Neurobiological Bases of Cue- and Nicotine-induced Reinstatement of Nicotine Seeking: Implications for the Development of Smoking Cessation Medications

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Abstract A better understanding of the neurobiological factors that contribute to relapse to smoking is needed for the development of efficacious smoking cessation medications. Reinstatement procedures allow the preclinical assessment of several factors that contribute to relapse in humans, including re-exposure to nicotine via tobacco smoking and the presentation of stimuli that were previously associated with nicotine administration (i.e., conditioned stimuli). This review provides an integrated discussion of the results of animal studies that used reinstatement procedures to assess the efficacy of pharmacologically targeting various neurotransmitter systems in attenuating the cue- and nicotine-induced reinstatement of nicotine seeking. The results of these animal studies have increased our understanding of the neurobiological processes that mediate the conditioned effects of stimuli that trigger reinstatement to nicotine seeking. Thus, these findings provide important insights into the neurobiological substrates that modulate relapse to tobacco smoking in humans and the ongoing search for novel efficacious smoking cessation medications.

Keywords Animal models · Nicotine · Cue-induced reinstatement · Nicotine-induced reinstatement · Drug seeking · Medication development

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1 Introduction

The negative impact of tobacco consumption on health remains one of the most urgent health issues (Alberg et al. 2014) because the global number of tobacco smokers continues to steadily increase (Ng et al. 2014). Although the health risks associated with tobacco smoking are greatly reduced by the cessation of tobacco consumption, fewer than 5 % of all quit attempts result in lifelong abstinence from tobacco smoking (Hughes et al. 2004). The vast majority of current smokers have considered or undertaken at least one quit attempt. Specifically, a recent survey of tobacco smokers in the USA reported that two-thirds of the respondents wished to quit their harmful habit and that over half of the respondents had undertaken one quit attempt in the previous year (Centers for Disease Control and Prevention 2010). However, despite the currently available smoking cessation medications and behavioral intervention treatments, an estimated half of smokers failed to quit their habit, despite multiple quit attempts during their lifetime (Centers for Disease Control and Prevention 2000). Relapse to tobacco seeking is thus one of the most defining features of tobacco dependence. To decrease relapse rates, the identification of novel pharmacological targets is needed. The development of these novel pharmacological targets in the treatment of tobacco dependence requires the use of procedures in experimental animals that mimic aspects of relapse in humans.

Nicotine is the main psychoactive ingredient in tobacco (Stolerman and Jarvis 1995). Therefore, experimental animal research that focuses on identifying pharmacological targets for novel smoking aids primarily assesses the effects of nicotine. The reinstatement procedure is one of the most widely used tools for screening the effects of pharmacological compounds on "relapse" to nicotine seeking in animals. The reinstatement of nicotine-seeking behavior is broadly defined as the continuation of the behavioral response that previously resulted in nicotine delivery

after noncontingent exposure to nicotine (nicotine-induced reinstatement) or the presentation of stimuli (e.g., cue light illumination and sounds associated with activation of the pump that delivers nicotine) that were previously associated with nicotine administration (cue-induced reinstatement) after a period of abstinence. In the reinstatement procedure, animals are allowed to self-administer nicotine for a prolonged period of time before undergoing extinction training. During extinction training, the animals are placed in the chambers where they were previously allowed to intravenously self-administer nicotine, while nicotine and its conditioned cues are withheld. Alternatively to extinction training, animals may also undergo a period of forced abstinence. During this period of abstinence, also referred to as the incubation of nicotine seeking (Abdolahi et al. 2010; Bedi et al. 2011), the animals remain in their home cages during the withdrawal period. Nicotine seeking in animals can then be reinstated by manipulations that have been associated with relapse in human smokers. Conditions that induce relapse to tobacco smoking in humans include tobacco smoking itself, conditioned cues, and stress (Doherty et al. 1995). In parallel to humans, rodent studies have shown that noncontingent nicotine administration (Dravolina et al. 2007), conditioned cues (Paterson et al. 2005), and stress (Bruijnzeel et al. 2009) all induce the reinstatement of nicotine-seeking behavior (see chapters entitled Behavioral Mechanisms Underlying Nicotine Reinforcement and The Role of Mesoaccumbens Dopamine in Nicotine Dependence; this volume). Importantly, the overlap in factors that induce relapse in humans and reinstatement in experimental animals suggests good etiological validity for the reinstatement model.

Predictive validity for the reinstatement procedure in terms of pharmacological isomorphism (Geyer and Markou 1995) is provided by various studies that identified compounds that attenuate both relapse in humans and the reinstatement of nicotine seeking in animals. For example, the opioid receptor antagonist naltrexone facilitated smoking cessation and reduced relapse rates in humans (Epstein and King 2004; King 2002; King et al. 2012, 2013; King and Meyer 2000) and effectively attenuated the reinstatement of nicotine seeking in rats (Liu et al. 2009). Another example is the cannabinoid CB_1 receptor antagonist rimonabant, which similarly decreased relapse to tobacco consumption in humans and reinstatement to nicotine seeking in rats (Cahill and Ussher 2011; Diergaarde et al. 2008; Forget et al. 2009). In contrast, however, two smoking cessation medications that are currently approved by the United States Food and Drug Administration (FDA) produced mixed results in studies of reinstatement of nicotine seeking in rats. Specifically, bupropion enhanced cue-induced reinstatement of nicotine seeking (Liu et al. 2008), while varenicline attenuated nicotine-induced, but not cue-induced, reinstatement of nicotine seeking (O'Connor et al. 2010). This variability in findings may reflect the different neurocircuits that probably underlie different aspects of the reinstatement of nicotine seeking. Results from reinstatement studies of drug seeking for other psychostimulant drugs, including cocaine, support the postulation that distinct neurocircuits are involved in the regulation of diverse aspects of the reinstatement of drug seeking (for reviews, see Kalivas and

McFarland 2003; See et al. 2003). The sections below briefly describe several neurocircuits that regulate diverse aspects of nicotine dependence, followed by discussions of the various neurotransmitter systems that are of interest in studies of the reinstatement of nicotine seeking.

2 Neurocircuits of Interest in Studies of the Reinstatement of Nicotine Seeking

2.1 Mesolimbic System

Dopaminergic projections from the ventral tegmental area (VTA) to nucleus accumbens (NAc) are critically involved in mediating the reinforcing and motivational properties of nicotine (Gerasimov et al. 2000; Laviolette and van der Kooy 2004). Nicotine directly activates these dopaminergic projections through β2-containing nicotinic acetylcholine receptors (nAChRs; see chapters entitled Structure of Neuronal Nicotinic Receptors and Genetics of Smoking Behaviour; volume 23) on VTA dopaminergic neurons (Mameli-Engvall et al. 2006) and indirectly through α7 nAChRs located on VTA glutamatergic neurons (Mansvelder and McGehee 2000). Pharmacological compounds that provide low levels of stimulation of dopaminergic projections to the NAc may therefore result in decreased nicotine-seeking behavior. In fact, the efficacy of the nicotinic receptor partial agonist varenicline, one of the few FDA-approved smoking cessation aids, in attenuating relapse to smoking in humans is assumed to partially result from low stimulatory actions at β2-containing nAChRs located on dopaminergic projections from the VTA to NAc (West et al. 2008). Alternatively, increased glutamatergic neurotransmission through the activation of excitatory α7 nAChRs, located on glutamatergic terminals that synapse on VTA dopamine neurons, activates dopaminergic projections from the VTA to NAc (Mansvelder and McGehee 2000). Moreover, a recent study by Gipson et al. (2013) demonstrated that glutamatergic neurotransmission in the NAc contributed to the cue-induced reinstatement of nicotine-seeking behavior, supporting an important role for the mesolimbic neurocircuit in the reinforcing and motivational effects of nicotine and the reinstatement of nicotine seeking. Findings from rat studies indicated changes in glutamatergic neurotransmission in the NAc during early nicotine withdrawal (i.e., 24 h after the cessation of nicotine self-administration; Knackstedt et al. 2009; Liechti et al. 2007). Subsequent studies by Gipson et al. (2013) revealed that these changes in NAc glutamatergic synaptic plasticity persist when the withdrawal period is extended to 2 weeks. Moreover, the cue-induced reinstatement procedure induced simultaneous increases in glutamatergic neurotransmission in the NAc and nicotine seeking (Gipson et al. 2013), further indicating the importance of glutamatergic neurotransmission in the mediation of cue-induced reinstatement.

2.2 Habenulo-interpeduncular Circuit

Opposite to the role of the corticolimbic neurocircuit in the reinforcing effects of nicotine, the habenulo-interpeduncular circuit appears to be important in mediating the aversive effects of nicotine (Fowler et al. 2011, 2013; Frahm et al. 2011). The medial habenula became of interest in the study of nicotine dependence when genetic linkage studies found that genetic variation in the gene cluster that encodes the α3, α5, and β4 nAChR subunits, which are densely located in the habenular circuit (De Biasi and Salas 2008), was associated with lung cancer and nicotine dependence in humans (Saccone et al. 2007, 2010). Mice null for the α5 nAChR subunit vigorously self-administered very high concentrations of nicotine (Fowler et al. 2011). Moreover, re-expression of the α5 nAChR subunit in the medial habenula in these knockout mice returned their increased self-administration rates of high nicotine doses back to rates observed in wild-type mice (Fowler et al. 2011), highlighting the involvement of the habenula-interpeduncular pathway in the high nicotine intake in these knockout mice. The effects of null mutation of the α5 nAChR subunit on nicotine consumption were explained in a later study by Fowler and colleagues. This study suggested that the reward-suppressing effects that high nicotine doses induce in wild-type mice were absent in α5 knockout mice (Fowler et al. 2013). Similarly, increased activity of β4 nAChR subunits in mice, in which the *CHRNA5-CHRNA3-CHRNB4* gene cluster was co-expressed with a bacterial artificial chromosome, resulted in the consumption of markedly less nicotine in a no-choice bottle procedure, presumably because of the aversion to nicotine that these mice exhibit in the conditioned place aversion procedure (Frahm et al. 2011; see also chapter entitled Genetics of Smoking Behaviour; volume 23). Lentiviral expression of the D398N α5 variant, which has been genetically associated with nicotine dependence and lung cancer in humans (Falvella et al. 2009; Hung et al. 2008; Wang et al. 2009), in the medial habenula reversed the aversion to nicotine in these mice (Frahm et al. 2011). These studies suggest the involvement of habenular α5 and β4 nAChR subunits in the aversive effects of nicotine, but the role of the habenulo-interpeduncular circuit in the reinstatement of nicotine-seeking behavior remains to be explored. Nevertheless, the somatic signs of nicotine withdrawal were attenuated in mice null for the both α5 and β4 nAChR subunits (Jackson et al. 2008; Salas et al. 2007; Stoker et al. 2012), suggesting that these nAChR subunits may be involved in mediating at least some of the aversive aspects of the nicotine withdrawal syndrome and that pharmacologically targeting these nAChR subunits may alleviate the negative withdrawal symptoms that ultimately result in the reinstatement of nicotine seeking.

2.3 Insular Cortex and Dorsal Striatum

Compared with the mesolimbic and habenulo-interpeduncular neurocircuits, the insula and dorsal striatum are thought to be recruited in later stages of drug dependence when drug-taking behavior becomes more habitual (for reviews, see Everitt et al. 2008; Naqvi and Bechara 2009). These brain structures are therefore particularly interesting in the study of drug reinstatement. The insular cortex became of interest in the study of relapse to tobacco smoking when Naqvi and colleagues reported that damage to the insular cortex facilitated spontaneous smoking cessation in humans, presumably by relieving symptoms of craving (Naqvi et al. 2007). Similarly, pharmacological or electrical inactivation of the insula attenuated the cue- and nicotine-induced reinstatement of nicotine-seeking behavior in animals (Forget et al. 2010a; Pushparaj et al. 2013). Subsequent studies provided additional evidence that the insula critically regulates different aspects of dependence on various psychostimulants and is particularly important in mediating the effects of conditioned cues associated with drug craving (Abdolahi et al. 2010; Contreras et al. 2007, 2012; Forget et al. 2010a; Hollander et al. 2008; Scott and Hiroi 2011). The insula projects to the dorsal striatum, a brain region implicated in the habitual and compulsive aspects of drug dependence. Interestingly, a recent case report described a patient in whom a lesion of the dorsal striatum resulted in the attenuation of nicotine intake (Muskens et al. 2012), similar to the effects of lesions of the insula on smoking cessation. In animals, studies of the involvement of the dorsal striatum in drug seeking have primarily focused on psychostimulant drugs other than nicotine, most notably cocaine. Lesions or pharmacological inactivation of the dorsal striatum in rats attenuated cocaine-seeking behavior (Fuchs et al. 2006; Fucile et al. 1997; Fung and Richard 1994; Gabriele and See 2011). The effects of conditioned cues associated with cocaine were shown to be mediated by dopaminergic neurotransmission in the dorsal striatum in animals (Ito et al. 2002) and humans (Volkow et al. 2006).

3 Role of Various Neurotransmitter Systems in Cue- and Nicotine-induced Reinstatement of Nicotine-seeking Behavior

3.1 Acetylcholine

All smoking cessation medications that are currently approved by the FDA (i.e., nicotine replacement therapy, varenicline, and bupropion) have some affinity at nAChRs (Coe et al. 2005; Slemmer et al. 2000; Thompson and Hunter 1998). While these medications are ineffective in approximately 80 % of smokers who attempt to quit smoking (Gonzales et al. 2006; Hughes et al. 2003; Jorenby et al. 2006), nAChRs have remained key targets in the research and development of

novel pharmacotherapies for smoking cessation. Bupropion, a medication widely used for smoking cessation, was initially used as an antidepressant therapy and primarily acts as a dopamine and norepinephrine reuptake inhibitor. Interestingly, bupropion was also found to act as an nAChR antagonist after it was marketed as a smoking cessation medication (Slemmer et al. 2000). bupropion has had mixed effects on smoking cessation rates in humans (Hurt et al. 1997) and actually enhanced the cue-induced reinstatement of nicotine seeking in rats (Liu et al. 2008). These results suggest that bupropion may have limited efficacy at treating the full spectrum of relapse and may primarily alleviate depressive-like symptoms during withdrawal (Cryan et al. 2003; Paterson et al. 2007).

Varenicline, a partial agonist at α4β2-containing nAChRs (Coe et al. 2005), was synthesized after studies suggested the crucial involvement of β2 nAChRs in nicotine dependence (Maskos et al. 2005; Picciotto 1998). Preclinical studies that assessed the effects of varenicline on the reinstatement of nicotine-seeking behavior demonstrated mixed effects on cue- and nicotine-induced reinstatement. Specifically, the nicotine-induced reinstatement of nicotine seeking was attenuated by varenicline in rats (see Fig. 1b adapted from O'Connor et al. 2010), similar to the effects of varenicline in humans. In contrast, varenicline did not affect the cue-induced reinstatement of nicotine-seeking behavior in rats (O'Connor et al. 2010; Wouda et al. 2011, see Fig. 1a adapted from Wouda et al. 2011), and higher doses of varenicline even enhanced cue-induced reinstatement (Wouda et al. 2011). Interestingly, varenicline attenuated the cue-induced reinstatement of nicotine seeking with a prolonged pretreatment time (Le Foll et al. 2012). When reinstatement was induced by both nicotine priming and the presentation of cues, varenicline also attenuated the reinstatement of nicotine seeking (O'Connor et al. 2010), presumably because of the attenuating effect of varenicline on nicotine-induced reinstatement. Altogether, preclinical studies on the effects of varenicline on nicotine seeking suggest the differential regulation of cue- and nicotine-induced reinstatement. Furthermore, Liu (2014) demonstrated that α7 nAChR antagonism with methyllycaconitine (MLA) but not α4β2-containing nAChR antagonism with dihydro-β-erythroidine (DHβE) reduced the cue-induced reinstatement of nicotine seeking. The results with varenicline and DHβE suggest that α4β2-containing nAChRs may be involved in the regulation of nicotine-induced, but not cue-induced reinstatement of nicotine seeking. In contrast, α7 nAChRs may be involved in mediating the cue-induced reinstatement of nicotine seeking. The enhancement of cue-induced reinstatement that results from administration of higher doses of varenicline (Wouda et al. 2011) may be explained by the activation of α7 nAChRs by varenicline, which acts as a full agonist at these receptors (Mihalak et al. 2006). This interpretation is further supported by results from the study by Liu (2014), which showed that α7 nAChR blockade attenuated cue-induced reinstatement. Further support for the involvement of α7 nAChRs in nicotine seeking reinstated by the presentation of conditioned cues, but not nicotine, is provided by the results of a study that reported that TAT-α7-pep2, a protein that interferes with the function of the α7nAChR–NMDA receptor complex, reduced the cue-induced reinstatement of

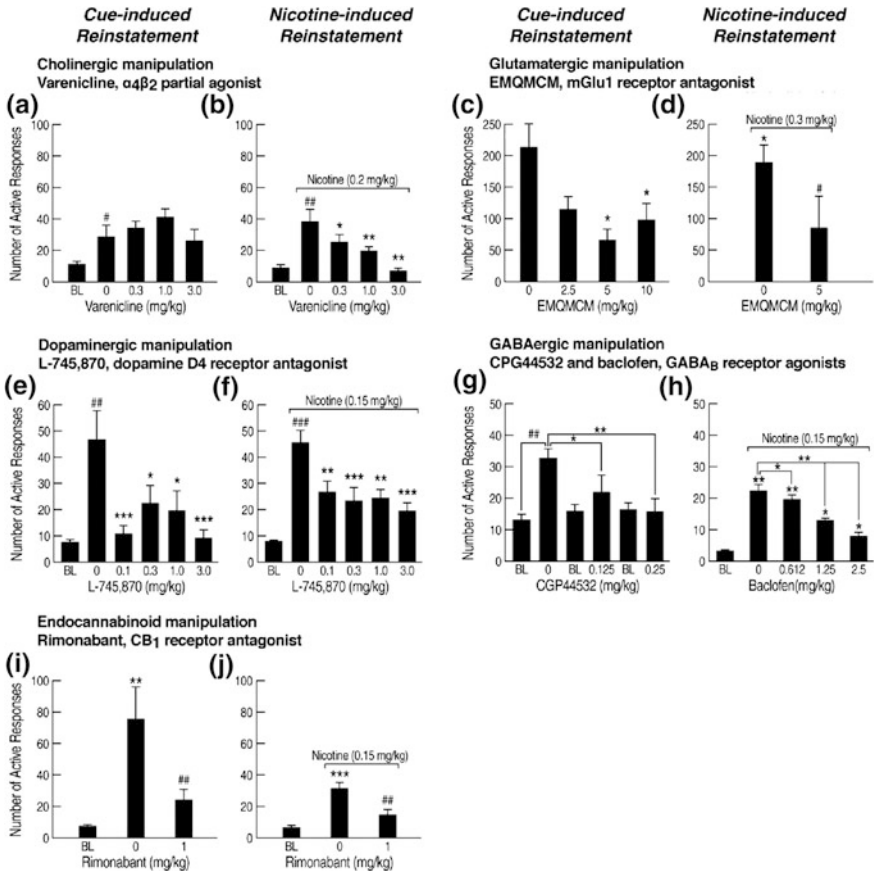

Fig. 1 Effects of manipulating various neurotransmitter systems on cue- and nicotine-induced reinstatement of nicotine-seeking behavior. The pharmacological targeting of a wide range of neurotransmitter systems attenuated reinstatement to nicotine seeking induced by the presentation of conditioned cues (*left panel*) and nicotine priming (*right panel*). Positive allosteric modulation of α4β2 nAChRs with varenicline had no effect on the cue-induced reinstatement of nicotine seeking (**a**, modified with permission from O'Connor et al. 2010), while varenicline attenuated the nicotine-induced reinstatement of nicotine seeking (**b**, modified with permission from O'Connor et al. 2010). The mGlu1 receptor antagonist EMQMCM attenuated both the cue-induced (**c**, modified with permission from Dravolina et al. 2007) and nicotine-induced (**d**, modified with permission from Dravolina et al. 2007) reinstatement of nicotine-seeking behavior. The dopamine D_4 receptor antagonist L-745,870 also attenuated the cue-induced (**e**, modified with permission from Yan et al. 2013) and nicotine-induced (**f**, modified with permission from Yan et al. 2013) reinstatement of nicotine seeking. The $GABA_B$ receptor agonists CPG44532 (**g**, modified with permission from Paterson et al. 2005) and baclofen (**h**, modified with permission from Fattore et al. 2009) similarly reduced the cue- and nicotine-induced reinstatement of nicotine seeking, respectively. Finally, the CB_1 receptor antagonist rimonabant attenuated the cue-induced (**i,** modified with permission from Forget et al. 2009) and nicotine-induced (**j**, modified with permission from Forget et al. 2009) reinstatement of nicotine seeking

nicotine seeking while not affecting reinstatement induced by nicotine priming (Li et al. 2012).

In addition to the direct activation of nAChRs, cholinergic neurotransmission can be increased by the inhibition of acetylcholinesterase, the enzyme that metabolizes the endogenous nAChR ligand acetylcholine. Galantamine, which acts both as an acetylcholinesterase inhibitor and positive allosteric modulator at α7- and α4β2-containing nAChRs, reduced the cue-induced reinstatement of nicotine seeking, suggesting that acetylcholinesterase inhibitors may be effective tools in the prevention of nicotine reinstatement (Hopkins et al. 2012). The potential therapeutic value of acetylcholinesterase inhibitors was supported by a study that demonstrated that donezipil, which acts exclusively as an acetylcholinesterase inhibitor, attenuated nicotine-induced reinstatement (Kimmey et al. 2012). Combined, the findings with galantamine and donezipil suggest that acetylcholinesterase inhibitors can attenuate both cue- and nicotine-induced reinstatement.

In summary, the pharmacological targeting of acetylcholinergic neurotransmission has been one of the most lucrative avenues in the search for smoking cessation aids to date. However, cue- and nicotine-induced reinstatement appears to be differentially regulated by pharmacological compounds that act on α7- and α4β2-containing nAChRs, potentially limiting their efficacy as pharmacological targets for smoking cessation medication. Exploring the efficacy of pharmacologically targeting diverse nAChR subtypes, including α3-, α5-, and β4-containing nAChR subunits, may thus be an interesting avenue in the identification of novel, highly efficacious smoking cessation medications.

3.2 Glutamate

Glutamatergic neurotransmission is modulated by two different types of receptors: ionotropic glutamate (iGlu) receptors and metabotropic glutamate (mGlu) receptors. iGlu receptors are located postsynaptically and modulate fast glutamatergic neurotransmission. Nicotine self-administration resulted in changes in iGlu and mGlu receptor levels, which likely contributed to the cue-induced reinstatement of nicotine-seeking behavior (Gipson et al. 2013; Liechti et al. 2007). Moreover, pharmacologically targeting iGlu receptors with the NMDA receptor antagonists ifenprodil and acamprosate attenuated the cue-induced reinstatement of nicotine-seeking behavior (Gipson et al. 2013; Pechnick et al. 2011). The development of novel pharmacotherapies for the treatment of drug dependence, however, has focused primarily on mGlu receptors because of the side effects of iGlu receptor antagonists in humans (for review, see Gass and Olive 2008). Metabotropic glutamate receptors have attracted much interest in recent years as targets for novel therapeutics in the treatment of nicotine dependence (Markou 2007). Compared with iGlu receptors, the activity of mGlu receptors is more slow acting and modulatory, presumably resulting in a reduced side effect profile. During nicotine withdrawal, presynaptic mGlu2/3 receptors were downregulated in the VTA and

NAc, and mGlu2/3 receptor activation in these brain areas induced by the agonist LY379268 attenuated the cue-induced reinstatement of nicotine seeking (Liechti et al. 2007). N-acetylcysteine, a compound that has been suggested to increase the glutamatergic tone of presynaptic mGlu2/3 receptors (Kupchik et al. 2012), similarly attenuated nicotine reinstatement elicited by environmental cues (Ramirez-Nino et al. 2013). Furthermore, the blockade of postsynaptic mGlu5 receptors (Bespalov et al. 2005) and mGlu1 receptors (see Fig. 1c adapted from Dravolina et al. 2007) decreased cue-induced reinstatement. Specifically, nicotine seeking was attenuated by administration of the mGlu5 receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine hydrochloride (MPEP; Bespalov et al. 2005) or mGlu1 receptor antagonist 3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate (EM-QMCM; Dravolina et al. 2007). In parallel to cue-induced reinstatement, EMQMCM also decreased the nicotine-induced reinstatement of nicotine-seeking behavior in rats (see Fig. 1d adapted from Dravolina et al. 2007). These results of experimental studies in animals on the role of mGlu receptors in nicotine reinstatement demonstrated that pharmacologically targeting glutamatergic neurotransmission effectively attenuates both cue- and nicotine-induced reinstatement and may attenuate relapse to tobacco smoking in humans. In fact, these experimental animal studies resulted in a Phase I clinical trial by Novartis that assessed the efficacy and safety of the mGlu5 receptor antagonist AFQ056 as a treatment option for voluntary smoking cessation. This clinical trial has been completed, but the results of the study have not yet been published (Clinicaltrials.gov 2007).

3.3 Dopamine

As described in Sects. 2.1 and 2.3, dopaminergic neurotransmission, which is mediated by G-protein-coupled dopamine receptors, in the mesolimbic circuit and striatum is critically involved in drug dependence (see chapter entitled The Role of Mesoaccumbens Dopamine in Nicotine Dependence; this volume). The cue-induced reinstatement of nicotine-seeking behavior can be attenuated by pharmacological compounds that decrease dopaminergic tone, including antagonists of dopamine D_1 and D_2 receptors (Liu et al. 2010), D_3 receptors (Khaled et al. 2010), and D_4 receptors (see Fig. 1e adapted from Yan et al. 2013). Consistent with these findings, a reduction of dopaminergic tone with the α-type peroxisome proliferator-activated receptor (PPAR-α) agonist clofibrate decreased cue-induced reinstatement in squirrel monkeys (Panlilio et al. 2012). These studies suggest that the pharmacological inhibition of dopaminergic neurotransmission consistently attenuates the cue-induced reinstatement of nicotine-seeking behavior. Furthermore, nicotine-induced reinstatement is similarly attenuated by dopamine D_3 and D_4 receptor agonists (Andreoli et al. 2003; Yan et al. 2013, see Fig. 1f adapted from Yan et al. 2013) and PPAR-α agonists (Mascia et al. 2011; Panlilio et al. 2012). The inhibition of dopaminergic neurotransmission, therefore, appears to be an interesting possibility in the identification for novel smoking cessation medication targets.

3.4 γ-Aminobutyric Acid (GABA)

GABA is the main inhibitory transmitter in the central nervous system. Inhibitory GABAergic activity attenuates dopaminergic mesocorticolimbic neurotransmission through GABA interneurons located in the VTA, medium spiny GABA neurons in the NAc, and GABAergic projections to the VTA from the NAc, ventral pallidum, and pedunculopontine tegmental nucleus (Klitenick et al. 1992). Inhibitory GABA receptors, therefore, would have to be activated by full agonists or positive allosteric modulators to decrease excitatory neurotransmission in the VTA which, as discussed above, generally attenuates the reinstatement of nicotine seeking. GABAergic neurotransmission is regulated through ionotropic $GABA_A$ and $GABA_C$ receptors and metabotropic $GABA_B$ receptors (Bormann 1986). Of these various GABA receptor subtypes, G-protein-coupled $GABA_B$ receptors are primarily of interest in the treatment of nicotine dependence (Li et al. 2014; Vlachou and Markou 2010). $GABA_B$ receptor activation induced by the $GABA_B$ receptor agonist CPG44532 attenuated the cue-induced reinstatement of nicotine seeking in rats (see Fig. 1g adapted from Paterson et al. 2005). Similar to the $GABA_B$ agonist, the $GABA_B$ receptor positive allosteric modulator BHF177 also decreased cue-induced reinstatement in rats (Vlachou et al. 2011). The effects of $GABA_B$ agonists on the nicotine-induced reinstatement of nicotine seeking have been less extensively explored. One study reported that baclofen decreased reinstatement induced by nicotine priming (see Fig. 1h adapted from Fattore et al. 2009). Furthermore, the $GABA_B$ receptor agonist baclofen was suggested to potentially facilitate smoking cessation in humans (Cousins et al. 2001). These studies indicate that $GABA_B$ receptors may be a promising target in the treatment of smoking cessation. Moreover, it has been proposed that $GABA_B$ positive allosteric modulators may be particularly effective in the treatment of nicotine dependence because of their modulatory actions at $GABA_B$ receptors that may result in an improved side effect profile and decreased development of tolerance to these compounds compared with $GABA_B$ full receptor agonists (Guery et al. 2007; Vlachou et al. 2011).

3.5 Endocannabinoids

Of the two endocannabinoid receptors cloned to date, CB_1 receptors are of primary interest in the treatment of dependence on drugs of abuse (Howlett et al. 2004) because these receptors are found on glutamatergic and GABAergic inputs to dopaminergic neurons (Gardner 2005). In contrast, CB_2 receptors are primarily localized on immune cells in both the central and peripheral nervous systems (Howlett 2002). As expected, the reinstatement of nicotine-seeking behavior was unaffected by the CB_2 receptor antagonist AM630 or CB_2 receptor agonist AM1241 (Gamaleddin et al. 2012b). CB_1 receptors located on presynaptic glutamatergic neurons in the VTA are hypothesized to decrease the inhibitory control that

GABAergic neurons exert on dopaminergic neurons (Schlicker and Kathmann 2001). Consequently, CB_1 receptor activation would result in the increased firing activity of VTA dopamine neurons (French 1997; French et al. 1997) and increased dopamine release in the NAc (Gardner and Vorel 1998; Tanda et al. 1997), suggesting therapeutic potential for CB_1 receptor antagonism in attenuating the reinstatement of nicotine seeking. Indeed, antagonism of the CB_1 receptor consistently attenuated the cue-induced reinstatement of nicotine-seeking behavior, demonstrated by the administration of rimonabant (Diergaarde et al. 2008; Forget et al. 2009, see Fig. 1i adapted from Forget et al. 2009), SR141716 (Cohen et al. 2005; de Vries et al. 2005), and AM404 (Gamaleddin et al. 2013) in rats. The $CB_{1/2}$ receptor agonist WIN 55,212-2 facilitated the cue-induced reinstatement of nicotine-seeking behavior (Gamaleddin et al. 2012a), presumably by activating CB_1 receptors. Furthermore, antagonism at CB_1 receptors attenuated nicotine-induced reinstatement in rats, demonstrated by the administration of rimonabant (see Fig. 1j adapted from Forget et al. 2009), AM251 (Shoaib 2008), and AM404 (Gamaleddin et al. 2013). Additionally, reinstatement induced by the combination of both cue presentation and nicotine priming was attenuated by administration of the CB_1 receptor antagonist AM251 (Shoaib 2008).

After various clinical trials assessed the efficacy of rimonabant as a smoking cessation medication, it was approved for this purpose in various European countries in 2006. Inopportunely, treatment of smoking cessation with rimonabant was halted in 2007 after reports of severe side effects that included anxiety and depression (Moreira and Crippa 2009). The development of pharmacological compounds that target the endocannabinoid system in smoking cessation is therefore currently directed toward developing compounds that indirectly target endocannabinoid neurotransmission, including anandamide transport inhibitors and fatty acid amid hydrolase (FAAH). Anandamide is one of the endogenous ligands that act at cannabinoid receptors (Giang and Cravatt 1997) and eliminated by reuptake into cells by anandamide transporters and subsequent hydrolysis by FAAH (Beltramo et al. 1997; Cravatt et al. 1996). The enhancement of endocannabinoid signaling by inhibiting the reuptake or hydrolysis of anandamide attenuated both cue- and nicotine-induced reinstatement of nicotine seeking (Forget et al. 2009; Gamaleddin et al. 2011). Notably, inhibiting the reuptake or hydrolysis of anandamide opposes the effects of CB_1 receptor antagonists. That is, CB_1 receptor antagonists attenuate endocannabinoid signaling, while FAAH inhibitors and anandamide transport inhibitors enhance endocannabinoid signaling. The same direction of effect (i.e., decrease) on the reinstatement of nicotine seeking by these seemingly opposing mechanisms may be due to the action of CB_1 receptor antagonists on neurocircuits that express endocannabinoid ligands other than anandamide (Scherma et al. 2008). Interestingly, compounds that target FAAH may exert dual actions on the reinstatement of nicotine seeking because FAAH also breaks down fatty acid amides that can activate PPAR-α (Fegley et al. 2005). As discussed above, the activation of PPAR-α decreases the cue-induced reinstatement of

nicotine seeking, presumably by decreasing dopaminergic neurotransmission, further emphasizing the potential of FAAH-inhibiting compounds in treating the reinstatement of nicotine seeking.

3.6 Other Neurotransmitter Systems

Whereas the aforementioned neurotransmitter systems have been the most extensively explored as targets for pharmacotherapy in attenuating the reinstatement of nicotine seeking, several other neurotransmitter systems have been suggested in the development of novel smoking cessation aids. Serotonergic receptors, for example, modulate dopaminergic neurotransmission and were suggested as potential targets in smoking cessation medications (for review, see Fletcher et al. 2008). The attenuation of serotonergic neurotransmission by the 5-HT_{2C} receptor antagonists Ro60-0175 and locaserin decreased both nicotine- and cue-induced reinstatement (Fletcher et al. 2012; Higgins et al. 2012). Similarly, the modulation of noradrenergic neurotransmission was shown to effectively reduce both cue- and nicotine-induced reinstatement with the noradrenergic α1 receptor antagonist prazosin (Forget et al. 2010b) and β-blocker propranolol, supporting the involvement of noradrenergic neurotransmission in cue-induced reinstatement (Chiamulera et al. 2010). Finally, the T-type calcium channel antagonist TTA-A2 also attenuated both cue- and nicotine-induced reinstatement (Uslaner et al. 2010), potentially by modulating glutamatergic or dopaminergic neurotransmission (Uslaner et al. 2012). Tricyclic antidepressants, which decrease both serotonergic and noradrenergic neurotransmission, have been suggested to facilitate smoking cessation in humans (Edwards et al. 1989; Hall et al. 1998; Prochazka et al. 1998). However, the severe side effects of tricyclic antidepressants, including cardiovascular effects and the severity of overdose symptoms (Biggs et al. 1977; Roose et al. 1991), make these compounds unfavorable as smoking cessation aids. The reversible monoamine oxidase-A (MAO-A) inhibitor moclobemide, which reduces both serotonergic and noradrenergic neurotransmission similarly to tricyclic antidepressants but with a more favorable side effect profile (Stabl et al. 1989), attenuated smoking cessation in a study group of heavy smokers (Berlin et al. 1995). These results suggest that MAO-A inhibitors may be preferred over tricyclic antidepressants as smoking cessation aids. However, bupropion remains the main antidepressant used as a smoking cessation medication (Tables 1 and 2).

4 Concluding Remarks

Relapse is one of the hallmarks of tobacco dependence, but the currently available smoking cessation medications only prevent the occurrence of relapse in a small percentage of people who attempt to quit tobacco consumption. The limited

Table 1 Animal studies of the pharmacological targeting of various neurotransmitter systems in cue-induced reinstatement of nicotine seeking

Compound	Mechanism	Species/strain	Reinstatement	Effect on reinstatement	References
Acetylcholine					
DHβE	α4β2 nAChR antagonist	Sprague-Dawley rats	Cue-induced	–	Liu (2014)
Mecamylamine	Wide-spectrum nAChR antagonist	Sprague-Dawley rats	Cue-induced	↓	Liu et al. (2007)
MLA	α7 nAChR antagonist	Sprague-Dawley rats	Cue-induced	↓	Liu (2014)
TAT-α7-pep2	α7nAChR–NMDAR complex interfering protein	Long-Evans rats	Cue-induced	↓	Li et al. (2012)
varenicline	α4β2 nAChR partial agonist	Hooded Lister	Cue-induced	–	(O'Connor et al. 2010)
		Wistar rats	Cue-induced	–/↑	Wouda et al. (2011)
varenicline (long pre-treatment time)	α4β2 nAChR partial agonist	Long-Evans rats	Cue-induced	↓	Le Foll et al. (2012)
Glutamate					
EMQMCM	mGlu1 receptor antagonist	Wistar rats	Cue-induced	↓	Dravolina et al. (2007)
MPEP	mGlu5 receptor antagonist	Wistar rats	Cue-induced	↓	Bespalov et al. (2005)
LY379268	mGlu2/3 receptor agonist	Wistar rats	Cue-induced	↓	Liechti et al. (2007)
Acamprosate	NMDA receptor antagonist, $GABA_A$ receptor agonist	Sprague-Dawley rats	Cue-induced	↓	Pechnick et al. (2011)

(continued)

Table 1 (continued)

Compound	Mechanism	Species/strain	Reinstatement	Effect on reinstatement	References
N-acetylcysteine	Cysteine pro-drug	Wistar rats	Cue-induced	↓	Ramirez-Nino et al. (2013)
GABA					
Acamprosate	$GABA_A$ receptor agonist, NMDA receptor antagonist	Sprague-Dawley rats	Cue-induced	↓	Pechnick et al. (2011)
BHF177	$GABA_B$ receptor positive allosteric modulator	Wistar rats	Cue-induced	↓	Vlachou et al. (2011)
CPG44532	$GABA_B$ receptor agonist	Wistar rats	Cue-induced	↓	Paterson et al. (2005)
Dopamine					
BP897	Dopamine D_3 receptor agonist	Long-Evans rats	Cue-induced	–	Khaled et al. (2010)
Clofibrate	α-type peroxisome proliferator-activated receptor agonist	Squirrel monkeys	Cue-induced	↓	Panlilio et al. (2012)
Eticlopride	Dopamine D_2 receptor antagonist	Sprague-Dawley rats	Cue-induced	↓	(Liu et al. 2010)
L-745,870	Dopamine D_4 receptor antagonist	Long-Evans rats	Cue-induced	↓	(Yan et al. 2013)
SB277011-A	Dopamine D_3 receptor antagonist	Long-Evans rats	Cue-induced	↓	(Khaled et al. 2010)
SCH23390	Dopamine D_1 receptor antagonist	Sprague-Dawley rats	Cue-induced	↓	Liu et al. (2010)
Endocannabinoid					
AM404	CB_1 receptor antagonist	Long-Evans rats	Cue-induced	↓	Gamaleddin et al. (2013)

(continued)

Table 1 (continued)

Compound	Mechanism	Species/strain	Reinstatement	Effect on reinstatement	References
AM630	CB_2 receptor antagonist	Long-Evans rats	Cue-induced	−	Gamaleddin et al. (2012b)
AM1241	CB_2 receptor agonist	Long-Evans rats	Cue-induced	−	Gamaleddin et al. (2012b)
Rimonabant (SR141716A)	CB_1 receptor antagonist	Wistar rats	Cue-induced	↓	Diergaarde et al. (2008)
		Long-Evans rats	Cue-induced	↓	Forget et al. (2009)
		Wistar rats	Cue-induced	↓	De Vries et al. (2005)
		Sprague-Dawley rats	Cue-induced	↓	Cohen et al. (2005)
URB597	Fatty acid amide hydrolase inhibitor	Long-Evans rats	Cue-induced	↓	Forget et al. (2009)
VDM11	Anandamide transport inhibitor	Long-Evans rats	Cue-induced	↓	Gamaleddin et al. (2011)
WIN 55,212-2	$CB_{1/2}$ receptor agonist	Long-Evans rats	Cue-induced	↑	Gamaleddin et al. (2012a)
Serotonin					
M100907	5-HT_{2A} receptor antagonist	Long-Evans rats	Cue-induced	↓	Fletcher et al. (2012)
Ro60-0175	5-HT_{2C} receptor agonist	Long-Evans rats	Cue-induced	↓	Fletcher et al. (2012)

(continued)

Table 1 (continued)

Compound	Mechanism	Species/strain	Reinstatement	Effect on reinstatement	References
Norepinephrine					
Prazosin	Noradrenergic α1 receptor antagonist	Long-Evans rats	Cue-induced	↓	Forget et al. (2010b)
Propranolol	β-blocker	Sprague-Dawley rats	Cue-induced	↓	Chiamulera et al. (2010)
Other					
bupropion	nAChR antagonist, dopamine and norepinephrine reuptake inhibitor	Sprague-Dawley rats	Cue-induced	↑	Liu et al. (2008)
Naltrexone	Nonselective opioid antagonist	Sprague-Dawley rats	Cue-induced	↓	Liu et al. (2009)
TTA-A2	T-type calcium channel antagonist	Long-Evans rats	Cue-induced	↓	Uslaner et al. (2010)
SB334867	Hypocretin receptor-1 antagonist	C57BL/6 J mice	Cue-induced	↓	Plaza-Zabala A et al. (2013)
TCSOX229	Hypocretin receptor-2 antagonist	C57BL/6 J mice	Cue-induced	-	Plaza-Zabala A et al. (2013)
2-SORA 18	Orexin 2 receptor antagonist	Long Evans rats	Cue-induced	↓	Uslaner et al. (2014)

Table 2 Animal studies of the pharmacological targeting of various neurotransmitter systems in nicotine-induced reinstatement of nicotine seeking

Compound	Mechanism	Species/strain	Reinstatement	Effect on reinstatement	References
Acetylcholine					
Donepezil	Acetylcholinesterase inhibitor	Sprague-Dawley rats	Nicotine-induced, cues available	↓	Kimmey et al. (2012)
Galantamine	α7 and α4β2 nAChR positive allosteric modulator and acetylcholinesterase inhibitor	Sprague-Dawley rats	Nicotine-induced, cues available	↓	Hopkins et al. (2012)
varenicline	α4β2 nAChR partial agonist	Hooded Lister rats	Nicotine-induced, cues available	↓	O'Connor et al. (2010)
		Hooded Lister rats	Nicotine-induced	↓	O'Connor et al. (2010)
Glutamate					
EMQMCM	mGlu1 receptor antagonist	Wistar rats	Nicotine-induced	↓	Dravolina et al. (2007)
GABA					
Baclofen	$GABA_B$ receptor agonist	Sprague-Dawley rats	Nicotine-induced	↓	Fattore et al. (2009)
Dopamine					
Clofibrate	α-type peroxisome proliferator-activated receptor agonist	Squirrel monkeys	Nicotine-induced	↓	Panlilio et al. (2012)
L-745,870	Dopamine D_4 receptor antagonist	Long-Evans rats	Nicotine-induced	↓	Yan et al. (2013)
methOEA	α-type peroxisome proliferator-activated receptor agonist	Sprague-Dawley rats and squirrel monkeys	Nicotine-induced, cues available	↓	Mascia et al. (2011)

(continued)

Table 2 (continued)

Compound	Mechanism	Species/strain	Reinstatement	Effect on reinstatement	References
SB277011-A	Dopamine D_3 receptor antagonist	Wistar rats	Nicotine-induced, cues available for 30 min before nicotine priming	↓	Andreoli et al. (2003)
WY14643	α-type peroxisome proliferator-activated receptor agonist	Sprague-Dawley rats and squirrel monkeys	Nicotine-induced, cues available	↓	Mascia et al. (2011)
Endocannabinoid					
AM251	CB_1 receptor antagonist	Hooded Lister rats	Nicotine-induced, cues available	↓	Shoaib (2008)
AM404	CB_1 receptor antagonist	Long-Evans rats	Nicotine-induced	↓	Gamaleddin et al. (2013)
AM630	CB_2 receptor antagonist	Long-Evans rats	Nicotine-induced	–	Gamaleddin et al. (2012b)
AM1241	CB_2 receptor agonist	Long-Evans rats	Nicotine-induced	–	Gamaleddin et al. (2012b)
Rimonabant	CB_1 receptor antagonist	Long-Evans rats	Nicotine-induced	↓	Forget et al. (2009)
URB597	Fatty acid amide hydrolase inhibitor	Long-Evans rats	Nicotine-induced	↓	Forget et al. (2009)
URB597	Fatty acid amide hydrolase inhibitor	Long-Evans rats and Sprague-Dawley rats	Nicotine-induced	↓	Scherma et al. (2008)
VDM11	Anandamide transport inhibitor	Long-Evans rats	Nicotine-induced	↓	Gamaleddin et al. (2011)

(continued)

Table 2 (continued)

Compound	Mechanism	Species/strain	Reinstatement	Effect on reinstatement	References
Serotonin					
Locaserin	5-HT_{2C} receptor agonist	Sprague-Dawley rats	Nicotine-induced, cues available	↓	Higgins et al. (2012)
M100907	5-HT_{2A} receptor antagonist	Long-Evans rats	Nicotine-induced	↓	Fletcher et al. (2012)
Ro60-0175	5-HT_{2C} receptor agonist	Long-Evans rats	Nicotine-induced	↓	(Fletcher et al. 2012)
Norepinephrine					
Prazosin	Noradrenergic α1 receptor antagonist	Long-Evans rats	Nicotine-induced	↓	Forget et al. (2010b)
Other					
TTA-A2	T-type calcium channel antagonist	Long-Evans rats	Nicotine-induced, cues available during extinction and reinstatement	↓	Uslaner et al. (2010)
2-SORA 18	Orexin 2 receptor antagonist	Long Evans rats	Nicotine-induced	-	Uslaner et al. (2014)

effectiveness of these medications may be explained by the differential regulation of diverse aspects of relapse by various neurotransmitter systems, as discussed in the introduction above, which has been extensively documented for relapse to cocaine seeking. Whereas the possibility of the regulation of the different types of reinstatement by different neurocircuits has not yet been widely explored for relapse to nicotine seeking, specific smoking cessation medications may only target one aspect of relapse, resulting in decreased overall effectiveness compared with pharmacological compounds that target the full spectrum of relapse. This concept is supported by studies of "relapse" to nicotine seeking in animals, which demonstrated that the reinstatement of nicotine seeking is most robust when it is elicited by both nicotine priming and exposure to conditioned cues compared with nicotine priming or conditioned cues themselves (Feltenstein et al. 2012; O'Connor et al. 2010). With less than 5 % of all smoking cessation attempts resulting in lifelong abstinence from tobacco (Hughes et al. 2004), novel medications that attenuate relapse rates are needed. Pharmacologically targeting the neurocircuits or neurotransmitters that are involved in multiple aspects of relapse to tobacco consumption may improve smoking cessation rates. Preclinical models of relapse are greatly important in this pursuit of novel pharmacological targets in the treatment of tobacco dependence. The reinstatement procedure, an animal model widely used to assess "relapse" to drug seeking in animals, has provided important insights into the neurobiological effects of stimuli that trigger relapse in humans, most notably nicotine and its conditioned cues (Shaham et al. 2003; but see Katz and Higgins 2003). The majority of nicotine reinstatement studies have assessed nicotine reinstatement primed by nicotine or its conditioned cues separately, allowing for differentiation of the neurotransmitters that regulate these two different manipulations that induce the reinstatement of drug seeking.

Preclinical studies suggest the limited effectiveness of two widely used smoking cessation medications, varenicline and bupropion, in attenuating the cue-induced reinstatement of nicotine seeking (Liu et al. 2008; O'Connor et al. 2010, Wouda et al. 2011). These results are consistent with the clinical observations that these two FDA-approved medications are not very efficacious in attenuating tobacco smoking in humans. Furthermore, these results suggest that the pursuit of the identification of novel smoking cessation medications would be best served by developing pharmacological compounds that effectively treat the various factors that can induce the reinstatement of nicotine seeking, including nicotine and cues. nAChR subunits other than the α4β2-containing nAChRs (the nAChR subtype on which varenicline acts), including α3, α5, and β4 subunits, may be interesting in the development of more efficacious smoking cessation medications. An increasing body of preclinical studies also suggests that exploring other neurotransmitter systems downstream from nAChRs may be lucrative in the quest for novel pharmacological targets to attenuate nicotine reinstatement.

Glutamatergic neurotransmitter systems are particularly appealing targets for the development of novel smoking cessation medications (Liechti and Markou 2008). Glutamate critically regulates the reinstatement of nicotine seeking (Bespalov et al. 2005; Gipson et al. 2013; Liechti et al. 2007) but also cocaine seeking (for reviews,

see Kalivas 2004; Wise 2009), suggesting that pharmacologically targeting glutamatergic neurotransmission may be particularly promising in the identification of novel targets for smoking cessation medications. Nicotine reinstatement studies found that pharmacological compounds that decrease glutamatergic neurotransmission effectively attenuated both the cue- and nicotine-induced reinstatement of nicotine seeking (Bespalov et al. 2005; Dravolina et al. 2007; Gipson et al. 2013; Liechti et al. 2007; Pechnick et al. 2011; Ramirez-Nino et al. 2013). The promise of targeting glutamatergic compounds as smoking cessation medications is further demonstrated by the success of N-acetylcysteine in reducing cigarette consumption in smokers (Knackstedt et al. 2009).

Other than glutamatergic neurotransmission, preclinical studies have suggested that both the cue- and nicotine-induced reinstatement of nicotine seeking can be attenuated by pharmacologically targeting various other neurotransmitters (Table 1). Dopamine receptor antagonists, $GABA_B$ receptor agonists or positive allosteric modulators, endocannabinoid receptor antagonists, serotonin receptor agonists, β-blockers, and opioid receptor antagonists have been identified as potentially efficacious as pharmacological smoking cessation medications. These preclinical studies of nicotine seeking have greatly benefited from the synthesis and characterization of novel pharmacological compounds that attenuate relapse to tobacco smoking in humans. Additionally, preclinical studies on the neurobiology of cue- and nicotine-induced reinstatement provide important insights into potential future study directions for clinical trials in ongoing efforts to repurposing medications that have been approved by the FDA for other neurobiological disorders to serve as smoking cessation aids.

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