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**REVIEW ARTICLE**

# Adolescent Substance Abuse, Transgenerational Consequences and Epigenetics

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**Abstract:** Adolescence is the transitional period between childhood and adulthood and a critical period in brain development. Adolescence in humans is also associated with increased expression of risk-taking behaviors. Epidemiological and clinical studies, for example, show a surge of drug abuse and raise the hypothesis that the adolescent brain undergoes critical changes resulting in diminished control. Determining how substance abuse during this critical period might cause long-term neurobiological changes in cognition and behavior is therefore critically important. The present work aims to provide an evaluation of the transgenerational and multi-generational phenotypes derived from parent animals exposed to drugs of abuse only during their adolescence. Specifically, we will consider changes found following the administration of cannabinoids, nicotine, alcohol and opiates. In addition, epigenetic modifications of the genome following drug exposure will be discussed as emerging evidence of the underlying adverse transgenerational effects. Notwithstanding, much of the new data discussed here is from animal models, indicating that future clinical studies are much needed to better understand the neurobiological consequences and mechanisms of drug actions on the human brains' development and maturation.

**Keywords:** Brain development, cannabinoids, opiates, alcohol, nicotine, adolescence.

## 1. INTRODUCTION

The *adolescence* period is a transitional phase from childhood to adulthood and characterized by behavioral manifestations such as novelty seeking, risk-taking and intense peer associations [1, 2]. In humans, this developmental stage occurs mainly between 10 and 19 years of age. In rodents, no precise boundary is established but is generally accepted to occur during postnatal days 28 and 42 [3]. There is extensive evidence that the brain undergoes significant developmental changes during this period [2, 4, 5], affecting regions associated with cognition, emotion and reward-seeking behaviors [6, 7]. The adolescent brain is thus more vulnerable to environmental perturbations such as drug abuse [4, 6, 8] with several groups, including our own, investigating the longer-term effects of adolescent drug exposure on brain development and neurophysiological function [9-11].

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In addition to recognizing that adolescent drug use may persistently influence susceptibility to drug abuse in adulthood, there is growing evidence for the *transgenerational* effects of drug-taking during adolescence [12-14]. These observations raise the hypothesis that epigenetic changes in one generation, following drug exposure in adolescence, promote the development of neurobiological changes in the next generation. Epigenetics is the molecular modification of genes without altering the DNA sequence (*i.e.*, the genetic code). Such epigenetic changes include the addition of methyl or histone groups to DNA, and change the way genes are read and expressed [15]. As such, several studies have identified a range of *transgenerational* physiological and behavioral consequences following parental exposures to environmental toxins and drugs of abuse [12, 14, 16, 17]. The direct effects of *in-utero* or adult pre-conception drug exposure on their offspring are not, however, the focus of this review, nor are the long-term effects of adolescent drug exposure on lifespan, which we have reviewed elsewhere [11]. Rather, we aim to provide the current view on the transgenerational effects of adolescent drug exposure prior to conception and parenthood on the neurobehavioral development of the subsequent generations. To this end, cannabinoids, nicotine, alcohol and opioids are reviewed and discussed here.

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## 2. CANNABINOIDS

Cannabis is one of the most common drugs of abuse in the world. Despite the public notion that cannabis consumption is *low risk*, there is recognition of the detrimental effects of this drug on cognition, increased risk of anxiety, depression and psychosis [18-20]. Studies have also shown that cannabis abuse frequently starts in adolescence, with a high rate of addictive behavior developing and this has become a serious medical concern over the past few years [21-23]. Evidence indicates that the brain endocannabinoid system undergoes maturational changes during adolescence and, as expected, these underlying neural circuits can be more vulnerable to the effects of exogenous cannabinoid exposure during this time window [24-26].

A number of studies have investigated the long-term impact of adolescent cannabinoid exposure on brain function and behavior in adulthood [10, 11, 25]. In addition, some researchers have suggested that exposure to cannabinoids during pregnancy can have a detrimental impact on their offspring's development [27, 28]. Moreover, a few studies have addressed, experimentally, the potential for cannabinoid exposure during adolescence to impact the generation subsequently born to these animals [12, 13, 29].

The endocannabinoid system is a potent regulator of reproductive function in females [30, 31], with significant development of the reproductive system occurring during adolescence [32]. Thus, exposure to exogenous cannabinoids during this dynamic period may cause persistent alterations in female reproductive organs with subsequent physiological changes in their offspring [33]. Most studies addressing cannabinoid transgenerational effects have therefore focused on female subjects. Byrens and colleagues (2012), for example, showed that exposure to the CB1/CB2 agonist, WIN 55,212-2 in adolescent female rats increased morphine-induced conditioned place preference (CPP) in their male rat offspring, suggesting an increased sensitization to the rewarding effects of opioids. This exposure also enhanced morphine-induced locomotor sensitization in their female offspring. These effects were found to be more pronounced at lower doses of morphine (1mg/kg) which represents a slight shift in the sensitivity of the endogenous opioid system in the offspring [34]. In a later study, these investigators also reported that adult female offspring of mothers exposed to WIN 55,212-2 in adolescence showed an increased expression of morphine-induced locomotor sensitization and increased mu opioid receptor expression in the nucleus accumbens [33].

Szutorisz and colleagues (2014) examined the behavioral and neurobiological characteristics of parental tetrahydrocannabinol (THC) exposure during adolescence on their offspring in rodents [35]. Their results demonstrated a significant increase in heroin self-administration among the F1 offspring compared with controls. At the molecular level, these F1 offspring showed dysregulation in striatal mRNA expression of cannabinoid, dopamine and glutamatergic receptors and reduced NMDA receptor binding. In addition, parental THC treatment was found to potentiate long-term depression (LTD) in dorsal striatum brain slices from the F1 offspring [35].

In a more recent study, adolescent female rats were administered either a *low* (0.1mg/kg) or *high* (1mg/kg) dose of delta-9-tetrahydrocannabinol (Δ9-THC) for 22 days [36]. Subsequently, the reward properties of Δ9-THC and d-amphetamine were attenuated in the adult male offspring, as indicated by the intracranial self-stimulation (ICSS) paradigm. However, this reduction in reward-related effects does not necessarily suggest a protective phenotype in the offspring towards a craving for such drugs of abuse. Rather, these results may indicate an anhedonic manifestation in the offspring, which are less sensitive to natural rewards and more vulnerable to addiction [36]. Together these data (Table **1**) suggest that parental exposure to cannabinoids during adolescence can impart a persistent and significant modification on brain development and behavioral phenotypes in their unexposed offspring.

## 3. NICOTINE

There are almost 40 million adults and about 4.7 million youth tobacco smokers in the United States (Centers for Disease Control and Prevention, 2020). This number is increasing with the popularity of electronic cigarettes [37, 38]. There is also epidemiological evidence for the possibility of nicotine-induced transgenerational effects [39, 40]. In most studies, offspring are directly exposed to nicotine *in utero,* which can cross the placental barrier to affect the developing fetus [41, 42]. *In utero,* nicotine results in hyperactivity, altered metabolism and increased susceptibility for respiratory diseases in the next two generations (F1 and F2) of mice offspring [43-45]. It is also documented that gametes and developing neural circuits are vulnerable to nicotine during the critical period of adolescence [9, 46]. Several studies have shown that nicotine during adolescence causes cognitive and behavioral impairments and the development of more severe dependence in later life [47, 48], but few studies have investigated the *transgenerational* impact of exposure to nicotine during adolescence.

Nicotine use and stress behavior are complex factors, which mutually influence each other. For instance, stress may increase nicotine addiction through the induction of stress signaling pathways and nicotine withdrawal is considered a stressful event that increases the release of stress hormones, like cortisol, and promotes nicotine relapse [49, 50]. In keeping with these notions, Yohn and coworkers (2019) found that environmental exposure to nicotine and stress during adolescence can cause multi-generational inheritance and produce unique phenotypes in their offspring [51]. Specifically, this group showed that nicotine delivered by osmotic minipump for 28 days during adolescence in (F0) male mice, followed by stress exposure in their offspring (F1) led to reduced nicotine sensitization in the F2 generation of both sexes, and increased sensitization only in the F3 generation of the female mice. Importantly, to exclude potential direct exposure of offspring to paternal nicotine, the drug-infusing minipumps were removed from the male mice 1 month prior to mating [51]. Interestingly, Renaud and Fountain (2016) have also reported that male, but not female parents, exposed to nicotine only during their adolescence, led to learning deficits and cognitive impairments in their F1 offspring when

**Table 1. A summary of the transgenerational impact of adolescent drug exposure on subsequent generations born to these parents, together with the species and the primary sources of these observations.**

| Drug | Parental Exposure (Maternal/Paternal) | Affected Generation | Transgenerational Manifestations | Species | References |
|---|---|---|---|---|---|
| **Cannabinoids** | Maternal | F1 | *Increased sensitization to rewarding effects of opioids* | Rat | Byrnes *et al.,* 2012 |
| | Maternal | F1 | *Increased expression of opioid receptors in NAc* | Rat | Vassoler *et al.,* 2013 |
| | Maternal | F1 | *Decreased THC and amphetamine reward effects* | Rat | Pitsilis *et al.,* 2017 |
| | Both | F1 | *Increased heroin self-administration* | Rat | Szutorisz *et al.,* 2014 |
| **Nicotine** | Paternal | F1, F2, F3 | *Increased locomotor sensitization* | Mouse | Yohn *et al.,* 2019 |
| | Both | F1 | *Learning deficits, cognitive impairments* | Rat | Renaud & Fountain, 2016 |
| **Alcohol** | Both | F1 | *Altered DNA methylation patterns in hypothalamus* | Rat | Asimes *et al.,* 2017 |
| | Both | F1 | *Changes in gene expression in hypothalamus* | Rat | Przybycien-Szymanska *et al.,* 2014 |
| | Paternal | F1 | *Impaired stress responsiveness* | Mouse | Rompala *et al.,* 2016 |
| | Paternal | F1 | *Increased anxiety & depression* | Mouse | Liang *et al.,* 2014 |
| **Opioids** | Maternal | F1 | *Impairment of maternal support* | Rat | Johnson *et al.,* 2011 |
| | Maternal | F1 | *Increased sensitivity to morphine analgesia; facilitation of morphine tolerance & sedation* | Rat | Byrnes *et al.,* 2011 |
| | Maternal | F1 | *Increase level of μ opiate receptors in NAc & VTA* | Rat | Vassoler *et al.,* 2016 |
| | Maternal | F1 | *Reduced corticosterone secretion* | Rat | Vassoler *et al.,* 2014 |
| | Maternal | F1, F2 | *Reduced locomotor sensitization* | Rat | Byrnes *et al.,* 2013 |
| | Paternal | F1 | *Altered electrophysiological features in VTA; Decreased sensitization to rewarding effects of opioids* | Rat | Azadi *et al.,* 2019 |
| | Paternal | F1 | *Changed pain-related behaviors* | Rat | Pachenari *et al.,* 2018 |
| | Paternal | F1 | *Altered electrophysiological features in LC* | Rat | Pachenari *et al.,* 2019 |
| | Paternal | F1 | *Altered electrophysiological features in LPGi; Increased opioid withdrawal syndrome* | Rat | Azadi *et al.,* 2020 |

measured using a serial multiple-choice task [52]. Currently, the mechanism(s) underlying the cross-generational consequences of nicotine exposure in adolescence are not well understood but suggest epigenetic modifications of the genome and future work should focus on the cellular events underlying the development of these phenotypic traits.

## 4. ALCOHOL

Alcohol consumption is considered a major health problem across the globe [53]. According to reports from the Center for Disease Control, over 60% of males and 44% of females are estimated to consume alcohol on a regular basis in the United States [54]. Alcohol drinking in the adolescent population in the United States is also increasingly recognized as a serious health concern; national surveys show that around 5 - 6% of adolescents (aged 12 to 17 years) report binge drinking, with a sharp increase to around 15% by 16 to 17 years of age [55].

There is also a correlation between parental drinking behavior and the onset and pattern of drinking in their offspring: heavy paternal drinking, for example, is associated with earlier as well as heavier drinking in their offspring [56]. Furthermore, adolescent alcohol use can lead to health problems in adulthood, including mood disorders, depression, drug dependence and neurodegenerative diseases [57, 58]. Moreover, adult paternal alcohol exposure can also lead to behavioral changes such as impaired stress responsiveness, increased rates of depression and anxiety in alcohol-naïve offspring of these animals [59, 60].

In contrast, much less is understood about the transgenerational consequences of exposure to alcohol during adolescence. Notably, parental binge alcohol consumption during adolescence in rodents leads to significant changes in the expression of genes that 'mediate neurogenesis and synaptic plasticity during neurodevelopment', chromatin remodeling and genes involved in the regulation of obesity and reproductive function in the hypothalamus of their F1 offspring [61]. DNA methylation is now considered as a heritable epigenetic mechanism which undergoes alterations during development and can be influenced by environmental factors, including alcohol [62, 63]. Along these lines, Asimes and coworkers (2017) have shown that adolescent binge ethanol exposure induces extensive changes in DNA methylation patterns in genes such as Rn5-8s, Bmp3 and Atg5 in the hypothalamus of alcohol-naïve offspring following both paternal and maternal exposure in rodents. These changes were

sex-dependent, with maternal ethanol treated offspring displaying 79 hypomethylated residues compared to 47 hypomethylated residues when only the father was exposed to ethanol. In offspring where both parents were exposed to ethanol, there were 105 hypomethylated differentially methylated cytosines compared to offspring from water-treated parents. These data suggest that changes in DNA methylation patterns are an epigenetic basis for the transgenerational effects of adolescent binge alcohol exposure in their offspring. Further studies are, however, clearly required to address this hypothesis [64].

## 5. OPIOIDS

Opioid use and abuse have surged substantially over the past two decades. The United States is now facing an opioid addiction crisis and opioid overdose events are growing at an alarming rate [65, 66]. In this respect, adolescents are more frequently exposed to legally prescribed opioid drugs such as hydrocodone (*Vicodin)*, oxycodone (*Percocet)* and fentanyl for a wide variety of reasons, including dental work, minor surgeries, the common cold and recreational consumption [67-69].

Brain opioid peptides and their receptors have essential roles in the modulation of neural, endocrine and immune systems [70-72]. For example, they regulate sexual maturation, stress responsiveness and numerous cognitive and reward-related processes during adolescence [73, 74]. Therefore, exposure to high levels of exogenous opioids may adversely affect a range of opioid-mediated functions within the CNS. There is strong evidence indicating that opioid exposure during adolescence persistently impairs brain development and functionality [1, 11]. Beyond this, it has been proposed that opiate exposure during this critical period may also leave effects on the next generations, even when exposure is discontinued prior to conception [12, 13].

Adolescent morphine exposure in rats is known to subsequently affect maternal behaviors during the nursing and non-nursing period and impair direct supportive contacts with their offspring [75]. Thus, the juvenile male offspring of these mothers are engaged in less *rough and tumble play* whereas females are engaged in more such behaviors [75]. In an open field behavioral test, F1 female offspring of mothers exposed to morphine in adolescence showed an increased level of anxiety-like behaviors [76]. In a subsequent study, the F1 male offspring of mothers exposed to morphine during adolescence displayed enhanced sensitivity to morphine analgesia and accelerated development of morphine tolerance [76, 77].

Vassoler and colleagues (2014) reported that adolescent female rats exposed to morphine was associated with potentiated morphine-induced sedation and attenuated corticosterone secretion in the male rat offspring and a significant increase in the expression of the proopiomelanocortin (POMC) gene in the arcuate nucleus and μ-opioid receptors in the ventral tegmental area (VTA) of these animals [12]. A later study reported the development of conditioned place preference to low doses (1mg/kg) of morphine was enhanced in F1 female rats whose mothers had been exposed to morphine during adolescence. Moreover, mu opiate receptors were increased in the nucleus accumbens and decreased in the ventral tegmental area [78]. Although the latter finding was not consistent with the change in conditioned place preference behavior, the authors hypothesized that protein expression does not measure the functional activity of the mu receptors.

Chronic exposure to escalating doses of morphine in adolescent male rats is associated with significant increases in formalin-evoked pain-related behaviors, including paw withdrawal and paw licking in the male offspring [79]. The same group also demonstrated that paternal morphine exposure during adolescence leads to attenuation in the rewarding effect of low dose morphine in the CPP paradigm, along with attenuation in spontaneous burst firing of ventral tegmental area dopamine neurons in male offspring of these animals [80]. Azadi and colleagues reported an enhancement in the development of the somatic and affective aspects of naloxone-precipitated morphine withdrawal mediated, at least in part, by alteration of lateral paragigantocellularis nucleus-related circuitry in the male offspring of sires exposed to morphine during adolescence. This study revealed that exposure to morphine in male rats during adolescence increases morphine-induced discharge inhibition in the lateral paragigantocellular nucleus (LPGi) neurons in male offspring [81]. Additionally, the decay slope of action potentials and the amplitude of after-hyperpolarizations increased in locus coeruleus neurons only in the rat offspring of males exposed to morphine during their adolescence [82].

Most studies addressing transgenerational effects of drugs of abuse have focused on the F1 generation. However, Byrnes and coworkers reported that adolescent opioid exposure might have effects across multiple generations. Thus, locomotor sensitization induced by quinpirole (a selective dopamine, D2 receptor agonist) was decreased in both F1 and F2 rat offspring following maternal morphine exposure in adolescence. At a molecular level, quinpirole-induced corticosterone secretion increased, and gene expression of kappa opioid receptors and dopamine D2 receptors (D2Rs) decreased within the nucleus accumbens [84]. Given the role of D2Rs in antipsychotic drug therapy, maternal exposure to opiates might increase the vulnerability of subsequent generations to neuropsychiatric disorders. Finally, following maternal morphine exposure during adolescence in Sprague Dawley rats, F1 and even F2 offspring displayed blunted relapsing and drug-seeking behaviors. Additionally, genes related to synaptic plasticity (*i.e*., Gria2, Snap25 and Zwint) and myelin basic protein (MBP) were dysregulated in F1 animals and some of these effects persisted even into the F2 generation [83]. Together, these data indicate that transient exposure to opioids in adolescence can have long-lasting and multi-generational consequences (Table **1**).

## 6. EPIGENETIC MODIFICATION: AN EMERGING HORIZON FOR FUTURE RESEARCH

The data reviewed here suggest a role for epigenetic modification of the genome in the transgenerational consequences of adolescent drug exposure. Conrad Waddington was first to introduce the concept of *epigenetics* with the notion that development originates from the 'casual interactions between genes and their products which bring the phe-

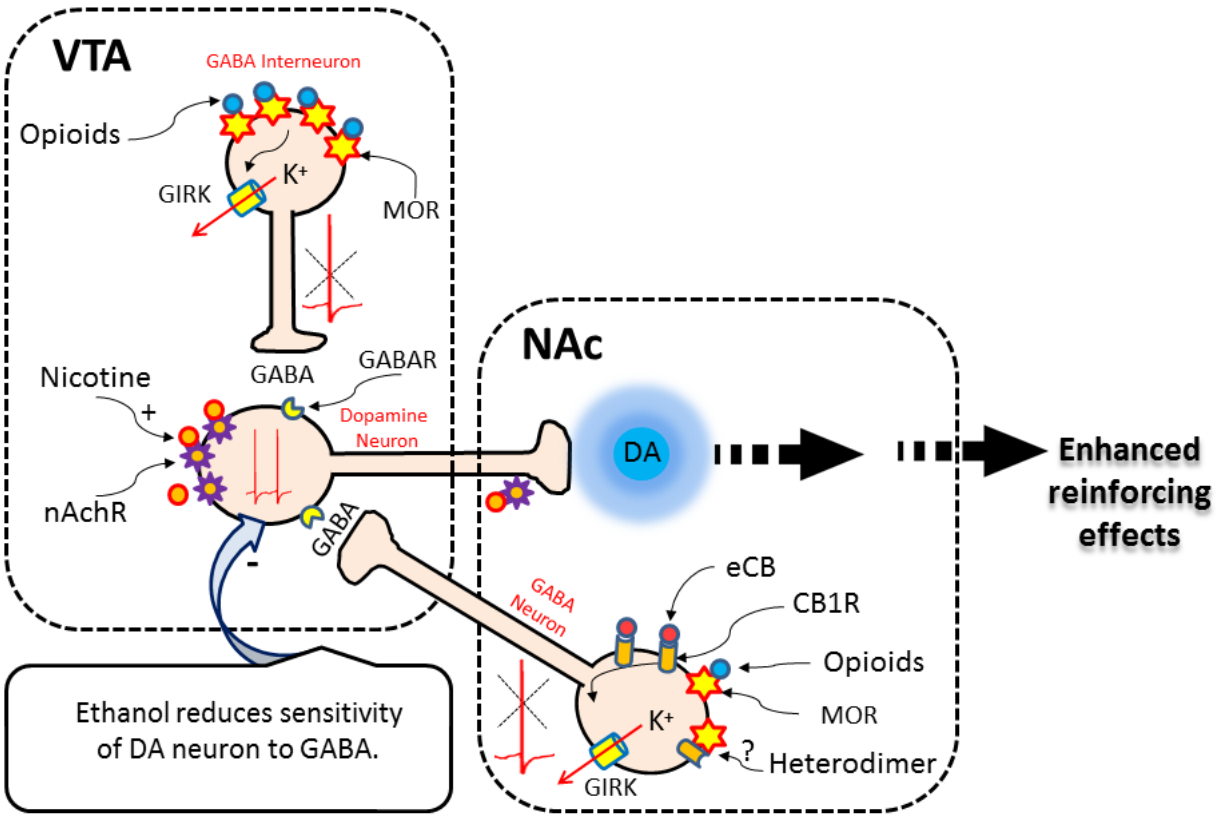


**Fig. (1).** A model depicting how common drugs-of-abuse (nicotine, cannabinoids, opioids and alcohol) can alter dopamine release within the brain reward circuit. VTA: ventral tegmental area, NAc: nucleus accumbens, GIRK: G protein-coupled inwardly-rectifying potassium channel, MOR: Mu-opioid receptor, DA: Dopamine, GABA: gamma-Aminobutyric acid, GABAR: GABA receptor, CB1R: Cannabinoid type 1 receptor, eCB: exogenous cannabinoid. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

notype into being' [85]. Today, the accepted definition of epigenetics is the study of modifications of DNA, including methylation, histone post-translational modifications and regulation by small non-coding RNAs that directly affect the expression of a gene but do not change the underlying DNA sequence [86, 87]. For instance, the acetylation of histone at specific lysine residues leads to relaxation of chromatin and consequently increased transcription of genes within the relaxed regions [88]. Epigenetic modifications can be inherited by the next generation in the absence of direct environmental challenges on germ cells. For example, in early life, variations in maternal licking and grooming behaviors can alter epigenetic markers throughout the genome and influence the level of care administered to the subsequent generation [89, 90]. Thus, daughters that received higher levels of maternal care impart increased care of their own offspring. Moreover, according to the *differential allocation* hypothesis, a drug-exposed male can also have confounding effects on subsequent maternal rearing behaviors toward offspring [91]: female mice, for example, that are mated with males that have experienced social enrichment across their lifespan also show elevated levels of post-natal maternal nursing and pup licking and grooming towards their offspring [92].

The epigenetic machinery is responsive to many variables and can shift the developmental trajectory of the CNS [93-95]. Interactions among epigenetic signatures, early life experience, environmental factors and drug-induced neuroplasticity can extend beyond an individual's lifespan [96, 97] and mediate vulnerability to drugs of abuse in subsequent generations [98]. For example, cocaine self-administration in male rats increased the association of acetylated histone H3 (H3K9K14ac2) with Brain Derived Neurotrophic Factor (BDNF) promoter IV in the medial prefrontal cortex (mPFC). Moreover, an increase was observed in total H3K9K14ac2 as well as associated with BDNF promoters in the sperm of F0 rats. Intriguingly, the same molecular alterations were measured in the mPFC of F1 male offspring. In addition, H3K9K14ac2 levels were also increased in the testes of the F1 animals, suggesting that H3K9K14ac2 may be a critical epigenetic mechanism for the transmission of this phenotype [99]. Notably, changes in BDNF expression are associated with affective disorders such as depression, normal and pathological aging, and structures important for memory, including the hippocampus and parahippocampal areas [100]. Additionally, Watson and colleagues also determined the transgenerational effects of THC exposure in the parents on the F1 epigenome of the nucleus accumbens and identified 1027 differentially methylated regions associated with parental THC, each represented by multiple cytosine-phosphate-guanine (CpGs) residues [101].

Parental exposure to opioid or cannabinoid agonists can upregulate the expression of Mu-opioid receptors (MORs) within the brain reward pathway (*i.e.*, the ventral tegmental area and the nucleus accumbens). The question, therefore, is

how these agents might promote the rewarding effects at the level of neural circuits. One hypothesis is that since opiates excite the VTA to nucleus accumbens (NAc) dopaminergic neurons through inhibition of local GABAergic interneurons, a disinhibitory mechanism [102, 103] is regulated enhancing dopamine release in NAc, and in turn, promoting the expression of reward behaviors. Alternatively, opioid and cannabinoid agonists hyperpolarize NAc to VTA inhibitory neurons [102, 103] and enhance dopamine release in the NAc. Notably, both CB1R and MORs are co-expressed in GABAergic neurons of NAc [104] and could also synergistically promote a disinhibitory mechanism through G-protein coupled heterodimer complexes [105] (Fig. **1**). Chronic exposure to nicotine on the reward circuit also stimulates an increased expression of nicotinic acetylcholine receptors within the VTA and NAc [106] which might increase DA release through still poorly understood mechanisms [107]. Prolonged alcohol drinking can also direct the reward pathway to an elevated level of activity by attenuating the potency of GABA on VTA dopaminergic neurons. Significantly, this effect is associated with epigenetic mechanisms, including histone acetylation [108, 109].

## CONCLUDING REMARKS

A growing body of evidence has emerged showing that drugs of abuse induce epigenetic changes that can remarkably have multi-generational effects. Offspring may therefore face altered levels of susceptibility to a variety of disorders because of parental exposure years, even decades, before they are conceived. The significance of maternal health for the unborn *in utero* is widely recognized; the potential that maternal and paternal drug exposure, even during adolescence, can also induce persistent effects in the offspring adds a new level of complexity. Even more challenging is the impact of multi-drug abuse, which is not uncommon during adolescence on subsequent generations. The US Preventive Services Task Force recognizes the '*negative health, social, and economic consequences of adolescent drug abuse in children (11 years and younger), adolescents (aged 12-17 years), and young adults (aged 18-25 years), including pregnant persons*' but concluded that the evidence was insufficient to assess the balance of benefits and harms of primary care-based behavioral counseling interventions to prevent illicit drug use, including non-medical use of prescription drugs [110]. Future work is therefore required at the genetic and epigenetic levels to provide insight into the underlying mechanisms of the transgenerational actions of drug abuse on neural development. In addition, more research is now clearly required to provide guidance for clinical treatments of a growing level of substance use disorders in society.

## CONSENT FOR PUBLICATION

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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