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ORIGINAL PAPER

Nicotine: Alcohol Reward Interactions

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Abstract It is well established that the continued intake of drugs of abuse is reinforcing—that is repeated consumption increases preference. This has been shown in some studies to extend to other drugs of abuse; use of one increases preference for another. In particular, the present review deals with the interaction of nicotine and alcohol as it has been shown that smoking is a risk factor for alcoholism and alcohol use is a risk factor to become a smoker. The review discusses changes in the brain caused by chronic nicotine and chronic alcohol intake to approach the possible mechanisms by which one drug increases the preference for another. Chronic nicotine administration was shown to affect nicotine receptors in the brain, affecting not only receptor levels and distribution, but also receptor subunit composition, thus affecting affinity to nicotine. Other receptor systems are also affected among others catecholamine, glutamate, GABA levels and opiate and cannabinoid receptors. In addition to receptor systems and transmitters, there are endocrine, metabolic and neuropeptide changes as well induced by nicotine. Similarly chronic alcohol intake results in changes in the brain, in multiple receptors, transmitters and peptides as discussed in this overview and also illustrated in the tables. The changes are sex and age-dependent—some changes in males are different from those in females and in general adolescents are more sensitive to drug effects than adults. Although nicotine and alcohol interact—not all the changes induced by the combined intake of both are additive—some are opposing. These opposing effects include those on locomotion, acetylcholine metabolism, nicotine binding, opiate peptides, glutamate transporters and endocannabinoid content among others. The two compounds lower the negative withdrawal symptoms of each other which may contribute to the increase in preference, but the mechanism by which preference increases—most likely consists of multiple components that are not clear at the present time. As the details of induced changes of nicotine and alcohol differ, it is likely that the mechanisms of increasing nicotine preference may not be identical to that of increasing alcohol preference. Stimulation of preference of yet other drugs may again be different –representing one aspect of drug specificity of reward mechanisms.

Keywords Chronic nicotine · Receptor subunits · Chronic alcohol · Transmitter metabolism · Neuropeptide changes · Endocrine influences · Adolescents · Drug interactions

Introduction

It has been well established that most drugs of abuse and also other stimulants such as food or sexual activity induce changes in the reward system of the brain, among others stimulating the mesolimbic dopamine system, releasing dopamine in the shell of the nucleus accumbens. This is not the only induced effect; other transmitters at other sites and other compounds, proteins, peptides, nucleic acids, are altered by the administration of rewarding drugs. The changes are complex and as we recently discussed are regionally heterogeneous and stimulus-specific [1, 2], that is the changes are different in different brain areas and are also different with different drugs. At least some of these changes induced by acute exposure to the stimulants are different from those induced by chronic exposure, and

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some are long-lasting. It is therefore to be expected that prior exposure would influence the changes induced by subsequent exposure of the same or of a different stimulant. Such interaction of nicotine and of alcohol administration was the subject of numerous studies after it was shown that alcohol use is a risk factor for nicotine use (smoking), and smoking is a risk factor for alcoholism. While some interaction is influenced by social, genetic, and psychological factors, the biological effects of one stimulus influencing the biological effects of the additional stimulus plays a major role in creating a risk factor.

In the following, we discuss such interactions in the reward system, in particular, the interactions of alcohol and nicotine as this interaction was examined more often than any other. We first will discuss the effects of chronic administration of each compound and then discuss the interactions, the effect of long-term exposure to one drug on the response to a different drug. We will focus on the effect of these drugs on the brain. We will not discuss many other effects of these drugs; such as alcohol effects on liver cells or other tissues. Other aspects such as withdrawal mechanisms, response to previous treatment with other drugs, prenatal effects are also outside the scope of this review. Clearly these drugs affect non-neural tissues in a complex manner, interact with other drugs—so they induce changes beyond those described here in the rest of the organism, which indirectly may affect the nervous system.

Effects of Chronic Nicotine Administration

Understandably the major effort examining chronic nicotine effects centered on changes of cholinergic receptors. Several changes in cholinergic receptors were reported. It was found some time ago that chronic nicotine administration results in increased nicotine binding in the majority of brain regions tested, it had no effect on the mRNA levels of nicotinic receptor subunits $\alpha 4$ or $\beta 2$ [3]. In cell cultures, these subunits and the total receptor expressed on the cell surface were increased by chronic nicotine [4]. More recently, upregulation of $\alpha 4$, $\beta 2$ nicotinic receptor subunits and $\alpha 7$ subunits were found. These changes were greater in adults than young animals. The upregulation of $\alpha 6$ nicotinic receptors was greater in periadolescents [5]. Looking at specific areas, chronic nicotine increased $\alpha 4$ and $\beta 2$ containing cholinergic receptors in the striatum and the superior colliculus, while $\alpha 7$ containing receptors decreased in the striatum only and there were no changes in $\beta 3$ containing receptors [6]. Mice lacking the $\beta 2$ subunit do not self-administer nicotine indicating that $\beta 2$ containing acetylcholine receptor is needed for nicotine reinforcement [7]. Heteromeric acetylcholine receptor binding is increased in the hippocampus, but not in the cerebellum, in addition, in the neuronal soma it is decreased [8]. The variation in subunits results in a number of nicotinic receptors with different affinity to nicotine. Many have a role in nicotine dependence [9]. A recent review discussed the mechanisms of chronic nicotine-induced upregulation of nicotinic receptors particularly in the ventral tegmental area from where these receptors modulate dopamine release. The change includes changes in subunit assembly and stoichiometry. Activation of nicotine receptors leads to increased sensitization response to nicotine and inhibition of mesoaccumbens dopaminergic activity [10]. Chronic nicotine increased the number of nicotinic receptors, but nicotine-induced dopamine and norepinephrine release were decreased in the hippocampus and striatum, but not in the frontal cortex. The regional differences are perhaps due to differences in the distribution of nicotinic receptor subtypes [11]. In general it seems nicotine upregulates the number of nicotinic acetylcholine receptors and desensitizes them, and it alters the subunit composition of cholinergic receptors, thereby altering the affinity and activity of the receptors. Presynaptic acetylcholine receptors stimulated by nicotine are on dopamine terminals and glutamatergic afferents and are involved in dopamine, noradrenaline and glutamate release, showing that GABA neurons are also involved [12]. There is regionally heterogeneity in subunit composition of the cholinergic receptors, nigrostriatal receptors differ from hippocampal ones which affects pharmacological receptors and noradrenaline release [13]. Opioid systems are also affected by nicotine [14] and transmitters are affected through nicotine-induced changes in catecholamine biosynthetic enzymes [15].

Chronic nicotine administration affects other receptor systems as well. Mesolimbic dopamine responses seem to be enhanced, while the nicotinic receptors are desensitized [16]. The behavioral sensitization (increased locomotor activity) is accompanied by increased dopamine D3 receptor binding and receptor mRNA level in the shell, but not in the core of the nucleus accumbens [17]. Dopamine D1 receptors levels are altered in the nucleus accumbens and the caudate-putamen. The mRNA of GABA receptors is increased, the one for GABAB1 increased more than the one for B2. The level of tyrosine hydroxylase, a key enzyme in transmitter formation is also altered [18]. GABA receptors participate in nicotine-induced effects—an agonist of GABAB receptors, baclofen extinguishes nicotine conditioned place preference [19]. There are chronic nicotine-induced changes in glutamate receptors, GluR2 is down-regulated and CREB the cAMP response element binding protein is activated [20]. There is an increase in benzodiazepine receptors [21] and a decrease in μ-opioid receptors [22]. In young, but not in adult rats, nicotine increased cannabinoid receptor density [23]. Nicotine first

activates, then desensitizes mid-brain nicotinic receptors on DA neurons, and also enhances glutamatergic excitation and decreases GABAergic inhibition on these neurons resulting in long-lasting increased activity of these neurons [24]. In the brainstem cholinergic, GABAergic, noradrenergic and serotonergic nuclei mediate nicotine effects [25]. Nicotine also affects serotonin formation and release [26]. In addition to transmitters, the levels of amino acids in brain areas are affected by nicotinic administration; increases in aspartate, glutamate, taurine, and glycine were noted—some others were not affected—the increase was not blocked by nicotinic, but was inhibited by muscarinic antagonists [27, 28]—such increase was noted in the nucleus accumbens [29]. Most likely a number of additional receptors are affected. These changes in other than nicotinic receptors play an important role in the reinforcing effects and in the tolerance to nicotine, and in turn further induce in a secondary action, representing indirectly nicotine-induced changes. Expression of proteins such as Fos and Jun-B are altered by nicotine selectively in some brain regions including the shell of the nucleus accumbens and medial prefrontal cortex [30]. Dynorphin levels are increased by nicotine [31]. It is also important to realize regional and substrate specificity of the changes even within the same small area—only a part of that there is the neurons show the changes with others remaining unaffected [32]. The region specific effects in nicotine-induced binding site changes have been observed some time ago [33]. Endocrine effects of nicotine include stimulation of adrenocorticotropin secretion [34] nicotine through muscarinic receptors decreases gastrin secretion [35], increases hypothalamic–pituitary–adrenal responses [36], upregulating orexins/hypocretin and neuropeptide Y and down-regulating leptin [37]. Nicotine stimulates Prolactin-releasing peptide containing neurons [38] and decreases LH levels [39]—most of these endocrine changes are involved in nicotine-induced changes in food intake and in stress response.

It has to be emphasized that acute as well as chronic effects of nicotine are different in chronic effects of nicotine are different in female as opposed to male animals, and depend on the dose of nicotine and is also age-dependent as it is different in young. During sensitive periods, nicotine influences brain development [40]. In general, nicotine was found to be more rewarding in adolescent as compared to adult animals. Adolescents were more sensitive to rewarding effects [41] and were less sensitive to aversive effects of nicotine [42]. Withdrawal produces a lower dopamine decrease in adolescents [43]. Nicotine induces mood improvements in adult, but not in adolescent rats [44]. Nicotine reward was found to be greater in female rats, with being rewarding at a lower dose in adolescents [45]. Under low dose conditions more females, than males, self-administered nicotine—responding was negatively associated with progesterone; positively associated with estradiol levels [46]. Nicotine induced anxiogenic response only in females, female mice were less sensitive to locomotor activity effects of chronic nicotine [47]. Sex differences in drug abuse were reviewed recently [48]. A brief summary is presented in Table 1.

Effects of Chronic Ethanol Administration

A number of studies showed that multiple changes are induced by chronic ethanol administration. One study found activation of GABAA receptors, release of dopamine and opioid peptides, inhibition of glutamate receptors, and interaction with serotonin systems [49]. Primary targets included NMDA, GABAA, glycine, serotonin, and nicotinic receptors followed by changes in most neurotransmission systems, Ca and K channels, and in neuropeptide systems, and a decrease in the function of reward neurocircuitry [50]. Chronic ethanol increased basal dopamine levels, down-regulated dopamine D2 receptors and NMDA 2B receptor phosphorylation. Additional changes observed

Table 1 Observations with chronic nicotine administration

Findings	References
Cholinergic receptor subunit composition	[3–9]
Cholinergic receptor regulation	[10–13, 32, 33]
Changes in other receptors	[14–25, 92]
Changes in transmitters	[11, 26–29, 130, 131]
Effects of antagonists	[19, 141, 142, 146]
Changes of peptides	[30–33]
Endocrine changes	[34–39]
Developmental changes	[40–44, 82, 83, 105, 123–125, 137–139]
Variations with sex	[45–48, 80, 84, 126]
Metabolic effects	[120–122, 127]

included those of histones H3 and H4 acetylation in the cortex and in the striatum, possibly chromatin remodeling changes, and changes in dopaminergic and glutamatergic neurotransmission [51]. Alcohol drinking altered dopamine and serotonin neurotransmission in the nucleus accumbens—these effects persisted for a time in the absence of ethanol [52]. Nicotinic receptor subtype levels were decreased by chronic ethanol administration [53], but the effect was limited to few brain regions [54]. Alcohol exposure alters other components of the cholinergic system as well choline acetyl-transferase, high affinity choline uptake also is altered with increase or decrease in some regions [55].

A number of studies found alcohol effects on the GABAA receptor. Its delta-subunit levels were down-regulated [56]; its function was decreased [57], also its localization was altered [58]. The mRNA levels of α2 and α3 subunits were decreased with no change in α4 mRNA [59]. GABAA receptor cell surface expression, subcellular and synaptic localization, phosphorylation, and subunit composition was changed by alcohol [60]. The α1 subunits were decreased while α4 were increased at synaptic and decreased at extrasynaptic GABAA receptors [61]. Thus, the changes were subunit and brain region specific [62]. It was suggested that different set of brain structures and circuits are involved in different stages of addiction—the ventral tegmental area and ventral striatum in the intoxication, the amygdala in the negative withdrawal, cortical areas with hippocampus and insula in craving and other cortical areas in disrupted inhibitory control [63]. Alcohol increased endocannabinoid levels in the limbic forebrain and decreased them in the midbrain, regional effects of chronic alcohol were different from the regional effects of nicotine on endocannabinoid levels, the effects of chronic cocaine differed from those of alcohol and nicotine—these changes are drug-specific [64]. Prolonged ethanol administration up-regulated NMDA glutamate receptor function [65]. It increased the level of NR1 and NR2B NMDA receptors, but not of NR2A level and their targeting to synaptic sites [66]. These changes cause structural alterations in dendrites and their spines in reward regions [67]. Of metabotropic glutamate receptors, chronic alcohol decreased mRNA expression of mGlu3, 5, and 7, but induced no change in mGlu2, 4, and 8 receptors. These changes may play a role in withdrawal-induced seizures and cognitive deficits [68]. Chronic alcohol down-regulated cannabinoid CB1 receptor and its signal transduction [69], and increased the levels of anandamide; decreasing its transport [70]. Neuropeptide Y agonists potentiated and antagonists inhibited alcohol induced effects [71]. Opioid receptors are also affected by alcohol; delta receptor expression was increased and mu receptor expression decreased in several areas [72]. Alcohol up-regulated the dynorphin/kappa-opioid receptor system [73], which may change the responsiveness of dopamine neurons [74]. Ethanol administration decreased kappa opiate receptor numbers, the numbers of mu receptors increased and the delta receptors were not changed, showing some specificity in alcohol effects on opioid receptors. Drug specificity is indicated as cocaine administration did not change the levels of these receptors [75]. A delta opiate agonist increased while a kappa agonist decreased ethanol intake. Morphine increased alcohol intake and naloxone decreased it [76]. Other systems are involved in alcohol effects. A serotonin receptor antagonist inhibits alcohol drinking [77]; so does an opiate antagonist [78]. There are sex differences in vulnerability by nicotine and alcohol [79]; women develop dependence on nicotine [80] or alcohol [81] more than men. The effects of nicotine in prenatal and adolescent stages are different from those in adults [82]. It has been often shown that adolescent brain is more sensitive to nicotine than adult brain [83], and prenatal exposure to nicotine sensitizes the adolescent response more in females than males [84]. In males, nicotine increased choline acetyltransferase, while ethanol reversed this effect. In females, nicotine decreased this enzyme [85]. The GABAergic and glutamatergic effect of alcohol was region-specific and sex-selective influenced by sex differences in the subunit compositions of the respective receptors [86]. During withdrawal, alcohol-induced hypothermia was greater in females [87]. In alcohol withdrawal, males showed handling induced kindling response—females did not [88]. Nicotine withdrawal increased; alcohol withdrawal decreased this enzyme, so did a combined administration of nicotine and alcohol [89]. There are also alcohol-induced changes in the brain that may not be mediated by effects on transmitters. It induces alteration in the neuronal cytoskeleton [90]. It affects a number of peptides in a complex manner for example, it elevates nerve growth factor and its expression, but decreases brain derived neurotrophic factor expression [91]. It is of interest that it does not influence nerve growth factor levels [92]. Alcohol induces an astroglial reaction, releasing glial derived trophic factors [90]. CREB protein, activity regulated cytoskeleton associated protein, and corticotrophin-releasing factors are affected by acute and by chronic ethanol exposure [93]. The production of pro-inflammatory cytokines is inhibited [94]. Ethanol affects a number of processes regulated by nucleocytoplasmic transport in astrocytes [95]. Alcohol induced changes are summarized in Table 2.

Interactions

Interaction of nicotine and alcohol is of significant interest as it was shown that dependence on both rather than just on

Table 2 Findings after chronic alcohol administration

Findings	References
Changes of receptor systems	[49–72, 97, 119, 136]
Changes in transmitters	[132–135]
Effect of antagonists	[143–146]
Effects of peptide systems	[73–78, 91]
Sex-dependent effects	[79, 81, 86–88]
Cellular changes	[90, 93, 95]
Biological systems affected	[94]

one of them has a more severe and unfavorable course [96], and dependence on one facilitates dependence on the other as indicated by smoking being among the strongest risk factors for alcoholism. The modulation of nicotinic acetylcholine receptor subunits may play an important role in this interaction [97]. Smoking is an important predictor of later heavy drinking among young women. Early age of sexual debut elevates their risk [98]. In people with past history of alcohol dependence, nicotine was a more potent reinforcer [99]. In rats a nicotinic antagonist reduced ethanol intake [100]. Other receptors, not only nicotinic receptors, are of importance. Impulsive behavior increases the likelihood of compulsive drug-seeking, thus drug effects on receptors that increase impulsive behavior (such as lowered dopamine receptors in the nucleus accumbens), would lead to greater drug preference [101]. The action of nicotine and alcohol is not identical. While chronic nicotine treatment increased nicotine and bungarotoxin binding in several brain regions, chronic ethanol treatment did not affect binding; thus the cross tolerance that develops is not completely dependent on nicotinic receptor changes [102]. The nicotine tolerance, part of the cross tolerance, may be dependent on nicotine binding changes, while the alcohol tolerance part may be due to increased ethanol metabolism [103]. Another study indicated that nicotine alcohol cross-tolerance is caused in part by each one increasing the metabolism of the other [104]. Nicotine pretreatment also increases nicotine preference. Animals given nicotine in early adolescence (but not at late adolescence or adulthood) show increased nicotine conditioned place preference when tested as adults [105]. Pre-treatment with nicotine (also with a cannabinoid agonist) decreased alcohol-induced dopamine release in the nucleus accumbens shell [106]. There are interactions in withdrawal as well. In animals dependent on both nicotine and alcohol, nicotine withdrawal increased choline acetyltransferase activity, which was reversed after alcohol withdrawal. The withdrawal of both up-regulated nicotinic receptors [89]. In human brain, genes altered by alcohol use participate in structural plasticity and in neurotransmitter transport and release. Smoking increased the expression of glutamate transporters—this was reduced by alcohol exposure [107]. Interactions of nicotine have been found with other drugs. Both cocaine and nicotine treatment produced tolerance to cocaine [108]. One way the nicotine alcohol interaction occurs is by smoking decreasing the aversive effects of alcohol, and by alcohol lowering nicotine withdrawal symptoms [109]. Interaction with different drugs is shown by adolescent rats pretreated with nicotine showing an increase in cocaine self-administration. There was a difference in rewards as responding to sucrose pellets was not influenced by nicotine pretreatment [110]. Chronic nicotine treatment increased the reinforcing effects of morphine. This was not mediated by mu-opioid receptors [111]. Both nicotine and alcohol utilize the endogeneous opioid system as a modulator of some of then effects releasing opioid peptides in specific brain regions [112]. The likelihood of substance use leading to use disorder is different with different drugs, higher with nicotine than with alcohol, lower with cannabis [113]. Exposure of newborn animals to ethanol caused an increase nicotine preference in adolescents indicating special sensitivity of the brain early in development [114]. In some aspects, nicotine and alcohol antagonize each other's effects. Nicotine counteracts alcohol enhanced locomotor activity and they counteract each other in the expression of transcription factors [115]. Alcohol- induced dopamine release was decreased by nicotine administration [106], although the effects on dopamine release in the nucleus accumben of alcohol and nicotine are additive [116]. As mentioned, prenatal drug influences are beyond the scope of this review, but it is of interest that prenatal exposure of both alcohol and nicotine decreased ethanol preference and consumption in males during adolescence in females during adulthood [117], nicotine exposure in early adolescence, but not later increased nicotine preference [105]. Some effects of alcohol differ from nicotine-induced effect so nicotine addition may alter some alcohol effects. Alcohol decreases acetylcholinesterase and choline acetyltransferase levels [118]. Choline acetyltransferase expression is also decreased by ethanol administration, together with decreasing acetylcholine release [119]. Nicotine increased cholinesterase levels in some systems [120, 121] and increased choline acetyltransferase [122]. The increase was regionally selective—some regions showed increase; others decrease [123]. Change in choline acetyltransferase was greater in adolescent rats [124]. A dopamine receptor antagonist decreased choline acetyltransferase, which was counteracted by nicotine [125]. In human placenta this enzyme was not affected by nicotine [126]. Genetic variants of this enzyme influenced nicotine dependence and ability to quit smoking in humans [127]. It was reported that acetaldehyde—the major metabolite of alcohol—decreases

Table 3 Nicotine-alcohol interactions

Findings	References
Receptor systems	[85, 89, 106, 112, 117, 118]
Transmitter changes	[64, 107, 108, 116]
Effects of antagonists	[140, 143–146]
Other interaction effects	[96, 98–106, 109, 112, 115]
Changes in development	[105, 113, 114, 117]
Effect on peptides	[129]
Other drug interactions	[108, 110, 111]

dopamine levels in the striatum [128] unlike nicotine. Preprotachykinin mRNA was decreased by nicotine and increased by alcohol [129]. The activity of combined nicotine and alcohol administration are summarized in Table 3.

Changes of Transmitters

Chronic nicotine or alcohol administration results also in changes in transmitter levels and also drug-induced transmitter release. Chronic nicotine administration evoked decrease in nicotine-evoked dopamine and norepinephrine release in the hippocampus and the striatum, but not in the cortex. KCl-evoked release was not altered [11]. Chronic nicotine decreased the basal extracellular level of dopamine in the nucleus accumbens, and dopamine uptake was significantly increased [130]. Changes in transmitter levels may be the result of alterations in their transporters by chronic drug administration. Among others, such chronic drug-induced changes in transporters of dopamine, norepinephrine, serotonin, and GABA have been reported [131]. Both chronic nicotine and alcohol affected the endocannabinoid contents of the brain, nicotine caused increases in the limbic forebrain and brainstem, decrease in the hippocampus, striatum, and cortex. Alcohol also increased levels in the limbic forebrain; it decreased them in the midbrain [64]. Chronic alcohol decreased dopamine levels in the nucleus accumbens and caudate putamen by stimulating dopamine uptake via alterations in autoreceptor function [132]. Ethanol enhanced cocaine-induced dopamine increase in the nucleus accumbens [133]. Ethanol induced increases in endocannabinoid levels; arachidonoylglycerol are increased by chronic ethanol administration, while the levels of anandamide are reduced by acute and reduced less by chronic alcohol administration [134]. The effects of nicotine on various transmitters in brain regions were examined in several studies. In addition to changes in dopamine, regionally heterogeneous changes in norepinephrine and serotonin have been found [135]. The concentrations of postsynaptic serotonin receptors were also affected [136]. We tested transmitter changes that would explain greater nicotine preference in young. Changes in dopamine were not likely to be responsible, while changes in serotonin were more significant [137]. Acetaldehyde stimulation of nicotine preference in young also indicated norepinephrine and serotonin, rather than dopamine involvement [138].

Antagonism of the Effects

Nicotinic and dopaminergic antagonists inhibited nicotine-induced changes not only in dopamine levels, but also in serotonin and norepinephrine levels [139].

A number of receptor antagonists were found to inhibit chronic drug-induced changes. *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist inhibited the effects of nicotine, alcohol, and opiates [140]. Blocking $\alpha 7$ or $\beta 2$ subunits of nicotinic receptors inhibited chronic nicotine effects [141]. Nicotine preference caused by chronic administration was blocked by a GABAB receptor agonist (baclofen) [19]. The nicotinic antagonist mecamylamine enhanced chronic nicotine-induced receptor upregulation, but inhibited nicotine tolerance [142]. Alcohol-induced dopamine release was inhibited by nicotinic antagonists (some of the α receptor subunit antagonists) [143]. Alcohol-seeking behavior after its chronic administration was inhibited by AMPA glutamate receptor antagonists [144]. Chronic alcohol-induced alcohol preference was inhibited by opioid receptor and CRF receptor antagonists [145]. Dopamine D3 receptor antagonists inhibit alcohol and nicotine-induced self administration while they do not influence food self administration [146]. The effects of antagonists blocking chronic drug effects on drug interactions have not been examined. Some of the differences in the effects of nicotine versus alcohol are summarized in Table 4.

Table 4 Differences between nicotine versus alcohol effects

Effect	References
Choline acetyltransferase, choline esterase	[89, 118–122]
Nicotine binding	[102]
Opioid peptide formation	[129]
Endocannabinoid content of some areas	[64]
Glutamate transporter expression	[107]
Locomotor activity, transcription factors	[115]
Cross tolerance	[102, 103]

Conclusions

It is clear that most drugs of abuse, nicotine and alcohol among them induce multiple changes in the brain. The changes include alteration in the level of transmitters, in the subunit composition, and distribution of receptors, metabolic changes including that of transmitters, endocrine, neuropeptide, and protein changes. The changes include decreases or inhibition as well as increases. Some of these changes are temporary, but many are of long duration. These changes are drug-specific, for example, some induced by nicotine and alcohol are opposite or some changes are only induced by one of them. Hence, some changes when both are administered are additive; others counter act and are inhibitory. Some of the changes increase sensitivity or preference when the same or a different drug is administered; then the administration of the first presents a risk for drug-seeking subsequently. At present, it is not clear which of the primary changes represent such risk; it is possible that such stimulation is also drug-specific, thus the risk may not be similar for all drugs. The identification of the longer term changes is advanced—the risk factors remain to be identified.

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