Functional interaction between presynaptic receptors on dopaminergic and noradrenergic nerve terminals of the rat central nervous system

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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 (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. It has been shown that dopaminergic and noradrenergic axon terminals in the nucleus accumbens and hippocampus possess nAChRs mediating enhancement of dopamine (DA) and noradrenaline (NA) release respectively. We investigated whether nAChRs and N-methyl-D-aspartic acid (NMDA) receptors interact on the same nerve endings using rat synaptosomes pre-labelled with [^{3}H]DA or [^{3}H]NA. 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 [^{3}H]DA overflow in the rat nucleus accumbens. This inhibitory effect was abolished when synaptosomes were pretreated with acetylcholine plus atropine (0.1 μM) and completely counteracted when nerve endings were pretreated in the presence of the selective antagonist DHβE indicating that the changes of the NMDA-dependent [^{3}H]DA release reported was dependent to the activation of a β_2* nAChR subtype. Similarly, the pre-exposure of synaptosomes to nicotine (from 0.01 μM to 30 μM) caused a significant reduction of the 100 μM NMDA-evoked [^{3}H]NA overflow in the rat hippocampus. Nicotine pre-incubation failed to modify the 10 μM 4-aminopyridine-induced [^{3}H]NA overflow suggesting that the changes in the exocytotic machinery of release does not account for the nicotine-induced modifications of the NMDAR function. The pre-exposure of synaptosomes to nicotine or acetylcholine also caused a marked reduction of the nicotine-induced [^{3}H]DA or [^{3}H]NA overflow (-85% and -91.2 % respectively) suggesting that these nAChRs could undergo an agonist-induced receptor desensitization.
To conclude our results show that the NMDA receptor function can be dynamically and negatively regulated in neurons in response to a brief incubation with different nicotinic agonists.

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