Title

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Journal

The American journal of drug and alcohol abuse, 43(2)

ISSN

0095-2990

Authors

Cross, Sarah J
Lotfipour, Shahrdad
Leslie, Frances M

Publication Date

2017-03-01

DOI

10.1080/00952990.2016.1209512

HHS Public Access

Author manuscript

Am J Drug Alcohol Abuse. Author manuscript; available in PMC 2017 June 30.

Published in final edited form as:

Am J Drug Alcohol Abuse. 2017 March ; 43(2): 171–185. doi:10.1080/00952990.2016.1209512.

Mechanisms and genetic factors underlying co-use of nicotine and alcohol or other drugs of abuse

Sarah J. Cross, BA[a], **Shahrdad Lotfipour, PhD**[b,c], and **Frances M. Leslie, PhD**[a,c]

[a]Department of Anatomy & Neurobiology, School of Medicine, University of California, Irvine, CA, USA

[b]Department of Emergency Medicine, School of Medicine, University of California, Irvine, CA, USA

[c]Department of Pharmacology, School of Medicine, University of California, Irvine, CA, USA

Abstract

Concurrent use of tobacco and alcohol or psychostimulants represents a major public health concern, with use of one substance influencing consumption of the other. Co-abuse of these drugs leads to substantial negative health outcomes, reduced cessation, and high economic costs, but the underlying mechanisms are poorly understood. Epidemiological data suggest that tobacco use during adolescence plays a particularly significant role. Adolescence is a sensitive period of development marked by major neurobiological maturation of brain regions critical for reward processing, learning and memory, and executive function. Nicotine exposure during this time produces a unique and long-lasting vulnerability to subsequent substance use, likely via actions at cholinergic, dopaminergic, and serotonergic systems. In this review, we discuss recent clinical and preclinical data examining the genetic factors and mechanisms underlying co-use of nicotine and alcohol or cocaine and amphetamines. We evaluate the critical role of nicotinic acetylcholine receptors throughout, and emphasize the dearth of preclinical studies assessing concurrent drug exposure. We stress important age and sex differences in drug responses, and highlight a brief, low-dose nicotine exposure paradigm that may better model early use of tobacco products. The escalating use of e-cigarettes among youth necessitates a closer look at the consequences of early adolescent nicotine exposure on subsequent alcohol and drug abuse.

Keywords

Adolescence; amphetamine; co-dependence; cocaine; e-cigarettes; ethanol; nicotinic acetylcholine receptors; tobacco

CONTACT Sarah J. Cross, BA, crosssj@uci.edu, Department of Anatomy & Neurobiology, University of California, Irvine, 367 Med Surge II, Irvine, CA 92697, USA.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

ORCID

Sarah J. Cross http://dx.orcid/0000-0002-6246-3815

Introduction

Nicotine, via tobacco and increasingly from electronic nicotine delivery systems, is often used in conjunction with alcohol or other abused drugs. The majority of alcoholics smoke (1,2) and non-alcoholic drinkers are more likely to smoke than non-drinkers (3). Tobacco use also occurs in ~90% of cocaine and methamphetamine users (4–6). The combined use of tobacco with other abused substances is associated with substantial negative health outcomes. These include reduced cessation (7–9) and increased risk of cancer, heart disease, and mood disorders (10–14).

Epidemiological data suggest that tobacco in particular can act as a “gateway” to further substance use (15–18), and recent preclinical work lends support to this hypothesis (18–21). However, much of the preclinical research on nicotine interactions with other drugs fails to take into account the age of exposure, despite strong age-dependent associations in epidemiological studies. Initiation of substance use typically occurs during adolescence, with tobacco and alcohol use beginning in early teen years before subsequent progression to illicit drugs (16,22,23). Indeed, almost 90% of adult smokers started before the age of 18 (24). Important sex differences in tobacco use and trajectories (25) are also frequently ignored, with adolescent females being more likely to start smoking and less likely to quit than adolescent males (26,27).

Adolescence is marked by major reorganization of limbic brain regions that are important for learning, memory, and reward processing and characteristic behaviors of increased risk-taking, novelty seeking, and peer associations (28–31). It is conserved across mammalian species, with many of the same physiological and behavioral changes occurring in both humans and rodents (28,30,32). This developmental period is conservatively estimated to last from 12 to 18 years in humans and postnatal (P) days 28–42 in rodents (28), although the boundaries may extend beyond these ages (33–36). The dopamine system, which is critically involved in the rewarding properties of abused drugs (37,38), undergoes substantial remodeling during adolescence (31,39). Nicotinic acetylcholine receptors (nAChRs), which are ligand-gated ion channels consisting of pentameric combinations of $\alpha 2 - \alpha 7$ and $\beta 2 - \beta 4$ subunits, are also critically involved in the dynamic maturation of adolescent brain (40–42). Nicotine exposure during this time can produce unique and long-lasting behavioral and neurochemical changes, including modifications of cholinergic, dopaminergic, serotonergic, and endorphin systems (31,42–46), which may lead to further drug use.

In this review, we discuss the neurobiological and genetic factors underlying concurrent use of nicotine and alcohol or psychostimulants. We highlight important sex differences in concurrent use and argue that adolescent exposure to nicotine, via tobacco or e-cigarettes, is an essential component in the high rates of subsequent drug co-abuse.

Concurrent use of nicotine and alcohol

Human studies

Approximately 6.2 million people report alcohol use and tobacco dependence in the United States (US) during a single year (2). The economic costs associated with tobacco and

alcohol use total nearly 500 billion dollars per year in the US (47). It is increasingly clear that both substances influence consumption of the other, likely due to common genetic and molecular sites of action. Dependent smokers are approximately 10 times more likely to be alcoholics than non-smokers (48), and 70–80% of alcoholics smoke (2). Even young adults who only smoke occasionally are very likely to drink and, when drinking and smoking occur together, significantly greater amounts of alcohol are consumed (49,50). An increasing number of reports demonstrate associations between e-cigarette use and alcohol use and misuse among adolescents (51–54), although one study did not see any effect of e-cigarette consumption on alcohol use (55). Cessation and relapse are also negatively impacted by co-use. Current alcohol use disorder is associated with lower likelihood of smoking cessation and increased relapse to smoking (56), and nicotine dependence is associated with decreased odds of alcohol cessation in alcoholics (57–59). Additionally, female smokers have significantly higher alcohol craving in a treatment setting than nonsmokers (60). Experimental studies in humans have shown that nicotine increases the rewarding value of alcohol (61,62), and vice versa (63,64). Epidemiologic data also show that early adolescent onset smokers are at the greatest risk of excessive alcohol consumption and severe alcohol abuse disorders (49,65,66). Furthermore, an assessment of 12th grader patterns of use, from 1976 to 2010, has shown that the association of tobacco and alcohol co-use has increased over time, even though overall drug use has declined (67). These findings suggest that the behavior of co-users is increasingly attributable to factors that concomitantly influence both smoking and drinking.

Genetic mechanisms may contribute to tobacco and alcohol co-use. There is substantial overlap in a variety of genes that contribute to alcohol or tobacco use alone (68–70), but a full discussion is beyond the scope of this review. Instead, our focus is on known genetic underpinnings of co-use. Twin studies have shown that a substantial proportion of alcohol and nicotine co-dependence results from genetic influences, with more modest environmental contributions (71,72). Subsequent studies have tried to identify specific genetic associations between smoking and drinking. An area on chromosome 2 has been identified as a possible common genetic vulnerability locus for smoking and alcohol co-dependence (73). Genetic studies have also shown that nAChR genes are associated with both tobacco and alcohol addictions. In particular, recent evidence highlights the importance of the human gene cluster CHRNA5/A3/B4, which encodes α3, β4, and α5 nAChR subunits, respectively, in mediating these disorders (74–77). However, although genetic variations in the α5 nAChR subunit have been shown to influence risk for both alcohol and tobacco dependence, different single nucleotide polymorphisms (SNPs) of the gene are responsible (76). SNPs in other nAChR subunit genes have also been implicated in drug co-use, with CHRNB2 linked to initial subjective responses to both alcohol and tobacco (78), and the CHRNA6 - CHRNB3 gene complex linked to both smoking and heavy alcohol consumption (79,80). SNPs in the CHRNA5/A3/B4 gene cluster have been shown to be significant predictors of early initiation of tobacco or alcohol use (81–84) as well as associated with the frequency of adolescent binge drinking (85).

Consistent with a possible role of nAChRs in alcohol use disorders, there have been reports of clinical efficacy of varenicline, which is a partial agonist at α4β2 nAChRs and a full agonist at the α7 nAChR (86). A recent meta-analysis of clinical trials found that varenicline

reduces alcohol craving and total alcohol consumption in patients with alcohol use disorders (87). Drug effects are mild, however, and are more evident in less heavy drinkers (88,89).

Animal studies

Genetic models—Genetic rodent models have helped provide evidence for the mechanisms mediating the associated addictions in humans and provided insight into possible therapeutic interventions. Our focus here is on genetic contributions to nicotine and alcohol consumption since it is most relevant to human drug use, but we also briefly discuss some other responses to ethanol. One approach involves the selective breeding of rats or mice for different responses to alcohol. For example, both rats and mice selectively bred for high sensitivity to alcohol's locomotor-stimulating or sedative effects have been found to be more sensitive to nicotine than low sensitivity animals (90–93). In another study, nicotine self-administration was examined in rats selectively bred for high (P) or low (NP) alcohol intake (94). Not only did P rats self-administer more nicotine than NP rats but, following extinction, they also exhibited greater cue- or drug-induced reinstatement of responding. Studies on mice selectively bred for differing sensitivity to the sedative effects of alcohol have linked alcohol effects on Y-maze activity to a region in mouse chromosome 2 that contains CHRNA4, the gene that encodes the α4 nAChR subunit (95). Subsequent biochemical analyses have confirmed that an A/T polymorphism at amino acid position 529 in the second intracellular loop of the α4 subunit protein influences the initial sensitivity of α4β2 nAChRs to alcohol exposure (96).

Use of transgenic mouse models with selective gene mutations has further confirmed a role for nAChR subunits in some alcohol-induced behaviors. The deletion of β2-containing nAChRs modifies anxiolytic and withdrawal behaviors to alcohol (97,98), but has no effect on alcohol drinking behavior (98) or alcohol preference (99). Deletion of the α7 nAChR subunit results in significant reduction of alcohol intake in female mice as compared to wild-type mice, with no effect in males (100). Knockout mice lacking the α7 nAChR subunit also have increased sensitivity to the hypothermic, sedative, and locomotor-stimulating effects of ethanol (101). Transgenic over-expression of α3, β4, and α5 nAChR subunit genes, which increases nicotine consumption, decreases alcohol intake in a two-bottle preference test (102). Although elimination of the α5 nAChR subunit does not modulate ethanol consumption in knockout mice, it results in slower recovery from ethanol-induced sleep (103).

Whereas gene deletion of α6 and β3 nAChR subunits, both highly expressed in midbrain dopamine neurons (104,105), does not influence alcohol consumption (106), a role for α6 nAChR subunits in alcohol reward has been demonstrated using transgenic mice (α6L9'S) expressing mutant, hypersensitive α6 nAChR subunits (107). Female α6L9'S mice show significantly elevated alcohol intake at low concentrations of alcohol in a two-bottle choice procedure, whereas α6L9'S of both sexes show significantly elevated alcohol intake in a drinking in the dark procedure and exhibit low dose alcohol-induced place preference not seen in control mice. Alcohol has been shown to activate dopamine neurons within the midbrain posterior ventral tegmental area (pVTA) that express higher levels of α4, α6 and β3 nAChR subunit genes than non-activated neurons (108). The role of α4 subunits in

alcohol reward has been further demonstrated by using two transgenic lines with either a deletion of the α4 subunit gene or an insertion of a hyperactive polymorphism (Leu9'Ala). Alcohol potentiates the electrophysiological response to acetylcholine in midbrain dopamine neurons in wild-type mice, an effect that is absent in α4 knockout mice (109). Furthermore, ethanol intake and preference are decreased in α4 knockout mice (108,110), whereas Leu9'Ala mice exhibit enhanced conditioned place preference (109). Infusion of varenicline into the pVTA has demonstrated the particular importance of α4 subunits in this brain region for alcohol reward. Whereas varenicline into the pVTA mildly decreased alcohol consumption in wild-type controls, it had no effect on animals with the α4 nAChR gene deletion. Conversely, low doses of varenicline that were ineffective in wild-type controls greatly reduced alcohol intake in Leu9'Ala hypersensitive mice. Together, these data show that α4-containing nAChRs are a critical element in varenicline reduction of alcohol consumption. In contrast, gene deletion studies have shown that β2 and α7 nAChR subunits have no role in varenicline actions (100).

Behavioral pharmacology—Pharmacological studies have also demonstrated a role for nAChRs in modulating ethanol reward and reinforcement, although they sometimes contrast with genetic rodent studies. Mecamylamine, a nonspecific nAChR antagonist, dose-dependently reduces ethanol consumption, blocks ethanol-induced conditioned place preference and inhibits ethanol activation of VTA dopamine neurons (111,112). Antagonism of α3β2-, β3-, and/or α6-containing nAChRs with α-conotoxin MII decreases ethanol-induced locomotion and dopamine overflow, as well as ethanol consumption and preference (113–115), although the α-conotoxin-PIA analogue that is selective for α6 nAChRs does not alter ethanol's locomotor or neurochemical effects (113). Blockade of α4β2 nAChRs with DHβE or α7 nAChRs with MLA has no effect on ethanol intake (111,115,116), but partial agonists of β4-containing nAChRs reduce ethanol consumption and seeking in rats (111,116).

As in humans, there are positive relationships between nicotine exposure and alcohol intake or self-administration in rodents (117–122), although this can depend on length and timing of exposure, strain, and route of administration. The opposite relationship, with alcohol influencing nicotine intake, has not been as thoroughly tested using animal models. Single systemic injections of nicotine have no effect on alcohol intake, while repeated exposure enhances both oral ethanol intake and self-administration (117–120). Nicotine pretreatment 3–4 hours prior to alcohol self-administration increases alcohol intake, whereas nicotine given immediately prior to the session has no effect or suppresses responding (121,122). The increased alcohol drinking 3–4 hours after nicotine exposure is accompanied by greater GABAergic inhibition of VTA neurons, resulting in decreased dopamine cell firing and lower nucleus accumbens (NAc) dopamine release that may increase the motivation for ethanol (122). Effects of extended nicotine pretreatment are eliminated by blocking stress hormone receptors, thus implicating corticosterone release in both behavioral and electrophysiological interactions. Concurrent nicotine and alcohol exposure, on the other hand, can have additive or synergistic effects within the mesolimbic dopamine system that may enhance their acute rewarding effects. Indeed, intravenous co-administration of nicotine and ethanol produces an additive increase in NAc dopamine (122), and systemic nicotine

plus intra-accumbens ethanol increases dopamine levels more than either drug alone (123,124). These studies serve to highlight potentially important differences in mechanism and pharmacology resulting from sequential versus concurrent drug exposure.

Recent preclinical studies have administered nicotine and alcohol together, with mixed results. While neither chronic exposure to nicotine or ethanol alone influences basal levels of glutamate in the medial prefrontal cortex of female rats, concurrent exposure produces long-lasting increases in basal glutamate without affecting clearance. This effect is accompanied by a heightened sensitivity to the rewarding effects of nicotine self-administered into the NAc-shell (125). Lê et al. (126) showed that concurrent intravenous nicotine and oral ethanol self-administration had no effect on alcohol intake and decreased nicotine intake. However, they suggest that this was due to patterns of within-session responding, where alcohol intake was highest in the first 20 minutes of the session but nicotine intake was steady across the entire session, preventing the nicotine-induced enhancement seen in other studies (117–119). Alcohol preferring rats will self-administer combined ethanol and nicotine directly into the pVTA at concentrations that do not support individual self-administration (127), while combinations of oral nicotine and ethanol are self-administered at levels similar to ethanol alone (121). Furthermore, microinfusion of nicotine into the pVTA of these rats will enhance ethanol self-administration, an effect that is blocked by antagonists for both nAChRs and 5-HT3 receptors (128).

Despite evidence that varenicline decreases alcohol intake (100,108,129), the effects on co-self-administration of nicotine and alcohol are not as clear (130,131). However, withdrawal from chronic concurrent exposure, which is more prolonged than withdrawal from either drug alone, can be attenuated by continued treatment with just one of the drugs (132). Furthermore, acute exposure to nicotine after chronic alcohol exposure, or vice versa, results in an attenuation of somatic withdrawal that is reversed by mecamylamine injections into the medial habenula or interpeduncular nucleus (132).

Adolescence—Whereas many preclinical studies use adult male animals, initiation of alcohol and tobacco use typically occurs during adolescence, with patterns of use differing between men and women (25,133). Brief pretreatment of male rats during early adolescence (P28–31) with low doses of nicotine enhances subsequent acquisition of alcohol self-administration (21). Periadolescent nicotine (P35–44) also enhances ethanol consumption in female mice (134), although one study reported no effect of adolescent nicotine exposure in rats on ethanol intake in adulthood (135). The discrepancy may be due to different age of testing for ethanol consumption or continuous versus intermittent exposure paradigms. Route of administration and metabolism rates may also influence behavioral responses. Adolescent rodents tend to have lower plasma cotinine or nicotine levels than adults with subcutaneous or intravenous drug administration (136,137), but are not different from adults following oral nicotine (138). Thus, depending on the route of administration, nicotine doses may need to be adjusted for adolescents to better match what adults are exposed to. Ethanol metabolism also seems to be faster in adolescents following oral intake (139), but potential age differences in metabolism have not been studied for intravenous ethanol. It should be noted that, although humans consume alcohol orally, intravenous exposure can be a valid

method for assessing age differences in ethanol's pharmacological effects because it bypasses chemosensory properties of taste and smell that might influence intake (140).

Individual differences may also underlie such discrepancies, since a prior study has shown that adolescent rats with high behavioral reactivity in a novel environment that are exposed to nicotine develop conditioned place preference to ethanol as adults, whereas low behavioral activity animals do not (141). In addition, concurrent acetaldehyde, the primary metabolite of ethanol, increases initial acquisition of nicotine self-administration in adolescent male rats (142). Whereas males exhibited a decrease in responding to nicotine-acetaldehyde combinations with age, females did not (143). More recent work demonstrates that adolescent males find concurrent intravenous nicotine and alcohol significantly more reinforcing than either drug alone. This enhanced reinforcement of co-administered drugs is not evident in adult males or females of either age, and seems to result from a functionally immature kappa opioid receptor system (44). Although research using adult animals has highlighted timing of drug exposure (i.e., whether nicotine is given as a pretreatment or concurrently with alcohol) as an important factor in behavioral and neurochemical responses to nicotine and alcohol, more work needs to be done in adolescents.

Flavor attributes of nicotine and alcohol may also contribute to co-use in adolescence. There is a positive relationship between acceptance of the negative chemosensory qualities of both drugs (i.e., bitter taste and aversive odor) and consumption (144,145), and recent work demonstrates that prenatal alcohol exposure decreases aversion to the taste and smell of nicotine (146) and alcohol (147,148) in adolescent rats. Similar changes in aversion to nicotine and alcohol may also occur following acute co-administration during adolescence, but this has not been studied.

Adolescent drug exposure also induces unique sex differences in markers of cholinergic function. While male adolescents display greater choline acetyltransferase (ChAT) activity after exposure to nicotine alone, ChAT activity is decreased in females (149). Ethanol co-exposure normalizes levels in both sexes. Since decreases in ChAT activity can mean a loss of cholinergic innervation (150), ethanol may have blocked compensatory axonal sprouting in males, while exerting a protective effect against nicotine-induced ChAT decreases in females. These findings may help explain sex differences in vulnerability to co-use in humans.

Concurrent use of nicotine and psychostimulants

Human studies

Concurrent use of nicotine/tobacco products with psychostimulants is a matter of clinical concern (6). Growing evidence demonstrates that cocaine and other psychostimulants interact with nicotine/tobacco use to influence brain, behavior and the overall health (4,151,152). Currently, over 1.5 million individuals use cocaine and 595,000 use methamphetamine in the US, with the majority starting prior to 18 years of age (153). The majority of cocaine (75%) and methamphetamine (87%) users are known to smoke (4,154), with use almost always occurring after smoking initiation (5,155). Cocaine or amphetamine use can increase the urge to smoke (151) and tobacco consumption (156). Individuals who

quit smoking also have a higher likelihood of remaining abstinent to illicit stimulants, particularly for cocaine dependence (157).

In contrast to nicotine and alcohol co-use, there is a paucity of genetic studies examining possible common genetic mechanisms underlying concurrent use of nicotine/tobacco products and psychostimulants. At the time of writing, only two studies have examined the genetic role of nAChRs in psychostimulant dependence, but both found a significant association of cocaine dependence with a nonsynonymous coding polymorphism, rs16969968, of the CHRNA5 gene (158,159). However, the association was in the reverse direction to that seen for nicotine dependence, with the polymorphism conferring a protective effect against cocaine dependence. In a more recent study of two ethnic populations with co-dependence to nicotine, alcohol and cocaine, significant roles and interaction effects were observed for SNPs in the genes encoding the two 5-HT3 receptors, HTR3A and HTR3B, and the serotonin transporter, SLC6A4 (160). These findings implicate a role for the serotonin system in the etiology of all three substance-use disorders.

Whereas this finding of a common genetic underpinning of all three substance use disorders may reflect a common liability for drug use (161,162), an alternative hypothesis is that early adolescent use of tobacco sensitizes the reward centers of the brain to other abused drugs (18). This “gateway” theory is largely the product of epidemiological observation of a strict temporal sequence of drug use initiation (15,23,163–165). However, there is also clinical evidence that adolescent tobacco use is strongly associated with positive initial response to cocaine in young adults and subsequent continued use (166). Furthermore, preclinical studies outlined below lend support for the gateway concept.

Animal studies

Genetic and pharmacological studies—As with alcohol, psychostimulant responses are often enhanced by nicotine exposure. Chronic pretreatment with nicotine enhances cocaine reward-related behaviors, including locomotor sensitization, place preference and self-administration (167–171). In contrast, nicotine pretreatment can decrease (172) or have no effect (173) on self-administration of methamphetamine. Associated psychostimulant-induced increases in dopamine neurotransmission are also altered by nicotine. Indeed, combinations of nicotine and cocaine or amphetamine have additive or synergistic effects on dopamine release in the nucleus accumbens (174–176). Cocaine and amphetamines also interact strongly with the cholinergic system. Endogenous acetylcholine levels are increased following cocaine exposure (177), and cholinergic inputs to the VTA from the laterodorsal tegmental nucleus are necessary for the development and expression of cocaine place preference (178). Conversely, the non-selective nAChR antagonist, mecamylamine, inhibits cocaine-induced place preference and self-administration (179,180).

Both genetic and pharmacological approaches are useful in assessing the identity of relevant nAChRs. Whereas deletion of the α4 nAChR subunit does not alter cocaine reward (181,182), there is substantial evidence for a role of α6β2-containing nAChRs. Mice lacking β2 nAChR subunits show reduced cocaine place preference (180), whereas those lacking α6 subunits do not exhibit cocaine reward at any dose tested (182). In this latter study, the involvement of α6β2-containing nAChRs was confirmed pharmacologically by the blockade

of cocaine reward with the intracerebral administration of the selective nAChR antagonist α-conotoxin MII. Other nAChR-regulated brain circuits may also be involved in cocaine reward, since the high affinity α3β4 nAChR functional antagonists, AT-1001 and AT-1012, can also attenuate cocaine place preference (183). A less selective α3β4 nAChR antagonist, 18-methoxycoronaridine, has also been shown to inhibit the self-administration of both cocaine and methamphetamine (184,185).

Adolescence—A critical limitation of many behavioral studies is the use of adult animals, even though adolescence is a period of vulnerability to the effects of nicotine and other drugs of abuse. In order to model early adolescent smoking, one group has delivered nicotine to rats intravenously once daily for four days at a dose (60 μg/kg) that produces nicotine blood levels equivalent to that of 1–2 cigarettes (19–21,45,137). This brief, low-dose nicotine exposure in early adolescence produces unique, age-specific effects not seen in adult rats. These effects include enhancement of cocaine-induced locomotor sensitization, and enhanced acquisition of cocaine and methamphetamine self-administration. Nicotine effects are long-lasting, still evident ten days after the last drug administration, and are only evident when treatment is during early (P28–31) but not later (P37–40) adolescence. Whereas presynaptic markers of dopamine function are largely unaltered by this nicotine pretreatment, serotonin function is markedly influenced, and the observed behavioral alterations result from 5HT-1A receptor-mediated increases in dopamine D2 receptor function (21,46). A recent study in mice has also demonstrated long-lasting effects of early adolescent (P28–34) nicotine treatment on psychostimulant reward in adulthood, with nicotine-exposed animals displaying enhanced cocaine and amphetamine conditioned place preference. The same nicotine exposure during late adolescence (P47–59) or adulthood had no effect on subsequent psychostimulant reward (186).

Other studies that have treated adolescent animals for longer periods, at higher doses, and/or with continuous infusion, have produced mixed findings. Adolescent nicotine treatment did not influence acquisition of cocaine self-administration in adult rodents (187,188), and either did not change (188) or decreased conditioned place preference (189). However, the overall cocaine intake was higher in nicotine-pretreated mice than controls (187). Brief nicotine pretreatment of rats during early adolescence increases subsequent locomotor response to amphetamine, both during later adolescence and in adulthood (190). Furthermore, low dose, but not high dose, nicotine pretreatment during adolescence increases subsequent self-administration of methamphetamine in adults (191). The discrepancies across these studies may reflect strain or species differences, as well as differing nicotine treatment protocols and age of assessment of psychostimulant effects. However, they serve to illustrate how critically important it is to have appropriate animal models that reflect human use patterns.

Guidance for future research, clinical practice, and policymaking

Epidemiological data have consistently shown that developmental tobacco or nicotine exposure can act as a gateway to subsequent substance abuse. As clinical studies are often unable to prove cause and effect (192), animal studies offer the ability to assess underlying neurobiological and neurochemical mechanisms. Indeed, both clinical and preclinical research has provided significant support for the “gateway” effect of nicotine and tobacco.

Even brief exposure to nicotine during early adolescence can produce long-lasting increases in sensitivity to the rewarding effects of alcohol, cocaine, and methamphetamine (19–21). The cholinergic and serotonergic systems, in particular, are likely mediators of co-use of these substances (Figure 1).

There are strong associations between the use of nicotine, alcohol, and other illicit substances throughout the lifespan, and the growing use of e-cigarettes among youth (193–195) represents a major public health concern. Recent evidence suggests that, although the use of traditional cigarettes is declining (196) and the majority of e-cigarette users in 8th and 10th grades do not abuse other substances, a unique class of polysubstance user emerges in 12th grade (197). Others have suggested that e-cigarette use increases the risk for alcohol use, and is therefore a public health risk for minors (52,198). Flavorings, such as bubble gum, mint, or fruit, are frequently added to e-cigarettes and may encourage use among teenagers. Data assessing how flavored e-cigarettes might influence subsequent risk of alcohol or psychostimulant abuse are not available yet, but recent work shows that adolescents who smoke mentholated cigarettes are more likely to binge drink than peers who smoke non-mentholated cigarettes (199). It is clear that longitudinal clinical studies will be required to evaluate whether e-cigarettes do pose a higher risk of subsequent substance abuse, but preclinical studies with nicotine alone suggest that this will be the case. Gaps in the pre-clinical assessment of co-occurring substance-use disorders still remain, however. The majority of the current animal research examines adult males only, ignoring important age and sex differences observed in both human and animal populations. For example, women have less success with cessation from tobacco products (27,200), escalate to heavy drinking faster, and develop alcohol-related brain damage more rapidly than males (201–203). Women also likely transition to dependence on psychostimulants faster and enter treatment earlier than men (204,205). In preclinical research, female rodents are more sensitive to the rewarding effects of nicotine (206) and have higher ethanol intake than male rodents (207,208). Acquisition of cocaine self-administration is also more rapid in females (205,209), and they exhibit higher motivation for cocaine under progressive ratio testing (210). However, few studies have examined the contribution of sex to nicotine and alcohol or psychostimulant co-use. Thus, future research should include both age and sex comparisons. Ultimately, doing so will assist in the development of more effective policies governing nicotine and tobacco, as well as the development of efficacious therapies tailored toward each unique population.

Acknowledgments

Funding

This work was supported by NIH grant DA 040440, Tobacco-Related Disease Research Program project grants 21RT-0136 and 22RT-0103, and the National Alliance for Research on Schizophrenia and Depression Young Investigator Grant 21517.

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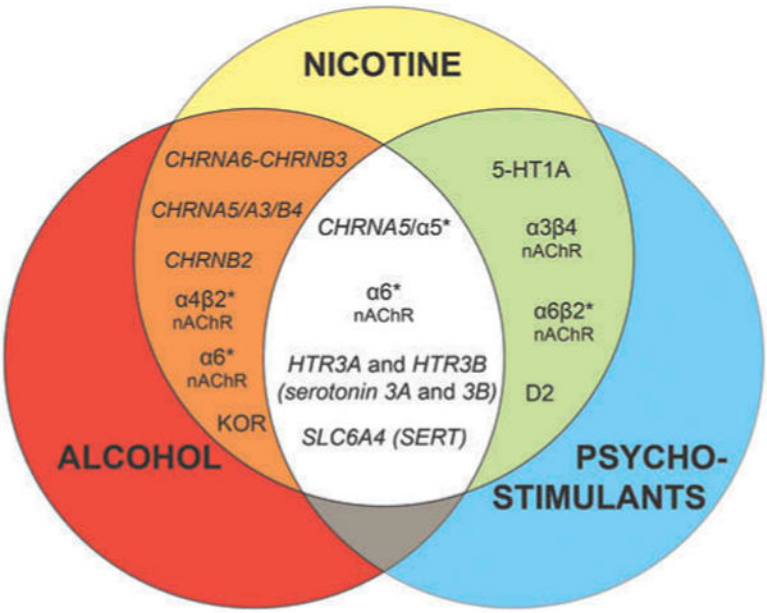

Figure 1.

Overlapping receptor systems involved in nicotine and alcohol or psychostimulant dependence. Genetic and pharmacological studies in both humans and rodents suggest that co-use of nicotine and alcohol or psychostimulants is mediated, in part, by activity at overlapping substrates. In particular, cholinergic and serotonergic systems underlie reward-related behaviors, including drug intake, preference, and dependence to all three drugs of abuse. Asterisks (*) indicate nAChRs containing other subunits. Italics indicate human genes. KOR = kappa opioid receptor.