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Exposure to nicotine and sensitization of nicotine-induced behaviors

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Abstract

Evidence for an important link between sensitization of midbrain dopamine (DA) neuron reactivity and enhanced self-administration of amphetamine and cocaine has been reported. To the extent that exposure to nicotine also sensitizes nucleus accumbens DA reactivity, it is likely that it will also impact subsequent drug taking. It is thus necessary to gain an understanding of the long-term effects of exposure to nicotine on nicotinic acetylcholine receptors (nAChRs), neuronal excitability and behavior. A review of the literature is presented in which different regimens of nicotine exposure are assessed for their effects on upregulation of nAChRs, induction of LTP in interconnected midbrain nuclei and development of long-lasting locomotor and DA sensitization. Exposure to nicotine upregulates nAChRs and nAChR currents and produces LTP of excitatory inputs to midbrain DA neurons. These effects appear in the hours to days following exposure. Exposure to nicotine also leads to long-lasting sensitization of nicotine's nucleus accumbens DA and locomotor activating effects. These effects appear days to weeks after drug exposure. A model is proposed in which nicotine exposure regimens that produce transient nAChR upregulation and LTP consequently produce long-lasting sensitization of midbrain DA neuron reactivity and nicotine-induced behaviors. These neuroadaptations are proposed to constitute critical components of the mechanisms underlying the initiation, maintenance and escalation of drug use.

Keywords

Dopamine; Nicotinic acetylcholine receptors; nAChR upregulation; LTP; Ventral tegmental area; Nucleus accumbens; Drug-abuse liability; Drug self-administration; Withdrawal; Locomotion

1. Introduction

Many abused drugs, including amphetamine, cocaine, opiates and nicotine, activate brain dopamine (DA) neurotransmission, increase locomotor activity and support self-administration in humans and laboratory animals. When repeatedly administered, these effects are enhanced so that re-exposure to the drug, weeks to months later, produces greater dopaminergic and behavioral activation than seen initially. This long-term enhancement in the ability of such drugs to activate DA neurotransmission and elicit appetitive behaviors is termed

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sensitization and may have relevance to the initiation, maintenance and escalation of drug use that is characteristic of the transition from casual experimentation with drugs to drug craving and abuse in humans. Sensitization may also contribute to the reinstatement of drug taking in individuals after prolonged abstinence. Understanding the mechanisms that underlie the induction and expression of sensitization may thus help elucidate the neural events and neuroadaptations underlying the development, maintenance and reinstatement of drug abuse and indicate how they may be prevented.

Among these drugs, nicotine has received far less attention and little is known about its long-term effects or their impact on the pursuit and self-administration of the drug. Considering that rats, like humans, will work to obtain this drug, and that its use is most often characterized by habitual, repeated intake over long periods of time, it is clear that the potential is present for the development of long-term effects with harmful consequences for the individual. This is underscored by the findings of epidemiological studies strongly suggesting that previous exposure to nicotine places individuals at risk for future nicotine use despite widespread appreciation of the dangers associated with continued exposure to tobacco.

This review focuses on sensitization as a potential adaptation that impacts the pursuit and self-administration of nicotine. As such, it is not meant to provide a comprehensive review of all adaptations that have been reported following exposure to the drug. Indeed, other adaptations like tolerance have received far more attention (Collins et al., 1988; Stolerman, 1999; Perkins, 2002). The contribution of other effects of nicotine, such as its ability to interact associatively and non-associatively with contextual stimuli, has been addressed by others (Caggiula et al., 2002; Donny et al., 2003) and will not be discussed here (for a discussion of conditioning-sensitization interactions, see Stewart and Vezina, 1988, 1991; Anagnostaras and Robinson, 1996). Rather, this review concentrates on describing the background and rationale for a model outlining how nicotine exposure can lead to long-lasting sensitization of midbrain DA neuron reactivity and nicotine-related behaviors. The neuroadaptations leading to this form of plasticity are proposed to constitute critical components of the mechanisms underlying the initiation, maintenance and escalation of drug use.

2. Exposure to nicotine and the subsequent pursuit of the drug

Tobacco use in humans is the leading cause of preventable, premature death in the United States (US Department of Human and Health Services, 1988). This 1988 report of the Surgeon General concluded that nicotine is the drug in tobacco that causes addiction and it has been reported that almost all smokers meet diagnostic criteria for dependence. The enormous negative impact of tobacco use on the health of the individual and society as a whole has created an urgent need to identify the neuronal mechanisms underlying the generation of nicotine seeking behaviors as well as those factors that place individuals at risk for such behaviors. Many social and family environmental risk factors have been identified that promote tobacco use. In addition, the contribution to smoking of identified nonnicotine factors including sensory cues, components of tar that reduce nicotine irritation, and MAO inhibitors contained in tobacco smoke must not be overlooked (Rose, 2006). However, such factors do not negate the primary reinforcing role of nicotine. Indeed, a number of studies point to the harmful impact exposure to nicotine, in and of itself, may have on the subsequent display of nicotine seeking behavior in the adult individual.

Several epidemiological studies have now shown that exposure to nicotine in utero (Kandel et al., 1994; Hofvendahl et al., 1997; Isohanni et al., 1991; cf, Fergusson et al., 1998), during childhood (Osler et al., 1995) or adolescence (Kandel, 1975; Kandel et al., 1992) can lead to a greater predisposition to use nicotine and other drugs in adulthood. Considering that the use of nicotine is most often characterized by habitual, repeated intake over long periods of time,

it is likely that short- and long-term drug effects are produced that would serve to perpetuate the pursuit of the drug in adults. It has been suggested, for example, that exposure to nicotine during development or in adulthood may induce modifications in the mesoaccumbens DA system that increase individuals' predisposition to initiate and maintain tobacco use (Kandel et al., 1994). Curiously, there have been few animal studies of the effect of nicotine exposure on the subsequent pursuit of the drug and consequently few attempts made to investigate such a possibility. In one study, adult rats were exposed to seven daily injections of nicotine and tested for self-administration of the drug starting the day following the last exposure injection. Slight but significant enhancements in the acquisition of nicotine self-administration were found in drug compared to saline exposed animals (Shoaib et al., 1997). In another study, again conducted in the adult rat, it was shown that previous exposure to nicotine enhanced this drug's ability to support conditioned place preference (Shoaib et al., 1994). These limited findings, suggesting that the pursuit of nicotine is enhanced by prior exposure to the drug, are reminiscent of the effects of other psychomotor stimulant drugs. These are reviewed below.

3. Mesoaccumbens DA, sensitization and drug seeking

Psychomotor stimulant drugs produce their locomotor effects and support self-administration behavior at least in part through their action on the mesoaccumbens DA system. VTA DA neurons that project to the NAcc are a central component of recent theories of drug taking and are a focus for many investigations of underlying mechanisms.

Wise and Bozarth (1987) argued, for example, that a wide range of addictive substances, including nicotine, have in common the ability to elicit approach behaviors by virtue of their actions on this system. For the psychomotor stimulants, there is considerable evidence to support this view (Deminiere et al., 1989; Bozarth, 1991), both for self-administration of (Roberts et al., 1980; Pettit et al., 1984; Woolverton and Virus, 1989; Caine and Koob, 1994) and locomotor responding to these drugs (Clarke at al., 1988b; McCreary and Marsden, 1993; Meyer et al., 1993; Vezina, 1996).

Robinson and Berridge (1993) have proposed that addictive drugs and associated environmental stimuli elicit excessive incentive salience and craving due to their ability to sensitize mesoaccumbens DA neuron reactivity, an effect known to accompany long-term locomotor sensitization to these drugs. Repeated exposure to amphetamine and cocaine is well known to lead to long-term enhancements in NAcc DA overflow and locomotor responding to these drugs (for references, see Vanderschuren and Kalivas, 2000; Vezina, 2004). In a manner paralleling this sensitization, previous exposure to these drugs not only promotes self-administration, but also enhances the acquisition and expression of conditioned place preference (Lett, 1989; Shippenberg and Heidbreder, 1995). Prenatal exposure to cocaine leads to enhanced self-administration of the drug in adult rats (Keller et al., 1996; cf, Hecht et al., 1998). Exposing adult rats to a regimen of amphetamine or cocaine injections known to produce locomotor and dopaminergic sensitization leads to long lasting enhancements in the subsequent self-administration of both low doses (Woolverton et al., 1984; Piazza et al., 1989, 1991; Horger et al., 1990, 1992; Valadez and Schenk, 1994; Pierre and Vezina, 1997, 1998) and high doses of these drugs (Lorrain et al., 2000; Mendrek et al., 1998; Vezina et al., 2002; for review, see Vezina, 2004). In addition, enhanced amphetamine self-administration is accompanied by enhanced extracellular DA levels in the NAcc (Lorrain et al., 2000; Vezina et al., 2002). Importantly, manipulations known to block the induction of locomotor and DA sensitization by amphetamine, such as preceding pre-exposure injections of this drug with antagonists for D_1 DA receptors, also block the facilitation of drug self-administration (Pierre and Vezina, 1998; Suto et al., 2002). Similarly, antagonists of AMPA, NMDA and mGlu receptors also block the facilitation of cocaine self-administration (Suto et al., 2003; for a review, see Vezina and Suto, 2003). Finally, previous exposure to drugs like Δ^9-THC, that fails to sensitize NAcc

DA overflow in response to amphetamine, does not enhance self-administration of amphetamine (Vezina et al., 2003). Taken together, these findings strongly support an important link between the sensitization of midbrain dopamine neuron reactivity and the facilitation of self-administration of psychomotor stimulant drugs. To the extent that exposure to nicotine produces sensitization of both its locomotor and NAcc DA activating effects, it is likely that it will also impact subsequent drug taking. These critical experiments with nicotine remain to be conducted and carefully evaluated.

4. Mesoaccumbens DA, sensitization and nicotine-induced behavior

In the rat, acute systemic administration of nicotine produces locomotor activation. This activation may sometimes be preceded by a period of locomotor depression depending on the dose administered and whether or not animals were first habituated to the test environment (Clarke and Kumar, 1983a,b; Ksir et al., 1985). When injections are repeated, tolerance develops to the depressant effect (see Collins et al., 1988) and sensitization of the stimulant effect of the drug is observed (Clarke and Kumar, 1983a; Ksir et al., 1985). It has also been demonstrated in several laboratories that intravenous nicotine can maintain stable levels of self-administration in the rat (Corrigall and Coen, 1989; Donny et al., 1995; Tessari et al., 1995; Shoaib et al., 1996, 1997; Shaham et al., 1997; cf, Dworkin et al., 1993).

4.a. Acute responding to nicotine

There are several lines of evidence indicating that nicotine, in a manner similar to the above stimulants, produces these behavioral effects via actions on the mesoaccumbens DA system (Pich et al., 1997; for a review, see Rose and Corrigall, 1997). Different subtypes of nAChRs are expressed both on the perikarya and the terminals of neurons in this system (Clarke and Pert, 1985; Pidoplichko et al., 1997) as well as by non-DA cells and afferent terminals in the VTA (Schilstrom et al., 1998a,b; Clarke et al., 1985; Dominguez et al., 1994; see below). Systemically or iontophoretically applied nicotine increases the rate of firing and the prevalence of burst firing in mesoaccumbens DA neurons (Lichtensteiger et al., 1982; Grenhoff et al., 1986; Mereu et al., 1987). Studies using a variety of techniques have also shown that locomotion-inducing systemic or local applications of nicotine increase DA utilization (Grenhoff and Svensson, 1988; Vezina et al., 1992) and release (Imperato et al., 1986; Mifsud et al., 1989; Rahman et al., 2003). These, as well as the locomotor effects of nicotine, are blocked by centrally but not peripherally acting nicotine receptor antagonists (Clarke and Kumar, 1983a). Nicotine preferentially stimulates activity in and release from DA neurons in the mesoaccumbens relative to the nigrostriatal system (Mereu et al., 1987; Imperato et al., 1986; Benwell and Balfour, 1997). Within the NAcc, acute nicotine-induced DA overflow is observed preferentially in the shell relative to the core (Pontieri et al., 1996). nAChR blockade in the VTA (but not in the NAcc) reduces the ability of systemically administered nicotine to increase NAcc DA release (Nisell et al., 1994a) and locomotion (Corrigall and Coen, 1994) and to support self-administration (Corrigall et al., 1994). Infusion of nicotinic agonists into this site produces locomotor activation (Reavill and Stolerman, 1990; Leikola-Pelho and Jackson, 1992; Museo and Wise, 1995; Panagis et al., 1996) and increases NAcc DA release (Nisell et al., 1994a,b). Finally, DA receptor blockade (Corrigall and Coen, 1991; O'Neill et al., 1991; Museo and Wise, 1995) and selective lesions of the mesoaccumbens DA system (Clarke et al., 1988a; Louis and Clarke, 1998; Corrigall et al., 1992) have each been reported to prevent the ability of nicotine to produce locomotor activation and support its self-administration. Thus, it is clear from these findings that the mesoaccumbens DA system, and particularly the VTA, plays a large and critical role in the ability of nicotine to impact behavior.

4.b. Sensitized responding to nicotine

Based on the findings outlined above, it is reasonable to expect that repeated exposure to nicotine would produce sensitization of its NAcc DA activating effect. Initial studies produced mixed results. Although some reported sensitized NAcc DA overflow in response to nicotine (Benwell and Balfour, 1992; Balfour et al., 1998), others observed either no change (DOPA accumulation: Mitchell et al., 1989; in vitro [^{3}H]DA release: Harsing et al., 1992; in vivo microdialysis: Damsma et al., 1989; Nisell et al., 1996) or decreased responding to the drug (DA utilization: Clarke et al., 1988a; Vezina et al., 1992; Lapin et al., 1989). Following exposure to nicotine and other drugs, enhanced DA overflow has also been reported by some to occur in the core rather than the shell of the NAcc (Cadoni and Di Chiara, 1999, 2000; Cadoni et al., 2000; Iyaniwura et al., 2001), although the opposite has been reported by others (Pierce and Kalivas, 1995). While attempts have been made to incorporate these findings into comprehensive models of drug addiction that attribute different specific functions to the NAcc subnuclei (e.g., Balfour et al., 2000; Di Chiara, 2002), it is important to note that, with the exception of the experiments by Pierce and Kalivas (1995), testing of NAcc DA responsivity in the above studies was conducted at short withdrawal times (usually one day) following the repeated nicotine injections. This point may be critical to the interpretation of these results. Enhanced NAcc DA overflow in response to amphetamine or cocaine is not observed one to two days but rather has been reported 10 days to three months following exposure to these drugs (Hamamura et al., 1991; Hurd et al., 1989; Segal and Kuczenski, 1992a,b; Paulson and Robinson, 1995; for reviews, see Vanderschuren and Kalivas, 2000; Vezina, 2004), indicating that it may be associated with the persistence of behavioral sensitization. Consistent with these findings, one recent report showed that previous exposure to nicotine three weeks earlier led to enhanced electrically evoked [^{3}H]DA release from NAcc slice (Schoffelmeer et al., 2002). Thus, it is conceivable that enhanced NAcc DA responding to nicotine is preferentially expressed after long withdrawal periods, similar to amphetamine and cocaine. Interestingly, sensitized locomotor responding to nicotine in the absence of enhanced NAcc DA overflow at early withdrawal times may be mediated, as proposed for amphetamine and cocaine (Wolf et al., 1994; Kim et al., 2001; De Vries et al., 2002), by functional upregulation of DA receptors in the NAcc (Suemaru et al., 1993; Birrell and Balfour, 1998; Le Foll et al., 2003).

Another factor that influences NAcc DA responding to nicotine is the intensity of the drug exposure regimen. One day following discontinuation of exposure to high drug concentrations delivered continuously over several days (as with an osmotic pump), rats show a decreased NAcc DA response to a drug challenge injection. Similar findings have been reported for several drugs of abuse including amphetamine (Wise and Munn, 1995), cocaine (Markou and Koob, 1991), heroin (Leri et al., 2003) and nicotine (Benwell et al., 1995). For nicotine, such regimens lead to expression, in the days following exposure, of a nicotine withdrawal syndrome characterized by somatic signs of withdrawal and elevated thresholds for intracranial self-stimulation (ICSS) that is proposed to motivate increased intake of the drug (Epping-Jordan et al., 1998). The mechanisms underlying these effects remain unknown but appear to involve alterations in both peripheral (somatic signs: Watkins et al., 2000) and central glutamate and ACh systems (ICSS thresholds and somatic signs: Watkins et al., 2000; Kenny et al., 2003). Increasing the dose and duration of exposure to nicotine increases the duration and magnitude of the withdrawal syndrome observed (Skjei and Markou, 2003; O'Dell et al., 2007). Conversely, ICSS thresholds are lowered (Kokkinidis and McCarter, 1990; Lin et al., 2000), locomotor (Leri et al., 2003) and NAcc DA (Benwell et al., 1995; Schoffelmeer et al., 2002) responses become elevated, and drug seeking increases (Sorge and Stewart, 2005) when sufficient time elapses between exposure to the drug and testing.

Taken together, these results suggest that tolerance to the appetitive effects of a drug occurs during and immediately following periods of intense exposure whereas sensitization requires

time to develop, and that the expression of either is dependent on the drug dose and exposure regimen. This is consistent with the view that sensitization of dopaminergic reactivity can exert long-lasting effects that promote the pursuit and self-administration of nicotine and other drugs (Stewart, 2003, 2004; Vezina, 2004; cf, Di Chiara, 2000; Laviolette and van der Kooy, 2004). It remains, however, that while many nicotine dose and exposure regimens have been tested for their effect on a number of measures, there has not yet been a systematic assessment of their impact on the induction and expression of behavioral and dopaminergic sensitization by nicotine at early and late withdrawal times.

5. nAChRs, mesoaccumbens DA and sensitization of nicotine-induced behavior

The neuronal nAChR is a pentameric ion channel that is permeable to Na^+, K^+ and Ca^{2+} (McGehee and Role, 1995). The nine nAChR subunit genes that are expressed in the mammalian nervous system include α2-α7 and β2-β4 (Le Novere and Changeux, 1995; Dani and Bertrand, 2007). In the CNS, high-affinity heteromeric receptors have been proposed to contain 3 α subunits and 2 non-α subunits (Anand et al., 1991), whereas low-affinity homomeric receptors contain α7 subunits and exhibit high Ca^{2+} permeability (Seguela et al., 1993). Current evidence indicates that mesoaccumbens DA neurons express both high-affinity α3, 4, 5, 6 and β2 and 3 subunit containing nAChRs, as well as low-affinity nAChRs consisting of the α7 subunit and that these receptors are expressed somatodendritically and on axon terminals (Marks and Collins, 1982; Clarke, 1993; Pidoplichko et al., 1997; Klink et al., 2001; Champtiaux et al., 2003; Cui et al., 2003). Both low- and high-affinity nAChRs are also expressed on afferent inputs to the VTA as well as by non-DA interneurons in this site (Dominguez et al., 1994; Schilstrom et al., 1998a,b; Mansvelder and McGehee, 2000; Mansvelder et al., 2002). It has been proposed that nicotine acts preferentially in the VTA to increase NAcc DA release, enhance locomotor behavior and promote self-administration by directly or indirectly activating mesoaccumbens DA neurons (Pidoplichko et al., 1997; see also Sorenson et al., 1998; Schilstrom et al., 1998a,b; Mansvelder et al., 2002). Indirect mechanisms of activation of VTA DA neurons include modulation of glutamatergic and GABAergic inputs to these cells to favor excitation (Mansvelder and McGehee, 2000; Mansvelder et al., 2002). Clearly, nAChRs in the VTA and perhaps other sites are well positioned to regulate the activity of mesoaccumbens DA neurons and to initiate long-term changes in their reactivity.

A number of phenomena have been associated with nAChRs including short-term activation and desensitization. Results from early radioligand binding studies both in vitro and in vivo suggested that nicotine exposure also increases the levels of [^{3}H]-acetylcholine and [^{3}H]-nicotine binding in several brain areas. This phenomenon, referred to as nAChR upregulation, was initially hypothesized to underlie both tolerance to this drug's locomotor depressant effect (Marks and Collins, 1985) as well as sensitization to its locomotor activating effect (Ksir et al., 1985, 1987). Subsequent studies showed, however, that a correlation does not always exist between increased binding and these behaviors. Rats, for example, have been shown to maintain tolerance to the locomotor depressant effect of nicotine for periods far exceeding those during which increases in binding are observed (Clarke and Kumar, 1983a; Collins et al., 1988, 1990; Stolerman et al., 1973). In addition, increased binding has been observed in the absence of enhanced locomotor responding to nicotine (Ksir et al., 1987).

5.a. Transient upregulation of nAChRs, LTP and the induction of sensitization

The lack of correlation between sensitized behaviors and nAChR upregulation excludes this phenomenon as the primary cause but it is possible that the transient upregulation of nAChRs observed following nicotine exposure represents an early step in a sequence of neuronal events that lead ultimately to sensitized responding. Chronic exposure to nicotine in vitro was recently

shown to produce an upregulation of ACh-evoked currents in rat and human α4β2 nAChRs expressed in human kidney epithelial cells (Buisson et al., 2000; Buisson and Bertrand, 2001; Vallejo et al., 2005) or cultured rat midbrain neurons (Nashmi et al., 2003). Similarly, exposing rat pups to nicotine in vivo was found to enhance ACh-evoked currents in α4β2- and α4β3-like nAChRs in hippocampal slices (Alkondon and Albuquerque, 2005). The importance of transient receptor desensitization in the upregulation of nAChRs remains to be determined (Pidoplichko et al., 1997). Within the VTA, receptor desensitization is important in the acute nicotine-induced decrease in GABAergic drive to DA neurons (Mansvelder et al., 2002). How this phenomenon is altered by chronic nicotine exposure and whether it is impacted by nAChR upregulation are questions that remain to be answered. It follows that upregulating nAChR responses on VTA DA neurons would be expected to increase the excitability of these cells directly and would favor the induction of drug-induced LTP of the excitatory inputs they receive. These processes could contribute to the induction of NMDA-dependent sensitization. DA neuron activation increases somatodendritic DA release creating a positive feedback on local glutamate release (Kalivas and Duffy, 1995; Wolf and Xue, 1998). The potentiation of excitatory inputs onto VTA DA neurons by drugs like cocaine and nicotine has been proposed as a possible component of sensitization (Ungless et al., 2001; Saal et al., 2003). Both are prevented by NMDA receptor blockade during drug exposure (Shoaib and Stolerman, 1992; Shoaib et al., 1994; Vezina and Queen, 2000; Ungless et al., 2001; Saal et al., 2003). However, drug-induced LTP persists for less than 10 days following drug exposure, independent of the number of exposure injections (Ungless et al., 2001; Borgland et al., 2004). In combination with the observation that sensitized DA release is seen in NAcc slices that contain DA neuron terminals but not their cell bodies (Schoffelmeer et al., 2002; for references, see Vezina, 1996), these findings indicate that LTP of excitatory inputs to VTA DA neurons may be important for the induction rather than the expression of sensitization.

5.b. Localization of relevant nAChRs necessary for the induction of sensitization

Activation of nAChRs is necessary for the induction of locomotor and dopaminergic sensitization not only by nicotine but also by other drugs such as amphetamine and cocaine (Schoffelmeer et al., 2002). These findings indicate a central role for nAChRs in drug sensitization. Upregulation of nAChRs is observed in a number of brain regions following exposure to nicotine (see Table 1) and appears to occur in receptors containing the α3, 4, 6 and β2 subunits (Ryan and Loiacono, 2001; Mugnaini et al., 2002; Parker et al., 2004). Results from some groups suggest that upregulation of the high-affinity nAChRs occurs through modifications in receptor assembly and trafficking, leading to a greater number of cell surface receptors (Peng et al., 1994; Harkness and Millar, 2002; Nashmi et al., 2003; Sallette et al., 2005). Alternatively, nAChR upregulation may involve a conformational change that hypersensitizes the receptor by increasing both its response and sensitivity to agonist (Vallejo et al., 2005; see also Buisson et al., 2000; Buisson and Bertrand, 2001; Alkondon and Albuquerque, 2005). Notably, either model would lead to increased reactivity in the cells expressing upregulated receptors.

As outlined above, there are several reasons to suspect that nAChRs in the VTA play a critical role in the induction of sensitization by nicotine. These receptors have been implicated in the ability of nicotine to increase locomotion and NAcc DA overflow as well as to support self-administration. They have also been implicated in cocaine place preference (Zachariou et al., 2001), the self-administration of methamphetamine and morphine (Glick et al., 2002) and, to some extent, in brain stimulation reward (Yeomans and Baptista, 1997). Nicotine is also known to upregulate these receptors and to enhance the synaptic strength and produce LTP of excitatory synapses onto VTA DA neurons (Mansvelder and McGehee, 2000; Saal et al., 2003). Consistent with these findings, it was recently shown that blocking nAChRs in the VTA, but not in the NAcc, during exposure to a moderate intermittent nicotine injection regimen

blocks the induction of long-term locomotor sensitization observed three weeks later. Importantly, the same nicotine exposure regimen also produced a transient upregulation of nAChRs in the VTA observed 3 hours but not 3 days or 3 weeks following exposure. No upregulation of nAChRs was observed in the NAcc at any time tested (Baker et al., 2005). These findings indicate that nAChRs in the VTA, but not the NAcc (in a manner reminiscent of the effects of amphetamine; Vanderschuren and Kalivas, 2000; Vezina, 2004), are necessary for the induction of sensitization by nicotine and that transient upregulation of nAChRs specifically in sites important for nicotine sensitization may be associated with this effect.

It should be noted that, unlike more intense exposure regimens that produce nAChR upregulation in several brain regions (see Table 1), the sensitizing regimen of nicotine injections used by Baker et al., (2005) above was relatively moderate and may be particularly well suited for characterizing the selective regulation of nAChRs in different brain areas and their participation in the induction of behavioral sensitization by nicotine. That said, the significance of nAChR upregulation observed in other sites must be assessed. For example, upregulation of nAChRs in the NAcc may enhance the ability of nicotine to amplify phasic relative to tonic firing induced DA release in this site (Rice and Cragg, 2004;Zhang and Sulzer, 2004). Both the PFC and amygdala are involved in the induction of sensitization by amphetamine (Wolf et al., 1995;Cador et al., 1999), although their contribution to nicotine sensitization remains unknown. Other sites include the pedunculopontine (PPT) and laterodorsal (LDT) tegmental nuclei. Upregulation of nAChRs following exposure to nicotine does not appear to have been assessed in either nucleus. However, both sites have been heavily implicated in the effects of nicotine. For example, pharmacological inhibition, selective cholinergic lesions of the PPT or blockade of nAChRs in this site reduce nicotine self-administration (Lanca et al., 2000a;Corrigall et al., 2001,2002), whereas non-selective lesions of the PPT block VTA nicotine induced conditioned place preference (Laviolette et al., 2002). Although most efferents from the PPT project to the substantia nigra (SN), this nucleus also sends some ACh, GABA and glutamate efferents to the VTA that could contribute to these effects (Oakman et al., 1995;Charara et al., 1996). The LDT on the other hand, sends major ACh projections to the VTA (Charara et al., 1996;Omelchenko and Sesack, 2005) that, together with glutamate inputs, modulate NAcc DA release (Blaha et al., 1996;Forster and Blaha, 2000;Forster et al., 2001). Nicotine and ICSS increase Fos immunoreactivity in both sites mostly in non-cholinergic cells (Lanca et al., 2000b;Nakahara et al., 2001). The latter has also been shown to increase ACh efflux in the VTA, an effect that may depend on inter-connectivity between the LDT and PPT (Semba and Fibiger, 1992;Forster et al., 2002;Miller et al., 2002).

The findings obtained thus far for nicotine sensitization are consistent with and extend current circuit models of sensitization proposed for other psychostimulants (e.g., Vanderschuren and Kalivas, 2000). In these models, descending glutamatergic projections from the infralimbic prefrontal cortex to the VTA are argued to play a critical role in the induction of sensitization by drugs such as amphetamine and cocaine. However, the fact that these projections do not form synapses with mesoaccumbens cells in the VTA (Carr and Sesack, 2000) has made it difficult to propose a direct role for these cortical afferents in the sensitization process. On the other hand, both the PPT and LDT receive afferents from the prefrontal cortex (Cornwall et al., 1990; Semba and Fibiger, 1992) and in turn send ACh, GABA and glutamate projections to the VTA (Charara et al., 1996; Forster and Blaha, 2000; Omelchenko and Sesack, 2005), positioning them well to play an important role in the induction of sensitization by nicotine. The circuit diagram in Figure 1 illustrates the interconnectivity between these and other nuclei that may be important for sensitization by nicotine.

6. Nicotine exposure and sensitization of nicotine-induced behaviors

Taken together, the findings reviewed above are consistent with the model of the impact of nicotine exposure proposed and outlined in the flowchart below. In this model, nicotine exposure first produces transient upregulation of nAChR function, leading to enhanced excitation of midbrain DA neurons and the induction of LTP. These successive events lead ultimately to long-lasting sensitization of midbrain DA neuron reactivity and to behavioral manifestations of sensitized responding to the drug.

exposure to nicotine → nAChR upregulation → LTP → DA sensitization → behavioral sensitization

As reviewed earlier, two factors interact to influence responding to nicotine after exposure to the drug: the intensity of the drug exposure regimen (as determined by the number of injections and the drug dose) and the time of testing following exposure to the drug. As illustrated in Figure 2, increases in the intensity of the drug exposure regimen would be expected to lead to temporally different outcomes in subsequent responding to nicotine. Moderate exposure regimens (Figure 2B) are known to lead to a progressive long-lasting increase in nicotine's locomotor effects and later enhancement of its DA activating effects (Clarke and Kumar, 1983a;Ksir et al., 1985,1987;Schoffelmeer et al., 2002;Baker et al., 2005), whereas intense exposure regimens (Figure 2C) are not associated with enhanced locomotor or DA responding (Ksir et al., 1987;Benwell et al., 1995) but rather with expression of somatic signs of withdrawal and elevated ICSS thresholds in the period soon after exposure (Epping-Jordan et al., 1998). Long-lasting increases in locomotor and DA responding to nicotine are likely to emerge later after the negative withdrawal effects have dissipated.

A critical element of this model is the role played by nAChR upregulation and LTP in the initiation of the long-lasting neuroadaptations underlying sensitization. Both moderate and intense nicotine exposure regimens are associated with transient upregulation of nicotine binding sites (see Table 1). Although less is known about functional nAChR upregulation and LTP following different nicotine exposure regimens, based on reports with cocaine (Borgland et al., 2004), it is likely that these effects are also transient. Thus, exposure regimens that produce nAChR upregulation and LTP would be expected to sensitize responding to and for nicotine (Vezina, 2004). With more intense drug exposure regimens, such as continuous exposure to high concentrations with an osmotic minipump, the sensitized phenotype would likely be established via the same mechanisms, but the expression of DA and behavioral sensitization would only be measurable after recovery from the drug withdrawal effects.

Findings obtained with psychomotor stimulants such as amphetamine support an important link between the long-lasting sensitization of midbrain DA neuron reactivity and the enhanced self-administration of these drugs (Vezina, 2004). To the extent that nicotine acutely increases locomotion and NAcc DA release, and that repeated exposure to the drug leads to sensitization of both effects, it is likely in light of these findings, that exposure to nicotine can also have long lasting effects on subsequent drug taking. This possibility has not yet been directly assessed. Interestingly, rats characterized as showing enhanced nAChR function in the VTA (High vs Low Responders to novelty; Fagen et al., in revision), also show enhanced drug-induced NAcc DA responses (Bradberry et al., 1991; Hooks et al., 1991) and enhanced nicotine self-administration (Suto et al., 2001). The potentiated excitatory input onto VTA DA neurons observed in High Responder rats does not, in and of itself, provide a good model for the long-lasting expression of sensitization as it is observed for only a short period after drug exposure in sensitization experiments (e.g., 5 days; Ungless et al., 2001). Nonetheless, conditions that enhance excitation of VTA DA neurons are conducive to the induction of sensitization (Vezina, 2004) and High Responder rats are more susceptible to develop sensitization (Pierre and Vezina, 1997). Thus, together, the above findings are consistent with the hypothesis that drug

exposure regimens that lead to nAChR upregulation and potentiation of excitatory synapses onto VTA DA neurons (or the presence of these conditions in High Responder rats) could lead to long lasting locomotor and dopaminergic sensitization that promotes self-administration of the drug. For a number of cultural and political reasons, along with the limited number of neurobiological investigations, nicotine addiction has been somewhat underestimated. Despite this history, it is clear that nicotine has profound long-term effects on behavior and it is likely that this drug induces lasting changes in neurochemistry analogous to those reported for cocaine and amphetamine.

Long-term neuroadaptations produced by previous exposure to nicotine or psychostimulants could thus exert critical impact on liability to initiate or resume excessive drug use (see also Koob and Le Moal, 1997). It has been argued, however, that the escalation of drug intake observed in rats given long (6-hr) rather than short (1-hr) access to cocaine in a self-administration paradigm (Ahmed and Koob, 1998) reflects tolerance (Ahmed et al., 2002) rather than sensitization of the appetitive (locomotor and DA activating) properties of the drug. This view is based in part on the lack of evidence for sensitized responding in tests conducted during or soon after the escalating phase of the experiments (Ahmed et al., 2003; Ahmed and Cador, 2006). Importantly, the absence of evidence for sensitization in these experiments is entirely consistent with the idea that sensitization develops gradually and is observed at later time points following drug exposure. If sensitization is not expressed in these animals, the escalation of drug intake observed could very well have been due to the incremental recruitment of opponent processes (Koob and Le Moal, 1997) or tolerance to the drug's aversive or suppressive effects (Robinson and Berridge, 1993, 2004; Zernig et al., 2004). It is argued here that sensitization may be a consequence of drug exposure in all of these cases, but that the timing of the behavioral and biochemical assays is critical for its assessment. According to the current model, sensitization could exert its impact on behavior during self-administration testing in rats previously exposed to the drug (e.g., Vezina et al., 2002), as well as long after drug exposure in these sessions. Interestingly, unlike cocaine, escalation of intake does not occur in rats given long (12-hr) access to nicotine (Kenny and Markou, 2006), which may reflect differences between the two drugs in the opponent processes or aversive effects each is associated with. It is important to note, however, that the total daily intake in this study (0.38mg/kg/1-hr and 1.36mg/kg/12-hr) was within the range previously observed to produce nAChR upregulation (see Table 1) and thus would be expected, according to the current model, also to lead to long-lasting sensitization in responding to nicotine.

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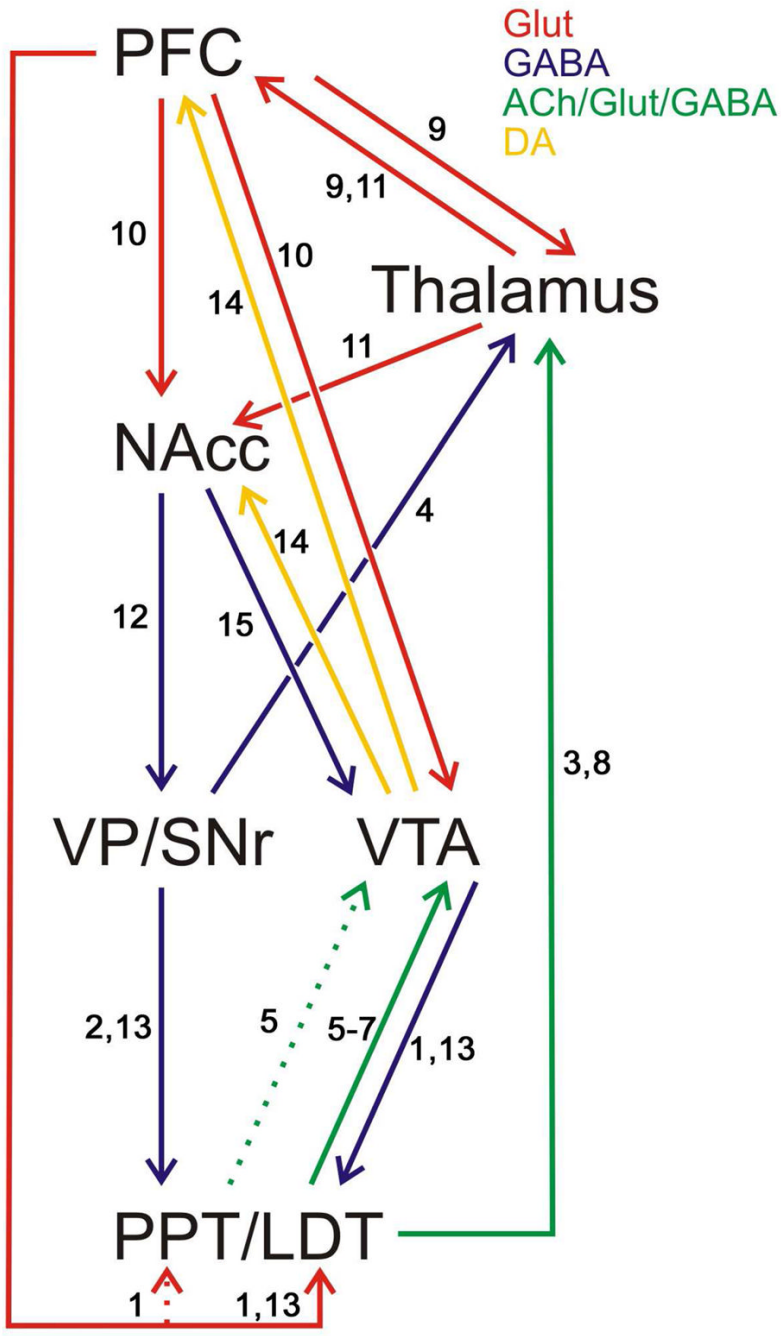

Figure 1.

Illustration of interconnectivity between nuclei and neurotransmitters in a thalamo-cortico-pontine-VTA-NAcc circuit proposed to be important for locomotor sensitization by nicotine. Data already support a role for part of this circuit (excluding the LDT/PPT) in sensitization by psychostimulants (Pierce and Kalivas, 1997; Vanderschuren and Kalivas, 2000). To date, findings indicate that activation of nAChRs in the VTA, but not the NAcc, is necessary for the induction of sensitization by nicotine. Exposure to a sensitizing regimen of nicotine injections also produces transient upregulation of nAChRs in the VTA but not the NAcc (Baker et al. 2005; see Section 4b). Dotted lines indicate weaker projections. 1. Semba and Fibiger, 1992. 2. Beckstead et al., 1979. 3. Cornwall and Phillipson, 1988, 4. Inglis et al., 1994. 5. Charara et

al., 1996. 6. Omelchenko and Sesack, 2005. 7. Forster and Blaha, 2000. 8. Woolf and Butcher, 1989. 9. Krettek and Price, 1977. 10. Sesack and Pickel, 1992. 11. Bubser and Deutch, 1998. 12. Jones and Mogenson, 1980. 13. Cornwall et al., 1990. 14. Swanson, 1982. 15. Zahm et al., 2001.

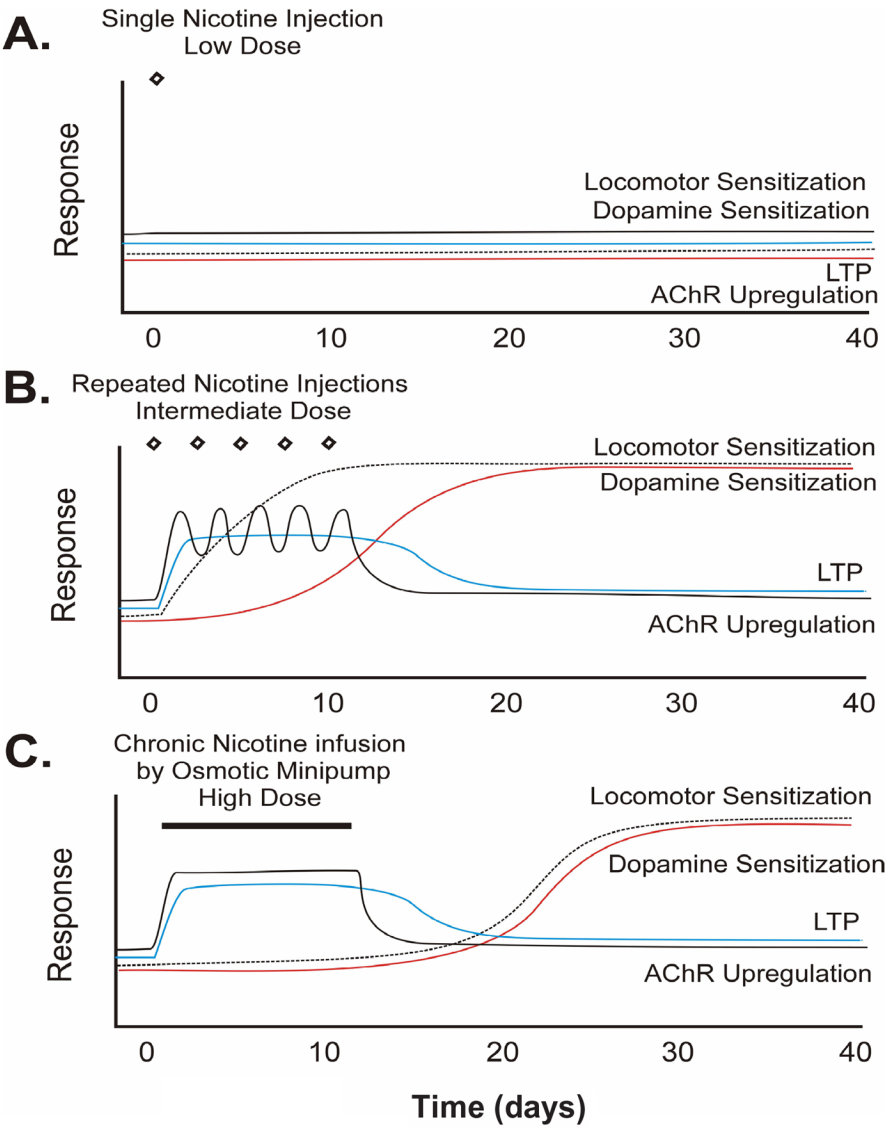

Figure 2.

Proposed model of the effect of increasingly intense exposure regimens on the induction and long-lasting expression of sensitization by nicotine. Plots show predictions by the model of effects produced by three examples of exposure regimens ranging from weak to intermediate to intense. **A. Weak.** Exposure to an insufficient number of injections or subthreshold doses of nicotine is without effect on any of the measures. **B. Intermediate.** Moderate exposure to nicotine (e.g., 5 injections of 0.4 mg/kg, i.p., one injection every other day) leads to the progressive enhancement of the drug's locomotor and later enhancement of the drug's DA activating effects. **C. Intense.** Prolonged and continuous exposure to nicotine (e.g., 15 days of continuous 3.0/mg/kg/day, s.c., or repeated injections of high doses) does not enhance responding in the days following termination of drug exposure. Enhanced responding is predicted to appear at later withdrawal times. Both intermediate and intense exposure regimens have been associated with transient nAChR upregulation. Transient expression of LTP has been reported following repeated injections of cocaine and is predicted to occur transiently following both nicotine exposure regimens. Both effects are proposed to be the initiating

neuroadaptations leading to long-lasting sensitization by nicotine. See text for supporting references.

Table 1

Exposure to nicotine leads to upregulation of brain nAChRs as indexed by increased ligand binding. These examples in rat brain show that nAChR upregulation is produced in a manner dependent on the intensity of the nicotine exposure regimen: low doses administered intermittently (1) or continuously (via osmotic minipump; 4) produce no effect while increasingly higher doses administered via either route produce upregulation (1, 4) that is observed in a greater number of brain regions (2, 3, 4, 5, 6) and persists for a longer period of time following exposure (2, 3). Note that enhanced locomotor responding to nicotine is observed in the period soon (1) and late (7) after intermittent exposure to moderate doses but not in the period immediately following exposure to a more intense regimen of nicotine injections (1). Exposure to a moderate intermittent nicotine injection regimen that leads to long-term locomotor sensitization produces transient nAChR upregulation in the VTA but not in the NAcc. Blockade of nAChRs in the VTA, but not the NAcc, during exposure prevents the development of locomotor sensitization by nicotine (7). These results are consistent with an important role for the transient upregulation of nAChRs in the VTA (and possibly other sites sending direct and indirect projections to this site) in the development of behavioral sensitization by nicotine. See text for additional references. All doses are expressed as base. Abbreviations: AuditC, primary auditory cortex; BLA, basolateral amygdaloid nucleus; CeAmyg, central amygdaloid nucleus; CingC, cingulate cortex; Cort, cortex; CPu, caudate putamen; Crb, cerrebellar cortex; Hb, hindbrain; Hip, hippocampus; Hyp, hypothalamus; LimbC, prelimbic and infralimbic cortex; Mid, midbrain; MotC, primary motor cortex; NAcc-C, nucleus accumbens core; NAcc-S, nucleus accumbens shell; NST, nucleus of the solitary tract; ParC, parietal cortex; PFC, prefrontal cortex; PirC, piriform/entorhinal cortex; SensC, primary sensory cortex; SNc, substantia nigra pars compacta; Str, striatum; Thal-c, central thalamic nucleus; Thal-pv, paraventricular thalamic nucleus; VTA, ventral tegmental nucleus. ↑, significant increase; →, no change; →↑, non-significant trend.

Nicotine Exposure Regimen	nAChR	Withdrawal	Locomotion	Reference
	[^{3}H]ACh - Cortex	1 day	loco-10min	1. Ksir et al., 1987
5 days sc - 1 X 0.01	→	0.2 nic at test	→	
0.03	↑		↑	
0.10	↑		↑	
0.30 mg/kg/day	↑		↑	
10 days sc - 2 X 1.6 mg/kg/day	↑	1 day	→	
		0.2 nic at test	cf saline exp	

	[^{3}H]Nic							2. Collins et al., 1988
	Str	Cort	Hip	Mid	Hyp	Hp		
7 days - 2 X 1.6 mg/kg/day	→	↑	→	↑	→	↑	0 day	
	→	↑	→	↑	→	↑	1 day	
	→	↑	→	↑	→	↑	2 day	
	→	↑	→	↑	→	↑	3 day	
	→	→	→	→	→	→	7 day	

	[^{3}H]Nic							3. Collins et al., 1990
	Str	Cort	Hip	Mid	Hyp	Hb		
7 days sc - continuous 0.8/mg/kg/hr	↑	↑	↑	↑	↑	↑	2 hr	
	↑	↑	↑	↑	↑	↑	1 day	
	↑	↑	↑	↑	↑	↑	2 days	
	↑	↑	↑	↑	↑	↑	4 days	
	→	↑	↑	→	→	→	8 days	
	→	→	→	→	→	→	21 days	

	[^{3}H]cytosine			< 1 day	4. Rowell & Li, 1997
	Striatum	PFC	Hip		
10 days sc - continuous 0.6	→	→	→		
1.2	→	↑	→		
2.4	↑	↑	↑		
4.8 mg/kg/day	↑	↑	↑		
- 2 X 0.3	→	→	↑		
0.6	→	↑	↑		
1.2	↑	↑	↑		
2.4 mg/kg/day	↑	↑	↑		
-4 X 0.6 mg/kg/day	→	↑	↑		

Nicotine Exposure Regimen		**nAChR**		**Withdrawal**	**Locomotion**	**Reference**
- 8 X 0.3 mg/kg/day	→	→	→			
		[^{3}H]nicotine		< 1 day		5. Mugnaini et al., 2002
15 days sc - continuous 3.0 mg/kg/day	AuditC ↑↑↑ LimbC ↑↑ MotC ↑↑ BLA ↑↑ SensC ↑↑ CingC ↑↑ CPu ↑↑		NAcc-C ↑↑ NAcc-S ↑↑ CeAmyg ↑ VTA ↑ SNc →↑ Thal-c →↑ Thal-pv →↑			
		[^{125}I]epibatidine		< 1 day		6. Parker et al., 2004
i.v. self-admin (5 days acq. + 13 days maint.) 13 days 1.5 mg/kg/day	NST ↑↑↑ VTA/SN ↑ ↑ ↑ NAcc ↑↑↑ Thal ↑↑ ParC ↑↑ Hyp ↑↑		Amyg ↑↑ PirC ↑ CPu ↑ Hip ↑ Crb →↑			
		[^{125}I]epibatidine			loco-2hr	7. Baker et al., 2005
5 days ip - 1 X 0.4 every other day	VTA		↑	3 hrs		
	NAcc		→			
	VTA		→	3 days - 3 weeks		
	NAcc		→			
5 days ip - 1 X 0.4 every other day				3 weeks	↑	
+ VTA mecamylamine				0.4 nic at test	→	
+ NAcc mecamylamine					↑	
					cf saline exp	