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Review Paper

Experimental Evidence on Age-related Differential Outcomes Associated With Substance Abuse

S Mohammad Ahmadi-Soleimani[1], Hamed Salmanzadeh[2], Hossein Azizi[3*]

1. Departments of Physiology, Neuroscience Research Center, School of Medicine, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran.
2. TJ Long School of Pharmacy, University of the Pacific, Stockton, The United States.
3. Department of Physiology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran.

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ABSTRACT

Growing evidence indicates that adolescent substance abuse is now an alarming concern that imposes a considerable socio-economic burden on societies. On the other hand, numerous studies have shown that due to specific neurophysiological features, the brain is more vulnerable to the adverse effects of psychoactive drugs at an early age. Unfortunately, these negative effects are not limited to the period of drug use, but can persistently affect the brain's responsiveness to future exposures to the same or other types of drug. For researchers to develop pharmacological strategies for managing substance abuse disorders, they need to gain a deep understanding of the differences in behavioral outcomes associated with each type of drug across different age groups. The present study was conducted to review the experimental evidence revealing the mentioned differential effects with an emphasis on common drugs of abuse, including cocaine, nicotine, cannabis, and opioids. Although the cellular mechanisms underlying age-related effects have not been exclusively addressed for each drug, the most recent results are presented and discussed. Future studies are required to focus on these mechanisms and reveal how molecular changes during brain development can result in differential responses to drugs at the behavioral level.

*** Corresponding Author:**
Hossein Azizi, Associate Professor.
Address: *Department of Physiology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran.*
Tel: *+98 (21) 8288 4587*
E-mail: *azizih@modares.ac.ir*

Highlights

- Adolescent substance abuse is a growing concern worldwide.
- Adolescent brain is highly vulnerable to the adverse effects of drugs.
- Adolescent drug exposure persistently affects brain responsiveness.
- Drugs of abuse cause age-related differential outcomes.

Plain Language Summary

Substance abuse disorder among adolescents is now a serious global concern. Some of the most common drugs of abuse include nicotine, alcohol and opium derivatives. People need to now the fact that from scientific point of view, adolescents' brain are more sensitive to the harmful effects of these drugs in comparison with adults. This is because during adolescence period many important chemical changes occur within the brain. In addition, drug abuse during this critical age causes long-term detrimental changes which may affect the individual's future vulnerability for addiction and various cognitive diseases. The present study was done to review the main findings about the side effects of drug abuse during adolescence in animal models. Taken together, in depth research is required how to find out how these side effects are induced and what policies could be adopted to prevent drug exposure during adolescence in society.

1. Introduction

In humans, adolescence (from 10 to 19 years old) includes various physiological, psychological, and social factors. Two behavioral features representing the childhood to adolescence transition are changes in the hormonal levels (characterized by partner-seeking behaviors) and increased manifestation of social, affiliative, and playful behavior. However, in rodents, adolescence is defined as the period between the postnatal days 21 to 60. More specifically, this interval can be divided into three stages, including early (paroxysmal nocturnal dyspnea [PND]=21–34), middle (PND=34–46), and late adolescence (PND=46–59) (Laviola et al., 2003). In particular, the middle stage has been shown as an effective model for studying behavioral complications associated with adolescence, including drug abuse. Substance abuse among adolescents is currently a growing social concern that imposes a great burden on both the individuals later in life and health care systems worldwide (Chassin et al., 2004; Pompili et al., 2012).

Normally characterized by increased locomotor activity, higher risk-taking and novelty-seeking behavior, all of which pave the way for a heightened appetitive drive for substance abuse (Doremus-Fitzwater et al., 2010; Feldstein & Miller, 2006). In this respect, drug intake may either occur as transitional periods of consumption (such as recreational/binge intake) or may continue into adulthood as an addiction or chronic consumption. Among the wide variety of drugs used by adolescents, more accessible ones, including nicotine, alcohol, opioids, and cannabis have extensively been studied (Barron et al., 2005; Botvin & Botvin, 1992; Salmanzadeh et al., 2021; Salmanzadeh et al., 2020). During the last decade, numerous studies have addressed the age-related physiological responses to drugs of abuse in adolescent vs adult animal models. Literature supports the idea that adolescents may exhibit a higher level of vulnerability to specific drugs compared to adult subjects (Chambers et al., 2003; Schramm-Sapyta et al., 2009; Wong et al., 2013). Current neurophysiological evidence indicates that even short/sporadic drug exposure in adolescence could result in persistent changes in the responsiveness of specific brain circuits to future drug exposure (Moazen et al., 2018; Sabuee et al., 2021; Salmanzadeh et al., 2021; Salmanzadeh et al., 2020, Salmanzadeh et al., 2017; Salmanzadeh et al., 2018; Torabi et al., 2019). Mechanistically, this results from the fact that many key brain structures undergo maturational refinements at the cellular level during adolescence. Furthermore, this period of life is associated with significant changes in brain neurotransmitter balance (Murrin et al., 2007; Pitzer, 2019; Wahlstrom et al., 2010), thus any alteration of brain function at this developmental stage may be persistently maintained until adulthood.

Although long-term complications of adolescent substance abuse have been thoroughly reviewed in recent years (Salmanzadeh et al., 2021; Salmanzadeh et al., 2020), the differential age-dependent effects of drugs on central nervous system (CNS) function have not been duly addressed. The present study reviews the current evidence on this concern and suggests that the researchers consider these discrepancies when investigating/interpreting the long-term complications of substance abuse in the context of early life exposure. To assist the readers to get acquainted with the literature, Table 1 presents a summary of the main results.

2. Differential drug effect in adolescent vs adult subjects

Cocaine, nicotine and cannabis

An experimental study on rats has revealed that cocaine alters both behavioral and neurochemical indices in an age-dependent manner (Collins & Izenwasser, 2002). In this study, rats received cocaine for 7 consecutive days, and after 10-day drug-free period, they were challenged again with cocaine injection, and locomotor activity was measured. In addition, in vitro tests were performed to determine dopamine and serotonin transporter densities in specific brain regions. Results indicated that adult rats, but not adolescents, have become sensitized to the locomotor-potentiating effects of cocaine. Furthermore, in adults treated with cocaine, dopamine transporter density was increased in caudate-putamen nuclei and serotonin transporter densities were increased in caudate-putamen nuclei, nucleus accumbens shell as well as the olfactory tubercle. In contrast, cocaine treatment did not affect the mentioned neurochemical markers in peri-adolescent rats. These results indicate that cellular adaptations to chronic cocaine administration differentially develop in young versus adult rats. Another similar study has suggested a developmental difference between the reinforcing and locomotor activating effects of cocaine in young versus adult rats (Frantz et al., 2007). In this research, locomotor activity was recorded to reveal the occurrence of motor sensitization to repeated cocaine injections, and the self-administration method was applied to reveal cocaine-induced reinforcing effects. Results indicated that, although motor sensitization to chronic cocaine more significantly occurs in adults versus peri-adolescent subjects, no age-dependent disparity was found in the acquisition of cocaine self-administration or the concentration of dopamine within the nucleus accumbens shell.

Differential behavioral responses to cocaine have also been addressed in association with nicotine pretreatment. Technically, cocaine-induced locomotor sensitization was observed in naïve adult (and not in adolescent) rats. However, when adolescent animals were pretreated with nicotine, they displayed the mentioned sensitized response similar to naïve adult subjects (McQuown et al., 2009). In another study, differential states of conditioned place preference (CPP) were assessed in adolescent vs adult rats. In this regard, researchers have demonstrated that adolescents require more extinction trials than adults to extinguish cocaine place preferences. Moreover, adolescents exhibit a higher preference for an environment that has been previously cocaine-paired representing stronger reinstatement (Brenhouse & Andersen, 2008). Regarding the differential sensitivity to the conditioned rewarding effects of cocaine, adolescent rats, regardless of gender, establish CPP at lower doses compared to their adult counterparts (Zakharova et al., 2009).

In the context of nicotine, evidence indicates that nicotine induces a dose-dependent CPP in peri-adolescent, but not in adult rats (Belluzzi et al., 2004; Shram et al., 2006). On the other hand, in the conditioned taste avoidance paradigm, adult animals, and not peri-adolescents subjects, exhibited a dose-dependent avoidance of saccharin when paired with nicotine (Shram et al., 2006). These results support an age-dependent shift of balance in the rewarding and aversive effects of nicotine in rats which may explain the higher susceptibility and inclination of adolescents to continued nicotine intake. In another study on rats, it was found that a single dose of nicotine (0.125–0.5 mg/kg) does not affect the locomotor response in adolescent animals while causing a significant suppression in adult subjects (Belluzzi et al., 2004).

Another set of commonly used psychoactive substances is cannabis derivatives among which tetrahydrocannabinol (THC) is the main constituent. Several studies have proposed that both acute and chronic doses of THC can cause a variety of changes, including a reduction of locomotor activity in rats (Romero et al., 1996; Whitlow et al., 2002). This effect has been observed in both adult and adolescent rats; however, it is less potent in adolescents (Schramm-Sapyta et al., 2007). However, evidence indicates that low doses of THC increase locomotor activity during adolescence and induce no effect in adults (Wiley et al., 2008). Therefore, it seems that the differential responsiveness to THC (at locomotor response) is both age- and dose-related in rats. It should be noted that such differential effects can affect the individual's future response to other drugs of abuse. For example, adolescent (and not adult) rats undergone THC exposure have

been reported to display increased locomotor responses to cocaine challenge compared to the vehicle-treated group (Dow-Edwards & Izenwasser, 2012). This may, at least in part, account for the enhanced susceptibility of transition to cocaine after early (rather than late) cannabis abuse. In the context of cognitive complications, THC has been shown to induce more potent anxiogenic and aversive effects in adult vs adolescent rats (Schramm-Sapyta et al., 2007). Clinically, this may somehow explain why cannabis use is less frequent among adult humans compared to teenagers. Furthermore, experimental studies have shown that cannabinoid pre-exposure in adolescent rats (but not adults) results in long-lasting tolerance to future exposure in dopaminergic neurons of the ventral tegmental area (VTA) (Pistis et al., 2004).

Alcohol

Similar to many other substances, alcohol drinking habits are often initiated during adolescence. Previous animal studies have revealed that the degree of control over alcohol seeking depends on the age of drinking onset and the level of consumption. In this regard, age-dependent differences have been suggested such that in adult rats, the level of previous alcohol exposure is negatively correlated with the future control over alcohol seeking. However, adolescent animals, even with a history of heavy alcohol consumption, can control their craving to seek alcohol (Labots et al., 2018). regarding blood alcohol levels, experimental studies have shown that two hours after the same dose of ethanol injection (0.75 g/kg, i.p.), adolescent rats indicate lower blood alcohol levels compared to their adult counterparts (Walker & Ehlers, 2009). This result was further confirmed by the observation of a higher alcohol elimination rate in adolescent animals at the dose of 1.5 g/kg. Numerous evidence support the differential cognitive outcomes of prolonged alcohol intake in adolescent vs adult animals. For example, adolescent rats exhibit lower sensitivity to the aversive effects of alcohol, such as drowsiness, nausea, and motor incoordination (Spear, 2011). In contrast, sensitivity to the alcohol's rewarding effects is enhanced in these animals (Spear, 2011). Clinically, these results may explain the biological basis for the higher inclination of adolescents for binge drinking compared to adults.

Animal studies have also revealed age-specific differences in response to prolonged intermittent ethanol injection (20 days, every other day, i.p.) (Acevedo et al., 2013). For example, the animals' body weight was markedly decreased in aged and adult rats, but not in adolescent subjects (Acevedo et al., 2013). This result may be explained by the evidence that adolescent rodents do not exhibit conditioned taste aversion as much as their elder counterparts (Holstein et al., 2011). In addition, adolescent rats are less affected by the alcohol-induced hangover, compared to adults and therefore, more expected to show feeding behavior (Brasser & Spear, 2002). Moreover, the results of the aerial righting reflex indicated that aged rats are more vulnerable to ethanol-induced ataxia, compared to adult and adolescent animals (Acevedo et al., 2013). Mechanisms underlying this heightened vulnerability are still controversial. While some studies have proposed that the higher blood alcohol levels in aged animals are due to more body fat and reduced hepatic metabolism (Vestal et al., 1977), some researchers have reported similar blood alcohol concentrations among various age ranges of rodents (Acevedo et al., 2013). In another study, sensitivity to the sedative effects of alcohol was tested in rats and results indicated that peri-adolescent (both 20 and 30 days old) animals could regain their righting reflex (which was reduced by alcohol) significantly earlier than adult (80 days old) subjects (Little et al., 1996). Furthermore, locomotor activity was also decreased in adult, but not in the peri-adolescent, rats following administration of 2.5 g/kg ethanol (Little et al., 1996). Another result of this study was the age-related difference in pharmacokinetics of ethanol such that adult rats display a significant delay in the time to peak serum ethanol level, compared to peri-adolescent animals (Little et al., 1996).

Opioid drugs

Age-related differential effects have also been noticed by researchers working on opioid drugs. For example, adolescent male rats exhibit higher locomotor activity and sensitization following chronic and acute morphine injections compared to adult animals (Koek et al., 2012; White & Holtzman, 2005; White et al., 2008). Also, adolescent male rats self-administer less morphine than adult animals during sessions on a schedule of reinforcement tests (Doherty et al., 2009). Similarly, in another research, adolescent male mice were found to self-administer less oxycodone than adults (Zhang et al., 2009). These results have raised the hypothesis that opioid drugs may act more potent in the adolescent brain. Consistent with this notion, it is evident that adolescent animals have higher levels of oxycodone-induced dopamine release within the striatum than adults. As measured by the locomotor activity test, the forced swim test, and the weight loss records, adolescent mice displayed less severe morphine withdrawal signs compared to adults (Hodgson et al., 2009; Koek, 2014). Thus, the lower intensity of negative consequences related to drug

Table 1. A summary of age-related differential effects associated with common drugs of abuse

Drugs	Subject	Differential Age-dependent Manifestations	References
Cocaine	Rat	Locomotor sensitization to cocaine occurs more significantly in adults vs adolescent animals.	Collins & Izenwasser, 2002; Frantz et al., 2007
	Rat	Adolescent animals require more extinction trials than adults to extinguish CPP.	Brenhouse & Andersen, 2008
	Rat	Adolescent animals establish CPP at lower doses of cocaine compared to their adult counterparts.	Zakharova et al., 2009
Nicotine	Rat	Nicotine induces CPP in peri-adolescent, but not in adult animals.	Belluzzi et al., 2004; Shram et al., 2006
	Rat	Adult, and not peri-adolescent, animals exhibit avoidance of saccharin when paired with nicotine.	Shram et al., 2006
	Rat	Nicotine does not affect the locomotor response in adolescent animals, while causes significant suppression in adult subjects.	Belluzzi et al., 2004
THC/Cannabinoids	Rat	THC reduces locomotor activity in rats, however, this effect is less potent in adolescent vs adult subjects. Anxiogenic and aversive effects of THC are more potent in adult vs adolescent rats.	Schramm-Sapyta et al., 2007
	Rat	Low doses of THC increase locomotor activity in adolescence and not in adult subjects.	Wiley et al., 2008
	Rat	Adolescent, but not adult, rats that received THC, display higher locomotor responses to cocaine.	Dow-Edwards & Izenwasser, 2012
	Rat	Cannabinoid exposure in adolescent rats (but not adults) results in long-lasting tolerance to future exposure in dopaminergic neurons of the VTA.	*Pistis et al., 2004*
Ethanol	Rat	Animals with adolescent onset of alcohol exposure exhibit better control over alcohol seeking, compared to those with an adult onset profile.	Labots et al., 2018
	Rat	Adolescent rats indicate higher elimination rates and lower blood levels compared to their adult counterparts.	Walker & Ehlers, 2009
	Rat	There is lower and higher sensitivity to the aversive and rewarding effects of alcohol in adolescent vs adult animals, respectively.	Spear, 2011
	Rat	Body weight decreases in aged and adult rats, but not in adolescents following chronic alcohol intake. Rats are more vulnerable to ethanol-induced ataxia, compared to adult and adolescent animals.	Acevedo et al., 2013
	Mouse	Adolescent mice do not show conditioned taste aversion as much as their elder counterparts.	Holstein et al., 2011
	Rat	Adolescent rats are less affected by alcohol-induced hang-over than adults.	Brasser et al., 2002
	Rat	Peri-adolescent rats are less sensitive to the sedative effects of ethanol than adults.	Little et al., 1996
Morphine/ Oxycodone	Mouse, rat	Adolescent male rats self-administer less morphine and oxycodone than adults. Adolescent rats have higher oxycodone-induced dopamine release within the striatum than adults.	Doherty et al., 2009; Zhang et al., 2009
Morphine	Mouse, rat	Adolescent rats exhibit higher morphine-induced locomotor activity and sensitization than adults.	Koek et al., 2012; White & Holtzman, 2005; White et al., 2008
	Mouse, rat	Adolescent mice show less morphine and heroine withdrawal signs than adults.	Doherty & Frantz, 2013; Hodgson et al., 2009; Koek, 2014
	Rat	Adolescent rats self-administer more heroin and show less heroin-seeking behavior than adults	Doherty & Frantz, 2012
	Mouse, rat	Opioid analgesic tolerance develops more rapidly in adolescent rats than adults.	Nozaki et al., 1975; Wang et al., 2005
	Rat	Adolescent, but not adult, morphine-treated rats display higher pain perception, compared to control subjects.	Ghasemi et al., 2019

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Abbreviations: THC: Tetrahydrocannabinol; VTA: Ventral tegmental area; CPP: Conditioned place preference.

abstinence during adolescence may contribute to the development of compulsive drug abuse behavior in teenagers (O'Dell et al., 2006). Some studies have addressed the effects of heroin in different age ranges of rodents. In this regard, heroin withdrawal signs have not been observed in adolescent rats as occur in adults. These mainly include physical signs of withdrawal as well as attenuation of locomotion, food intake, and body mass. However, locomotor sensitization induced by heroin is not significantly affected by age (Doherty & Frantz, 2013). Consistent with this result, adolescent rats have been observed to self-administer more heroin than adults and show less heroin-seeking behavior than adults following drug abstinence (Doherty & Frantz, 2012). Regarding the analgesic effects of opioids, age-related differences are still a matter of controversy, and depending on the method of analgesia assessment, inconsistent/opposing results have been reported. For example, in one study, researchers found that morphine analgesic effect is greater in adult (12-weeks-old) than adolescent (4 or 7-weeks-old) rats (Nozaki et al., 1975). However, another study showed that older mice experienced less morphine analgesic effect than their older counterparts in the tail-flick test (Webster et al., 1976). In addition, this study has reported a slower rate of absorption and longer half-life of morphine following i.p. injection in older animals. However, there seems to be a consensus on the point that opioid analgesic tolerance develops more rapidly in adolescent, rather than adult, animals following repeated drug exposure (Nozaki et al., 1975; Wang et al., 2005). In the context of pain perception, formalin test results have revealed that adolescent rats who received morphine pre-treatment exhibit higher pain-related signs compared to the control (saline-treated) group; however, this result was not observed in morphine-treated adult rats compared to their control counterparts (Ghasemi et al., 2019).

Researchers have also addressed the cellular and molecular mechanisms underlying age-dependent differential responsiveness to opioid drugs. For example, the protein expression and distribution of endogenous opioids (such as preproenkephalin, preproendorphin, preprodynorphin, and prepronociceptin) are related to age (De Vries et al., 1994; Tseng et al., 1995) and expression of opioid receptors also vary among different developmental stages (Hoskins et al., 1998; Volterra et al., 1986). Moreover, expression of arrestin-2 (Gurevich et al., 2004), protein kinase C (Pascale et al., 1998), inhibitory G proteins (Ihnatovych et al., 2002), RGS proteins (Ingi & Aoki, 2002; Wilson et al., 2005), all of which are key molecules mediating opioid receptor activation and desensitization, are affected by age. Finally, another less addressed issue is to reveal whether developmental changes in the pharmacokinetics of opioid drugs may cause differential responsiveness to these drugs when tested at different ages.

3. Conclusion and Future Directions

Nowadays, growing evidence indicates that the human brain undergoes progressive maturational changes critical for survival and promotion of cognitive functions. These include structural and functional changes at the level of neural circuits, neurotransmitter systems, and signaling molecules. As mentioned earlier, such neurobiological changes finally define how the brain responds to a wide variety of stimuli, such as hormones and drugs. During the last decade, numerous studies have demonstrated the growing rate of adolescent substance abuse as an alarming concern in societies. It is now well established that adolescents' brains are more vulnerable than adults to the adverse effects of most drugs and recent evidence indicates that many drug-induced changes in the function of CNS are rather persistent and in some cases, can affect the brain responsiveness to other drugs of abuse even when taken later in life. Therefore, researchers seeking therapeutic strategies to manage substance abuse disorder should first get well acquainted with the age-related disparities associated with the effect of each specific drug. In other words, the brain of an adolescent subject may respond quite differently to the effects of a drug compared to that of an adult individual, even when the drug dose and administration route are the same. Therefore, adopting a similar approach to manage subjects belonging to different age ranges may lead to ineffective or in some cases detrimental outcomes. The present study was conducted to review the most recent experimental evidence demonstrating age-related differences in responsiveness to common drugs of abuse, including cocaine, nicotine, alcohol, and opioid drugs. It should be noted that the current literature lacks in-depth research on the cellular mechanisms underlying the age-related effects of drugs. However, in the case of opioid drugs, the upcoming horizon is more promising, since strong evidence supports age-related changes at the level of receptors and signaling molecules, as discussed earlier. Indeed, future research needs to focus on these mechanistic gaps in CNS and reveal how developmental changes at molecular levels can result in differential behavioral responses to drugs.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization, methodology and writing the original draft: Mohammad Ahmadi-Soleimania and Hamed Salmanzadeh; Conceptualization, review, editing and supervision: Hossein Azizi.

Conflict of interest

The authors declared no conflict of interest.

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