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REVIEW

THE EFFECTS OF ABUSED DRUGS ON ADOLESCENT DEVELOPMENT OF CORTICOLIMBIC CIRCUITRY AND BEHAVIOR

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Abstract—Adolescence is a period of significant neurobiological change that occurs as individuals transition from childhood to adulthood. Because the nervous system is in a relatively labile state during this stage of development, it may be especially sensitive to experience-induced plasticity. One such experience that is relatively common to adolescents is the exposure to drugs of abuse, particularly alcohol and psychostimulants. In this review, we highlight recent findings on the long-lasting effects of exposure to these drugs during adolescence in humans as well as in animal models. Whenever possible, our focus is on studies that use comparison groups of adolescent- and adult-exposed subjects as this is a more direct test of the hypothesis that adolescence represents a period of enhanced vulnerability to the effects of drug-induced plasticity. Lastly, we suggest areas of future investigation that are needed and methodological concerns that should be addressed.

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Key words: adolescent, young adult, neuroanatomy, neurophysiology, psychostimulants.

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Abbreviations: BLA, basolateral amygdala; CRH, corticotropin-releasing hormone; EEG, electroencephalography; LTD, long-term depression; LTP, long-term potentiation; mPFC, medial prefrontal cortex; MRI, magnetic resonance imaging; NAc, nucleus accumbens; NMDA, *N*-methyl-D-aspartate; P, postnatal day; PFC, prefrontal cortex.

INTRODUCTION

Adolescence, the transition from the juvenile period to adulthood, is marked by puberty and numerous physical and neural changes. In humans, adolescence begins at approximately 12 years of age and may extend to the mid-twenties (Dahl, 2004). In rats, adolescence has been conservatively defined as beginning around postnatal day (P) 28 and extending to P42 (Spear, 2000) or perhaps as late as P60 (Tirelli et al., 2003; Brenhouse and Andersen, 2011). This is based, in part, on the rise of pubertal hormones which leads to the vaginal opening in female rats between P29 and P37 (Castellano et al., 2011) and preputial separation in male rats between P39–47 (Korenbrot et al., 1977). During this time, there is substantial behavioral and neural development (Spear, 2000; Sisk and Foster, 2004), with corticolimbic brain regions such as the prefrontal cortex (PFC), nucleus accumbens (NAc), and basolateral amygdala (BLA) being among the last brain circuits to fully mature in both humans and rodents (Casey et al., 2000; Brenhouse and Andersen, 2011). Because the brain is undergoing this programed period of dramatic change, it might be especially sensitive to outside influences that have the ability to induce plasticity in the nervous system.

One such influence that is pervasive during human adolescence is exposure to drugs such as alcohol and psychostimulants. Recent data from the nationwide Monitoring the Future study (Johnston et al., 2012), which sampled from over 46,000 eighth to 12th grade students, suggests that approximately 70% of young people have consumed alcohol by the end of the 12th

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grade and 33% have been intoxicated within the last month. Nicotine (via cigarette smoking) is consumed at least once by about 40% of adolescents by the 12th grade, and nearly 20% of 12th graders report being current smokers. Nearly 1% and 3% of adolescents report they are current users of cocaine and amphetamines, respectively. These relatively high levels of use are of concern because these drugs are known to produce significant and long-lasting changes in brain structure and function (Luscher and Malenka, 2011) that have been linked to long-term changes in cognitive functioning and the development of addiction (Goldstein and Volkow, 2002). In this review, we will highlight recent findings on the long-lasting effects of alcohol and psychostimulant exposure during periadolescence. Although some evidence from humans is available, we will primarily focus on studies in animal models. In doing so, we will place particular emphasis on those that utilize both adolescent and adult exposure groups since these directly assess the potential for age of exposure-dependent effects.

ADOLESCENCE: THE LAST DEVELOPMENTAL PHASE OF PFC MATURATION

The scientific community and the general public were startled when human structural magnetic resonance imaging (MRI) studies showed that the cortex, including the PFC, decreases in size between 11and 22 years of age (Giedd et al., 1999; Sowell et al., 1999). Previous to this finding, most neural development in humans was thought to be completed by 12 years of age, which is approximately when overall brain volume is at adult levels (Courchesne et al., 2000). The continuation of development during adolescence suggests greater vulnerability than adults to many of the effects of environmental influences, including those produced by exposure to drugs of abuse. This is a major problem because adolescence is also a time of high novelty and sensation seeking (Spear, 2000), which often includes experimentation with drugs.

Prior to the advent of MRI studies, there were indications of cellular changes in the PFC during adolescence. Periadolescent anatomical refinement of circuitry in the primate PFC was described in both excitatory and inhibitory circuits (reviewed by Lewis, 1997; Woo et al., 1997). Synaptic density in this area was also found to decline during adolescence in both monkeys (Bourgeois et al., 1994; Anderson et al., 1995) and humans (Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997); however, this decrease in synaptic number would have a small effect on cortical volume, as was noted by Bourgeois and Rakic (1993). Here, we suggest that a loss of neurons could readily account for the MRI finding of volume loss in human adolescence.

Neuron number in the medial prefrontal cortex (mPFC)

The number of neurons (density × volume) during development and adolescence has not been examined in the frontal cortex or any other cortical region in primates. This is due in part to the technical difficulties of parcellating regions of the cortex in large brains that have variable gyri. However, subtle declines in neuronal density between 2 and 16 years of age in human frontal cortex have been noted (Huttenlocher, 1979). The rat PFC is a more practical model than that of the primate for exploring the cellular basis for pruning during adolescence because the rat PFC is less differentiated and segregated. Furthermore, on the basis of the reciprocity of specific thalamic as well as other connections, embryological development, and electrophysiological and behavioral characteristics, rats do have a PFC that is homologous to that of the primate (Brown and Bowman, 2002; see Uylings et al., 2003 for an extensive review). Interestingly, like humans, the rat PFC undergoes a decrease in volume during the periadolescent period (van Eden and Uylings, 1985; Markham et al., 2007).

To investigate the possibility of cell loss, we (Markham et al., 2007) quantified the number of neurons in the mPFC of male and female rats that were either peripubertal (P35) or adults (P90). No sex differences were found in the number of neurons at P35, but sex differences did appear at P90. This was because females had lost more neurons between these ages

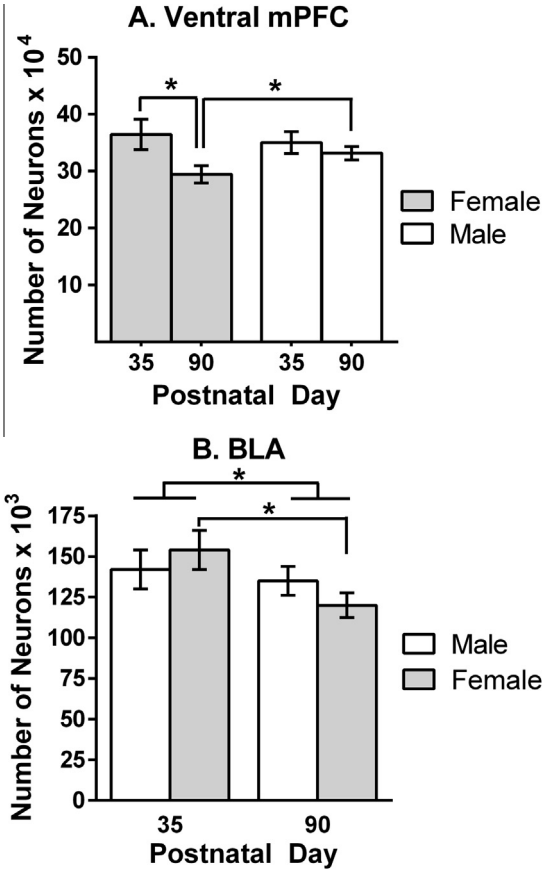

Fig. 1. (A) The number of neurons in the ventral portion of the rat mPFC at periadolescence (P35) and adulthood (P90) in both sexes. Adapted from Markham et al. (2007). (B) The number of neurons in the basolateral amygdalar nucleus at periadolescence and adulthood. Adapted from Rubinow and Juraska (2009). $^{*}p < 0.04$.