Neuropharmacology 76 (2014) 269–275

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

The impact of exposure to addictive drugs on future generations: Physiological and behavioral effects

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ARTICLE INFO

Article history:
Received 7 March 2013
Received in revised form
30 April 2013
Accepted 7 June 2013

Keywords:
Transgenerational
Epigenetic
Drugs of abuse
Alcohol
Nicotine
Marijuana
Opioids
Cocaine

ABSTRACT

It is clear that both genetic and environmental factors contribute to drug addiction. Recent evidence indicating trans-generational influences of drug abuse highlight potential epigenetic factors as well. Specifically, mounting evidence suggests that parental ingestion of abused drugs influence the physiology and behavior of future generations even in the absence of prenatal exposure. The goal of this review is to describe the trans-generational consequences of preconception exposure to drugs of abuse for five major classes of drugs: alcohol, nicotine, marijuana, opioids, and cocaine. The potential epigenetic mechanisms underlying the transmission of these phenotypes across generations also are detailed.

This article is part of a Special Issue entitled 'NIDA 40th Anniversary Issue'.

1. Introduction

Drug addiction is a serious medical and social issue in the United States and around the world. There is consistent evidence that substance use disorders run in families (Bierut et al., 1998; Brook et al., 2002; Cloninger et al., 1981; Merikangas et al., 1998). Adoption, twin, and sibling studies implicate genetic factors in the heritability of abuse (Cloninger et al., 1981). However, simple genetic mechanisms of inheritance cannot explain all results (Cloninger et al., 1981; Schuckit et al., 1972). Societal differences in drug use and consumption patterns vary from different time periods and between countries suggesting a large environmental component (UNODC, 2012). Thus, vulnerability to develop an addiction is dependent on both genetics and the environment. The sum of separate genetic and environmental contributions cannot fully explain the heritability either. Therefore, the interaction between genetics and the environment may help explain some of the discrepancies (Cloninger et al., 1981).

Epigenetics is a key mechanism by which the environment can influence and interact with genetics. In recent years, the term epigenetics has been used to describe myriad processes (Haig, 2004). For example, modifications to the structure of chromatin or DNA without changes in the sequence that affect gene transcription even in non-dividing cells such as DNA methylation or histone acetylation are described as epigenetic modifications (Holliday, 1989). However, some definitions of epigenetics emphasize that the modifications in gene expression that do not involve alterations in the DNA sequence must be heritable, spanning multiple generations. There has recently been an increase in studies examining the transgenerational effects of environmental toxins on offspring. The goal of the current review is to examine the available literature regarding the effects on offspring of parental drug exposure in the absence of any direct fetal exposure for five major drugs of abuse. While offspring susceptibility to drug use is of particular interest, all behavioral, molecular, and physiological changes in the offspring will be reported. The majority of the studies available on this topic focus on paternal transmission of epigenetic phenotypes, as this model eliminates any direct fetal exposure and ostensibly avoids maternal rearing effects. With regard to maternal transmission, there is certainly an extensive body of literature documenting offspring effects following prenatal exposure to drugs of abuse (Malanga and Kosofsky, 2003; Sithisarn et al., 2012). Due to the possible direct effects of *in utero* exposure on the fetus, as well as the numerous confounds that drug use

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http://dx.doi.org/10.1016/j.neuropharm.2013.06.016

during pregnancy introduces (e.g. changes in nutritional status, renal function, vascular perfusion, etc.), prenatal substance use models will not be included in the current review. We will, however, include data from studies examining transgenerational effects of female drug use occurring prior to conception. Thus, the current review will examine the effects of parental exposure to drugs of abuse prior to conception on the development of subsequent generations.

2. Alcohol

Currently, alcohol is the most commonly abused drug in the United States. In 2011, the center for disease control estimated that 60% of males and 44% of females engage in chronic alcohol drinking (Edward J. Sondik et al., 2012). While the neurobehavioral effects of fetal alcohol exposure are well described, less is known about the effects of parental exposure to alcohol prior to conception. It should be noted, however, that reports and writings as early as the 1720's, during the so-called gin epidemic, observed that both maternal and paternal alcohol use had detrimental effects on offspring (Warner and Rosett, 1975). While few studies have examined maternal alcohol use prior to pregnancy (i.e. in the absence of prenatal use), several findings have demonstrated effects of paternal alcohol exposure on offspring development. Indeed, as early as 1913 animal studies found that offspring sired by alcohol inhaling rats demonstrated malformations, low birth weight, retarded growth and increased neonatal mortality across several generations (Friedler, 1996). Clearly the concept that alcohol use by the father, and not solely his genetic composition, can affect future progeny is not novel. The interest in paternal effects, however, has been reinvigorated by the emergence of the field of epigenetics, with a number of preclinical findings suggesting transgenerational epigenetic effects of paternal alcohol use.

Several of the initial animal studies on paternal alcohol effects focused on basic parameters of reproductive success, such as fertility and fecundity, following exposure to alcohol in peripubertal males. These studies observed a significant reduction in the number of successful pregnancies which decreased from 92% in controls to 75% in naïve females mated with alcohol-drinking sires (Emanuele et al., 2001). Litter size was also substantially reduced (Cicero et al., 1990; Emanuele et al., 2001). It was determined that alcohol exposure during puberty modified sexual maturation and resulted in decreased testes and secondary sex organ weight, eliminated the typical pubertal surge in testosterone, decreased beta-endorphin levels in the hypothalamus, and enhanced testicular oxidative injury (Cicero et al., 1990; Emanuele et al., 2001). Interestingly, offspring of these pubertal alcohol-exposed sires demonstrated similar alterations, including decreased serum testosterone levels, reduced seminal vesicle weights, and lower levels of hypothalamic beta-endorphin (Abel and Lee, 1988; Cicero et al., 1990).

Alcohol-sired offspring also demonstrate abnormalities in development. In an elegantly designed rodent study, Jamerson and colleagues revealed that paternal alcohol exposure that was ongoing, or that had ceased weeks prior to conception resulted in more rapid development of various reflexes, differences in gait, and thicker cortical layers (Jamerson et al., 2004). It was also noted that timing of alcohol exposure in relation to conception impacted the neurobehavioral effects of the offspring (Jamerson et al., 2004). For example, one study found that a single exposure to alcohol just prior to conception resulted in a significant increase in small for gestational age offspring as well as an increase in offspring demonstrating significant malformations (Bielawski and Abel, 1997). Moreover, alcohol-exposed sires also produced offspring displaying increased adrenal cortex and decreased spleen weights (Abel, 1993b). Finally, there is evidence that metabolic and immune functioning may be disrupted in alcohol-sired offspring, given that they display reductions in leptin levels (Emanuele et al., 2001) and a diminished immune response (Berk et al., 1989; Hazlett et al., 1989).

In terms of behavioral effects, both increases and decreases in activity have been noted in offspring of alcohol-consuming sires (Abel, 1989a,b; 1993a, b; Abel and Lee, 1988), with the direction of these effects mediated by a number of factors including the level of alcohol consumption, the time between exposure and conception (Jamerson et al., 2004), and the age at the time of testing (Abel, 1989a). Alterations in behavioral activity following amphetamine were also noted in male offspring (Abel, 1993a), with some evidence suggesting that increased activity was dependent on the cholinergic system (Abel, 1994). Potential modifications in the cholinergic system of alcohol-sired offspring are notable given that deficits in learning and memory have also been reported. For example, offspring sired by alcohol treated males demonstrated impairments in spatial learning (Wozniak et al., 1991) and had increased latencies to reach a choice point in a T-maze (Abel, 1994; Abel and Lee, 1988). In addition to deficits observed in males, alcohol-sired female offspring showed impaired performance in a two-way shock avoidance learning task (Abel and Tan, 1988). Finally, offspring of alcohol-consuming sires demonstrated decreased grooming as well as decreased immobility in a forced swim test, an effect that was rescued by imipramine and propranolol and exacerbated by yohimbine and metergoline (Abel, 1991a, b; Abel and Bilitzke, 1990). Together, these results indicate a detrimental behavioral phenotype of paternal alcohol consumption on both male and female offspring.

Examining epigenetic parental effects in human populations can be difficult. Human studies have, however, revealed correlations between parental drinking behavior and offspring initiation and drinking patterns. Thus, heavy paternal drinking or heavy-episodic drinking in both parents predicts earlier onset of offspring drinking as well as heavier drinking (Vermeulen-Smit et al., 2012). Children born with characteristics associated with fetal alcohol syndrome whose mother's did not drink but fathers were alcoholics have also been observed (Lemoine et al., 2003). Additionally, there is evidence that sons of early-onset (adolescent) alcoholic fathers perform more poorly on tests of verbal intelligence and attention than late onset (adult) alcoholics (Tarter et al., 1989). While this may suggest that adolescence, or periods of significant neural and endocrine development, are particularly important in determining the effects of paternal alcohol exposure, one cannot exclude the possibility that early-onset drinking may be a marker of genetic vulnerability or additional comorbid pathologies. Finally, in addition to deficits in cognition, attention, and visuospatial capacity observed in children of alcoholic fathers, increased hyperactivity has also been noted (Goodwin et al., 1975), although the relationship between hyperactivity and paternal alcohol consumption remains equivocal (Knopik et al., 2009). Much less work has been done examining the effects of maternal preconception alcohol consumption. However, a decreased birth weight has been observed in children of alcoholic women that abstain from use during pregnancy (Little et al., 1980; Livy et al., 2004; Ramsay, 2010). While human studies remain more difficult to interpret than preclinical research due to many aspects that are impossible to control, it is important that both lines of research continue in order to fully understand the scope of preconception alcohol use and abuse.

3. Nicotine

Nicotine is the second most abused substance in the United States. In 2011 it was reported that 21.6% of adult men and 16.5% of