Functional interaction between nicotinic and NMDA receptors on dopaminergic synapses.

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It is well-known that cross-talk between receptors represent an important mechanism of neuromodulation and plasticity. Although, these interactions have been mostly localized post-synaptically, receptors cross-talk which involves common intracellular pathways have been reported to occur also at the presynaptic level (for a review see Marchi et al 2015). Neuronal nicotinic acetylcholine receptors (nAChRs) in the CNS are located mostly presynaptically and have been implicated in facilitating release of neurotransmitter. Moreover, it has been shown that dopaminergic axon terminals in the nucleus accumbens possess nAChRs mediating enhancement of dopamine (DA) release. We investigated whether nAChRs and N-methyl-D-aspartic acid (NMDA) receptors interact on the same nerve endings using rat (male Sprague–Dawley, 200–250 g) synaptosomes and slices pre-labelled with [3H]DA. The in vitro short-term pre-exposure of synaptosomes (10 min) to different concentrations of acetylcholine (from 0.01 μM to 10 μM) caused a significant reduction (maximal effect: -54 % at 10 μM) of the 100 μM NMDA-evoked [3H]DA overflow in the rat nucleus accumbens. This inhibitory effect was completely abolished when nerve endings were pretreated with acetylcholine plus dihydro-b-erythroidine indicating a mechanism that involved the activation of β2* nAChR subtypes. Conversely, the pre-exposure to acetylcholine in presence of atropine (0.1 μM) was ineffective; these results completely excluded a role of muscarinic receptors.

In vitro washout-experiments clearly demonstrated that the nicotinic modulation of NMDA receptors function was time dependent and completely restored after 16 min. Interestingly, a pharmacological characterization of these receptors after washout period revealed a strong modification of the subunits composition.

Our results show a new modulatory effect of nicotine on NMDA receptors function.

Marchi M, Grilli M, Pittaluga AM.Nicotinic modulation of glutamate receptor function at nerve terminal level: a fine-tuning of synaptic signals. Front Pharmacol. 2015 Apr 29;6:89. doi: 10.3389/fphar.2015.00089.