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Cellular mechanisms of nicotine addiction

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Abstract

In developed countries, tobacco use is estimated to be the largest single cause of premature death [Lancet 339 (1992) 1268]. Nicotine is the main addictive component of tobacco that motivates continued use despite the harmful effects. Nicotinic acetylcholine receptors (nAChRs) are widely distributed throughout the mammalian central nervous system (CNS), where they normally respond to acetylcholine (ACh) and modulate neuronal excitability and synaptic communication. Nicotinic receptors are structurally diverse and have varied roles. Presynaptic and preterminal nAChRs enhance neurotransmitter release. Postsynaptic and somal nAChRs mediate a small proportion of fast excitatory transmission and modulate cytoplasmic second messenger systems. Although the impact of nicotine obtained from tobacco is not completely understood, a portion of nicotine's addictive power is attributable to actions upon the dopaminergic systems, which normally help to reinforce rewarding behaviors. As obtained from tobacco, nicotine activates and desensitizes nAChRs, and both processes contribute to the cellular events that underlie nicotine addiction.

Keywords: Acetylcholine; Nicotinic receptor; Tobacco; Smoking; Cigarettes; Presynaptic; Postsynaptic; Synaptic plasticity; Dopamine; Tolerance; Reward; Reinforcement

1. Introduction

It is now clear that tobacco use is a major worldwide health problem (Leshner, 2000). The World Health Organization estimates that one-third of the global adult population smokes. Because tobacco usage is on the rise in less developed countries, it is one of the very few causes of mortality that is increasing (Peto et al., 1996). It is common to begin smoking as an adolescent, and about half of those who continue throughout life will die from smoking-related diseases (WHO, 1997). In developed countries, smoking causes 20% of all premature deaths, and is the cause of more than one-third of all deaths in men aged 35–69. Therefore, it is not surprising that in developed countries tobacco use is estimated to be the largest single cause of premature death (Peto et al., 1992).

Tobacco is addictive, and it is difficult to quit smoking. More than 80% of the attempts to quit smoking fail within a year, and those who succeed usually have tried to quit repeatedly (Balfour and Fagerstrom, 1996; Schelling, 1992). In the United States, 70% of smokers say that they would like to quit, but only 3% are successful each year (Benowitz, 1999). The accumulated evidence from a wide range of studies indicates that nicotine is the major addictive component of tobacco that drives continued use despite the harmful consequences (Balfour et al., 2000; Dani et al., 2001; Dani and Heinemann, 1996; Di Chiara, 2000; Schelling, 1992; Stolerman and Shoaib, 1991).

When studied under laboratory conditions in the absence of smoke or other extraneous factors, nicotine elicits behaviors associated with addictive drugs. Under restricted doses, nicotine functions as a reinforcer for both animals and humans. At higher doses, however, there are aversive effects caused by nicotine that complicate its reinforcing effectiveness when compared with other drugs, which serve as reinforcers over a wider range of doses and test situations. Despite these complications, nicotine elicits drug-seeking behavior in animal studies, where it supports self-administration and reinforces place preference (Corrigall, 1999; Corrigall and Coen, 1989; Di Chiara, 2000; Stolerman and Shoaib, 1991). In drug discrimination tasks, there is some cross-generalization between nicotine and other addictive drugs, i.e., nicotine is mistakenly discriminated in place of a different addictive drug (Di Chiara, 2000; Stolerman and

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Jarvis, 1995). Nicotine cessation also produces a withdrawal syndrome, and those symptoms can be relieved by nicotine replacement (Stolerman and Jarvis, 1995). In summary, nicotine produces effects that are commonly seen with other addictive drugs such as amphetamines and cocaine: nicotine reinforces self-administration, increases locomotor activity, enhances reward from brain stimulation and reinforces place preference (Clarke, 1990, 1991; Corrigall, 1999; Dani and Heinemann, 1996; Di Chiara, 2000; Goldberg and Henningfield, 1988; Stolerman and Jarvis, 1995; Stolerman and Shoaib, 1991).

2. Neuronal nicotinic acetylcholine receptors (nAChRs)

Nicotine initiates its action by binding to nAChRs. Nicotinic receptors belong to a superfamily of ligand-gated ion channels that include glycine, $GABA_A$ and $5\text{-}HT_3$ serotonin receptors (Albuquerque et al., 1997; Broide and Leslie, 1999; Buisson and Bertrand, 1998; Dani, 2001; Dani et al., 2001; Jones et al., 1999; Lena and Changeux, 1998; Lindstrom, 1997; Lindstrom et al., 1996; Luetje et al., 1990; McGehee and Role, 1995; Paterson and Nordberg, 2000; Role and Berg, 1996; Sargent, 1993; Wonnacott, 1997). The receptor–channel complex is composed of five polypeptide subunits assembled like a rosette around a central water-filled pore (Cooper et al., 1991). Various subunit combinations produce many different nAChR subtypes. The biggest distinction is between homo-oligomeric nAChRs and those formed from $\alpha\beta$-subunit combinations. Many subunit combinations of $\alpha2-\alpha6$ and $\beta2-\beta4$ are possible, but some of these subtypes share similar pharmacological and physiological properties. Only $\alpha7$, $\alpha8$ or $\alpha9$ subunits are known to form homo-oligomeric nAChRs, and only $\alpha7$ is widely distributed in the mammalian central nervous system (CNS).

The main endogenous agonist for all of these nAChRs is acetylcholine (ACh), but nicotine obtained exogenously from tobacco also is an agonist. Upon binding an agonist, a nAChR briefly enters the open conformation of the ion channel, which provides a water-filled pathway through the membrane for cations. After a couple milliseconds, the receptor undergoes another conformational change that closes the channel, and the receptor returns to the resting conformation or enters into a desensitized conformation that is unresponsive to agonists. The speed of activation, the ionic current, the rates of desensitization and recovery from desensitization, the pharmacology and the regulatory controls of the agonist response all depend on the subunit composition of the nAChRs as well as other local factors. For example, $\alpha7$ homo-oligomeric receptors have faster kinetics and higher calcium permeabilities than other nAChRs, whereas $\alpha4\beta2$ receptors have higher affinity for nicotine. To add further complexity, the three basic conformational states (closed, open and desensitized) do not account for the complete kinetic behavior of nAChRs. Particularly, desensitization can encompass more than one time constant, having both short and longer lasting states (Dani et al., 2000; Fenster et al., 1999a). The overall process is a dynamic one. At each moment, the population of nAChRs will distribute among the possible conformational states depending on the differences in free energy that separate those states. The binding of agonists or allosteric modulators will shift that distribution (Buisson and Bertrand, 1998; Changeux et al., 1998).

When examining the function of nAChRs and the effects of smoking, it is important to consider that the probability of a nAChR being in a particular conformational state depends on the agonist concentration and the rate of agonist exposure. At a synapse in the CNS, which is about 1 μm in diameter, ACh is delivered by the presynaptic terminal at a concentration of about 1 mM for a couple of ms before the ACh is hydrolyzed by acetylcholinesterase. This rapid pulse of agonist causes synchronized activation of nearby nAChRs with little or no desensitization. Nicotine obtained from tobacco arrives much more slowly at a concentration near or below 0.1 μM, and it is present much longer, in part, because nicotine is not broken down by acetylcholinesterase. This longer exposure to a low concentration of agonist favors desensitization. In fact, a slow application of a low agonist concentration can cause some desensitization without activation because the desensitized conformation of the nAChR has a higher affinity for agonist than the resting or open conformation. The higher affinity of the desensitized receptor for agonist and the changing distribution of nAChRs among the various functional conformations must be considered to understand what takes place during sustained nicotine use. Nicotinic receptors can exist on the cell surface as nonfunctional receptors (Margiotta et al., 1987) or can enter long-lived desensitized states (Lester and Dani, 1994). Knowledge of long-term forms of desensitization may be especially important for understanding the phases of withdrawal symptoms and the development of tolerance to nicotine. Aspects of tolerance and withdrawal could be explained by nAChRs slowly recovering to functional states from various nonfunctional states of desensitization.

3. Nicotinic cholinergic mechanisms in the brain

Cholinergic neurons project throughout the CNS, providing diffuse, sparse innervation to practically all of the brain, but a relatively small number of cholinergic neurons innervate each neural area (Kasa, 1986; Oh et al., 1992; Woolf, 1991). Thus, the activity of a rather small number of cholinergic neurons can influence diverse and relatively large neuronal structures. Although cholinergic cell bodies are distributed in a loosely contiguous axis running from the spinal cord and brain stem to the basal telencephalon, there are two major cholinergic projection subsystems that can be identified. One cholinergic system arises in the basal forebrain and makes broad projections mainly throughout the

cortex and hippocampus. The second major cholinergic system arises from neurons in the pedunculopontine tegmentum and the laterodorsal pontine tegmentum. This system provides widespread descending innervation that reaches to the brain stem. It also sends ascending innervation mainly to the thalamus and midbrain areas, including the dopaminergic neurons of the substantia nigra and ventral tegmental area (VTA).

At present, the most widely observed synaptic role of nAChRs in the CNS is to influence neurotransmitter release. Activation of presynaptic nAChRs has been shown to initiate a calcium increase in presynaptic terminals that enhances the release of nearly every neurotransmitter that has been examined (Albuquerque et al., 1997; Alkondon et al., 1997a; Gray et al., 1996; Guo et al., 1998; Ji et al., 2001; Jones et al., 1999; Li et al., 1998; McGehee and Role, 1995; McGehee et al., 1995; Mansvelder and McGehee, 2000; Radcliffe and Dani, 1998; Radcliffe et al., 1999; Role and Berg, 1996; Wonnacott 1997; Wonnacott et al., 1990). Because α7* nAChRs are the most highly permeable to calcium, they often mediate the increased release of neurotransmitter; but in some cases different nAChR subtypes are involved (Gray et al., 1996; Ji et al., 2001; McGehee and Role, 1995; McGehee et al., 1995; Mansvelder and McGehee, 2000; Radcliffe and Dani, 1998).

Direct, fast nicotinic synaptic transmission has been detected as a small excitatory input at several areas in the brain (Alkondon et al., 1998; Frazier et al., 1998; Hefft et al., 1999; Roerig et al., 1997). Where it has been reported, fast nicotinic transmission is a minor component of the excitatory input. This result is expected because cholinergic projections and cholinergic synapses are present at low densities. Although direct nicotinic excitation of a neuron usually does not predominate, nicotinic cholinergic inputs could influence the excitability of groups of neurons owing to the broad cholinergic projections into an area (Ji and Dani, 2000). In addition to those direct cholinergic synaptic connections, there also is evidence for significant nonsynaptic, volume transmission for ACh in the CNS (Umbriaco et al., 1995). For example, cholinergic varicosities in the hippocampus do not always match with synaptic specializations, indicating that the majority of cholinergic release may be via diffuse, volume transmission. Thus, beyond their specific roles at discreet synapses, nAChRs may normally modulate neuronal circuits over wide areas. Nicotine from tobacco bathes all of the brain and, therefore, reaches nAChRs at synaptic and nonsynaptic locations. The diverse distribution and roles of nAChRs ensures that nicotine from tobacco will influence many neuronal regions and functions.

Nicotinic receptors also have roles during development and neuronal plasticity (Broide and Leslie, 1999; Dani et al., 2001; Ji et al., 2001; Mansvelder and McGehee, 2000; Role and Berg, 1996). The density and distribution of nAChRs varies during development, and nAChRs can contribute to activity-dependent calcium signals that influence cellular processes (Rathouz et al., 1996). Smoking during pregnancy and nursing carries risk to the fetus and to the infant during the rapid phases of development (Haustein, 1999). Despite publicity of the adverse effects, mothers use tobacco in 25% of pregnancies in the United States. Tobacco use and nicotine may have greater influence on the fetus and developmental health than cocaine, which has received much more attention (Slotkin, 1998). Although the causes are not understood, smoking during pregnancy can produce deficits in learning and can increase psychopathology in offspring (Frydman, 1996; Haustein, 1999; Slotkin, 1998). Furthermore, nicotine is passed to the infant in the milk from nursing mothers that smoke, increasing the direct exposure to the drug. Evidence indicates that nicotine can abnormally alter cell proliferation and differentiation, and thereby affect synaptic and circuit activity (Slotkin, 1998).

4. Nicotinic influences on dopaminergic neurons

Many recent addiction studies have focused on reward circuitry and modifications of those pathways during drug use (Berke and Hyman, 2000; Dani et al., 2001; Di Chiara, 1999; Wise, 2000). Although many psychopharmacological factors contribute to addiction, dopaminergic systems have received much attention because of their roles in reward. Reward, motivation and the roles of the dopaminergic systems are far from completely understood, and are active areas of experimental and theoretical research (see Schultz et al., 1997; Spanagel and Weiss, 1999; Tzschentke, 2001). It is accepted, however, that dopaminergic systems have roles in arousal, cognition, and motor function, and they have complex participation in the processes associated with reinforcing behaviors that lead to reward (Berke and Hyman, 2000; Spanagel and Weiss, 1999; Wise, 2000). The mesolimbic dopaminergic system is important for the acquisition of behaviors that are reinforced by the salient drives of the normal environment or by the inappropriate stimuli of addictive drugs. An important dopaminergic pathway originates in the VTA of the midbrain and projects to forebrain structures, including the prefrontal cortex, and areas such as the olfactory tubercle, the amygdala, the septal region and the striatum, which ventrally includes the nucleus accumbens.

A role for the mesolimbic system in nicotine addiction is supported by a number of findings (Balfour et al., 2000; Clarke, 1991; Corrigall et al., 1992; Dani et al., 2001; Di Chiara, 2000). Many addictive drugs, including nicotine, elevate dopamine in the nucleus accumbens, and that elevation reinforces drug use, particularly during the acquisition phase (Balfour et al., 1998, 2000; Benwell and Balfour, 1992, 1997; Clarke, 1991; Corrigall et al., 1992; Di Chiara, 2000; Di Chiara and Imperato, 1988; Koob, 1992; Nestler, 1992, 1993; Nisell et al., 1994; Pontieri et al., 1996; Spanagel and Weiss, 1999; Wonnacott et al., 1990). Blocking dopamine release in the nucleus accumbens with antagonists or lesions attenuates the rewarding effects of nicotine, as indicated by reduced self-administration in rats (Corrigall

et al., 1992; Stolerman and Shoaib, 1991). In rat brain slices, it was directly shown that the concentration of nicotine obtained from tobacco can activate nAChRs on VTA dopamine neurons, and thereby potently modulate the firing of VTA neurons (Calabresi et al., 1989; Pidoplichko et al., 1997). A major component of the nicotinic currents from VTA neurons was from nAChRs containing the β2 subunit (Picciotto et al., 1998), but other components of the current were mediated by other nAChRs subtypes, including α7* nAChRs (Pidoplichko et al., 1997). Furthermore, Mansvelder and McGehee (2000) showed that nicotine also helps initiate synaptic plasticity in the VTA by enhancing the release of glutamate (see Nisell et al., 1994; Schilstrom et al., 1998). When the enhanced glutamate release was coupled to a postsynaptic depolarization to relieve Mg^{2+} block of the NMDA receptors, then long-term synaptic potentiation was induced. Thus, nicotinic activity is capable of influencing synaptic plasticity in the dopaminergic system. In addition, multiple forms of synaptic plasticity in the hippocampus have been shown to be influenced by nAChR activity (Ji et al., 2001). Evidence is accumulating that nicotinic mechanisms influence forms of synaptic plasticity that are thought to underlie learning and memory, providing the initial support for a link between nicotine addiction and learned associates within the context of tobacco usage (Dani et al., 2001). Other circuitry is involved in the rewarding effects, neuroadaptations and learned or associative behaviors linked with nicotine addiction, but the mesolimbic dopamine neurons play an important role during the addiction process.

5. Nicotine activates and desensitizes nAChRs on mesolimbic neurons

Smoking a cigarette delivers about 50–300 nM nicotine to the brain (Gourlay and Benowitz, 1997; Henningfield et al., 1993; Rose et al., 1999). Fig. 1A shows that nicotine, in exactly the range experienced by smokers, both activates and desensitizes nAChRs on dopaminergic neurons from the VTA (see Pidoplichko et al., 1997). A dopamine neuron from a rat brain slice was whole-cell voltage clamped near its resting potential at −60 mV. A pipette filled with 1 mM ACh was positioned next to the neuron, and brief pressure injections of ACh onto the soma were used to activate nicotinic currents (downward arrows of Fig. 1). Before nicotine was applied to the bath, a brief pressure application of ACh activated a relatively large current: I_1, equal to 50 pA. Then, 0.1 μM nicotine was infused with the solution that was constantly flowing into the bath (solid bar). As the nicotine reached the neuron in the slice, nAChRs were activated, producing a whole-cell inward current seen as a downward deflection in the trace (Fig. 1A).

The nicotine also caused a great deal of desensitization. Three minutes after bath application of 0.1 μM nicotine, a second pressure application of ACh activated a much smaller current: I_2, equal to 17 pA. Comparing the nAChR

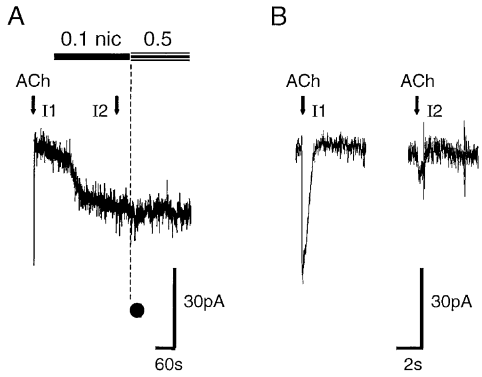

Fig. 1. Nicotine, at the concentration experienced by smokers, activates and desensitizes nAChRs. (A) Bath application of 0.1 μM nicotine activated an inward current through nAChRs on the surface of the patch-clamped dopaminergic neuron (downward deflection in the current trace). After 3 min in 0.1 μM, applying 0.5 μM nicotine activated very little additional current. If there had been no desensitization, the filled circle marks the average size of the current activated by 0.5 μM nicotine. Pressure applications of ACh (1 mM, 30 ms, downward arrows) onto the soma of the neuron were applied before (I_1) and near the end (I_2) of the 0.1 μM nicotine. (B) The nAChRs currents activated by the pressure application of ACh are shown on an expanded scale to indicate the extent of desensitization (adapted from Pidoplichko et al., 1997).

current activated by the first and second ACh applications indicates that greater than 65% of the nAChRs were desensitized. This degree of desensitization is rapid and large given that it takes some time for nicotine in the bathing solution to penetrate the slice and reach the nAChRs on the dopamine neuron under study. When the nicotine in the bathing solution was increased to 0.5 μM nicotine (striped bar, Fig. 1), no further increase in the whole-cell current was seen, indicating significant desensitization. The filled circle shows the size of the whole-cell current that would have been obtained if 0.5 μM nicotine had been applied without the desensitizing preexposure to 0.1 μM nicotine.

6. Hypotheses to extrapolate the cellular results to smokers

Based on these results (Pidoplichko et al., 1997), we can infer some of the effects of smoking a cigarette, which will deliver about 0.1 μM nicotine to the brain (Gourlay and Benowitz, 1997; Rose et al., 1999). Initially, the brain is free of nicotine, and the nAChRs should be responding normally to cholinergic synaptic activity. When the nicotine first arrives, nAChRs are activated, causing the neurons to depolarize and fire action potentials. This process occurs throughout the brain, with multiple consequences. The results of Fig. 1 indicate that VTA dopamine neurons are activated (Pidoplichko et al., 1997), contributing to the increase in dopamine that has been detected in the nucleus accumbens (Balfour et al., 2000; Benwell and Balfour, 1997; Clarke, 1991; Corrigall et al., 1992; Di Chiara, 2000; Di Chiara and Imperato, 1988; Imperato and Di

Chiara, 1986; Nisell et al., 1994; Pontieri et al., 1996; Wonnacott et al., 1990; Schilstrom et al., 1998). Present theories indicate that these neuronal events reinforce the behaviors that produced the dopamine release (Di Chiara, 1999; Schultz et al., 1997). Thus, smoking and associated behaviors, whether incidental or meaningful, will be reinforced (in a type of learning process). Desensitization of nAChRs also will begin, which decreases the impact obtained by smoking more than a couple cigarettes in a row (Fenster et al., 1999a; Pidoplichko et al., 1997; Dani et al., 2000). The onset of desensitization will produce some acute tolerance to further cigarettes. However, the desensitization process is not complete. There is considerable variability in desensitization of the various nicotinic receptor types, leading to significant differences in the level of desensitization even when comparing similar, neighboring neurons under the same experimental conditions (Dani et al., 2000).

Nicotinic receptor desensitization also will have other effects. Because the delivery and removal of ACh at synapses is normally very rapid, desensitization is usually not thought to be important in the CNS. However, this topic has not been investigated well (Dani et al., 2000), and choline at concentrations that are achievable in the CNS can cause some activation and greater desensitization of some subtypes of nAChRs (Alkondon et al., 1997b; Papke et al., 1996; Zwart and Vijverberg, 2000). When nicotine obtained from tobacco is present, particular nAChR subtypes are likely to desensitize, such as the high affinity nicotine sites that include $\alpha4\beta2$* nAChRs (Fenster et al., 1999a). Also, nAChRs at rapidly firing cholinergic synapses will be more likely to desensitize. At those cholinergic synapses, nAChRs will experience repeated exposures to ACh and will be exposed to nicotine from the cigarette. The combination of agonist exposures will increase the probability for nAChRs at active cholinergic synapses to enter desensitization. Thus, smoking will turn down the gain for information arriving via nicotinic cholinergic synapses because fewer nAChRs will be able to respond to the released ACh. In summary, nicotine not only sends inappropriate information through the mesolimbic dopamine system (reinforcing addictive behaviors), but it also decreases the amplitude for normal nicotinic cholinergic information processing.

Another important piece of information about long-term nicotine exposure is that it causes an increase in the number of nAChRs in brains of humans, rats and mice (Marks et al., 1992; Perry et al., 1999; Wonnacott, 1990). This increase is specific to nAChRs, especially those subtypes with a high affinity for nicotine (Buisson and Bertrand, 2001; Fenster et al., 1999b; Wang et al., 1998; Yates et al., 1995). Those same nAChRs, mainly of the $\alpha4\beta2$* type, are the ones that are most important for nicotine self-administration in mice (Picciotto et al., 1998). Although the explanation is not complete (Rowell and Li, 1997), the increase in nAChRs seems to occur because long exposures to nicotine cause nAChRs to enter states of desensitization much more often (Lester and Dani, 1994; Fenster et al., 1999a; Pidoplichko et al., 1997). In those desensitized conformations, the nAChRs are turned over in the cell membrane more slowly, leading to an overall increase in number (Peng et al., 1994, 1997). Along with other factors that alter excitation and inhibition of dopamine neurons (Mansvelder and McGehee, 2000), this increase in the number of nAChRs may contribute to nicotine sensitization (Balfour et al., 1998, 2000; Cadoni and Di Chiara, 2000). When nicotine is removed from the brain, the excess of nAChRs recovers from desensitization, resulting in an excess excitability of the nicotinic cholinergic systems of smokers. This hyperexcitability at cholinergic synapses could contribute to the unrest and agitation that contributes to the smoker's motivation for the next cigarette. In part, the next cigarette "medicates" the smoker by desensitizing the excess number of nAChRs back toward a more normal level.

Taking all this information together, it is possible to speculate about a common pattern of cigarette smoking. Most smokers report that the first cigarette of the day is the most pleasurable (Russell, 1989). After a night of abstinence, nicotine concentrations in the brain are at their lowest level. Thus, smoking the first cigarette most strongly activates nAChRs, likely inducing the greatest dopamine release and contributing to the most pleasurable impact. After a few cigarettes, there is much (though incomplete) desensitization, causing some acute tolerance and less impact from additional cigarettes. This process of activation and desensitization affects different nAChR subtypes differently, and influences synaptic plasticity (Dani et al., 2001; Ji et al., 2001; Mansvelder and McGehee, 2000) that contributes to the long-term changes associated with addiction. Cigarettes are smoked throughout the day driven by smaller, variable reward and by the agitation arising, in part, from the excess nAChRs and hyperexcitability at cholinergic synapses. Often, episodes of cigarette smoking are separated by 2–5 h of abstinence, during which nicotine levels drop and some nAChRs recover from desensitization (Balfour et al., 2000; Dani and Heinemann, 1996; Jarvik et al., 2000; Schuh and Stitzer, 1995). Smokers often report that cigarettes smoked during the day help them to focus and relax so that they can work more efficiently. As the occasions of smoking continue throughout the day, the background level of nicotine slowly increases (Benowitz et al., 1989; Russell, 1989). Therefore, a smoker experiences some exposure to nicotine throughout the day, ensuring that some subtypes of nAChRs visit states of desensitization. Those episodes of nAChR desensitization ensure that the number of nAChRs becomes and remains elevated. If nicotine were avoided for a few weeks, the number of nAChRs would return toward the lower value seen in nonsmokers. The process of quitting would then be well underway. However, most attempts to quit fail, and this topic is a very active area of research (Balfour and Fagerstrom, 1996; Dani et al., 2001; Schelling, 1992). During the years of smoking, neuroadaptations

occurred and long-term synaptic changes resulted in the learned behaviors, some of which were associated with smoking and with the context in which smoking took place. Because those behaviors were reinforced by repeated variable reinforcements from cigarettes and linked to sensory cues, the desire for cigarettes extinguishes slowly and sometimes incompletely. Cravings for cigarettes can be experienced even years after having quit.

Certainly, nicotine's effects and the addiction process have many more complex components that were not discussed or that are not known. Nicotine obtained from tobacco bathes the whole brain. Given that cholinergic projections and nAChRs are so widely distributed in the brain, it is difficult to imagine all the processes that are influenced. In addition, nicotine bathes the rest of the body, and fast nicotinic synaptic transmission is used throughout the peripheral nervous system and at the neuromuscular junctions. Despite the progress, there is still much to learn about nicotine addiction.

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