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Synaptic Plasticity and Nicotine Addiction

Minireview

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Nicotine, the main addictive component of tobacco, activates and desensitizes nicotinic acetylcholine receptors (nAChRs). In that way, nicotine alters normal nicotinic cholinergic functions. Among the myriad of psychopharmacological effects that underlie the addiction process, nicotine influences nAChR participation in synaptic plasticity. This influence has particular importance in the mesocorticolimbic dopamine system, which serves during the reinforcement of rewarding behaviors.

Nicotine obtained from tobacco is addictive, and tobacco use is a major health problem that is estimated to cause 4 million deaths a year worldwide. Nearly a third of the world's adults smoke, and tobacco use is on the rise in developing countries. As a consequence, tobacco is one of the few causes of death that is rapidly increasing. In developed countries, smoking is estimated to be the largest single cause of premature death. In the United States alone, smoking-related illness causes more than 430,000 deaths and $50 billion in medical costs annually (Epping-Jordan et al., 1998).

Nicotine binds to nicotinic acetylcholine receptors (nAChRs). In the central nervous system (CNS), nAChRs normally respond to acetylcholine (ACh) and modulate neuronal excitability and synaptic communication (Albuquerque et al., 1997; Dani, 2001; Jones et al., 1999; McGehee and Role, 1995; Role and Berg, 1996; Wonnacott, 1997). Presynaptic and preterminal nAChRs enhance neurotransmitter release. Postsynaptic and somal nAChRs mediate a small proportion of fast excitatory transmission and modulate intracellular second messengers. Recent studies have shown that nicotinic mechanisms influence forms of synaptic plasticity that are thought to underlie learning and memory (Ji et al., 2001; Mansvelder and McGehee, 2000). After briefly summarizing evidence that nicotine is addicting, this minireview will examine the potential link between nicotine addiction and nicotinic mechanisms that influence synaptic plasticity.

Nicotine Separated from Tobacco Is Addictive

The mechanisms underlying addiction to tobacco are not completely understood, but the accumulation of evidence indicates that nicotine is the major addictive component (Balfour et al., 2000; Dani and Heinemann, 1996; Di Chiara, 2000). The motivating power of tobacco is anecdotally supported by the difficulty encountered when a smoker attempts to quit. Only about 20% of the attempts to quit smoking are successful, and those who succeed usually have tried to quit repeatedly (Balfour et al., 2000).

Under controlled laboratory conditions, nicotine elicits the hallmark behaviors observed with addictive drugs. Nicotine reinforces intravenous self-administration and elicits place preference by animals and humans (Corrigall, 1999; Di Chiara, 2000). In addition, nicotine cessation produces a withdrawal syndrome with both somatic and affective symptoms (Epping-Jordan et al., 1998; Watkins et al., 2000). Those withdrawal symptoms can be relieved by nicotine replacement. As is seen with other addictive drugs, nicotine also increases locomotor activity and enhances reward from brain stimulation.

Addiction Is Linked to Neuroadaptations and Learning

The addiction process acts upon molecular and cellular mechanisms that are present to subserve the normal functions of the brain. Long-term exposure to an addictive drug produces neuroadaptive changes that are, in part, homeostatic reactions to the abnormal stimulation by the drug (Berke and Hyman, 2000; Watkins et al., 2000). For example, long-term exposure to nicotine results in an increased expression of nAChRs, and that change is likely to be a homeostatic response arising from increased nAChR desensitization (Buisson and Bertrand, 2001). Molecular and cellular neuroadaptations are often invoked to explain tolerance, sensitization, and dependence, but they do not readily explain the long-lasting cravings that arise after years of abstinence. Cravings and relapse are often linked to the people, context, and cues that were associated with the original drug use. The addictive drug reinforces salient and extraneous factors that are consistently a part of the drug experience, and eventually they become independent motivators for drug use (Balfour et al., 2000; Berke and Hyman, 2000; Di Chiara, 2000). Associative learning arises as addictive drugs initiate, influence, and alter normal mechanisms, including those that produce synaptic plasticity. In particular, addictive drugs are hypothesized to remodel circuits of the brain that normally reinforce rewarding behaviors.

Although many areas of the brain participate, the mesocorticolimbic dopamine (DA) system serves a vital and fundamental role in the acquisition of behaviors that are inappropriately reinforced by addictive drugs (Balfour et al., 2000; Dani and Heinemann, 1996; Di Chiara, 2000). An important dopaminergic pathway originates in the ventral tegmental area (VTA) of the midbrain and projects to the prefrontal cortex, as well as limbic and striatal structures, including the nucleus accumbens (NAc) (Figure 1). A role for the mesocorticolimbic DA system in nicotine addiction is supported by a number of findings (Balfour et al., 2000; Dani and Heinemann, 1996; Di Chiara, 2000; Watkins et al., 2000). Although it is an over simplification, the accumulated evidence can be summarized as follows: nicotine elevates DA in the NAc, and that elevation reinforces drug use, particularly during the acquisition phase. Blocking DA activity in the NAc with antagonists or lesions attenuates the rewarding

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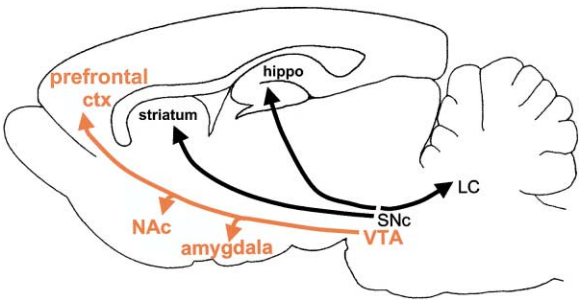

Figure 1. Schematic Representation of Some Major Dopaminergic Pathways

Some dopaminergic projections from the midbrain substantia nigra compacta (SNc) and the ventral tegmental area (VTA) are depicted in a sagittal section of a rat brain. Addiction research has particularly focused on the importance of the pathway from the VTA to the nucleus accumbens (NAc) and the prefrontal cortex.

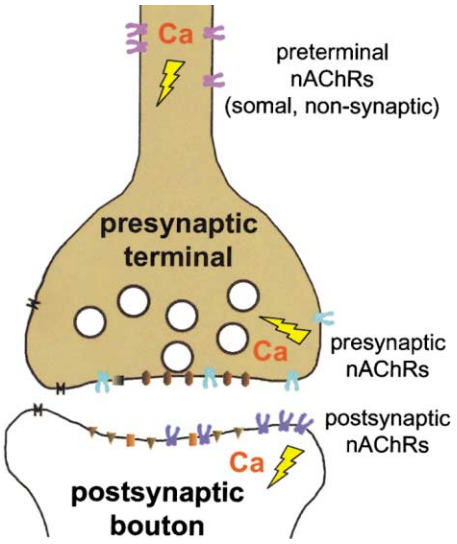

Figure 2. Sites of Influence by nAChR Activity

Nicotinic receptors are depicted at synaptic and nonsynaptic locations. The different shades of blue represent different subtypes of nAChRs. At each location, nAChR activity can induce a depolarization (lightning bolt) and a Ca^{2+} influx. The size of the signals will depend on many factors, including the subtypes of nAChRs that are present and activation versus desensitization by agonists and modulators. The Ca^{2+} influx can influence subsequent Ca^{2+} release from intracellular stores and initiate intracellular cascades, while the depolarization electrically excites the cell.

effects of nicotine, as indicated by reduced self-administration (Corrigall, 1999).

More sophisticated theories of how DA participates in the reinforcement of rewarding behaviors have evolved during the last few years (Berke and Hyman, 2000; Di Chiara, 2000; Schultz et al., 1997). DA concentrations in the NAc are not a scalar indication of reward. More likely, the DA signal conveys novelty and reward expectation or serves to indicate the deviation of the environmental input from the animal's expectations, which were constructed by experience. Thus, DA may participate in the ongoing associative learning of adaptive behaviors as an animal continually updates a construct of environmental saliency (Schultz et al., 1997). These hypotheses for the roles of DA further indicate that drugs of addiction can act upon the mechanisms that normally serve during short-term and long-term synaptic plasticity underlying learning and memory. In the case of nicotine, the influence over synaptic plasticity, learning, and memory begins at the nAChRs.

Neuronal Nicotinic Acetylcholine Receptors

There are many nAChR subtypes, and they are all formed from combinations of five subunits (Dani, 2001; Jones et al., 1999; McGehee and Role, 1995; Role and Berg, 1996). Twelve different neuronal nAChR subunits have been cloned: α2–α10 and β2–β4. Usually, the subunits form α and β combinations, but α7, α8, and α9 subunits are capable of forming homooligomeric nAChRs. Of those three, only α7 is widely distributed in the mammalian CNS.

The main endogenous agonist for nAChRs is ACh, and nicotine obtained from tobacco also is an agonist. The three basic conformational states of the nAChR ion channel are rest (closed), open, and desensitized (closed). The populations of various nAChR subtypes distribute among these conformations based upon the relative free energies of the states. The overall process is a dynamic one, with nAChRs responding to local conditions and to the binding of agonists and allosteric modulators (Changeux et al., 1998). Binding an agonist transiently favors the open conformation of the channel. The open channel permeates mainly sodium and potassium ions, but calcium also carries about 1%–10% of the current, depending on the nAChR subtype. After being open for a couple of milliseconds, the channel closes again to the resting state, or, under some circumstances, it enters a desensitized state in which the channel is closed and unresponsive to agonist. The functional characteristics of a nAChR, such as the pharmacology and kinetics, vary depending on the subunit composition.

Nicotinic Mechanisms that Can Influence Synaptic Plasticity

ACh or nicotine acting through nAChRs mainly initiates a membrane potential change and an intracellular Ca^{2+} signal. Despite this apparently simple action, nicotinic influences are extremely diverse because of inherent properties of the nicotinic cholinergic systems. Nicotinic AChRs are located on the soma and on neuronal processes, and they are depicted at preterminal, presynaptic, and postsynaptic locations in Figure 2. Because nAChRs of varying subtypes are widely distributed in the brain, any particular neuron can have nAChRs at any or all of those locations. At each location, a different nAChR subtype may be positioned either alone or in combination with other subtypes. The magnitude and sign of the membrane potential change or the Ca^{2+} signal depend upon which subtypes are present and whether the nAChRs are mainly activated or desensitized.

The intracellular Ca^{2+} signal initiated by nAChR activity deserves some further attention because it is different from that mediated by voltage-gated Ca^{2+} channels and by the NMDA subtype of glutamate receptors. At a cell's negative resting potential, voltage-gated Ca^{2+} channels

generally do not open, and extracellular Mg^{2+} blocks NMDA receptors. Nicotinic receptors, however, open and pass current freely at negative potentials that provide strong voltage forces to drive cations into the cell. Thus, calcium currents mediated by nAChRs have a different voltage-dependence than other Ca^{2+}-permeable ion channels. Furthermore, incoming Ca^{2+} has a different temporal and spatial distribution that depends on the timing of cholinergic activity and on the cellular location of nAChRs. For these reasons, Ca^{2+} signals initiated by nAChR activity serve specific and characteristic roles. Nicotine influences those roles by introducing nonphysiological activation and desensitization.

At a cholinergic synapse, approximately 1 mM ACh is released into the cleft, causing nearly synchronous activation of the nAChRs. In about a millisecond, the ACh diffuses away and is hydrolyzed by acetylcholinesterase. The rapid delivery and removal of ACh usually precludes significant desensitization. Cigarette smoking delivers nicotine to the brain in a much different way. About 50–300 nM nicotine arrives much more slowly (Gourlay and Benowitz, 1997), bathes the whole brain, and is present much longer because it is not hydrolyzed by acetylcholinesterase. The nicotine can potentially activate nAChRs at any location, not just at synapses. In this way, the nicotine-induced activity may supercede the normal nicotinic cholinergic afferent excitation. In addition, long exposure to a low nicotine concentration causes profound desensitization, which is very dependent on the particular subtype of nAChR.

Keeping in mind the complexities that have just been described, consider the most straightforward mechanisms indicated by Figure 2, and consider how they influence synaptic plasticity. Presynaptic nAChRs initiate a Ca^{2+} signal that boosts the release of neurotransmitters (Albuquerque et al. 1997; Jones et al., 1999; McGehee and Role, 1995; Wonnacott, 1997). By boosting release at glutamatergic synapses, presynaptic nAChR activity has been shown to enhance the induction of synaptic potentiation (Ji et al., 2001; Mansvelder and McGehee, 2000). Postsynaptic nAChR activity also can enhance the induction of synaptic potentiation when the nicotinic postsynaptic excitation and Ca^{2+} signal coincides with presynaptic glutamate release (Ji et al., 2001). In both these examples, nAChR activity reinforces the coincidence between presynaptic glutamate release and a postsynaptic response. That coincidence of presynaptic and postsynaptic activity can initiate potentiation of glutamatergic synapses. However, if nAChR activity were to cause a postsynaptic response that preceded presynaptic glutamate release, then synaptic depression is expected to be favored. Also, as depicted in Figure 2, preterminal or somal nAChRs can depolarize neurons and produce action potential firing.

Nicotinic Influence over Synaptic Plasticity at Dopamine Neurons

At the concentration obtained from cigarettes, nicotine increases the firing rate of DA neurons in the VTA (Pidoplichko et al., 1997). This activation is mainly mediated by $\beta2^*$ nAChRs (Picciotto et al., 1998). After a few minutes, particularly the high-affinity $\alpha4\beta2^*$ receptors desensitize, which tends to terminate the direct stimulation of the DA neurons by nicotine. Microdialysis studies have shown, however, that a single injection of nicotine elevates DA in the NAc for about 2 hr (Di Chiara, 2000). This prolonged DA signal is sustained, in part, because there is a wide range of responses by the DA neurons. In many DA neurons, desensitization of nAChRs is rapid and strong, causing the nicotine-induced firing to terminate in several minutes. In a minority of DA neurons, however, the desensitization is less complete, and a single nicotine dose induces prolonged firing.

Recently, Mansvelder and McGehee (2000) showed that nicotine also helps initiate synaptic plasticity in the VTA. Application of a relatively low nicotine concentration to a midbrain slice activated presynaptic $\alpha7^*$ nAChRs that enhanced the release of glutamate onto the postsynaptic DA neurons. If that nicotine-induced glutamate release was paired with a postsynaptic depolarization of the DA neuron to relieve Mg^{2+} block of the NMDA receptors, then long-term synaptic potentiation was induced. Once the afferent glutamatergic transmission was potentiated, it continued to excite the DA neurons after the direct nicotine stimulation had ended owing to desensitization.

These results suggest a cellular scenario that contributes to nicotine's misdirection of normal synaptic mechanisms in the VTA. Nicotine from tobacco directly activates the DA neurons mainly via $\beta2^*$ nAChRs distributed throughout the cell surface. Because nicotine initially excites and depolarizes the DA neurons, the Mg^{2+} block of the NMDA receptors is removed. At the same time, nicotine enhances glutamate release mainly via presynaptic $\alpha7^*$ nAChRs. The enhanced release of glutamate is better able to activate postsynaptic NMDA receptors, and therefore, is more likely to produce long-term potentiation of the glutamatergic afferents onto DA neurons. In a few minutes, most of the $\beta2^*$ nAChRs on the soma of the DA neurons are desensitized, and much of the direct nicotine stimulation of the DA neurons ceases. The potentiated excitatory glutamatergic afferents, however, continue to drive the DA neurons. In addition, the presynaptic $\alpha7^*$ nAChRs are much less susceptible than the somal $\alpha4\beta2^*$ nAChRs to desensitization by low nicotine concentrations. Therefore, the presynaptic nAChRs continue to enhance glutamate release onto DA neurons while nicotine is present. These results help to explain the microdialysis finding that DA is elevated in the NAc for hours after a nicotine injection.

Future Issues

A central question of addiction is what mechanisms underlie the long-term changes of the brain that lead to craving and relapse years after abstinence from the drug. It is hypothesized that during the addiction process the drug misdirects the mechanisms that usually subserve learning and memory. Thus, we have seen that nicotine influences synaptic plasticity of the kind associated with learning and that plasticity occurs in pathways pertinent for addiction.

There are many other ways in which nicotine influences information processing in the brain. For example, the $\alpha4\beta2^*$ nAChRs are the most numerous in the CNS, and after a short time, they are significantly desensitized by nicotine. The normal synaptic mechanisms mediated by those nAChRs will be impaired throughout the brain, and loss of function is likely to be a component of nicotine's effect. Also, nAChRs are highly expressed on inhibitory GABAergic neurons where they can alter circuit

activity and indirectly enhance or diminish synaptic potentiation (Ji et al., 2001). Finally, presynaptic nAChR activity modulates the release of many neurotransmitters. The nAChR effects on GABAergic activity and on the release of other transmitters have not yet been integrated into the addiction process. Nicotine influences upon synaptic plasticity are likely to make diverse contributions to the complex psychopharmacological effects that underlie nicotine addiction.

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