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Review article

Consequences of adolescent use of alcohol and other drugs: Studies using rodent models

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ABSTRACT

Studies using animal models of adolescent exposure to alcohol, nicotine, cannabinoids, and the stimulants cocaine, 3,4-methylenedioxymethampethamine and methamphetamine have revealed a variety of persisting neural and behavioral consequences. Affected brain regions often include mesolimbic and prefrontal regions undergoing notable ontogenetic change during adolescence, although it is unclear whether this represents areas of specific vulnerability or particular scrutiny to date. Persisting alterations in forebrain systems critical for modulating reward, socioemotional processing and cognition have emerged, including apparent induction of a hyper-dopaminergic state with some drugs and/or attenuations in neurons expressing cholinergic markers. Disruptions in cognitive functions such as working memory, alterations in affect including increases in social anxiety, and mixed evidence for increases in later drug self-administration has also been reported. When consequences of adolescent and adult exposure were compared, adolescents were generally found to be more vulnerable to alcohol, nicotine, and cannabinoids, but generally not to stimulants. More work is needed to determine how adolescent drug exposure influences sculpting of the adolescent brain, and provide approaches to prevent/reverse these effects.

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1. Introduction

Drug use is frequently initiated during adolescence. The latest Monitoring the Future survey reported that 13, 20 and 31% of 8th, 10th and 12th graders endorse having tried cigarettes, with over 10% of 12th graders affirming that they have smoked cigarettes within the past month (Johnston et al., 2016). Annual prevalence rates for use of alcohol and marijuana/hashish across these age ranges were 21, 42 and 58% and 12, 25 and 35%, respectively. Some of this use reaches high levels with, for instance, >10% of 12th grade students reporting consumption of 10 or more alcohol drinks in a row in the past 2 weeks, and >5% reporting consumption of >15 drinks per occasion over the same 2 week interval (Patrick et al., 2013). Illicit drugs other than marijuana used by adolescents include psychostimulants such as cocaine and the "club drugs" 3.4-methylenedioxymethamphetamine (MDMA, commonly called "ecstasy") and methamphetamine (METH), with 2.5% of high school seniors in the United States reporting annual use of cocaine, 3.6% reporting MDMA use, and 0.6% endorsing use of METH (Johnston et al., 2016).

Among the likely contributors to the elevation of alcohol and drug use during adolescence are maturational changes occurring in the brain at this time—many of which are described in detail in other reviews in this special issue. Although notably oversimplified for the purposes here, prominent among these brain changes is a developmental dissociation between earlier maturation or even enhanced reactivity to rewarding and motivationally relevant stimuli in subcortical regions during adolescence that contrasts with relatively delayed maturation throughout adolescence of frontal brain regions that are critical for control of these subcortical regions (e.g., see Casey et al., 2011; Doremus-Fitzwater et al., 2010). That is, on the one hand, reactivity and cross-reactivity appears to be enhanced during adolescence in mesolimbic regions such as the nucleus accumbens (nAc) and amygdala (AMYG) that are critical for processing and responding to rewarding, aversive, and emotionally arousing stimuli, including social stimuli (e.g., Ernst and Fudge, 2009; Spear, 2011). This enhanced reactivity contrasts with delayed development of prefrontal cortex (PFC) and other frontal regions that mature only slowly during adolescence and are critical for cognitive control (Casey et al., 2011). These and other developmental changes occurring in the adolescent brain, such as developmental declines in cortical gray matter, and increases in myelination and in the portion of the brain partitioning as white matter, appear to have been highly conserved evolutionarily. That is, similar developmental alterations are evident during this ontogenetic transition across a variety of mammalian species, despite notable species differences in overall brain complexity and the relative length of the adolescent period (see Spear, 2000, 2016a; for review). For instance, in rats, the two week period between postnatal days (P) 28–42 is thought to roughly subsume the early-mid adolescent period (~12–17 years in humans), with the interval from ~P43–55 more comparable to the late adolescence/emerging adulthood period in humans (~18–25 years) (see Spear, 2015). The conserved nature of the brain transformations of adolescence support the use of animal models to explore some of the critical questions regarding contributors to drug use and consequences of that use that may be challenging to study empirically and ethically in underage humans (see Spear, 2016a).

Alcohol and other drugs exert many of their effects through action in mesolimbic and frontal cortical regions undergoing particularly marked remodeling during adolescence. Hence, the maturational state of these regions could potentially influence the propensity for experimentation and continued drug use during adolescence. To the extent that initiation/escalation of alcohol/drug use during adolescence has a biological basis, and because the developmental timing is similar across species (see Spear, 2000, 2016a; for review), one would predict that enhanced propensities for drug initiation and elevated use seen in human adolescents would also be evident in adolescents of other species. Indeed, studies in laboratory animals have shown that voluntary self-administration of and sensitivity to the effects of alcohol and other drugs differs during adolescence from that seen in adulthood. Using alcohol as an example, adolescent rats (like their human counterparts) (SAMHSA, 2013) often drink 2–3 times more per drinking occasion than do adults (e.g., Doreumus et al., 2005; Vetter et al., 2007; but see also Bell et al., 2006). Along with this elevation in intake, studies with adolescent rats have shown them to be less sensitive to many of the effects of alcohol (ethanol [EtOH]) that presumably serve as cues to limit intake (such as EtOH-induced motor impairing, sedative, aversive, and socially impairing effects), along with an enhanced sensitivity to desired effects of EtOH, including its rewarding and social facilitating effects (e.g. Spear, 2016b). Adolescents show an enhanced sensitivity to the rewarding effects not only of alcohol, but also nicotine and cocaine, with aversive effects attenuated during adolescence not only to alcohol, but also to nicotine, cocaine, amphetamine and delta-9-tetrahydrocannabinol ([THC]—one of the major cannabinoids in marijuana) (see Doremus-Fitzwater et al., 2010; for review). Collectively, these age-related propensities for accentuated appetitive and attenuated aversive properties of drugs could contribute to the enhanced susceptibility for initiation and escalation of drug use during adolescence.

That alcohol and drug use is often initiated (and sometimes escalates into high levels of use) during the time of the notable brain remodeling during adolescence leads to the question of whether drug exposure during this time may influence that development and exert persisting neural and behavioral alterations. For an extensive review of human imaging studies of adolescent alcohol and drug users, see Silveri et al. in this special issue. Studies using animal models have also proven useful in examining this question empirically and with a rapidity of data accumulation that is often not possible in cross-sectional or time-consuming longitudinal studies with human adolescents (see Spear, 2016a; for review). From studies in laboratory animals, the evidence is mounting that indeed