Nicotine Addiction: From Molecules to Behavior

Marina R. Picciotto

Neuroscientist 1998; 4; 391
DOI: 10.1177/107385849800400610

Nicotine Addiction: From Molecules to Behavior

MARINA R. PICCIOTTO

Drugs of abuse, including nicotine, activate common pathways in the brain that lead to reinforcement and addiction. Each drug, however, has unique molecular targets. This article describes what is known about the neurobiological processes underlying the reinforcing actions of nicotine that ultimately lead to nicotine dependence. The pathway starts with binding of nicotine to nicotinic acetylcholine receptors, its biochemical targets in the brain, which results in altered dopamine physiology and, ultimately, smoking behavior. Experiments using genetically altered mice have begun to identify the molecules involved in this pathway. This type of experiment will ultimately allow identification of the individual molecules in the brain that carry out the steps leading to nicotine addiction and may identify sites of intervention that could lead to novel treatments for nicotine addiction.
NEUROSCIENTIST 4:391–394, 1998

KEY WORDS *Nicotine, Addiction, Mouse*

Cigarette smoking is a major public health issue, and much evidence points to nicotine as the ingredient that is responsible for tobacco addiction (1). A great deal of research has contributed to understanding the mechanisms by which nicotine exerts its effects in the brain (2). This research has included biochemical experiments to identify individual molecules that transduce the nicotine signal, physiological experiments that have shown how neurons respond to the drug, and behavioral experiments that demonstrate that nicotine causes dependence in animal models. This article reviews what is known about the pathway leading to nicotine dependence and then describes recent experiments on genetically engineered mice that lack a single subunit of the neuronal nicotinic acetylcholine receptor (nAChR) which have shown that biochemical, physiological and behavioral responses correlated with nicotine dependence require the functioning of the b2 subunit of the nAChR (3).

Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut

Address reprint requests to: Marina R. Picciotto, Department of Psychiatry, Yale University School of Medicine, 34 Park Street–3rd Floor Research, New Haven, CT 06508 (Email: marina.picciotto@yale.edu).

This work was supported by grants from National Institute on Drug Abuse, The National Alliance for Research on Schizophrenia and Depression, and the Donaghue Foundation.

Biochemical Properties of Brain Nicotinic Receptors

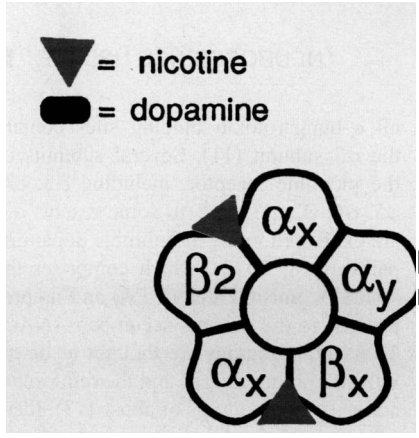
The first step in the pathway to nicotine addiction is binding of the drug to a subclass of acetylcholine receptors in the brain (Fig. 1). These receptors are termed *nicotinic* because of their ability to bind to and be activated by nicotine. Brain nicotinic receptors are pentameric proteins, one family of which is made up of two agonist-binding subunits (α2–α6) and three structural subunits (non-α; β2–β4) (4), whereas the α7–α8 subfamily of nAChRs can form functional homo-oligomers on their own (5). Eleven different neuronal nicotinic subunits have been cloned to date; these can be divided into subfamilies based on pharmacological and physiological properties, sequence homology, and phylogeny (6). One family is composed of α2–α6 combined with β2–β4; the second comprises α7–α8, which are able to bind to the snake toxin α-bungarotoxin. α9 has distinct pharmacological properties, is primarily expressed in the hair cells of the inner ear, and is likely to be part of a third family (7). The most widely expressed subtypes of nAChR in the brain are the α4/β2 subunit-containing receptor and the α7 subunit-containing receptor (8, 9). Minor populations of nAChRs contain combinations of other α and β subunits, sometimes in addition to the most common subunits. Receptor autoradiography experiments in the brains of knock-out mice have shown that all high-affinity nicotine binding sites in the brain contain the β2 subunit of the nAChR (10), whereas all α-bungarotoxin binding sites contain the α7 subunit (11). Several subunits of the nicotinic receptor, including α3, α4, α5, α6, β2, β3, and (to some extent) α7, are expressed in the mesolimbic dopamine pathway (8, 9, 12), which comprises the ventral tegmental area (VTA) and its projections to the nucleus accumbens (NAc). These brain regions are thought to be involved in brain reward and the reinforcing actions of many drugs of abuse (13). Identification of the particular receptor subtypes that mediate this first step in the action of nicotine in the mesolimbic dopamine system will be very useful in developing drugs that might block nicotine addiction without disrupting general reward pathways.

Physiological Effects of Nicotine

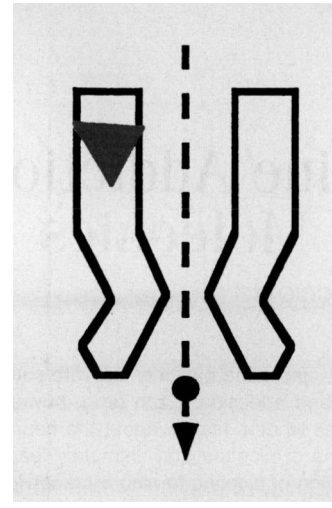
After binding of nicotine to a subtype of the nAChR in the brain, the next step in the pathway leading to nicotine dependence is likely to be activation of dopaminergic neurons in the mesolimbic dopamine system, which results in an increase in dopamine turnover and in the level of extracellular dopamine in these areas (Fig. 1). In support of this hypothesis, nicotine has been shown to increase the firing rate of dopaminergic neurons in the substantia nigra and the VTA both in vivo and in vitro (14, 15). Low concentrations of nicotine consistent with the levels found in the brains of smokers can also stimulate the firing of dopaminergic neurons (3, 16) as well as the release of dopamine from striatal synaptosomes (17). These data are consistent with the hypothesis that nicotine from tobacco use exerts its reinforcing properties through activation of nAChRs on dopamine cell bodies and terminals. The effect of nicotine on dopamine levels is likely to be at least partly caused by nAChRs on dopamine terminals; nicotine-elicited dopamine release can be seen in purified synaptosome preparations from the NAc that can be considered to be highly enriched in presynaptic elements (17, 18). The result of activation of the mesolimbic dopamine system is thought to be reinforcement of the activating behavior, leading ultimately to addiction to the drug of abuse (19).

Rodent Self-Administration as a Model of Drug Abuse

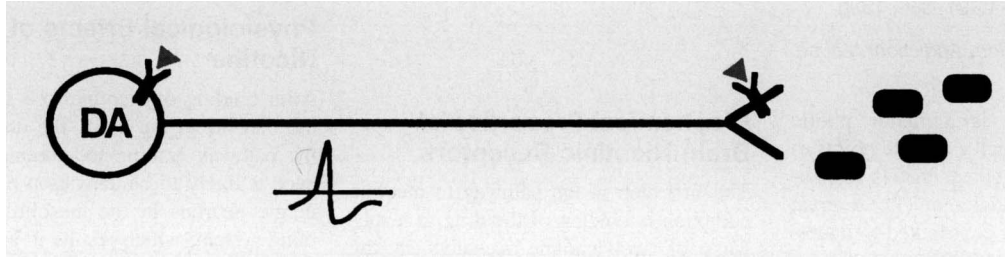
After binding to a subtype of the nAChR and activation of dopamine neurons, the



Step one -
two molecules of nicotine bind to the pentameric receptor...

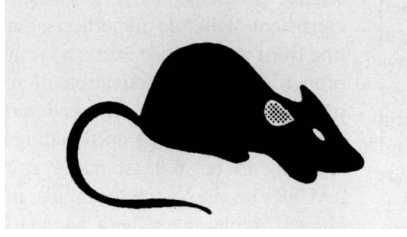


...and the nAChR changes conformation allowing ions to flow into the cell



Step two -
nAChRs are activated on cell bodies and terminals of dopamine neurons...

... leading to an increase in extracellular dopamine levels



Step three -
activation of the dopamine system leads to nicotine self-administration in mice...

... or smoking in humans.

Fig. 1. Schematic diagram of the pathway leading to nicotine addiction. *A*, A hypothetical nicotinic receptor is shown as a heteropentamer of different nicotinic subunits containing at least one β2 subunit. Nicotine binds at the interface between an α subunit and a β subunit. This receptor has an intrinsic ion channel that opens upon nicotine binding to allow flux of sodium, potassium, and calcium. *B*, Nicotine can activate nAChRs on the cell bodies and nerve terminals of dopaminergic neurons. Activation at these sites leads to an increase in the firing rate of dopaminergic neurons, an increase in dopamine release, and an increase in dopamine levels in the extracellular space. *C*, As a result of activation of the meso-limbic dopamine system, rodents will self-administer nicotine, which is an animal model of nicotine reinforcement. This might correspond smoking behavior in humans.

next step in the pathway for nicotine reinforcement is a behavioral output (Fig. 1). Nicotine is known to be highly addictive to humans (1), but is less effective than opiates in rodent models of addiction, which led to early speculation that nicotine was not acting like other classically addictive drugs. This is clearly not the case however, because nicotine has been shown to be self-administered intravenously by many species, including rats (20) and mice (3). The self-administration paradigm measures whether an animal will work by pressing a lever or poking its nose in a hole to attain infusions of the drug being tested. Smoking might be considered to be a human form of self-administration. The conditions under which rodents will self-administer nicotine seem to be more limited than for cocaine self-administration but resemble the episodic nature of cigarette smoking (20). Nicotine self-administration has been shown to involve activation of the mesolimbic dopamine system (21) and, as with other drugs of abuse, it increases extracellular levels of dopamine in the NAc (22, 23). In addition, lesions of the mesolimbic dopamine neurons attenuate nicotine self-administration in rats (21), which implies that action of nicotine on dopaminergic neurons in this area is necessary for at least some of its reinforcing properties.

Evidence That the β2 Subunit is Part of the nAChR Mediating Nicotine Addiction

Genetically altered mice that lack a particular protein—termed *knock-out mice*—have been very powerful tools for the identification of molecules involved in complex behaviors. Recent experiments have been performed using knock-out mice that lack the β2 subunit of the nAChR but retain expression of all other subunits of the neuronal nAChR (10). Each of the steps described above in the pathway leading to nicotine addiction has been examined in these animals (3), leading to the conclusion that this subunit of the nAChR is a necessary component of the receptor that mediates the reinforcing properties of nicotine in the brain. First, high-affinity nicotine binding is completely absent in the mesolimbic system of mice lacking the β2 subunit, which implies that in the absence of the β2 subunit, nicotine cannot bind to at least one of its targets in this region (10). Second, both the electrophysiological response to nicotine of dopaminergic neurons, as well as nicotine-induced dopamine release, were absent in β2 mutant mice, which suggests that this effect is dependent on an nAChR that contains the β2 subunit (3). Finally, β2 mutant mice will self-administer cocaine; when nicotine is substituted for cocaine, however, the mice extinguish self-administration behavior, which implies that these animals cannot experience the reinforcing properties of nicotine in this paradigm. Although these experiments identify binding of nicotine to nAChRs containing the β2 subunit as the first step in the pathway toward nicotine addiction, future experiments using mice deficient in various α subunits of the nAChR are necessary to identify the other subunits that make up this receptor.

Conclusions

The neuronal pathway underlying nicotine dependence is now fairly well understood. Like other drugs of abuse, nicotine leads to activation of the mesolimbic dopamine system and can result in behaviors in rodents that model drug abuse. The use of new tools, such as knock-out mice, allows the molecular components of that neuronal pathway to be identified. The β2 subunit of the nAChR is the first component of the pathway to be identified in this way, but the tools now exist to provide a complete characterization of the nAChRs responsible for nicotine addiction. Identification of molecules in the pathway leading to nicotine addiction will allow for rational drug design of nicotine-like compounds that could be used to treat nicotine dependence in the future.

Acknowledgments

I thank M. Zoli, D. Russell, and T. George for helpful discussions about this work.

References

1. US Department of Health and Human Services. The health consequences of smoking: Nicotine addiction. A report of the Surgeon General. US DHHS, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 1988.
2. Dani JA, Heinemann S. Molecular and cellular aspects of nicotine abuse. Neuron 1996;16:905–908.
3. Picciotto MR, Zoli M, Rimondini R, et al. Acetylcholine receptors containing the beta 2-subunit are involved in the reinforcing properties of nicotine. Nature 1998;391:173–177.
4. Anand R, Conroy WG, Schoepfer R, Whiting P, Lindstrom J. Neuronal nicotinic acetylcholine receptors expressed in *Xenopus* oocytes have a pentameric quaternary structure. J Biol Chem 1991;266: 11192–11198.
5. Sargent PB. The diversity of neuronal nicotinic acetylcholine receptors. Annu Rev Neurosci 1993;16:403–443.
6. Le Novère N, Changeux J-P. Molecular evolution of the nicotinic acetylcholine receptor: an example of multigene family in excitable cells. J Mol Evol 1995;40:155–172.
7. Elgoyhen AB, Johnson DS, Boulter J, Vetter DE, Heinemann S. Alpha 9: an acetylcholine receptor with novel pharmacological properties expressed in rat cochlear hair cells. Cell 1994;79:705–715.
8. Zoli M, Le Novère N, Hill JAJ, Changeux J-P. Developmental regulation of nicotinic receptor subunit mRNAs in the rat central and peripheral nervous systems. J Neurosci 1995;15:1912–1939.
9. Wada E, Wada K, Boulter J, et al. Distribution of Alpha 2, Alpha 3, Alpha 4, and Beta 2 neuronal nicotinic subunit mRNAs in the central nervous system: a hybridization histochemical study in rat. J Comp Neurol 1989;284:314–335.
10. Picciotto MR, Zoli M, Léna C, et al. Abnormal avoidance learning in mice lacking functional high-affinity nicotine receptor in the brain. Nature 1995;374:65–67.
11. Orr-Utreger A, Goldner FM, Saeki M, et al. Mice deficient in the alpha 7 neuronal nicotinic acetylcholine receptor lack alpha-bungarotoxin binding sites and hippocampal fast nicotinic currents. J Neurosci 1997;17:9165–9171.
12. Le Novère N, Zoli M, Changeux J-P. Neuronal nicotinic receptor alpha 6 subunit mRNA is selectively concentrated in catecholaminergic nuclei of the rat brain. Eur J Neurosci 1996;8:2428–2439.
13. Nestler E. Molecular mechanisms of drug addiction. J Neurosci 1992;12:2439–2450.
14. Lichtensteiger W, Hefti F, Felix D, Huwyler T, Melamed E, Schlumpf M. Stimulation of nigrostriatal dopamine neurones by nicotine. Neuropharmacology 1982;21:963–8.
15. Calabresi P, Lacey MG, North RA. Nicotinic excitation of rat ventral tegmental neurones in vitro studied by intracellular recording. Br J Pharmacol 1989;98:135–40.
16. Pidoplichko VI, Debiasi M, Williams JT, Dani JA. Nicotine activates and desensitizes midbrain dopamine neurons. Nature 1997;390:401–404.
17. Grady S, Marks MJ, Wonnacott S, Collins AC. Characterization of nicotinic receptor-mediated [^{3}H]dopamine release from synaptosomes prepared from mouse striatum. J Neurochem 1992;59:848–56.
18. Wonnacott S, Drasdo A, Sanderson E, Rowell P. Presynaptic nicotinic receptors and the modulation of transmission release. In: Block G and Marsh J, editors. The biology of nicotine dependence. Chichester: Wiley; 1990. p. 87–105.
19. Wise RA, Rompre PP. Brain dopamine and reward. Annu Rev Psychol 1989;40: 191–225.

20. Corrigall WA, Coen KM. Nicotine maintains robust self-administration in rats on a limited-access schedule. Psychopharmacology 1989;99:473–478.
21. Corrigall WA, Franklin KB, Coen KM, Clarke PB. The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. Psychopharmacology 1992;107:285–289.
22. Imperato A, Mulas A, Di Chiara G. Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats. Eur J Pharmacol 1986;132: 337–338.
23. Pontieri FE, Tanda G, Orzi F, Di Chiara G. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. Nature 1996;382:255–257.