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Molecular mechanisms underlying the motivational effects of nicotine

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PREFACE

In addition to the primary rewarding properties of nicotine and the alleviation of withdrawal symptoms, cues associated with smoking are critical contributors to maintenance of smoking behavior. Nicotine-paired cues are also critical for precipitating relapse after smoking cessation. An accumulation of evidence suggests that repeated exposure to tobacco, including the primary psychoactive ingredient, nicotine, changes brain neurochemistry in a way that promotes the control that cues associated with smoking or other rewards have over behavior. This chapter will consider the neurochemical mechanisms underlying these neuroadaptations. Targeting these molecular alterations may provide novel treatments for smoking cessation.

INTRODUCTION

Cues and Nicotine Dependence

Nicotine reinforcement is important for the initiation of smoking behavior, however, brain systems important for incentive motivation, such as those that control responses to reward-associated cues, may play a predominant role in maintenance of tobacco use and relapse to smoking (Robinson & Berridge, 1993). It is interesting that sensory cues provided by tobacco smoke result in increased pleasure in smokers while smoking denicotinized cigarettes (Perkins, Gerlach, Vender, Grobe, Meeker, & Hutchison, 2001; Rose & Behm, 2004) and the success of behavioral therapies that devalue cigarettes is dependent on providing the flavor that matches smokers' regular brands (Rose & Behm, 2004). Smoking-associated cues that induce craving activate brain areas associated with liking nicotine (Brody, Mandelkern, London, Childress, Lee, Bota, Ho, Saxena, Baxter, Madsen, & Jarvik, 2002; Due, Huettel, Hall, & Rubin, 2002; Franklin, Wang, Wang, Sciortino, Harper, Li, Ehrman, Kampman, O'Brien C, Detre, & Childress, 2007). Together these studies suggest that smoking-associated cues can gain control over the areas of the brain that stimulate reward and such cues can be manipulated to aid in smoking cessation.

Animal studies also suggest that cues play a prominent role in nicotine dependence. In the absence of cues, rats self-administer nicotine at a steady rate, limiting their intake to approximately 10 infusions per hour (Caggiula, Donny, Chaudhri, Perkins, Evans-Martin, & Sved, 2002a). Nicotine appears to be a weak reinforcer on its own; however, simultaneous presentation of a cue with the same dose of nicotine greatly increases self-administration (Caggiula et al., 2002a; Caggiula, Donny, White, Chaudhri, Booth, Gharib, Hoffman, Perkins, & Sved, 2001, 2002b). Environmental cues previously paired with nicotine can support self-administration behavior in the absence of nicotine reward for weeks after removal of the nicotine reinforcer (Caggiula et al., 2002a; Cohen, Perrault, Griebel, & Soubrie, 2005). Not only do such cues promote the maintenance of smoking behaviors, but

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smoking-associated cues can also promote relapse to smoking (Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996; Waters, Shiffman, Bradley, & Mogg, 2003). Indeed, a nicotine-associated cue is a more efficient primer than the drug itself in reinstating nicotine self-administration in an animal model of relapse (Lesage, Burroughs, Dufek, Keyler, & Pentel, 2004). By virtue of being paired with nicotine, cues gain incentive salience value (Robinson & Berridge, 1993): they become conditioned reinforcers capable of eliciting self-administration behavior on their own and they become triggers that lead to craving for the drug with which they were paired (Tiffany & Drobles, 1990).

Prior chronic nicotine exposure enhances conditioned reinforcement—

Although environmental cues paired with smoking can drive nicotine intake, it is also the case that nicotine, acting through $\beta 2^*$ nAChRs, increases the ability to make associations between rewards and novel cues in rats and mice (i.e., conditioned reinforcement), even several weeks after nicotine has been withdrawn (Brunzell, Chang, Schneider, Olausson, Taylor, & Picciotto, 2006; Olausson, Jentsch, & Taylor, 2003, 2004a, 2004b). Nicotine also facilitates the association of cues with reward by acting as an occasion setter (Palmatier, Peterson, Wilkinson, & Bevins, 2004). Thus, nicotine can increase the salience of environmental cues, which in turn increase the drive to seek nicotine, resulting in a vicious cycle that is likely to drive both smoking behavior and relapse after smoking cessation (See Fig 1).

The nicotine dosing regimens that lead to enhanced conditioned reinforcement have also been shown to result in locomotor sensitization, changes in intracellular signaling, upregulation of nicotine binding and increased mesolimbic dopamine turnover (Brunzell & Picciotto, 2004; Gaddnas, Pietila, & Ahtee, 2000; King, Caldarone, & Picciotto, 2004; Sparks & Pauly, 1999). Like other drugs of abuse, sensitization of the DA system might regulate nicotine associated conditioned reward (Robbins & Everitt, 2002; Robinson & Berridge, 1993; Taylor & Robbins, 1984). The ability of nicotine to promote conditioned reinforcement is blocked by systemic administration of mecamylamine (Olausson et al., 2004a). In addition, studies using knockout mice suggest that the ability of prior chronic nicotine exposure to enhance conditioned reinforcement as well as nicotine-mediated enhancement of context conditioning is mediated through nicotinic acetylcholine receptors containing the $\beta 2$ subunit ($\beta 2^*$ nAChRs) (Brunzell et al., 2006; J.A. Davis & Gould, 2006; J. A. Davis & Gould, 2007).

There is an apparent dissociation between the role that $\beta 2^*$ nAChRs play in nicotine-associated enhancement of conditioned reward and conditioned reward at baseline. $\beta 2$ KO mice have a tendency towards enhanced responding for a cue over wild type mice, but only when the cue was previously paired with a primary reward. This suggests that $\beta 2^*$ nAChRs modulate conditioned reinforcement at baseline (Brunzell et al., 2006). It is known that baseline conditioned reinforcement and psychostimulant-mediated enhancement of conditioned reinforcement are controlled by DA projections to the NAc core and shell, respectively (in Robbins & Everitt, 2002) and recent data suggest that baseline contextual fear conditioning and nicotine-dependent enhancement of contextual fear are modulated by different nAChRs (J.A. Davis & Gould, 2006). It is therefore possible that baseline conditioned reinforcement and nicotine-mediated enhancement of conditioned reinforcement are regulated by nAChRs in different neuronal populations, or that long-term desensitization and activation of nAChRs is important for the ability of nicotine to increase conditioned reinforcement.

Desensitization of nAChRs may underlie the ability of nicotine to enhance cue salience—While it is clear that activation of nAChRs can depolarize and increase the firing rate of DA neurons acutely (Grenhoff, Aston-Jones, & Svensson, 1986; Klink, de

Kerchoue d'Exaerde, Zoli, & Changeux, 2001; Picciotto, Zoli, Rimondini, Lena, Marubio, Pich, Fuxe, & Changeux, 1998; Svensson, Grenhoff, & Engberg, 1990), electrophysiological studies show that continuous nicotine exposure, as might be seen in smokers who have significant blood levels of nicotine throughout the day, results in desensitization of midbrain nAChRs (Pidoplichko, DeBiasi, Williams, & Dani, 1997). Further, in striatal synaptosomes, lower doses of nicotine are required for desensitization than for activation of nAChRs as measured by nicotine-dependent DA release (S. Grady, Marks, Wonnacott, & Collins, 1992; S. R. Grady, Marks, & Collins, 1994; Rowell & Duggan, 1998; Rowell & Hillebrand, 1994). The progressive desensitization of nAChRs may explain why smokers generally report that the first cigarette of the day is the most pleasurable (Russell, 1989).

Using a PET ligand recognizing $\beta 2^*$ nAChRs, it has been shown that very low levels of nicotine are sufficient to displace the majority of nAChR binding in human brain (Brody, Mandelkern, London, Olmstead, Farahi, Scheibal, Jou, Allen, Tiongsong, Chefer, Koren, & Mukhin, 2006). This observation may be due to the fact that the high affinity nicotinic binding sites visualized using these ligands represent the subset of nAChRs that are already desensitized, and therefore in an allosteric state that binds nicotinic ligands more tightly (Changeux, Devillers-Thiery, & Chemouilli, 1984). Another possibility is that smokers take in nicotine both to initially activate and then to inactivate their nAChRs. Electrochemical studies using cyclic voltammetry suggest that desensitization and inactivation of nAChRs in the NAc may be a mechanism that tunes DA neurons (Rice & Cragg, 2004; Zhang & Sulzer, 2004). Nicotine or a nicotinic antagonist result in similar effects on this tuning process, suggesting that desensitization is the critical molecular event (Rice & Cragg, 2004; Zhang & Sulzer, 2004). Desensitization of $\beta 2^*$ nAChRs decreases DA release when the DA neurons are firing tonically, but enhances DA release when DA neurons are in a phasic state (Rice & Cragg, 2004), as one would expect during the presentation of a reward (Schultz, 2002). As environmental cues gain more control over behavior following repeated presentation of cues with a primary reinforcer, there is a transition from phasic activity of DA neurons in response to the primary reinforcer, to phasic activity in response to the cue (Schultz, 2002). Thus, desensitization of nAChRs may enhance the response to environmental cues paired with smoking and make them more salient.

Brain areas important for nicotine's effects on cue responding

It is clear that nAChRs in the VTA are critical for behaviors related to nicotine addiction (Corrigall, Coen, & Adamson, 1994; Maskos, Molles, Pons, Besson, Guiard, Guilloux, Evrard, Cazala, Cormier, Mameli-Engvall, Dufour, Cloez-Tayarani, Bemelmans, Mallet, Gardier, David, Faure, Granon, & Changeux, 2005). The terminals of VTA neurons project to the NAc, but significant projections also go from the VTA to other brain regions implicated in responding for drug-paired cues, including the hippocampus, prefrontal cortex (PFC), and amygdala (Jentsch & Taylor, 1999; Robbins & Everitt, 2002). PET studies in human subjects show that DA is released in the NAc following cigarette smoking (Brody, Olmstead, London, Farahi, Meyer, Grossman, Lee, Huang, Hahn, & Mandelkern, 2004) and animal studies have shown that both systemic and VTA administration of nicotine result in increased extracellular DA levels in the NAc (Benwell & Balfour, 1992; Di Chiara & Imperato, 1988; Ferrari, Le Novere, Picciotto, Changeux, & Zoli, 2002). The VTA, NAc, amygdala, and PFC, are activated in human imaging studies in response to craving and presentation of cigarette-associated cues (Brody et al., 2002; Due et al., 2002) even in the absence of nicotine withdrawal (Franklin et al., 2007), suggesting that these brain areas regulate incentive salience of cues for smoking. Interestingly, cigarette cues also activate the insular cortex (Franklin et al., 2007) which when lesioned, abolishes the desire to smoke without any symptoms of craving or (Naqvi, Rudrauf, Damasio, & Bechara, 2007).

Animal imaging studies show that acute administration of nicotine or the $\beta 2^*$ nAChR agonist 5IA-85380 activate the PFC and the basolateral amygdala (Gozzi, Schwarz, Reese, Bertani, Crestan, & Bifone, 2005), brain areas known to have glutamatergic inputs to the NAc and to be necessary for expression of conditioned reinforcement (Robbins & Everitt, 2002). Psychostimulant-mediated enhancement of conditioned reinforcement is dependent on DA release in the NAc shell (Cador, Taylor, & Robbins, 1991; Taylor & Robbins, 1986) where both $\alpha 4/\beta 2^*$ nAChRs and $\alpha 6/\beta 2/\beta 3^*$ nAChRs are found on DA terminals, and is regulated by the central nucleus of the amygdala and the subiculum (Robbins & Everitt, 2002) where $\alpha 4/\beta 2^*$ nAChRs predominate (Cui, Booker, Allen, Grady, Whiteaker, Marks, Salminen, Tritto, Butt, Allen, Stitzel, McIntosh, Boulter, Collins, & Heinemann, 2003; Pauly, Marks, Gross, & Collins, 1991).

Contextual cues paired with nicotine administration result in immediate early gene activation of the NAc, amygdala, hippocampus, and PFC (Kelley, 2006; Schiltz, Kelley, & Landry, 2005, 2007; Schochet, Kelley, & Landry, 2005; Schroeder, Binzak, & Kelley, 2001), suggesting that changes in both neuronal activity and gene expression in these mesolimbic structures is likely to be involved in behavioral responses to nicotine-associated conditioned reinforcers. The DA projection areas also receive glutamate stimulation, and it is likely that these neurotransmitters are important for encoding the salience of drug-paired cues since coordinate input of these two neurotransmitters onto NAc neurons is thought to be essential for both drug reinforcement and response to natural rewards (Kelley, 2004; Robbins & Everitt, 2002).

The role of glutamate signaling in nicotine reward has been demonstrated pharmacologically using antagonists of metabotropic glutamate receptor subtype 5 (mGluR5) which decrease self-administration, progressive ratio responding and cue-induced reinstatement of nicotine (Bespalov, Dravolina, Sukhanov, Zakharova, Blokhina, Zvartau, Danysz, van Heeke, & Markou, 2005; Paterson & Markou, 2005; Paterson, Semenova, Gasparini, & Markou, 2003). With respect to the DA system, the DA D3 receptors are up-regulated in the NAc shell following repeated nicotine exposure, and blocking this class of DA receptors decreases both the locomotor response resulting from exposure to a nicotine-paired context and nicotine conditioned place preference (Le Foll, Diaz, & Sokoloff, 2003; Le Foll, Schwartz, & Sokoloff, 2003; Le Foll, Sokoloff, Stark, & Goldberg, 2005). Thus, both glutamate and DA signaling are likely to be important for the control of nicotine-paired cues over behavior.

Role of DA in nicotine-mediated behaviors—The mesocorticolimbic DA system is thought to regulate various behaviors that contribute to incentive motivation for drugs of abuse (for detailed review see Jentsch & Taylor, 1999; Robbins & Everitt, 2002; Robinson & Berridge, 2001). Like other drugs of abuse, nicotine regulates mesolimbic DA release and is thought to act in part via this mechanism to control behaviors associated with nicotine addiction (Di Chiara & Imperato, 1988). DA receptor activity is necessary for nicotine self-administration (Corrigall, Franklin, Coen, & Clarke, 1992), conditioned place preference (Shoaib, Stolerman, & Kumar, 1994), locomotor activation (Benwell & Balfour, 1992; Di Chiara & Imperato, 1988; King et al., 2004) and conditioned locomotor activation (Bevins, Besheer, & Pickett, 2001; Palmatier & Bevins, 2002); all of these behaviors are sensitive to manipulation of cues. Blockade of nAChRs in the VTA (Corrigall et al., 1994; Laviolette & van der Kooy, 2003) or lesions of DA neurons (Corrigall et al., 1992) reduce nicotine self-administration and conditioned place preference. $\beta 2^*$ nAChRs on dopaminergic cell bodies increase their firing rate (Klink et al., 2001; Picciotto et al., 1998; Sorenson, Shiroyama, & Kitai, 1998; Wu, George, Schroeder, Xu, Marxer-Miller, Lucero, & Lukas, 2004), and in addition, presynaptic nAChRs in both the VTA and NAc can modulate DA release (Mansvelder, Keath, & McGehee, 2002; Pidoplichko, Noguchi, Areola, Liang, Peterson,

Zhang, & Dani, 2004; Salminen, Murphy, McIntosh, Drago, Marks, Collins, & Grady, 2004; Wooltorton, Pidoplichko, Broide, & Dani, 2003) and regulate DA transporter activity (Middleton, Cass, & Dwoskin, 2004).

NACHR subtypes involved in modulating the DA system—Knockout mouse studies have shown that $\alpha 4/\beta 2^*$ nAChRs are critical for nicotine-elicited increases in DA release, DA-dependent locomotor activation, nicotine conditioned place preference and nicotine self-administration in studies using knockout mice lacking these individual subunits (King et al., 2004; Marubio, Gardier, Durier, David, Klink, Arroyo-Jimenez, McIntosh, Rossi, Champtiaux, Zoli, & Changeux, 2003; Picciotto et al., 1998; Walters, Brown, Changeux, Martin, & Damaj, 2006). Correspondingly, knockin mice with $\alpha 4^*$ nAChRs that are hypersensitive to nicotine show nicotine conditioned place preference at a very low dose of nicotine (Tapper, McKinney, Nashmi, Schwarz, Deshpande, Labarca, Whiteaker, Marks, Collins, & Lester, 2004). It would be interesting to determine whether these mice show increased incentive salience as well. Both nicotine-mediated DA release and local self-administration of nicotine into the VTA can be rescued by lentiviral-mediated expression of the $\beta 2$ subunit in the VTA of $\beta 2$ KO mice (Maskos et al., 2005). These studies in genetically modified mice are in accord with pharmacological studies showing that rats will self-administer a selective $\alpha 4/\beta 2^*$ agonist, 5IA-85380 (Liu, Koren, Yee, Pechnick, Poland, & London, 2003) and that VTA administration of antagonists of $\alpha 4/\beta 2^*$ nAChRs decrease nicotine self-administration (Corrigall et al., 1992; Grottick, Trube, Corrigall, Huwyler, Malherbe, Wyler, & Higgins, 2000).

Another nAChR that may be important for nicotine reward is the $\alpha 6/\beta 3^*$ nAChR subtype. An antisense oligonucleotide against the $\alpha 6$ nAChR subunit blocks nicotine-dependent locomotor activation in rats (le Novere, Zoli, Lena, Ferrari, Picciotto, Merlo-Pich, & Changeux, 1999). $\alpha 6/\beta 2/\beta 3^*$ nAChRs are located on DA terminals and contribute to nicotine-stimulated DA release (Champtiaux, Gotti, Cordero-Erausquin, David, Przybylski, Lena, Clementi, Moretti, Rossi, Le Novere, McIntosh, Gardier, & Changeux, 2003; Salminen et al., 2004), and thus could contribute behaviors mediated through NAc DA signaling, including conditioned reinforcement and psychostimulant-mediated enhancement of conditioned reinforcement. Upregulation of $\alpha 6/\beta 2/\beta 3^*$ nAChRs in the NAc could be responsible for the ability of nicotine to enhance conditioned reinforcement (Parker, Fu, McAllen, Luo, McIntosh, Lindstrom, & Sharp, 2004); however, several studies suggest that these nAChRs are downregulated in the NAc following chronic nicotine exposure (Lai, Parameswaran, Khwaja, Whiteaker, Lindstrom, Fan, McIntosh, Grady, & Quik, 2005; McCallum, Parameswaran, Bordia, Fan, McIntosh, & Quik, 2006; Mugnaini, Garzotti, Sartori, Pilla, Repeto, Heidbreder, & Tessari, 2006), so sensitization at the level of $\alpha 6/\beta 2/\beta 3^*$ nAChRs may not underlie lasting effects of nicotine on behavior, such as enhancement of conditioned reinforcement. $\alpha 6/\beta 2/\beta 3^*$ nAChRs are also located on DA cell bodies in the VTA (Klink et al., 2001). As α -conotoxin-MII sensitive (i.e. $\alpha 6/\beta 2/\beta 3^*$ nAChRs) and insensitive $\beta 2^*$ nAChRs respond similarly to DH β E and 5IA-85350 (Kulak, Sum, Musachio, McIntosh, & Quik, 2002; Mogg, Whiteaker, McIntosh, Marks, Collins, & Wonnacott, 2002; Salminen et al., 2004), it is possible that $\alpha 6/\beta 2/\beta 3^*$ nAChRs are required for nicotine self-administration (Corrigall et al., 1994; Liu et al., 2003). In fact, a single nucleotide polymorphism in the $\beta 3$ subunit is linked to tobacco dependence in smokers (Bierut, Madden, Breslau, Johnson, Hatsukami, Pomerleau, Swan, Rutter, Bertelsen, Fox, Fugman, Goate, Hinrichs, Konvicka, Martin, Montgomery, Saccone, Saccone, Wang, Chase, Rice, & Ballinger, 2007).

Although $\alpha 7^*$ nAChRs are important for synaptic plasticity following nicotine exposure in the VTA (Mansvelder et al., 2002; Pidoplichko et al., 1997) it is still not clear what role these nAChRs play in nicotine reward. Local VTA administration of methyllycaconitine

(MLA), an antagonist which was thought to be selective for $\alpha 7^*$ nAChRs, blocks nicotine conditioned place preference (Laviolette & van der Kooy, 2003) and high doses of MLA attenuate nicotine self-administration in rats (Markou & Paterson, 2001). Although these studies suggest that $\alpha 7$ nAChRs might contribute to nicotine reward, $\alpha 7$ knockout mice show normal nicotine place preference across a range of doses (Walters et al., 2006). Because MLA competes with α -conotoxin-MII binding at doses that are behaviorally effective (S. R. Grady, Meinerz, Cao, Reynolds, Picciotto, Changeux, McIntosh, Marks, & Collins, 2001; Salminen, Whiteaker, Grady, Collins, McIntosh, & Marks, 2005), it is possible that antagonism of $\alpha 6^*$ nAChRs might be responsible for MLA-dependent attenuation of nicotine reward.

Intracellular signaling downstream of nAChRs

The ability of nicotine to change synaptic strength of mesolimbic DA neurons (Mansvelder et al., 2002; Pidoplichko et al., 1997; Rice & Cragg, 2004; Zhang & Sulzer, 2004) is likely to be critical for the long-lasting changes in behavior that result from repeated nicotine administration. Long-term changes in synaptic transmission result from activation of intracellular signaling cascades (Greengard, 2001). A number of intracellular signaling pathways are known to be critical for synaptic plasticity in the hippocampus and contribute to learning and memory (for detailed review see Silva, Kogan, Frankland, & Kida, 1998; Sweatt, 2004). Among those signaling molecules regulated by nicotine are the extracellular-regulated protein kinase (ERK) and cyclic AMP responsive element binding protein (CREB) (Brunzell, Russell, & Picciotto, 2003; Pandey, Roy, Xu, & Mittal, 2001; Valjent, Pages, Herve, Girault, & Caboche, 2004; Walters, Cleck, Kuo, & Blendy, 2005). *In vitro* studies show that ERK is activated following nicotine exposure and is necessary for nicotine-dependent activation of CREB (Chang & Berg, 2001; Dineley, Westerman, Bui, Bell, Ashe, & Sweatt, 2001; Nakayama, Numakawa, Ikeuchi, & Hatanaka, 2001). *In vivo*, nicotine has region- and treatment-dependent effects on the levels and activation state of ERK and CREB (Brunzell et al., 2003; Valjent et al., 2004). Acute nicotine administration increases activation of ERK in amygdala and PFC (as measured by levels of phosphorylated ERK (pERK)) (Valjent et al., 2004). In contrast, chronic nicotine administration increases pERK in the PFC, but decreases both ERK and pERK in the amygdala (Brunzell et al., 2003).

The transcription factor CREB appears to be essential for nicotine-associated cue-dependent learning. Wild type mice show increased pCREB in VTA in response to acute nicotine exposure, a nicotine conditioned place preference paradigm or exposure to a novel environment that had been paired with nicotine, and knockout mice lacking CREB do not show nicotine conditioned place preference (Walters et al., 2005). The ability of the nicotine-paired chamber to increase phosphorylated or active CREB (pCREB) in the NAc (Walters et al., 2005) suggests that this neuroadaptation could be associated with the ability of nicotine to increase conditioned reinforcement. Chronic nicotine exposure results in upregulation of total CREB levels in the NAc of mice (Brunzell et al., 2003), perhaps further promoting incentive salience of nicotine-associated cues. Post mortem studies on human brain indicate that protein kinase A (PKA) activity is elevated in the NAc and ventral midbrains of smokers (Hope, Nagarkar, Leonard, & Wise, 2007). PKA could promote synaptic plasticity via phosphorylation of CREB leading to CRE-mediated transcription. Reductions in NAc pCREB observed following chronic nicotine in rodents, however, suggest that homeostatic mechanisms occur in the NAc (Brunzell et al., 2003; Pandey et al., 2001).

Both nicotine exposure and withdrawal modulate pCREB levels in the NAc, PFC, VTA, and amygdala (Brunzell et al., 2003; Pandey et al., 2001; Walters et al., 2005). Increases in pCREB in the PFC occur only after chronic nicotine exposure in mice (Brunzell et al., 2003) and decrease in rats following nicotine withdrawal (Pandey et al., 2001), suggesting that

CREB activity may be recruited in the PFC after repeated pairing of nicotine exposure and environmental cues. As indicated above, nicotine-associated cues elicit arc and c-fos immediate early gene activity in the PFC, amygdala, and nucleus accumbens (Schiltz et al., 2005; Schroeder et al., 2001), suggesting that by virtue of their association with nicotine, cues become capable of altering new gene transcription in areas of the brain that regulate reward.

Conclusions

An incentive motivation theory of nicotine reward can explain why smokers experience intense craving to smoke despite the relatively modest reinforcing value of nicotine (Robinson & Berridge, 1993). Though studies using other psychostimulants provide insights into the mechanisms underlying nicotine-associated effects on incentive motivation, the systems that control incentive motivation for nicotine are less understood. $\beta 2^*$ nAChRs appear to modulate cue-dependent behavior as well as nicotine-associated enhancement of conditioned reinforcement. nAChRs are expressed in mesolimbic structures that contribute to conditioned reinforcement, but further studies are necessary to identify the specific role that various nAChR subtypes, and their downstream signaling targets, play in incentive sensitization.

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Figure 1. Nicotine drives associations with environmental cues that, in turn, drive nicotine intake

Exposure to environmental cues paired with nicotine self-administration greatly increases nicotine intake. Conversely, exposure to nicotine increases the ability of cues to drive responding for rewarding stimuli (conditioned reinforcement). It is clear that $\alpha 4/\beta 2^*$ nAChRs are important for both nicotine reinforcement and for the ability of nicotine to increase conditioned reinforcement. Other nAChR subtypes, including $\alpha 6/\beta 3^*$ and $\alpha 7^*$ nAChRs may also contribute to these processes. D3 type dopamine receptors (D3R), μ -opioid receptors (μR), and the transcription factor CREB can contribute to the ability of nicotine-paired cues to drive behavior. Targeting these molecular processes could result in novel treatments for smoking cessation.