

Pharmacological Activity of the Tobacco Nitrosamine N-nitrosornicotine on Nicotinic Acetylcholine Receptors

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The addictive effect of tobacco has been mostly attributed to nicotine as agonist of nicotinic acetylcholine receptors (nAChR). However, the discovery of other active compounds in tobacco with even higher affinities for some nAChR subtypes has raised doubts whether addiction and adverse effects are solely due to nicotine action. Therefore, our aim is to elucidate some of the pharmacological characteristics of N-nitrosornicotine (NNN), present in tobacco and possibly involved in smoke addiction. NNN, in millimolar concentrations, inhibited the activity of a wide range of nAChR subtypes in PC12 cells, but did not affect whole-cell currents generated in response to stimulation of muscular nicotinic receptors present in BC₃H1 cells. In HEK cells expressing recombinant $\alpha 3\beta 4$ nAChR channels, NNN at millimolar concentrations acted as a non-competitive antagonist. The obtained data led to suggest that the inhibitor bound with higher affinity to the closed-channel form of the receptor and with less affinity to its open-channel form. The characterization of a non-competitive inhibitor in tobacco leaves may change the general-accepted concept of attributing smoke-related effects predominately to nAChR activation. However, more studies are necessary for elucidation of the cellular and molecular mechanism of NNN action.

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