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Positive and Negative Effects of Alcohol and Nicotine and Their Interactions: A Mechanistic Review

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Abstract

Nicotine and alcohol are two of the most commonly abused legal substances. Heavy use of one drug can often lead to, or is predictive of, heavy use of the other drug in adolescents and adults. Heavy drinking and smoking alone are of significant health hazard. The combination of the two, however, can result in synergistic adverse effects particularly in incidences of various cancers (e.g., esophagus). Although detrimental consequences of smoking are well established, nicotine by itself might possess positive and even therapeutic potential. Similarly, alcohol at low or moderated doses may confer beneficial health effects. These opposing findings have generated considerable interest in how these drugs act. Here we will briefly review the negative impact of drinking–smoking co-morbidity followed by factors that appear to contribute to the high rate of co-use of alcohol and nicotine. Our main focus will be on what research is telling us about the central actions and interactions of these drugs, and what has been elucidated about the mechanisms of their positive and negative effects. We will conclude by making suggestions for future research in this area.

Keywords

Alcoholism; Smoking; Alcohol; Nicotine

Introduction

Two of the biggest threats to world health come from the negative effects of using tobacco and alcohol. It has become clear over the last few decades that heavy use of tobacco and/or alcohol leads to serious health consequences such as development of cardio- and cerebro-vascular diseases, gastric ulcers, various cancers, particularly those of the head, neck, esophagus, and even liver (Castellsagué et al. 1999; Franceschi et al. 1990; Johnson and Jennison 1992; Ko and Cho 2000; Koob and Le Moal 2006; Mitrouska et al. 2007; Olsen et al. 1985; Pelucchi et al. 2008). The high use of alcohol and tobacco products likely stems in part from their abundant and legal availability, but also from other factors that can lead to users' abusive and addictive use. In recent years it has been elucidated that abuse of alcohol and nicotine (from tobacco products) can be attributed in part to genetic, rewarding, and possibly the analgesic effects the drugs have. Furthermore, high incidence of co-morbidity can be linked by these same factors, as well as possible pharmacokinetic and pharmacodynamic interactions (e.g., enhancement of the rewarding and analgesic effects) and counteracting mechanisms that co-use affords the consumer. This article first reviews

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and evaluates current evidence of these contributory factors to co-use, then looks at how dosing should be considered when evaluating the impacts of these drugs. The main focus will be on central effects of alcohol and nicotine, and how dosing level and combination of these drugs can alter the effects of both drugs. Finally, we will comment on how these research findings potentially impact suggestions for cessation treatment for addicts and general heath management, and suggest lines of study that need to be pursued.

Contributory Factors to Alcohol and Tobacco Co-morbidity

Epidemiological studies have demonstrated that in adolescents and adults high rates of smoking correlate highly with alcohol use, with smoking rates in alcoholics estimated to be at least two times higher than the general population (Falk et al. 2006), and the rate of cigarette consumption to be higher in alcoholic smokers than nonalcoholic smokers (Dawson 2000). Research involving this phenomenon has given rise to four prominent explanations for the high incident rate of alcohol and tobacco co-use. The depth of research in each field is varied, but begins to paint a picture of how alcohol and nicotine possibly interact to contribute to their co-morbidity.

Genetic Influence

In recent years studies have focused on the nature side of addiction over the nurture, by following addiction rates in twins (mono- vs. dizygotic) and siblings raised in different environments (Ball 2008; Enoch and Goldman 2001). It has become clear that there is a strong genetic component to addiction, which may account for addictive behavior more than environmental influences. Current estimations for heritability of all major addictive disorders range between 40 and 80% (Goldman et al. 2005). This suggests strongly that there is an underlying genetic vulnerability for alcohol–nicotine co-morbidity. It is estimated that genetic factors account for about 50% of nicotine or alcohol dependence (Maes et al. 1999; Sartor et al. 2010; True et al. 1999), but this number can vary with gender, race, culture, and religion. The influence of genetic factors on addiction to these drugs appears to vary with the age that drinking or smoking was initiated (Rose 1998), hinting on a possible epigenetic influence. Alcohol–nicotine co-morbidity appears to be equally dependant on genetic factors in men and women, but the same does not appear to be true in nonaddicted users (males more genetically predicated: Han et al. 1999; Kendler et al. 1994, 2000).

Genetic studies of addiction have focused on dysfunctions of several neurotransmitter systems that in some way contribute to alteration of the reward (e.g., dopaminergic) or mood (e.g., glutamatergic, opioidergic, serotonergic, or cholinergic) pathways in the brain. The hypothesis being that alteration to these systems could alter an individual’s experience or tolerance to a drug, and therefore change the likelihood that the person becomes addicted to or have difficulty quitting. However, the search for candidate genes in these pathways (via various methods such as Whole Genome Association) has turned up many genes on various chromosomes that act on and alter a variety of functions including enzymatic activity, protein translation, transcriptional regulation, and receptor function. Changes in these functions could alter susceptibility to alcohol, nicotine, or drug addiction in general (Ducci and Goldman 2008; Uhl 2004; Uhl et al. 2008). Still the genetic basis of alcohol and nicotine addiction is unknown. Some studies suggest that even subtle changes in genetic makeup (different strains of rats) can alter sensitivity to drugs and the rewarding release of dopamine (see “Reward Pathway Activation” section: Cadoni et al. 2009). However, the most promising have been studies of mutations of genes involved in alcohol metabolism (e.g., ADH/ALDH: alcohol/aldehyde dehydrogenase), nicotine metabolism (e.g., CYP2A6: cytochrome P450 2A6) or nicotinic receptor.

It is the belief of some scientists that polymorphisms in ADH/ALDH are the only ones that truly alter the risk of alcoholism (Crabbe et al. 2006). ADH and ALDH are enzymes that metabolize alcohol to acetaldehyde and then to acetate, respectively. Isoform variation of either gene appears to reduce the risk of alcoholism, with additive effects when both vary (Ball 2008; Dick and Foroud 2003; Köhnke 2008). It is unclear why variations cause decreased alcohol abuse and alcoholism, but it might be in part due to increased negative side effects of the alcohol consumption. These side effects are likely tied to accumulation of acetaldehyde, leading to acetaldehyde syndrome-like symptoms, including palpitations, skin flushing, nausea, and severe hangovers (Ball 2008; Luczak et al. 2002; Müller et al. 2010; Tu and Israel 1995). These polymorphisms appear most predominantly in East Asian populations, but studies are finding similar mutations in ADH and ALDH that likely alter rates of alcoholism in non-Asian populations (Liu et al. 2011).

CYP2A6 is part of an enzyme subfamily involved in the oxidative metabolism and detoxification of various compounds. Therefore, polymorphisms within this subfamily can dramatically alter drug effects (Johansson and Ingelman-Sundberg 2011). CYP2A6 specifically, is the primary enzyme responsible for the oxidation of nicotine to cotinine (Benowitz and Jacob 1994; Messina et al. 1997; Nakajima et al. 1996a, b). Polymorphisms of CYP2A6 alters nicotine metabolism resulting in increased or decreased smoking rate depending on the mutation. For example, individuals with inactivated CYP2A6 are less likely to smoke or smoke very little (Messina et al. 1997; Pianezza et al. 1998; Rao et al. 2000), whereas duplication of the gene increases smoking (Rao et al. 2000). This suggests that length of time nicotine is bioavailable in the system due to CYP2A6 mutations can dramatically influence smoking rates and possibly age of smoking initiation and cancer risk (Ariyoshi et al. 2002; Thorgeirsson et al. 2010).

Recent exciting discoveries emanating from genome wide association studies have identified polymorphisms localized to chromosome 15q24 (gene cluster encoding α3, α5, β4 nicotinic acetylcholine receptor (nAChRs) subunits) variants of which are associated with nicotine dependence as well as risk for lung cancer and peripheral arterial disease (Berrettini et al. 2008; Thorgeirsson et al. 2008). Moreover, emerging evidence suggest that nAChRs containing α5, α6, β3, and β4 subunits regulate nicotine intake (Fowler et al. 2011; Frahm et al. 2011; Hoft et al. 2009b). Interestingly, polymorphisms within the cluster encoding for nAChRs are also associated with alcohol dependence and early initiation of alcohol use (Hoft et al. 2009a; Schlaepfer et al. 2008; Wang et al. 2009). See below for more detailed discussion of nicotinic receptors.

Nicotinic Receptors

Nicotinic receptors belong to ionotropic class of receptors. These receptors act by regulating directly the opening of a cation channel in the neuronal membrane (see Changeux et al. 1998; Gotti and Clementi 2004; Rathouz et al. 1996; Wu and Lukas 2011 for reviews). Considerable information on interaction between these receptors and other neurotransmitter systems is now available. Indeed, therapeutic potentials for selective nicotinic receptor agonists in various neuropsychiatric and neurodegenerative disorders have been suggested. Various subtypes of these receptors with distinct anatomical, physiological, and pharmacological characteristics have been identified (see reviews by: Albuquerque et al. 1995; Changeux et al. 1998; Clarke 1995; Conti-Fine et al. 1995; Gotti and Clementi 2004; Lukas and Bencherif 1992; Miwa et al. 2011; Olale et al. 1997; Picciotto 2003; Wu and Lukas 2011). The most predominant and most extensively studied subtype in the brain has a high affinity for cytisine, nicotine or acetylcholine and is formed from α4 to β2 subunits (see Clarke et al. 1985; Flores et al. 1992; Pabreza et al. 1991). This subtype is commonly referred to as high-affinity binding site. The other major class with a high affinity for α-bungarotoxin but low affinity for nicotine is formed from α7 subunits and can be labeled by

[^{125}I]α-bungarotoxin. This subtype is commonly referred to as low-affinity binding site. It should be noted that [^{125}I]α-bungarotoxin also binds with high affinity to neuro-muscular nicotinic receptors and in some cases to ganglionic nicotinic receptors (Zigmond and Loring 1988). However, the subunit structures of the nicotinic receptors in the muscle are different from those in the ganglia which are different from those in the CNS.

Further distinction between nicotinic receptor subtypes is evident in their central distribution as well as their physiological roles. For example, [^{125}I]α-bungarotoxin binding sites in the brain are most abundant in hippocampus (see Clarke et al. 1985 for detailed distribution) and are believed to have a prominent role in neuronal growth and survival (De Fiebre et al. 1995). Furthermore, these receptors appear to be involved in cognitive functions, particularly attentional processes (Freedman et al. 1997; Matsuyama et al. 2001; Miwa et al. 2011). A role for α7 receptor subtype in central reward pathway has also been suggested (Schilström et al. 1998; Jones and Wonnacott 2004). High-affinity nicotinic receptors (e.g., α4–β2 or α3 containing receptors), on the other hand, are more prominent in mesolimbic or nigro-striatal pathways and appear to be more involved in rewarding or addictive behavior, locomotor activity and antinociception (Changeux et al. 1998; Damaj et al. 1998; Lindstrom 1997; Olale et al. 1997; Stolerman et al. 1997). Both receptors appear to be involved in neuroprotection as well (Belluardo et al. 2000; Picciotto et al. 2000; Tizabi et al. 2003, 2004). Studies with Flinders and WKY rat models of depression and Fawn-Hooded rat model of alcoholism and depression also suggest involvement of high-affinity nicotinic receptor subtypes in these behavioral characteristics (Tizabi et al. 1999, 2000, 2009).

Epigenetic Influence

Another consideration is that changes are not occurring within the genes themselves, but through activation or deactivation of more than one gene. In other words, it is possible that environmental factors are causing modulation of gene activation through epigenetic changes (i.e., change in gene expression controlled by alteration of DNA methylation and/or chromatin structure). Strong evidence supports the idea that epigenetic mechanisms exist that can alter gene expression in neurons that can lead to changes in behavior including psychiatric disorders such as depression, schizophrenia, and drug addiction (reviewed Tsankova et al. 2007). In terms of drug addiction, these epigenetic changes may provide reasons for why addictive behaviors arise, persist long after drug cessation, and have high rates of relapse. Epigenetic effects of drug abuse has been extensively studied in cocaine (Renthal and Nestor 2008; reviewed Tsankova et al. 2007), but poorly studied in alcohol and nicotine. Nicotine has been shown to have longterm effects after intrauterine exposure: both immediate (Dickson et al. 2011; Lotfipour et al. 2009; Toledo-Rodriguez et al. 2010) and transgenerational (Holloway et al. 2007). Furthermore, it has been seen in humans that nicotine has lasting effects on demethylation of monoamine oxidase-B promoters (altering serotonin metabolism: Launay et al. 2009), and is associated with high CYP2A6 activity due to full demethylation of the gene site (Al Koudsi et al. 2010). Recent studies, using a mouse model to study nicotine abuse in schizophrenics, have demonstrated the likelihood of nicotine playing a role in regulating epigenetic alterations of GABAergic neurons seen in this disease (Maloku et al. 2011). The link may be through activation or alteration of the α4β2 nicotinic receptor subtype (Maloku et al. 2011). Ethanol has been more directly studied, with both chronic and acute exposure causing chromatin changes (Bönsch et al. 2005; Kim and Shukla 2006; Mahadev and Vemuri 1998). Chronic alcohol exposure leads to changes in protein expression in astrocytes and neurons (Mahadev and Vemuri 1998), and withdrawal from chronic exposure can cause chromatin remodeling that leads to withdrawal related anxiety (Pandey et al. 2008; Moonat et al. 2010). In one study no changes were seen in the brain after acute alcohol exposure, but other tissues did show epigenetic changes via histone modification (Kim and Shukla 2006). Another study showed anxiolytic effects of

alcohol, possibly in relation to chromatin modification (Pandey et al. 2008). Studies in *Drosophila* have shown that acute exposure to alcohol caused gene regulation changes that altered drug sensitivity (Ghezzi et al. 2004; Wang et al. 2007). Collectively, these findings suggest epigenetic/genetic mechanisms by which drug tolerance and dependence may develop.

Pharmacokinetic Interactions

There are several pharmacological interactions between alcohol and nicotine that may explain how use of one drug might lead to increased co-use of the other. For example, nicotine and alcohol interact to alter the effect either drug has alone, and chronic use of either or both drugs alters this interaction (reviewed Lajtha and Sershen 2010). Aside from the pharmacokinetic interactions between these two drugs, where either drug may alter the peripheral metabolism of the other (Parnell et al. 2006; Yue et al. 2009), a primary contributory factor to co-use of alcohol and nicotine, is likely the additive or synergistic activation of the reward system. In addition, the analgesic properties of the combination and possible counteraction of adverse effects when the drugs are used together may also promote co-use of alcohol and nicotine.

Reward Pathway Activation

A number of animal and some human studies, provide strong evidence that alcohol and nicotine are interacting to potentiate the rewarding effects of one another through activation of the dopamine reward pathway. In short, this pathway is comprised of dopaminergic neurons in the ventral tegmental area (VTA) which possess nAChRs, that when stimulated cause release of dopamine in several brain areas including the nucleus accumbens (NAcc). Activation of the NAcc has been implicated in changes in emotional and cognitive behaviors, especially in relation to regulation of reward-induced addiction (reviewed in Ikemoto and Panksepp 1999; Willuhn et al. 2010). Specifically, nicotine and ethanol have been shown to increase dopaminergic neuron firing (Kleijn et al. 2011; Mereu et al. 1984, 1987), and dopamine release (Kleijn et al. 2011; Löf et al. 2007; Nisell et al. 1994a, b; Tizabi et al. 2002, 2007).

Nicotine appears to activate mesolimbic reward pathway through nAChRs (especially $\alpha 4/\alpha 6\,\beta 2$ and $\alpha 7$ subunits: Exley et al. 2011; Gotti et al. 2010; Mansvelder and McGehee 2000; Maskos et al. 2005; Pidoplichko et al. 1997; Pons et al. 2008). Moreover, the sensitivity to nicotine reward may be modulated by dopamine signaling through its interactions with D1 and D2 receptors (Laviolette et al. 2008). However, the exact pre- or post-synaptic nicotinic receptors that activate dopamine release are not known.

Alcohol (ethanol) may influence the reward pathway by a number of mechanisms including interactions with nicotinic receptors (Blomqvist et al. 1993, 1996; Jerlhag et al. 2006; Larsson and Engel 2004). Co-administration of alcohol and nicotine produces an additive release of dopamine in the NAcc (Tizabi et al. 2002, 2007) which may reflect additive rewarding effect and hence a possible mechanism contributing to the co-use of alcohol and nicotine. It is also conceivable and likely that interactions of alcohol and nicotine with other transmitter systems may influence their individual as well as their combined rewarding and addictive nature.

In humans it has been reported that smoking of normal nicotine cigarettes versus denicotinized cigarettes increased alcohol consumption (Barrett et al. 2006), and that alcohol consumption can increase self-reported pleasure derived from cigarette smoking (Rose et al. 2004). The strength of this effect is dynamic and can be altered by a number of factors including age and gender (Acheson et al. 2006; Grant et al. 2006). These influences may

stem from alteration of nAChR activation as the brain ages and after long-term smoking (Hellström-Lindahl and Court 2000; Teaktong et al. 2003, 2004), especially if changes occur in the dopamine reward pathway. Chronic smoking globally increases nAChRs, probably due to desensitization to repeated nicotine exposure instead of enhanced receptor function (Grady et al. 1994; Ke et al. 1998; Marks et al. 1993; Sabbagh et al. 2002; Wonnacott 1990), although in some unique cases the up-regulation of receptors may also be associated with an increase in function (Nguyen et al. 2004). One theory postulates that desensitization occurs to protect neurons from uncontrolled excitation, as mice with mutated $\alpha 7$ receptor show decreased desensitization and an increased rate of mortality (Mudo et al. 2007; Wang and Sun 2005). Further research is needed to understand this phenomenon, as desensitization and alteration in numbers vary with receptor subtype and location (Buisson and Bertrand 2001; Fenster et al. 1997; Gentry and Lukas 2002; Olale et al. 1997; Perry et al. 2007; Picciotto et al. 2008; Teaktong et al. 2003, 2004; Yu and Wecker 1994).

It has been shown in rats with moderate ethanol preference that consumption of ethanol increases after nicotine treatment (Blomqvist et al. 1996), and application of a nicotinic antagonist reduces ethanol intake (Bell et al. 2009). This response may be from the fact that ethanol and nicotine together appear to increase and sustain dopamine release significantly over that seen when they are administered alone (Tizabi et al. 2002, 2007). However, pre-treatment with mecamylamine, a nicotinic receptor antagonist, blocked the additive effect of combined alcohol and nicotine on dopamine release (Tizabi et al. 2007), and decreased ethanol intake in rats (Blomqvist et al. 1996; Ericson et al. 1998; Le et al. 2000). Similarly, in some human studies it was shown that use of mecamylamine caused a decrease in euphoric effects of alcohol and the desire to consume it (Chi and de Wit 2003; Young et al. 2005). More recently it has been demonstrated that the FDA approved varenicline, a nicotinic partial agonist at $\alpha 4$–$\beta 2$ subtype, for smoking cessation may also be effective in reducing alcohol intake as suggested by preclinical as well as limited clinical trials (Ericson et al. 2009; Fucito et al. 2011; Hendrickson et al. 2010; Kamens et al. 2010; McKee et al. 2009; Steensland et al. 2007). Thus, further elucidation of the roles of specific nicotinic receptors in pathways involved in reward enhancing effects of alcohol–nicotine co-use could lead to novel interventions in drinking–smoking co-morbidity (see also Chatterjee and Bartlett 2010).

Analgesia

Pain is a broad term that now refers to both a physical and emotional experience (Price 2000). Beyond the activation of nAChRs and possible dopamine re-enforced pleasure in alcohol–nicotine co-use another contributory factor could be the analgesic (or antinociceptive) effect of such a combination. Nicotine in itself appears to be effective as a reducer of pain and inflammation in many situations (Decker et al. 2001; Yagoubian et al. 2011; Yoshikawa et al. 2006). Nicotine's analgesic ability was first demonstrated before the identification of nAChRs (Davis et al. 1932), but the activation of the nAChRs has long been suggested as a key component in mediation of analgesic effects of nicotine and other nicotinic agonists (e.g., epibatidine, see below: Damaj et al. 1999; Khan et al. 1998; Simons et al. 2005; Vincler 2005). Many brain nuclei express a diverse number of nAChR subtypes, and areas regulating pain are no exception (Millar and Gotti 2009; Tracey and Mantyh 2007). Nicotine activation of nAchRs containing $\alpha 4$, $\beta 2$, and possibly $\alpha 7$ subunits appear to be a key part to regulating pain (Damaj et al. 2000; Flores 2000; Gao et al. 2010). In support of this idea, mice with $\alpha 4$ and $\beta 2$ mutations demonstrate no analgesic effect to nicotine administration (Marubio et al. 1999). Treatment with $\alpha 4$ and $\beta 2$ agonists show similar, although not complete, analgesic effects to nicotine administration (Flores 2000; Gao et al. 2010), but administration of epibatidine and ABT-594, both $\alpha 4\beta 2$ agonists, produce effects 200 times more potent than morphine (Bannon et al. 1998; Spande et al. 1992). Although it

has been suggested that the analgesic effect that comes from activation of the nAChR receptors by nicotine may be due to opioid release (Galeote et al. 2006), the majority or finding suggest that it is independent of the opioid system when given alone (Campbell et al. 2006; Cooley et al. 1990; Damaj et al. 1999; Khan et al. 1998; Rogers and Iwamoto 1993; Tripathi et al. 1982).

Alcohol has historically been used to dull central nervous system responses to pain before development of more sophisticated pain medications. Basic pain tolerance studies have shown that even low doses of alcohol work to alleviate physical pain (James et al. 1978; Perrino et al. 2008; Woodrow and Eltherington 1988). This antinociceptive effect of alcohol appears to be primarily regulated by the opioid system (Boada et al. 1981; Campbell et al. 2006), and may be influenced by factors such as family history of alcoholism and personality (Ralevski et al. 2010). In fact, individual history of alcohol use may be key in how it works as an analgesic, as continued alcohol use may affect pain modulation by altering dopamine and opioid function (Cowen et al. 2004; Cutter and O'Farrell 1987; Koob et al. 1998; Vanderah et al. 2001). This contention is supported by human studies showing a positive relationship between chronic pain and substance abuse, and that alcoholics are more sensitive to pain—especially when sober—compared to non-alcoholics (Askay et al. 2009; Brown and Cutter 1977; Rosenblum et al. 2003). The altered analgesic effect in those that are addicted to nicotine or alcohol, may contribute to co-use of both drugs for their analgesic properties.

Simultaneous administration of alcohol and nicotine causes additive or synergistic analgesic effects (Franklin 1989, 1998), and appears to occur primarily—but not exclusively—by activation of the opioid system (Campbell et al. 2006). Alleviation of pain—emotional and physical—may be what leads to increased use and co-abuse of nicotine and alcohol. This increased use combined with developing tolerance—especially if the user becomes fully or partially cross-tolerant (i.e., the chronic use of one substance resulting in tolerance to effects of the other: Burch et al. 1988; Collins et al. 1988; de Fiebre and Collins 1993)—may be a key component in making the user vulnerable to addiction. Co-use of alcohol and nicotine (smoking) may therefore arise from a user seeking to find additional pain relief.

Counteracting Mechanisms

In addition to the above, one contributing factor to comorbid use of alcohol and nicotine may be the counteracting of adverse effects of one drug by the other drug. Thus, certain deleterious effects of alcohol (e.g., cognitive impairment, subjective intoxication, and sedating properties) appear to be alleviated by tobacco's nicotine (Ceballos 2006; Perkins et al. 1995). Early studies of this interaction showed that smoking improved alcohol-induced cognitive impairment by shortening temporal distortion in the form of overestimation of time elapsed and improving decrements in divided attention tasks (Leigh and Tong 1976; Leigh et al. 1977). This decrease in negative effects of alcohol by nicotine may actually lead to an increase in alcohol consumption and dependence (Schuckit and Smith 2004). Specific testing of alcohol-induced impairment shows that nicotine in the cigarette smoke is likely what causes the amelioration of impairments or deficits (Al-Rejaie and Dar 2006; Dar et al. 1993, 1994; Gould et al. 2001; Taslim et al. 2011; Tracy et al. 1999). Chronic smokers report feeling less intoxicated than non-smokers after consumption of the same dose of alcohol (Madden et al. 2000). The beneficial effect of nicotine may be limited to acute exposure dosing (Craddock et al. 2003; Ernst et al. 2001; Lawrence et al. 2002; Rezvani and Levin 2001), and may be lost in chronic co-morbid users (Cervilla et al. 2000; Durazzo et al. 2010; Glass et al. 2006, 2009). Thus, chronic consumers of combination of alcohol and cigarettes may show increased cognitive impairment (Durazzo et al. 2010; Glass et al. 2006, 2009). Even acute dosing of nicotine in some animal studies appears to work synergistically with alcohol to cause impairment at doses where alcohol alone caused little to no deficit

(Bizarro et al. 2003; Rezvani and Levin 2002). The variations seen in experimentation, and between acute and chronic dosing, are likely due to differential pharmacokinetic interactions causing cross-tolerance or sensitization (Gulick and Gould 2008). A recent study has revealed that $\alpha 4\beta 2$ and $\alpha 7$ nAChR subtypes are key in behavioral cross-tolerance between nicotine and ethanol-induced ataxia, with nitric oxide signaling being a potential mechanism to this effect (Taslim et al. 2011).

Dosing Consideration

Chronic smoking (the primary route of tobacco consumption) and drinking both have well documented long-term impacts on cardiovascular system and smoking in particular, causes a variety of obstructive airway diseases (Koob and Le Moal 2006; Mitrouska et al. 2007). Both habits also have been attributed to cerebrovascular diseases such as transient ischemic attacks and stroke, and can increase the risk of a number of cancers (Castellsagué et al. 1999; Franceschi et al. 1990; Johnson and Jennison 1992; Ko and Cho 2000; Koob and Le Moal 2006; Mitrouska et al. 2007; Olsen et al. 1985; Pelucchi et al. 2008). The multitude and severity of these detriments can be synergistically exacerbated when the two are combined. However, the majority of the populations are not heavy alcohol and/or nicotine consumers, and on average would have only low-level exposure to one or both compounds. Recent evidence shows that alcohol or nicotine alone at low to moderate levels can have health and therapeutic benefits. Specifically, both compounds at low concentrations have demonstrated the ability to act as neuroprotectants (Belmadani et al. 2004; Collins et al. 2009; Ferrea and Winterer 2009; Quik et al. 2008; Ramlochansingh et al. 2011; Tizabi et al. 2003, 2005, 2007; see also below). However, when low doses of alcohol and nicotine are combined this protection appears to be reversed in at least some in vitro studies (Ramlochansingh et al. 2011; Smith et al. 2006). Although, further in vivo interactions between these two compounds are necessary, it is noteworthy that a study in adolescent mice did not detect toxicity by co-administration of alcohol and nicotine (Oliveira-da-Silva et al. 2009, 2010). Thus, it is important to elucidate the extent of acute and chronic interactions between alcohol and nicotine in various in vitro and in vivo paradigms.

Nicotine in low doses has been seen in in vitro cell (primary and immortal) cultures to protect against or attenuate damage induced by β-amyloid, lipopolysaccharide (LPS)-induced inflammation, glutamate, alcohol, N-methyl-D-aspartate (NMDA), hypoxia, and salsolinol (Copeland et al. 2005, 2007; Dajas-Bailador et al. 2002; Das and Tizabi 2009; Guan et al. 2003; Hejmadi et al. 2003; Kihara et al. 1998; Liu and Zhao 2004; Park et al. 2007; Ramlochansingh et al. 2011; Stevens et al. 2003; Tizabi et al. 2003, 2004). The action of this protection is unclear, but it appears to be mediated by activation of nicotinic receptors (discussed above: Dajas-Bailador et al. 2002; Das and Tizabi 2009; Hejmadi et al. 2003; Picciotto and Zoli 2008). The signal transduction mechanisms underlying the neuroprotection may involve direct or indirect nicotinic receptor mediated modulation of calcium and other antiapoptotic mechanisms (Donnelly-Roberts et al. 1996; Kihara et al. 2001; Liu and Zhao 2004; Ren et al. 2005; Stevens et al. 2003; reviewed in Buckingham et al. 2009), but these potential pathways are still poorly understood.

Alcohol given in low to moderate doses also appears to provide neuroprotection. Epidemiological studies show trends that light to moderate drinkers have reduced risk of dementia and cognitive decline in comparison to nondrinkers (reviewed in Collins et al. 2009). Some of these benefits could be attributed to anti-oxidant polyphenols (e.g., resveratrol in red wine), but it is likely that alcohol in moderate levels has its own direct neuroprotective effect. However, empirical data to support this claim is limited, especially in in vivo models. Studies have shown that giving low doses of alcohol (ethanol) protects in vitro and ex vivo neural cultures exposed to toxins that cause neurodegeneration such as

HIV-1 glycoprotein gp120 (gp120: Collins et al. 2000), homoquinolinic acid (Cebere and Liljequist 2003), and NMDA (Cebere and Liljequist 2003; Chandler et al. 1993; Wegelius and Korpi 1995). Similarly, pre-treatment of SH-SY5Y cells, a cell line commonly used to model nigral dopaminergic neurons for Parkinson's disease with low ethanol concentrations caused attenuated salsolinol-induced toxicity (Ramlochansingh et al. 2011). Salsolinol (1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline) is an endogenous dopamine metabolite that has structural similarity to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) which is especially toxic to nigral dopaminergic neurons, a cluster of cells implicated in Parkinson's disease (Maruyama et al. 2004; Naoi et al. 2004; Storch et al. 2002). Since many Parkinson patients show high levels of salsolinol in their cerebrospinal fluid, it has been suggested that salsolinol might be involved in the etiology or loss of dopamine neurons in at least some of these patients (Maruyama et al. 2004; Storch et al. 2002). SH-SY5Y cells, derived from human neuroblastoma cells express high level of dopaminergic activity and are used extensively as a model to study nigral dopaminergic neurons (Maruyama et al. 2004; Naoi et al. 2004; Storch et al. 2002). Although the exact neuroprotective mechanism of low alcohol concentration is not fully understood, it appears that several mechanisms may be at work.

Alcohol in low to moderate concentration has also been shown to dampen the inflammatory processes within the brain or in culture (Belmadani et al. 2001; Collins et al. 2000), possibly by influencing increased release of heat shock proteins (HSPs: Belmadani et al. 2004; Sivaswamy et al. 2010; reviewed in Collins et al. 2010). Studies in ex vivo models have shown that preconditioning with alcohol for more that 4 days provided significant protection against neurodegeneration caused by gp120 and β-amyloid exposure (Belmadani et al. 2001, 2004). The current theory of how this preconditioning may work is that alcohol exposure translates an upstream signal that causes an increase in select HSPs (reviewed in Collins et al. 2010). Interestingly, HSPs increase differentially in neurons and astrocytes, with HSP70 primarily located in neurons and HSP27 diffusely elevated in both (Sivaswamy et al. 2010). This suggests that alcohol is differentially interacting with each cell type, and/or affecting the communication between them.

Future Considerations

The story of why there is such a high incidence of alcohol and nicotine co-morbidity is still being unraveled, and there are still many gaps in our knowledge about how the interaction of these two drugs may lead to this co-morbidity. Moreover, the full consequences of alcohol–nicotine co-use—especially at low doses—are far from clear. We have discussed that studies have found additive, synergistic, or contradicting effects of nicotine and/or alcohol on some measures. Obviously, differences in models (in vivo vs. in vitro) and in between in vivo (e.g., different species, age, sex, etc.) and in vitro models (e.g., different cell lines) have to be taken into consideration. Thus, future studies are needed to: establish dose equivalency in humans as compared to rodents; evaluate effects of acute versus chronic treatment in both sexes and in different age groups; and address the mechanism of action (e.g., receptor involvement). Moreover, epigenetic influences of the single or combined effects of alcohol and nicotine have yet to be determined. It is expected that future findings will not only enhance our understanding of basic mechanisms leading to co-use of alcohol and nicotine, but also shine more light on possible therapeutic interventions in drug addiction in general and co-morbid condition of alcoholism and smoking in particular.

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