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Research update

Tobacco and alcohol use during adolescence: Interactive mechanisms in animal models

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ABSTRACT

There is a strong association between tobacco smoking and the consumption of alcoholic beverages. When compared to the effects of either drug on its own, the combined use may lead to worsened outcomes, such as less successful quitting attempts and increased likelihood of developing mood disorders. Co-consumption most frequently begins during adolescence, a developmental period that is characterized by an increased risk for substance use disorders. However, to date, most studies that have contributed to the current state of knowledge on the mechanisms that underlie tobacco or alcohol use/abuse, and their consequences, adopted adult animal models. Besides, the available literature hardly addresses the effects of co-exposure, irrespective of age. Since adolescence is a period of transition between infancy and adulthood that is characterized by unique brain maturational events and behavioral traits, the mechanisms that drive drug use/abuse in adolescents differ in several aspects from those proposed to underlie adult consumption. This review summarizes and consolidates recent findings on common molecular targets and neuropharmacological mechanisms of action associated with nicotine/tobacco smoke and ethanol co-exposure in animal models, highlighting the effects that culminate in behavioral dysfunctions. To that effect, we discuss the role of mesocorticolimbic system maturation events, cross-tolerance and cross-reinforcement, stress, and sex differences in the context of adolescent co-exposure, identifying gaps in knowledge regarding the interactions between these habit-forming drugs. Finally, we suggest future directions for research on epigenetic mechanisms associated with nicotine and ethanol co-exposure as well as on potential pharmacological therapies for co-addiction.

Contents

Abbreviations: 5HT, serotonin; ACh, acetylcholine; AMPAR, a-amino-3-hydroxy-5-methylisoxazolepropionic acid receptor; BECs, blood ethanol concentrations; Ca^{2+}, calcium; ChAT, choline acetyltransferase; CRF, corticotropin-releasing factor; DA, dopamine; DAergic, dopaminergic; GABA, gamma-aminobutyric acid; HPA, hypothalamic pituitary adrenal axis; nAChR, nicotinic acetylcholine receptor; NAcc, nucleus accumbens; NMDA, N-methyl-D-aspartate; NP, non-preferring; msP, Marchigian Sardinian alcohol-preferring; AA, ALKO alcohol accepting; P, alcohol preferring; PN, postnatal day; PFC, prefrontal cortex; SNc, substantia nigra pars compacta; SRY, sex-determining region Y; VTA, ventral tegmental area.

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1. Introduction

Tobacco is often used in conjunction with alcoholic beverages. Most individuals that have alcohol use disorders smoke [1] and even social drinkers are more likely to smoke than non-drinkers [2]. Besides, smoking increases the risk of alcohol use disorders [3] and alcohol drinking enhances both smoking urge and smoking satisfaction [4,5]. The interactions between these drugs also impact cessation and relapse behavior. Both current and past alcohol-related problems reduce the likelihood to quit smoking and increase that of relapse [6].

The association between tobacco smoking and alcoholic beverage drinking is most frequently established during adolescence [7–9]. Adolescents who begin consuming one of these drugs are more likely to shortly after initiate the use of the other one [10]. As an example, in the United States, the average age of initiation of alcohol use is 17.0 years and of tobacco is 17.6 years, with "early initiators" beginning at ages 12–14 [11]. It is important to note that alcohol consumption during adolescence is frequently characterized by binge episodes [12]. Interestingly, co-consumption is a two-way street: Not only adolescent smokers are likely to be binge drinkers, but adolescent binge drinkers are likely to be smokers [12]. There are also long-term consequences of early initiation, since adolescent smokers and heavy drinkers are especially at risk for developing hazardous substance use later in adolescence or in young adulthood [13].

These findings demonstrate a strong and complex interaction between tobacco and alcohol. While psychosocial factors contribute to this association [14], there is mounting evidence that neurobiological mechanisms also play an important role. Human studies have recently begun to identify shared genetic factors such as the pleiotropic effects of nicotinic acetylcholine receptor (nAChR) subunit genes on nicotine- and alcohol-related phenotypes [15–17] and the overlap in polygenic risk factors between smoking behavior and alcohol use [18] However, most studies that aimed to identify the underlying cellular and molecular components that contribute to co-use focused on pharmacological interactions. Accordingly, much of the mechanistic work has been done in rodents, in which social and genetic factors can be minimized and/or controlled, so that neuropharmacological factors are the main determinants of the outcomes of drug exposure.

A good starting point for understanding the neuropharmacological mechanisms involved with the frequent association between tobacco and alcohol consumption during adolescence is provided by experimental evidence on the synergistic and less-than-additive interactions between nicotine, a major psychoactive component of tobacco smoke, and ethanol (e.g. [19–22]). These interactions result not only in immediate changes in brain function but also in effects that are manifested even long after the end of adolescence. Considering that several mechanisms have been proposed to explain co-consumption, this review limits it scope to the discussion of studies that were carried out in rodents, summarizing recent findings on common molecular targets and neuropharmacological mechanisms of action between nicotine and ethanol. We also highlight the effects of the combined exposure that culminate in behavioral dysfunction and identify gaps in knowledge pertaining to the interactions between these two drugs during adolescence. Finally, we suggest future directions for research concerning epigenetic targets that are known to be affected by both drugs, as well as for the development of potential pharmacological therapies for ethanol and nicotine co-addiction and relapse.

Considering that most studies that use rodent models to examine the biological bases of adolescent tobacco and alcoholic beverage co-consumption combine nicotine and ethanol, here, the emphasis placed on nicotine, not on tobacco smoke, is justified by the fact that the former is the major addictive component of the latter. Besides, nicotine consumption via replacement therapy and electronic delivery systems (e-cigarettes) has experienced a rapid growth [23,24] and there is already evidence that e-cigarette use increases alcohol consumption among adolescents [25,26]. Nonetheless, non-nicotine components may play important roles in tobacco effects in the central nervous system [27–31]. Therefore, whenever relevant, findings on rodent models of tobacco smoke (or tobacco smoke extracts) and ethanol co-exposure will be discussed. Also, although not a focus of this review, to the extent that data are available in human research, these will be compared to data obtained from studies in rodents.

2. The adolescent brain

Adolescence is a period of transition between childhood and adulthood for which temporal boundaries are difficult to define. Conservative estimates define adolescence to extend from 12 to 18 years of age in humans and from postnatal day (PN) 28 to PN42 in rats and mice [32]. However, its onset and offset vary among individuals, so that signs of adolescence may be identified as early as at 8 years of age and may be present up until 25 years of age in humans whereas, in rats and mice, this age range extends from PN21 to PN55 [32,33].

The human brain is structurally and functionally complex, which helps to explain our highly developed capacity for abstract thought and emotional depth, among other characteristics. However, despite its higher complexity, the human brain is like the rodent brain regarding several aspects of its morphology and functional organization [34,35]. In addition, behavioral, neurochemical and morphological hallmarks of adolescence are greatly conserved throughout evolution, being identified both in humans and in rodents [36]. As examples, both humans and rodents exhibit greater preference for social stimuli during adolescence than during adulthood, as well as greater novelty-seeking and risk-taking behaviors. Interestingly, while social behavior has a protective role [37], high levels of novelty-seeking and risk-taking behavior are associated with increased risk of drug use and abuse [38,39]. Moreover, adolescents show increased sensitivity to drug reward and insensitivity to the direct negative effects of drugs such as nicotine [40] and ethanol [9], which, together with the aforementioned behavior similarities, drive drug consumption.