CURRENT CONCEPTS ON THE EFFECTS OF NICOTINE ON
NEUROTRANSMITTER RELEASE IN THE CENTRAL NERVOUS SYSTEM

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ABSTRACT

In this overview, the present knowledge about the effects of nicotine on neurotransmitter release in the central nervous system has been evaluated. Five characteristics relating to nicotine mechanisms and sites of action in the brain are presented. These are the following: the site of action of nicotine at the neuronal level; the areas of the brain in which nicotine has been shown to affect neurotransmitter release; the neurotransmitter affected by nicotine; the mechanistic characteristics of release such as receptor mediation, calcium dependence, and subcellular pools affected; and, the pharmacological characteristics of nicotine such as potency, efficacy, time course, stereoselectivity, and structure-activity relationships. Experimental information is presented concerning the effects of nicotine on $[^{3}H]$dopamine release from rat striatal synaptosomes and tissue punches from mesolimbic nuclei. These include concentration-response relationships, the effects of agonists and antagonists, and the time-course and efficacy of nicotine on the stimulation of $[^{3}H]$dopamine release.

An assimilation of the results indicates that nicotine stimulates the release of neurotransmitters, particularly the catecholamines, from selective brain areas, notably the hypothalamus and striatum. Nicotine is able to release these neurotransmitters at concentrations likely to be present in the brains of cigarette smokers. The effect appears to be mediated by presynaptic receptors which resemble, but are not identical to, the $\mathrm{N}_1$-type cholinergic receptors. This indicates that there are presynaptic neural connections at selective nerve terminals in the brain where an endogenous nicotinic neuromodulator acts to facilitate neurotransmitter release. Whether the neuromodulator is acetylcholine or another unidentified nicotinic compound is unknown. It is quite likely that the ability of nicotine to stimulate catecholamine release in selective brain areas such as the mesolimbic system is involved in the pleasurable aspects associated with smoking. The discovery of new agents that mimic or block the effects of nicotine on neurotransmitter release may lead to the identification of endogenous reinforcing compounds as well as permit the design of successful low-tar, low-nicotine cigarettes with a diminished risk associated with the pharmacological effects of nicotine.
Investigations into the reasons why people smoke and the mechanisms accounting for the pleasurable aspects of smoking have continued to be of major interest to neurobiologists for obvious reasons. The identification and characterization of why people smoke could have practical implications such as the design of more effective smoking cessation programs and the production of safer cigarettes.

Although a number of factors appear to be involved in the reason for cigarette smoking, such as subjective pleasurable sensations, decreased anxiety, improvement of memory, repetitive motor activity, social elements, and learned responses (1), most investigators would agree that the underlying pharmacological basis for smoking is due to the presence of nicotine. Not only is nicotine the most abundant and pharmacologically active component of cigarette smoke (2), but also it has been shown that nicotine is a positively reinforcing agent which is associated with the pleasurable experiences associated with cigarette smoking (3-5). Further, nicotine appears to be the component of cigarette smoke that correlates with the frequency of smoking (6-9), and substitution of nicotine with other compounds results in a decrease in cigarette smoking (7,10-12). It is also thought that the dependence, tolerance, and withdrawal symptoms that are characteristic of chronic cigarette smoking are due to the actions of nicotine (9,13-15). From all these studies it would appear that the rewarding stimuli associated with cigarette smoking are centered on the pharmacological effects of nicotine.

It is also generally accepted by neuroscientists that the site of nicotine's action is the central nervous system. Although it is not inconceivable that at least part of nicotine's pleasurable stimuli is mediated by its autonomic effects in the peripheral nervous system, it is far more likely that nicotine's actions are due to its effects in the CNS. Unlike most neurons in the peripheral nervous system, however, central neurons have no effector organ but instead function to integrate and transfer information to adjacent neurons. The process by which this takes place involves the release of neurotransmitters from the nerve terminal. Therefore, it is evident that any drug which has CNS activity must, either directly or indirectly, influence the release of some neurotransmitter in the brain. Even drugs with a purely postsynaptic site of action must eventually affect neurotransmitter release to have CNS activity. If neurotransmitter release were not affected by a substance, it is difficult to see how CNS activity could be influenced. Therefore, from the premises that (a) the pleasurable aspects of smoking are due to nicotine, (b) the site of nicotine's action is the CNS, and (c) centrally neuroactive substances have effects on neurotransmitter release, it is evident that one of the most fruitful areas of investigation into why people smoke is the study of the effects of nicotine on neurotransmitter release in the central nervous system.

In studies of neurotransmitter release, it is obviously not sufficient to simply measure the effects of nicotine administration in vivo or in vitro in order to define nicotine's mechanism and site of action in the brain. Instead, a number of characteristics should be considered which, taken together, will provide useful information about nicotine's central neuroactive effects. In this overview, five of these characteristics are presented and the studies that address these considerations are evaluated. The five major considerations are (1) the neuronal site of action of nicotine; (2) the areas of the brain in which nicotine has been shown to affect release and the relationship of these structures to CNS function; (3) the neurotransmitters affected by nicotine; (4) the mechanistic characteristics of release such as receptor mediation, calcium dependency, and subcellular pools affected; and, (5) the pharmacological characteristics of the drug such as potency, relative activity, time