Metamodulation of NMDA receptors in central nervous system

A. Pittaluga¹,², S. Di Prisco¹, E. Merega¹, T. Bonfiglio¹, M.C. Padolecchia¹, G. Olivero¹, M. Marchi¹,²

¹Dept of Pharmacy, University of Genoa
²Center of Excellence for Biomedical Research, University of Genoa, Italy

Metamodulation refers to the possibility that different neurotransmitters can cooperate to modulate neurotransmission in the CNS. Actually, although neurotransmitters are often analyzed individually for their mediated effects, it is largely recognized that they can cooperate to reciprocally interact in controlling neuronal activity. The complexity that originates from that converging action is impressive and might account for the modulation of synaptic plasticity as well as for aberrant responses in selected CNS regions. Neurotransmitter bioavailability in the synaptic biophase is tightly regulated by receptors and it can be influenced by environmental stimuli, by proinflammatory signaling molecules (such as chemokines and cytokines) the overproduction of which usually can be observed in pathological conditions, by drug of abuse (i.e. nicotine) and by therapeutics. These adaptation can in turn reverberate of the receptor-receptor interaction occurring at the single neuron, then having a profound impact on central chemical connections and should be taken in consideration when considering the apparent changes in affinity and efficacy of receptors controlling neuronal activity. That is, in other words, that the composition of the synaptic milieu primes the receptor-receptor mediated interaction, then modifying neuronal activity and synaptic plasticity.

NMDA receptors exist both presynaptically and postsynaptically, where they colocalize with other receptors (i.e. both ionotropic and metabotropic receptors), the activation of which can influence NMDA-mediated responses. In particular, these receptor-receptor interactions might cause either upregulation or down regulation of NMDA receptors by influencing the trafficking of NMDA receptors in-out the synaptic membranes as well as by changing the phosphorilation of the receptor subunits. In particular, the talk will focus on the consequences on release-regulating NMDA receptors located presynaptically in nerve endings due to the activation of non-glutamatergic receptors (i.e. nicotin receptor, somatostatinergic receptors, chemokinergic receptors, noradrenergic receptors) co-localized with NMDA receptors. A more extensive and detailed knowledge of these mechanisms of control of synaptic plasticity may eventually enable us to develop specific therapeutic interventions for central disease as well as for mechanism(s) of addiction and dependence.