In vitro pre-exposure to nicotine: modulation of presynaptic NMDA receptors present on dopaminergic terminals in rat Nucleus Accumbens.

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Here we provide functional and immunocytochemical evidence supporting the presence on Nucleus Accumbens (NAc) dopaminergic terminals of N-methyl-D-aspartic acid (NMDA) receptors colocalized with nicotinic acetylcholine receptors (nAChRs). Immunocytochemical studies showed that a significant percentage of NAc terminals were dopaminergic and that most of these terminals also posses nAChRs which contain the a4 subunit. The *in vitro* short-term pre-exposure of synaptosomes to 30 μM nicotine or 10nM 5IA85380 caused a significant reduction of both the 30 μM nicotine and the 100 μM NMDA-evoked [^{3}H]Dopamine (DA) overflow. This reduction was completely counteracted when synaptosomes were pretreated with nicotine plus mecamylamine. In synaptosomes transiently stimulated with 100 μM NMDA before and after pretreatment with 100 μM nicotine or 10 nM 5IA85380 the time course of FURA-2 AM fluorescence emission changes shows a significant decrease of the NMDA-evoked calcium transients. The inhibitory effect of 5IA85380 was completely counteracted when synaptosomes were pretreated in the presence of the selective antagonist DHβE indicating that the changes of the NMDA-dependent DA release reported was dependent to the activation of a β2* nAChR subtype. The NMDA-evoked overflow was almost completely antagonized in presence of MK801 and partially inhibited in presence of the non specific antagonist CGS-19755 and by RO 25-6981 and Ifenprodil, two specific GluN2B antagonists. CPP-19755 and $ZnCl_2$ (1 nM), two compounds showing preferring affinities at GluN2A subunits did not antagonized the NMDA effect. A significant decrease in GluN2B biotin tagged proteins was observed following exposure of NAc synaptosomes to nicotine pretreatment when compared to control. Therefore, our results show that the NMDA receptor function can be dynamically and negatively regulated in neurons in response to a brief incubation with nAChRs agonists.

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