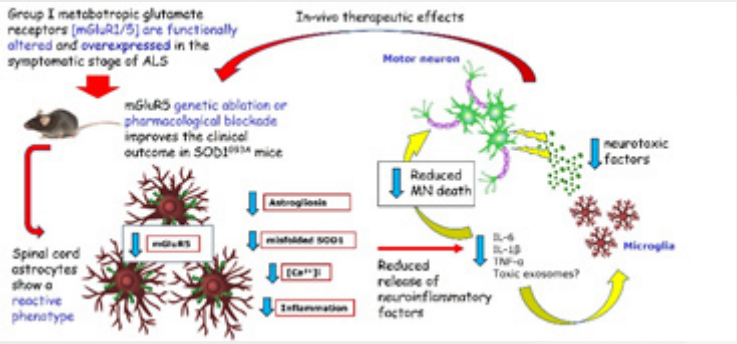
In-vivo and in-vitro evidence supporting the mGlu5 receptor as a pharmacological target for amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is fatal neurodegenerative disease characterized by a progressive degeneration of motor neurons (MNs). The etiology is still largely obscure, and several mechanisms have been proposed, including glutamate-mediated excitotoxicity. In this context, group I metabotropic glutamate receptors (mGluR1/5) play an active role, since their expression and functions are altered during the progression of the disease.

Behavioral, histological, and functional experiments have been performed to characterize the effects of mgluR5 modulation in both in-vivo and in-vitro ALS models. We investigated the effect of a partial or total genetic ablation of mGlu5 receptor in the SOD1G93A mouse model of ALS. We tested in-vivo the pharmacological blockade of mGluR5 by the negative allosteric modulator CTEP. Finally, we studied the effects of mGluR5 genetic or pharmacological modulation, on spinal cord astrocytes isolated from SOD1G93A mice.

The in-vivo genetic ablation of mGluR5 translates into a delayed disease onset and prolonged survival probability, in SOD1G93A ALS mice. This effect was paralleled by a significant MNs preservation and a decreased astrocytes and microglia activation. Subsequently, behavioral studies showed that also the oral pharmacological treatment with CTEP significantly slowdown the progression of the pathology and increased the survival probability in SOD1G93A treated mice respect to vehicle treated animals. Moreover, we observed a reduced glial activation and a significant MNs preservation. In-vitro experiments with primary spinal cord astrocytes cultured from SOD1G93A mice genetically lacking mGluR5 showed a marked modulation of astrocyte's reactive phenotype and a reduced neurotoxic effect toward co-cultured MNs, with a diminished release of neuroinflammatory factors.

Overall, the constitutive genetic downregulation, or the pharmacological blockade of mGlu5 receptor, have a positive outcome in SOD1G93A mice. The effects can be mainly ascribed to a reduced glial activation, supporting the role of mGluR5 as a multifactorial therapeutic target to counteract the progression of ALS.



Biography

Marco Milanese is Associate Professor at the Department of Pharmacy of the University of Genoa. The scientific interest of Milanese Marco focuses on various aspects of neurotransmission and the molecular mechanisms involved in neurodegenerative processes; the research activity of Milanese Marco is characterised by the study of glutamatergic neurotransmission linked to excitotoxicity in neurodegenerative diseases, with particular interest to amyotrophic lateral sclerosis (ALS). The current research lines of Marco Milanese are aimed at studying the etiopathological mechanisms of ALS and develop translational strategies, by exploiting in-vivo behavioural analyses on experimental mouse models of ALS as well as functional in-vitro studies on motoneuron, astrocyte and microglia primary cell cultures. In this framework, very recently, Milanese Marco demonstrated the pivotal role of Group I mGluR receptors supporting the progression of ALS pathology. This research topic might pave the way for new therapeutic approach to counteract MN degeneration and ALS course.