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Neuropharmacology of the Interoceptive Stimulus Properties of Nicotine

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Abstract

Preclinical drug discrimination techniques play a significant role in advancing our knowledge of the receptor mechanisms underlying the interoceptive effects of nicotine. Early reports confirmed that nicotinic acetylcholine receptors (nAChRs) are critical for transduction of the nicotine cue. In recent years, advances in molecular biology and the discovery of novel ligands with greater selectively for specific nAChR subtypes have furthered our understanding of these mechanisms. There is now evidence regarding the specific nAChR subtypes involved in nicotine discrimination; in addition, there is also evidence suggesting that other systems (i.e., adenosine, cannabinoid, dopamine, glutamate and serotonin) may play a modulatory role. The neuroanatomical structures mediating the nicotine cue have also begun to be elucidated. However, much remains to be learned about the predictive validity of the drug discrimination procedure, particularly with regard to the relation between interoceptive and reinforcing effects and individual differences in vulnerability to tobacco dependence. Recent data also suggests that the mechanisms involved in the conditional and discriminative stimulus properties of nicotine may be dissociable. Avenues for future research should include assessing the mechanisms of the subjective effects of nicotine withdrawal, factors contributing to individual differences in sensitivity to the nicotine cue, and the role of behavioral factors involved in drug cross-substitution.

Keywords

nicotine; drug discrimination; conditional stimulus; nicotinic acetylcholine receptor

1. Introduction

Drugs of abuse can alter behavior in a number of ways, including strengthening ongoing behavior that precedes their delivery (i.e., reinforcing effects) or guiding behavior between concurrently-available, differentially-reinforced response options with their interoceptive effects. The latter property can be studied with drug discrimination, one of the most commonly used procedures for investigating the neuropharmacology of psychoactive drugs in the behaving animal [1–3]. In contrast to self-administration, which is restricted to investigations of drugs that function as reinforcers, drug discrimination is generally amenable to studying any compound that generates a perceptible internal state that can be associated with appetitive or aversive events in the environment. Thus, one can study the interoceptive cueing effect of nicotine by using nicotine as the training stimulus, or by

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administering nicotine to subjects trained to recognize a related ligand (e.g., cytisine) thought to act on similar neurotransmitter systems as nicotine. Early investigations in the field used procedures such as the shock-escape T-maze task [4], although the two-lever operant drug discrimination protocol is currently the most widely-used procedure [5]. In this latter method, experimental subjects are trained to earn a reinforcer (e.g., food) by emitting one response (e.g., pressing the left of two levers) following injection of a training drug; a different response is reinforced (e.g., pressing the right of two levers) following placebo injection [6–8]. Thus, subjects are required to first recognize the presence or absence of the training drug cue (often referred to as a discriminative stimulus, or S^D), and to then complete the requisite response requirement [e.g., 25 presses on the drug lever] to earn a reinforcer.

More recently, two different variants of a Pavlovian drug discrimination procedure have been used to study the interoceptive stimulus effects of nicotine in rats (see [9] for recent discussion of these protocols). One procedure conceptualizes nicotine as an interoceptive context cue or conditioned stimulus (CS) that signals when intermittent access to liquid sucrose unconditioned stimulus (US) will occur; placebo indicates that sucrose will be withheld. Sucrose delivery occurs regardless of ongoing behavior. Nicotine thereby comes to acquire the ability to evoke anticipatory approach to the goal area (i.e., goal tracking; [10]) relative to the placebo state [11]. The other procedure conceptualizes nicotine as an occasion setter (OS) that signals when a CS-US association is or is not in force. The procedure is similar to the nicotine CS protocol, except that a brief exteroceptive stimulus such as illumination of a cue light is added to nicotine and placebo sessions. If nicotine is trained as a feature positive OS, then sucrose follows each light presentation only on nicotine sessions. If trained as a negative feature, the sucrose occurs only on placebo sessions. The light comes to differentially evoke a goal-tracking CR depending on the drug state [12, 13].

Regardless of the protocol, two types of tests can be conducted once the discrimination has been established. In substitution testing, varying doses of the training drug or a test drug are administered alone to determine the degree to which they generalize to the training drug. In interaction testing, a pretreatment drug is administered in combination with the training drug to determine whether responding controlled by the training drug is altered. Substitution and interaction tests can be used to determine the receptor mechanisms mediating the interoceptive effects of a drug, as a test drug typically substitutes for a training drug within a similar, but not a distinct, pharmacological class. For example, a stimulant drug (e.g., *d*-amphetamine) would be expected to substitute for the cue of another stimulant such as cocaine, but not for the cue produced by a sedative/hypnotic such as pentobarbital. An important advantage of drug discrimination is that similar cross-species findings are typically obtained when comparing the results of animal and human studies [14]. Thus, the excellent predictive validity and pharmacologic specificity of drug discrimination studies have led to the widespread adoption of these procedures to probe the neuropharmacology of many psychoactive drugs.

The purpose of the present review is to synthesize current knowledge regarding the receptor mechanisms of nicotine action as revealed by drug discrimination studies. A review of the operant drug discrimination based on a literature survey conducted in 2007 has been published recently in book form [15]. Therefore, the focus of the present article will be on recent findings obtained with laboratory animals using Pavlovian procedures, as well as operant methodology. Since the initial work in the field conducted several decades ago [16–18], studies conducted with genetically-altered mice [19] and the discovery of novel ligands with enhanced selectivity for specific receptor subtypes [20, 21], have further illustrated the diverse mechanisms of the interoceptive stimulus properties of nicotine, including recent

insights into the role of specific nicotinic receptor subtypes. Work across these areas will be integrated and issues in need of further investigation will be discussed.

2. Acetylcholine

In the central nervous system, acetylcholine (ACh) acts on two distinct classes of receptors, muscarinic acetylcholine receptors (mAChRs) and nicotinic acetylcholine receptors (nAChRs). The mAChR family includes 5 subtypes (M_1-M_5), each of which is a G protein-coupled metabotropic receptor. The nAChRs are ligand-gated ionotropic pentamers consisting of various combinations of the eight α (α2-α7, α9, and α10) and three β (β2-β4) subunits identified in mammalian brain to date [22].

2.1. Peripheral AChRs

The interoceptive stimulus properties of nicotine appear to be centrally-mediated. The peripheral nAChR agonist methylcarbamylcholine does not substitute for nicotine [23]. The ganglionic blockers hexamethonium and chlorisondamine, which do not readily penetrate the blood-brain barrier, also fail to block nicotine discrimination [11, 13, 24–27], although a single intraventricular administration of chlorisondamine blocks the nicotine cue for up to 4 weeks [27, 28].

2.2. Central AChRs

There is ample evidence indicating that central nAChRs are a critical component of the nicotine cue. The classical central nAChR antagonists mecamylamine and dihydro-β-erythroidine (DHβE) block nicotine discrimination completely without disrupting response rates, whereas the mAChR antagonist atropine fails to block the nicotine cue [11, 13, 21, 27, 29–31]. Nicotine also fails to generalize to the S^D effects of the mAChR agonists arecoline, physostigmine, pilocarpine or oxotremorine [32–35] or the S^D effects of the mAChR antagonist scopolamine [36]; physostigmine also fails to alter the nicotine cue [37].

Conversely, a variety of nAChR agonists, including 1-acetyl-4-methylpiperazine (AMP), 3-pyridylmethylpyrrolidine, anabasine, anatoxin, cotinine, cytisine, isoarecolone, and nornicotine generalize fully to nicotine in rats [23, 38–45] and/or squirrel monkeys [46]. Nicotine also elicits full substitution for cytisine in rats that have been trained using cytisine as a S^D [47]. Combined, these findings indicate that central nAChRs, but not mAChRs, mediate nicotine's interoceptive stimulus effects. However, each nAChR subtype may not contribute equally to this effect, given the diversity in subunit composition and regional distribution of these receptors.

2.2.1. α4β2* nAChRs—The α4β2* nAChR (note that "*" refers to the possible inclusion of additional native nAChR subunits) is the most abundant heteromeric subtype in mammalian brain, and nicotine binds to α4β2* nAChRs with high affinity [48]. Unlike wild-type (WT) mice, β2 subunit knockout (KO) mice are unable to discriminate nicotine from saline regardless of the training dose and despite extensive training [49]. In addition, the extent to which α4β2 nAChR agonists generalize to the nicotine cue appears to be associated with affinity for α4β2* nAChRs in receptor binding assays and/or the ability to evoke nAChR-mediated [^{3}H]neurotransmitter release in functional assays. Specifically, partial α4β2 agonists such as cytisine, the smoking cessation agent varenicline (Chantix®), and SSR591813 substitute partially for nicotine [50–54], whereas full α4β2 agonists such as ABT-418, ABT-594, A85380, TC2559, epibatidine and 5-iodo-3-(2(S)-azetidinylmethoxy)pyridine (5-IA) substitute fully [51, 55, 56]. Interestingly, the α4β2 nAChR desensitizing agent sazetidine-A also produces full generalization to the nicotine cue [57], consistent with the notion that both nAChR activation and desensitization contribute to

the behavioral effects of nicotine [58]. The naturally-occurring nicotine enantiomer, S(−)nicotine, is ~9 times more potent than R(+)nicotine in substitution tests [59], consistent with the greater potency of the former enantiomer at displacing [^{3}H]nicotine binding in rat brain homogenates [60]. Finally, administering nicotine via oral, subcutaneous, or intraperitoneal routes produces equipotent substitution for an oral nicotine S^{D}, although transdermal administration reduces the potency of nicotine by ~1 log unit [52].

In interaction tests, the α4β2 nAChR antagonist DHβE blocks fully the nicotine cue in mice [61] and rats [21, 50, 54, 62, 63], as well as the nicotine-like S^{D} effects of 5-IA [64]. In contrast to mecamylamine, however, the inhibitory effects of competitive nAChR antagonists such as DHβE and erysodine are surmounted by higher doses of nicotine [62, 63, 65]. The partial α4β2 nAChR agonists cytisine, varenicline and SSR591813 also attenuate nicotine discrimination [50, 51], but to a lesser extent than classical antagonists. Thus, α4β2* nAChRs are a critical transduction mechanism for producing the nicotine cue.

2.2.2. α6β2* nAChRs—The α6 nAChR subunit is expressed primarily on the soma and axon terminals of midbrain DA neurons [66–68]. The functional significance of α6-containing receptors was unknown until the peptide toxin α-conotoxin MII (α-Ctx MII) was isolated from the marine snail *C. magus* [69]. The complete loss of [^{125}I]α-Ctx MII binding sites in α6 KO mice [66] spurred research leading to recognition of the critical role of this subtype in regulating basal and nicotine-evoked DA release [68, 70], as well as nicotine self-administration [71]. Although α-Ctx MII cannot be tested systemically because it does not cross the blood-brain barrier, a novel series of *N,N'*-alkane-diyl-*bis*-3-picolinium (bAPi) analogs appear to represent the first systemically-effective α6β2 antagonists [21]. Based on initial findings that two bAPi analogs (*N,N'*-decane-1,10-diyl-*bis*-picolinium diiodide, bPiDI; and *N,N'*-dodecane-1,12-diyl-*bis*-picolinium dibromide, bPiDDB) attenuate nicotine-evoked DA release in nucleus accumbens and nicotine self-administration [72–74], each of the bAPi analogs has been tested for blockade of nicotine discrimination. Although several bAPi analogs selectively inhibit nicotine-induced hyperactivity, none block the S^{D} or CS effects of nicotine [21, 75]. Thus, it appears that while α6β2* nAChRs play a critical role in the DA-mediated reinforcing and stimulant properties of nicotine, this subtype does not seem to be important for the interoceptive stimulus effects of nicotine.

2.2.3. α3β4* nAChRs—There are only a few reports examining the role of α3β4* nAChRs in nicotine discrimination. The α3β4 nAChR agonist WO 03/062224 does not substitute for nicotine or serve as a S^{D} [56]. The *N*-methyl-D-aspartate (NMDA) glutamate receptor and α3β4 nAChR antagonist dextromethorphan (DXM) also fails to substitute for or alter the S^{D} effects of nicotine [76, 77]. However, DXM partially blocks the CS, and fully blocks the locomotor, effects of nicotine [75]. This antagonism may be mediated by DXM antagonism of NMDA receptors, rather than α3β4* nAChRs, given that pretreatment with MK-801, a noncompetitive NMDA receptor antagonist, fully blocks the CS effects of nicotine [30; see later]. Regardless, these findings indicate a need for more research, as well as improved pharmacological tools, to better assess the involvement (or lack thereof) of α3β4* nAChRs in the nicotine cue.

2.2.4. α7* nAChRs—Although α7* nAChRs are the most abundant homomeric subtype, there is only limited support of a role for these receptors in generating the nicotine stimulus. In contrast to β2 KO mice, α7 KO mice readily learn to discriminate nicotine from saline [78]. In substitution tests, the α7 agonists GTS-21 and WO 01/60821A1 do not substitute for nicotine in rats [56, 78]. In interaction tests, GTS-21 and the α7 antagonist methyllycaconitine (MLA) fail to alter the stimulus effects of nicotine in rats [50, 64, 75, 79, 80]. However, a recent study demonstrated that nicotine substitutes more readily in WT mice than in α7 KO mice trained to discriminate *d*-amphetamine, and that MLA attenuates

the S^D effects of nicotine in nicotine-trained WT mice, as well as the S^D effects of nicotine and *d*-amphetamine in WT mice trained to discriminate *d*-amphetamine [19]. Thus, the *d*-amphetamine-like S^D effects of nicotine may involve α7* nAChRs, although MLA appears to block the nicotine cue in nicotine-trained mice only.

3. Dopamine

Dopamine (DA) is a critical mediator of the reinforcing and stimulant effects of abused drugs, including nicotine [81–85]. The two primary classes of DA receptors are the D_1-like (i.e., D_1 and D_5) and the D_2-like (i.e., D_2, D_3 and D_4) receptors. Nicotine initially activates, but then desensitizes, high-affinity β2 subunit-containing nAChRs on DA neurons that evoke release. In addition, a relatively prolonged reduction of inhibitory GABA input, combined with potentiation of excitatory glutamate input to these neurons, promotes DA release in the synapse [83]. While these effects are critical for nicotine self-administration [86], the contribution of DA to the interoceptive stimulus effects of nicotine remains a matter of debate [87, 88].

3.1. D_1 receptors

Some evidence supports a role for D_1-like DA receptors in nicotine discrimination. The D_1 agonists SKF-38393, SKF-81297 and SKF-82958 substitute partially for nicotine using the common 0.4 mg/kg nicotine training dose [29, 89, 90], whereas SKF-82958 substitutes fully in rats trained to discriminate 0.1 mg/kg nicotine [29]. However, when rats are trained in a 3-choice discrimination procedure using nicotine, saline, and SKF 812897 as S^D, SKF 81297 alone no longer evokes nicotine-appropriate responding [89]. Although the D_1 antagonist SCH-23390 partially attenuates the S^D effects of nicotine [91], as well as the generalization of *d*-amphetamine to nicotine [89], reductions in response rate are also observed (see also [92]), indicating that the attenuation by SCH-23390 may represent nonspecific effects due to behavioral impairment. Thus, only limited findings [29] support the notion that D_1 receptors are involved in the S^D effects of a low nicotine dose.

3.2. D_2 receptors

There are also mixed results on the role of D_2 receptors in the nicotine cue. The D_2 agonist R(−)-10,11-dihydroxy-N-*n*-propylnoraporphine hydrochloride (NPA), the mixed $D_{2/3}$ agonists bromocriptine, (±)-7-hydroxy-N,N-di-n-propyl-2-aminotetralin (7-OH-DPAT) and quinpirole, and the DA autoreceptor antagonist (+)-AJ-76, do not substitute for nicotine [29, 89, 90]. The D_2 antagonists haloperidol and spiperone, and the DA release inhibitor CGS 10746B, partially attenuate the nicotine S^D in some studies [27, 29, 91, 93], but haloperidol and the nonselective DA antagonist *cis*-flupentixol are not effective in other studies [94]. Finally, the $D_{2/3}$ antagonist eticlopride attenuates nicotine-evoked conditioned responding, but only at doses that also decrease activity [92]. Collectively, it appears that the attenuation of nicotine's interoceptive effect by DA antagonists occurs only at doses that reduce either response rates or general activity, which complicates interpretation [91].

3.3. D_3 receptors

There are no results supporting D_3 receptor involvement in nicotine discrimination. The D_3 agonist PD 128, 907, the D_3 partial agonist BP-897, and the D_3 antagonists ST 198 and nafadotride do not generalize to, or alter, the responding controlled by the stimulus effects of nicotine [29, 39, 92, 95].

3.4. D_4 receptors

There also does not appear to be a role for D_4 receptors in the stimulus effects of nicotine. Although the atypical antipsychotic clozapine (an antagonist of D_4 receptors) attenuates

nicotine discrimination [39], the more selective D_4 antagonist U-101,387 fails to alter the S^D effects of nicotine [89]. The effect of clozapine may therefore be attributable to its actions on other neurotransmitter systems (e.g., serotonin) that appear to play a greater role in the nicotine cue.

3.5. DA agonists

Stronger evidence for a role of DA in nicotine discrimination is derived from investigations of the effects of nonselective DA agonists (i.e., DA transporter [DAT] inhibitors and DA releasers), although the diverse actions of such compounds precludes speculation on the role of any particular receptor(s).

3.5.1. Dopamine transport inhibitors—The S^D effects of several DAT inhibitors (i.e., bupropion, cocaine, GBR 12909 and methylphenidate) have been assessed in nicotine-trained rats. The nonselective monoamine uptake inhibitor cocaine elicits no substitution [26, 96, 97] or partial substitution [89, 98, 99] in nicotine-trained rats, pigeons, or squirrel monkeys. Further, cocaine pretreatment fails to alter the effects of nicotine in nicotine-trained rats [100]. On the other hand, nicotine generalizes fully in rats [23, 101] or rhesus monkeys [102] trained to discriminate cocaine. The cocaine-like S^D effects of nicotine are blocked by the nonselective DA receptor antagonist *cis*-flupentixol [98], although mecamylamine does not alter cocaine discrimination [98, 101]. Thus, the generalization of nicotine to the cocaine cue appears to be mediated by nAChRs and DA, whereas the generalization of cocaine to the nicotine cue is mediated by DA but not nAChRs.

The S^D effects of the DAT and norepinephrine transporter (NET) inhibitor bupropion (which also blocks nAChRs [103]), have also been examined in nicotine-trained rats. Bupropion substitutes partially or fully for nicotine in some studies [99, 104–106], but not others [98, 107]. Also, nicotine fully substitutes for bupropion when it is trained as a feature positive OS in rats [104]. The bupropion metabolite S,S-hydroxybupropion, as well as (+) and (−) *threo* bupropion, elicit partial substitution for the S^D effects of nicotine [108]. However, S,S-hydroxybupropion does not substitute for a nicotine CS in rats [104]. In interaction tests, bupropion shifts the nicotine dose-response curve leftward based on one study [106], but not based on another study [107]. There is no shift in the CS effects of nicotine after pretreatment with 5 or 10 mg/kg of bupropion, although 20 mg/kg of bupropion decreases nicotine-controlled responding [104]; similarly, the bupropion metabolite R,R-hydroxybupropion attenuates the S^D effects of the nicotine training dose by ~50% [108]. While the nicotine-like S^D effects of bupropion are not blocked by mecamylamine [105, 106], the nicotine-like CS effects of bupropion are blocked by the dopamine D1 antagonist SCH-23390 and the D2/3 antagonist eticlopride [104]. Thus, DA receptors appear to regulate the nicotine-like CS effects of bupropion, although nAChRs are not involved in the nicotine-like S^D effects of bupropion.

Mixed findings have also been obtained with the DAT and NET inhibitor methylphenidate. Although methylphenidate (1.25–10 mg/kg) does not substitute in rats trained to discriminate 0.3 mg/kg of nicotine, it dose-dependently enhances the S^D effects of a lower 0.056 mg/kg nicotine dose [109]. In contrast, 10 mg/kg of methylphenidate substitutes partially in rats trained with 0.2 mg/kg of nicotine as a CS [99].

The nicotine-like S^D effects of the selective DAT inhibitor GBR 12909 have also been examined. GBR 12909 produces either partial [91] or full [29] generalization to the S^D effects of nicotine. In contrast, GBR 12909 does not substitute for the CS effects of 0.2 mg/kg of nicotine [99]. Interestingly, GBR 12909 does not substitute for the S^D effects of nicotine if caffeine (3 mg/ml) is added to the rats' daily drinking water [29].

3.5.2. Dopamine releasers—There are conflicting reports regarding whether DA releasers produce nicotine-like stimulus effects. For example, *d*-amphetamine produces partial [11, 26, 89, 110] or full [111] substitution for the S^D or CS effects of nicotine in rats; *d*-amphetamine also substitutes partially in nicotine-trained C57BL/6 mice [112]. In contrast, *d*-amphetamine does not substitute for 0.4 mg/kg nicotine trained as a feature positive OS [113, 114]. Methamphetamine also elicits partial substitution for nicotine [94], whereas cathinone elicits full substitution [93]. On the other hand, the nonselective DA agonist apomorphine does not substitute for nicotine [26]. In tests of cross-substitution in stimulant-trained rats, nicotine either fails to substitute [115, 116], or substitutes only partially [47, 113], for *d*-amphetamine or cathinone [93]. However, nicotine substitutes fully for methamphetamine [94], and for the S^D effects of a low 0.3 mg/kg dose of *d*-amphetamine [101]. The α4β2 nAChR partial agonist cytisine [47] and the nicotine metabolite nornicotine [38] also evoke partial substitution for *d*-amphetamine. Interestingly, the nicotine-like S^D effects of *d*-amphetamine are not blocked by haloperidol [89], although haloperidol attenuates the partial substitution of methamphetamine [94]. The DA release inhibitor CGS 10746B also prevents the partial substitution of cathinone for nicotine [93]. On the other hand, mecamylamine and hexamethonium do not alter the S^D effects of *d*-amphetamine [101] or methamphetamine [94], although mecamylamine (but not haloperidol) blocks the substitution of nicotine for methamphetamine [94]. Finally, nicotine potentiates the S^D effects of *d*-amphetamine in *d*-amphetamine-trained rats [117]. While there clearly is not a complete overlap in the S^D effects of nicotine and stimulant drugs, the stimulant-like S^D effects of nicotine involve both DA and nAChRs, whereas the nicotine-like S^D effects of stimulant drugs are mediated primarily by DA.

4. Norepinephrine

There is limited evidence supporting a role for NE in the interoceptive stimulus effects of nicotine. Although one early study found that depleting central NE levels with the tyrosine hydroxylase inhibitor α-methyl-para-tyrosine (AMPT) attenuates the discriminative stimulus effects of nicotine [118], AMPT also depletes DA, making it difficult to conclude that blockade depends specifically on NE depletion. Further, the NET inhibitor desipramine [89], the β2 adrenergic agonist clenbuterol [41], and the α2 adrenergic antagonists agmatine [119] and yohimbine [89], do not substitute for nicotine. Further, the α1 adrenergic antagonist dibenamine [120], the α2 adrenergic antagonist agmatine [119], and the nonselective β adrenergic antagonist propranolol [120] do not alter nicotine's S^D effects. Although the NET inhibitor atomoxetine does not substitute for the CS effects of nicotine, atomoxetine blocks partially the nicotine CS without altering activity [99]. This observation has also been extended to the NET inhibitor reboxetine (R.A. Bevins, unpublished data). Thus, NE does not appear to be a component of the S^D effects of nicotine, although atomoxetine and reboxetine partially attenuate the CS property of nicotine at doses that do not produce nonspecific behavioral impairments.

5. Serotonin

Some early attempts to determine the role of serotonin (5-hydroxytryptamine; 5-HT) in the S^D effects of nicotine produced negative results. Depletion of central 5-HT levels with para-chlorophenylalanine does not alter rats' ability to discriminate nicotine from saline [118]. The mixed 5-HT receptor antagonist methergoline does not alter the nicotine cue [120], and the mixed 5-HT receptor agonist quipazine does not substitute for nicotine [26]. More recently, nicotine was shown to generalize partially to a compound S^D composed of both the 5-HT releaser fenfluramine and the DA releaser phentermine, but not when fenfluramine or phentermine alone is used as the training stimulus [121]. Fenfluramine alone also does not

substitute for nicotine [89]. In contrast to these results, however, there is recent evidence supporting a role for specific 5-HT receptor subtypes in modulating the nicotine cue.

5.1. 5-HT$_{1A}$ receptors

The 5HT$_{1A}$ agonist (±)-8-hydroxy-2-(di-n-propylamino)tetralin hydrobromide (8-OH-DPAT) dose-dependently attenuates nicotine-appropriate responding [122], although the 5HT$_{1A}$ partial agonist buspirone does not alter the nicotine cue [123].

5.2. 5-HT$_{2A/C}$ receptors

There appears to be a role for 5-HT$_{2A/c}$ receptors in the interoceptive stimulus effects of nicotine. The 5-HT$_{2A}$ antagonist R-(+)-alpha-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol (M100,907), the 5-HT$_{2A/C}$ agonist (+/−)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane HCl (DOI), the 5-HT$_{2C}$ receptor antagonist 6-chloro-5-methyl-1-to indoline (SB 242,084), and the 5-HT$_{2C}$ agonists Ro-60–0175 and (7bR, 10aR)-1,2,3,4,8,9,10,10a–octahydro-7bH-cyclopenta-[b][1,4]diazepino[6,7,1hi]indole (WAY 163,909) lack nicotine-like S^{D} effects [124]. However, DOI and 1-(4-bromo-2, 5-dimethoxyphenyl)-2-aminopropane (DOB) attenuate the nicotine cue [122, 124]. The 5-HT$_{2A/C}$ antagonists ketanserin or M100,907, but not SB 242,084, reverse the DOI blockade [122, 124], whereas the blockade by Ro-60–0175- or WAY 163,909 is reversed by SB 242,084, but not by M100,907 [124]. The 5-HT$_{2C}$ agonists 6-chloro-2-(1-piperazinyl) pyrazine hydrochloride (MK 212) and Ro-60–0175 also attenuate responding controlled by nicotine, although response rates were decreased at the highest test dose of each drug [122, 124, 125]. Similarly, the generalization to nicotine by the α4β2 nAChR agonist 5-IA is also blocked partially by WAY 163,909 and completely by DOI and Ro 60–0175 [124]. Interestingly, chronic nicotine treatment in ICR mice reduces cortical 5-HT$_{2A}$ receptor density, an effect that was suggested to reflect a potential 5-HT$_{2A}$ antagonist effect of nicotine [126]. If such a notion is true, it appears that the ability of 5-HT$_{2A/C}$ agonists to attenuate the S^{D} effects of nicotine may be due to reversal of nicotine-induced 5-HT$_{2A}$ receptor antagonism, providing further support of a 5-HT mechanism in the stimulus effects of nicotine.

5.3. 5-HT$_{3}$ receptors

A limited number of studies have failed to support a role for 5-HT$_{3}$ receptors in the nicotine cue, as the 5-HT$_{3}$ antagonists ICS-205930, MDL 72,222, and ondansetron each fail to alter nicotine-maintained responding [123, 127].

5.4. 5-HT$_{6}$ receptors

One study [124] demonstrated that the 5-HT$_{6}$ antagonist MS-245 does not substitute for nicotine alone. However, pretreatment with MS-245 prior to the ED$_{50}$ dose of nicotine elicits full generalization, suggesting 5-HT$_{6}$ antagonism augments the discriminative cue of a low nicotine dose [128].

6. γ-aminobutyric acid

There have been few investigations of a potential role for γ-aminobutyric acid (GABA) in the stimulus effects of nicotine. The benzodiazepine site GABA$_{A}$ positive modulator chlordiazepoxide, the GABA$_{A}$ agonist topiramate, and the GABA$_{B}$ agonist baclofen do not generalize to nicotine or alter its stimulus effects [26, 113, 129, 130; but see section 15 below for an interesting exception). While the noncompetitive GABA$_{A}$ antagonist picrotoxin does not elicit nicotine-appropriate responding in rats [26], the benzodiazepine site GABA$_{A}$ partial inverse agonist ethyl-β-carboline-3-carboxylate elicits partial or full substitution in squirrel monkeys trained to discriminate intravenous nicotine from saline

[131]. Withdrawal from 21 days of chronic nicotine treatment elicits partial generalization to the discriminative stimulus effects of the $GABA_A$ antagonist pentylenetetrazole (PTZ) [132], although nicotine itself does not generalize to PTZ [133]. Interestingly, the substitution of nicotine withdrawal for PTZ is reversed by the $GABA_A$ positive modulator diazepam, but not mecamylamine [132]. These results suggest a relatively limited role of GABA in the cueing effect of nicotine, although the interoceptive cue of nicotine withdrawal may reflect, in part, a reduction in GABA transmission.

7. Glutamate

The role of glutamate has also not been addressed fully. The *N*–methyl-D-aspartate (NMDA) ionotropic glutamate receptor subtype channel blockers dextromethorphan (DXM), MK-801 and memantine, and the metabotropic 5 glutamate receptor (mGluR5) subtype antagonist MPEP, do not generalize to nicotine in substitution tests, although memantine and MPEP, but not MK-801 or DXM, produce a slight attenuation in responding controlled by the nicotine S^D [76, 77, 134]. In contrast, using a CS procedure in nicotine-trained rats, MPEP produces no effect in substitution or interaction tests, although MK-801 blocks nicotine-evoked responding at doses that do not alter general activity [92]. Finally, nicotine does not generalize to an NMDA S^D [135]. Thus, results to date do not appear to support a primary role for glutamate in the discriminative stimulus properties of nicotine, although NMDA and/or mGluR5 glutamate receptors may play a minor role. Further, the results reported in [92] suggest the possibility that NMDA receptors play a greater role in the CS properties of nicotine, although further work is needed before conclusions can be accepted fully.

8. Cannabinoids

The role of endogenous cannabinoids and the CB_1 and CB_2 cannabinoid receptor subtypes in the stimulus effects of nicotine has been addressed in several recent investigations.

8.1. Endogenous cannabinoids

The endogenous cannabinoid anandamide, the anandamide uptake/fatty acid amide hydrolase (FAAH) inhibitor AM-404, and the FAAH inhibitor URB 597 lack nicotine-like discriminative stimulus effects, although combinations of AM-404 + anandamide or URB 597 + anandamide produce modest leftward shifts in the nicotine dose-response curve [64]. On the other hand, in rats trained to discriminate the CB_1 agonist Δ^9-tetrahydrocannabinol (Δ^9-THC; 3 mg/kg) from vehicle, a combination of nicotine (0.1–0.56 mg/kg) + URB-597 (0.3 mg/kg) evokes ~75% Δ^9-THC-appropriate responding that is reversed by the CB_1 antagonist/inverse agonist SR141716 (rimonabant) [136].

8.2. CB_1/CB_2 receptors

Three studies have shown that SR141716 does not substitute for, or alter, the S^D effects of nicotine in nicotine-trained rats [64, 137, 138]. In contrast, SR141716 partially blocks conditioned responding evoked by a nicotine CS [139]. The non-selective cannabinoid CB1/2 receptor agonist CP 55,940 substitutes partially for the nicotine CS and enhances conditioned responding evoked by a lower nicotine dose. Interestingly, SR141716 dose-dependently attenuates the generalization of nicotine in *d*-amphetamine-trained rats without disrupting response rates [137]. In rats trained to discriminate Δ^9-THC from vehicle, nicotine (0.1–0.56 mg/kg) alone does not elicit Δ^9-THC-appropriate responding but a low 0.1 mg/kg dose of nicotine enhances the discriminative stimulus effects of Δ^9-THC, an effect reversed by co-administration of either SR141716 or mecamylamine with nicotine [136]. Finally, the mixed $CB_{1/2}$ agonists CP 55,940 and WIN 55,212, and the CB_2 antagonist SR144528 lack nicotine-like discriminative stimulus properties in substitution

tests [64]. Collectively, it appears that cannabinoid receptor activation does not produce a nicotine-like cue, but can augment the effects of nicotine.

9. Adenosine

The role of adenosine in nicotine discrimination has been examined using the nonselective adenosine receptor antagonist caffeine, as well as with ligands selective for the A_1 and A_{2A} adenosine receptor subtypes. In rats provided with normal drinking water or with drinking water containing caffeine, there are no differences in the rate of acquisition, nicotine dose-effects, or mecamylamine blockade of nicotine discrimination, although several DAergic compounds generalize to nicotine in rats with normal water, but not when caffeine is added [29]. Further, the putative DA release inhibitor CGS 10746B attenuates the nicotine cue in rats with normal water, but not in rats with caffeine added to the drinking water [29]. Chronic exposure to 0.25 mg/ml of caffeine, but not 1.0 mg/ml of caffeine, also enhances acquisition of learning to discriminate nicotine from saline [29]. In substitution tests in nicotine-trained rats, depending on the study, caffeine either lacks nicotine-like stimulus effects [140], substitutes partially [141] or fully [113]. Caffeine also potentiates the effects of a low nicotine dose in interaction tests [140]. Finally, the A_1 adenosine receptor antagonist CPT and the A_{2A} adenosine receptor antagonist MSX-3 also produce partial generalization to nicotine, while shifting the nicotine dose-response curve leftward [141].

10. Opioids

The role of opioid systems has not been addressed extensively. The nonselective opioid receptor agonist morphine does not substitute for nicotine [41, 111], and the μ opioid receptor antagonists naloxone and naltrexone do not block the nicotine cue [142]. In contrast, the stimulus effects of nicotine trained as a positive OS are fully blocked by the μ opioid receptor antagonist naloxone [13]. However, the doses required for such blockade (2 to 6 mg/kg) are higher than those typically used to block the stimulus effects of morphine, and leave open the possibility for a non-specific account of this antagonism. Further, rats can discriminate between the μ opioid receptor agonist fentanyl and nicotine [143], indicating that these drugs produce distinct discriminative stimulus effects.

11. Ion channel blockers

One study demonstrated that the dihydropyridine Ca^{2+} channel blocker isradipine reduces levels of nicotine-appropriate responding elicited by nicotine by ~50%, although effects on response rate were not reported [127].

12. Monoamine oxidase

Tobacco smoke also delivers psychoactive compounds that inhibit monoamine oxidase (monoamine oxidase inhibitors; MAOIs) in human smokers [144], and recent evidence has shown that MAOIs can dramatically increase nicotine self-administration in rodents [145–148]. Two studies have examined the discriminative stimulus effects of MAOIs in nicotine-trained rats [89, 149]. The selective MAO_B inhibitor deprenyl produces a maximum of ~20% nicotine-appropriate responding in substitution testing (deprenyl was not examined in interaction tests; [89]). The selective MAO_A inhibitor clorgyline, the selective MAO_B inhibitor pargyline, and the nonselective MAO_{AB} inhibitor phenelzine also do not evoke nicotine-appropriate responding (with the exception of 17 mg/kg of phenelzine, which produces ~43% nicotine-appropriate responding, although response rates were suppressed; [149]). In interaction testing, 10 mg/kg of phenelzine enhances the effects of a low 0.056 mg/kg dose of nicotine and prolongs the time course effect of the 0.3 mg/kg nicotine

training dose [149]. Thus, these findings suggest that concurrent inhibition of each MAO isozyme can potentiate the nicotine cue, although the underlying mechanisms are unknown.

13. Neuroanatomical mediation of the nicotine cue

Drug discrimination has also been used to elucidate the brain regions mediating the stimulus effects of nicotine. The involvement of cholinergic-innervated regions such as dorsal hippocampus (HPC), mesencephalic reticular formation (MRF), and medial habenula (mHB) in the nicotine cue has been investigated. Local infusion of nicotine into the MRF or HPC substitutes partially for nicotine, and systemic mecamylamine eliminates completely the substitution of intra-HPC nicotine and attenuates the substitution by intra-MRF nicotine [150]. Intra-HPC administration of nicotine substitutes in rats trained to discriminate systemic nicotine [151]. Interestingly, substitution for intra-HPC nicotine is obtained in normal rats, but not in rats treated with 6-hydroxydopamine as neonates [152]. In contrast, others have found no substitution of intra-HPC nicotine [153, 154]. Those latter studies also reported that intra-HPC mecamylamine fails to block responding controlled by the systemic nicotine cue. Finally, nicotine infused into the mHB fails to elicit nicotine-appropriate responding [155].

The involvement of DA neurons and terminal fields in the ventral tegmental area (VTA), nucleus accumbens (NAcc), and medial prefrontal cortex (mPFC) have also been investigated. Intra-VTA nicotine does not evoke nicotine-appropriate responding and intra-VTA mecamylamine does not block responding controlled by the systemic nicotine cue in one report [153], although partial substitution with intra-VTA nicotine was obtained in another report [154]. Partial to full substitution for systemic nicotine is obtained with intra-NAcc nicotine [153, 154, 156], and intra-NAcc mecamylamine blocks responding controlled by systemic nicotine [153, 156]. However, intra-NAcc nicotine did not substitute for nicotine in another report [151]. Finally, intra-mPFC nicotine has been shown to substitute for systemic nicotine [155].

Together, it appears that the MRF, VTA, NAcc and mPFC, but not HPC or mHB, play a role in mediating the cueing effects of nicotine in operant procedures. The reasons for the discrepant findings among some studies are unknown, although it is possible that differences in the nicotine training doses used, and/or subtle variations in the location of brain infusion sites, may play a role. The brain regions mediating the Pavlovian CS properties of nicotine also warrant investigation.

14. Individual differences

There is a large body of literature indicating that individual difference variables play important roles in drug abuse vulnerability [157–159]. However, little work has been conducted to examine the potential for these variables to influence the interoceptive stimulus properties of drugs. Some evidence suggests that the drug discrimination procedure is amenable to studying individual differences. For example, genetic factors play a role, as Lewis rats acquire a nicotine-saline discrimination at a dose of 0.4 mg/kg, whereas a higher dose of nicotine (0.9 mg/kg) is needed with Fischer-344 rats; in addition, the ED_{50} value for nicotine generalization is lower for Lewis rats than for Fischer-344 rats [160]. There is also evidence that nicotine is generalized to an ethanol stimulus in alcohol-preferring rats to a greater extent than in alcohol-nonpreferring rats [156]. There is also evidence that inbred C57BL/6 mice are more sensitive to nicotine than DBA/2 mice [162]. Regarding sex differences, nicotine substitutes for a PTZ stimulus more readily in male and ovariectomized female rats than in intact female rats [163]. Further, environmental differences are also important, as preliminary results suggest that rats raised in an enriched condition (EC) are less sensitive to the discriminative stimulus effects of nicotine compared to rats raised in an

impoverished condition (IC), and that EC rats are more sensitive to mecamylamine attenuation of the nicotine cue than IC rats [164]. Given that IC rats also showed a greater density of [^{125}I]epibatidine-sensitive nAChR binding sites in the VTA [164], it is possible that individual differences in nAChR expression could predict sensitivity to nicotine's S^D effects. Based on recent findings showing that baseline expression of α4β2* nAChRs predicts motivation to self-administer nicotine under a PR schedule in squirrel monkeys [165], future research should also attempt to address the potential role of differential baseline expression of nAChR subtypes in acquisition of, and/or sensitivity to, nicotine's interoceptive stimulus properties.

15. Functional rather than pharmacological substitution

As described previously, an important strength of drug discrimination as a tool for studying neuropharmacological processes is that control of responding is relatively specific to the training drug. For instance, when nicotine is trained as a feature positive OS, neither amphetamine nor chlordiazepoxide substitutes for the nicotine stimulus [113]. Notably, recent research has shown that substitution crosses pharmacological classes and occurs as a result of shared learning history [114]. In that latter study, rats had nicotine trained as a feature positive OS to indicate when a discrete 15-sec cue (e.g., illumination of a light) would be followed by sucrose. In the same rats, chlordiazepoxide signaled when a separate and distinct stimulus (e.g., white noise) would be followed by sucrose. In the placebo (saline) state, the white noise and the light were presented but never reinforced. Not surprisingly, under these conditions, the discrete stimulus evoked a robust conditioned response when tested in the drug state in which it had been previously reinforced (i.e., nicotine:light and chlordiazepoxide:noise in this example). More importantly, the ability to evoke responding transferred to the other stimulus. Thus, nicotine is able to substitute for chlordiazepoxide, and vice versa, with the discrete stimulus evoking ~100% conditioned responding that it had never been trained with. Notably, this transfer is not the result of intermixed training with 2 different drug states producing a drug versus no-drug discrimination, as no responding is seen in substitution tests with amphetamine. Future research will need to examine the generality of such a finding, as well as the necessary learning conditions to establish generalization across drug classes. For instance, a similar outcome does not appear to occur when two drug states (rather than placebo) are used in the two-lever drug discrimination task. Perhaps having the incorrect lever present on all sessions with its stimulus and response controlling properties under extinction prevents such an effect. Alternatively, does the same US (sucrose in [114]) need to be used for both drug states trained as a positive feature, or is it sufficient to use a US within the same class of outcomes (appetitive or aversive)?

16. Summary and future directions

The drug discrimination procedure has been an important tool for elucidating the receptor mechanisms that mediate the interoceptive effects of nicotine. The critical initial transduction mechanism of the nicotine cue is activation of high-affinity β2 subunit nAChRs, although it appears that α4, rather than α6, is the complementary subunit involved; a role for other nAChR subunits has yet to emerge. However, since activation of α4β2* nAChRs modulates the activity of many neurotransmitter systems [166], it seems likely that the mechanisms underlying the interoceptive stimulus effects of nicotine are complex. Accordingly, recent findings suggest that adenosine, cannabinoid, and 5-HT systems are important elements of the nicotine cue; in addition, dopamine and glutamate may also be involved. Ongoing technical advances in the use of neurochemical techniques such as fast-scan cyclic voltammetry or rapid microdialysis could perhaps eventually be used to measure

behavior and neurotransmitter fluctuations concurrently as a way of further refining our understanding of the neural correlates mediating the stimulus effects of nicotine.

The drug discrimination procedure has also been employed in medication development. A particularly useful application of the procedure has been the characterization of nAChR agonists and antagonists for the treatment of tobacco dependence. For example, rats pretreated with a nAChR agonist (i.e., nicotine) or nAChR antagonist (i.e., mecamylamine) show similar decreases in rates of nicotine self-administration; thus, a drug that decreases nicotine self-administration may due so by acting either as a "substitute" agonist or as a "blocking" antagonist. Thus, it is important to also evaluate novel nAChR ligands in the drug discrimination procedure in order to identify the mechanism underlying decreases in nicotine intake. As shown in Fig. (**1**), drug discrimination dissociates the effects of nAChR agonists and antagonists more readily than self-administration (M.T. Bardo and T.E. Wooters, unpublished observations); nicotine and mecamylamine each decrease the number of nicotine infusions earned in a dose-related manner (Fig. 1A), whereas only nicotine elicits a dose-dependent increase in nicotine-appropriate responding in rats trained to discriminate nicotine from saline (Fig. 1B). Interestingly, however, compounds from several drug classes that do not alter the S^D effects of nicotine have been shown to reduce nicotine self-administration. Notable examples of this phenomenon include the DA antagonists SCH23390 and spiperone [86], the CB_1 receptor antagonist/inverse agonist SR141716 [137] (but see [139]), the $GABA_B$ agonist baclofen [177] and the putative α6β2 nAChR antagonists bPiDI and bPiDDB [21, 72, 74]. A number of other drugs that either generalize to or augment the S^D effects of nicotine have been shown to increase nicotine self-administration; these include bupropion [167], GBR-12909 [168], methamphetamine [167], methylphenidate [109] and nonselective MAO inhibitors [145, 148]. Thus, while the S^D and reinforcing effects of nicotine are clearly dissociable, drugs that produce nicotine-like interoceptive effects appear to reliably increase nicotine self-administration, although this notion requires further evaluation.

Drug discrimination techniques may also prove amenable to investigate of the subjective effects of nicotine withdrawal. Drug discrimination has been used widely to characterize the discriminative effects of withdrawal from *d*-amphetamine [169], benzodiazepines [170, 171], opioids [172, 173], and Δ^9-THC [174]. Although studies of nicotine dependence/withdrawal have relied primarily on somatic (e.g., somatic signs) or affective (e.g., conditioned place aversion, intracranial self-stimulation) measures, it seems plausible that rats could learn to discriminate injections of a nAChR antagonist (e.g., mecamylamine) following acute nicotine pretreatment or during chronic nicotine exposure. In fact, rats are able to discriminate mecamylamine following acute pretreatment with nicotine, but not saline [51]. In addition, the partial α4β2 nAChR agonist SSR591813 substitutes partially for mecamylamine, and attenuates the mecamylamine cue, when administered after nicotine and prior to mecamylamine [51]. It would be of interest to determine whether clinically-available smoking cessation agents (e.g., bupropion and varenicline) also attenuate the discriminative stimulus effects of nicotine withdrawal, and whether or not such results predict a compound's ability to alter nicotine self-administration. Such a procedure could potentially provide further insight into the receptor mechanisms involved in nicotine withdrawal. Finally, the involvement of the corticotrophin-releasing factor [175] and hypocretin/orexin [176] systems in nicotine reinforcement has been demonstrated recently; thus, the possibility that such systems also mediate the interoceptive effects of nicotine could help to clarify the nature of the relation between the interoceptive and reinforcing properties of nicotine.

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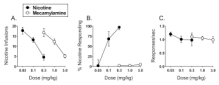

Fig. (1).

Effects of the nAChR agonist nicotine and the nAChR antagonist mecamylamine on nicotine self-administration and nicotine discrimination. Panel **A** demonstrates that nicotine (0.03–0.3 mg/kg, SC; 15-min pretreatment interval [PTI]) and mecamylamine (0.3–3.0 mg/kg, SC; 15-min PTI) both decrease the (mean ± SEM) number of nicotine (0.03 mg/kg/infusion) infusions earned in rats (n = 6) trained to self-administer nicotine under a fixed ratio 5 (FR5) reinforcement schedule during daily 60-min sessions. Panel **B** demonstrates that nicotine (0.03–0.3 mg/kg, SC; 5-min PTI), but not mecamylamine (0.3–3.0 mg/kg, SC; 15-min PTI), produces a dose-dependent increase in the percentage of nicotine-appropriate responses in rats (n = 6) trained to discriminate nicotine (0.3 mg/kg, SC) from saline under a FR10 reinforcement schedule during daily 15-min sessions. Panel **C** illustrates the effects of nicotine and mecamylamine on response rates (responses/sec) corresponding to the data presented in panel B.