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Nicotine, adolescence, and stress: A review of how stress can modulate the negative consequences of adolescent nicotine abuse

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Abstract

In order to continue the decline of smoking prevalence, it is imperative to identify factors that contribute to the development of nicotine and tobacco addiction, such as adolescent initiation of nicotine use, adolescent stress, and their interaction. This review highlights the biological differences between adolescent and adults in nicotine use and resulting effects, and examines the enduring consequences of adolescent nicotine administration. A review of both clinical and preclinical literature indicates that adolescent, but not adult, nicotine administration leads to increased susceptibility for development of long-lasting impairments in learning and affect. Finally, the role stress plays in normal adolescent development, the deleterious effects stress has on learning and memory, and the negative consequences resulting from the interaction of stress and nicotine during adolescence is reviewed. The review concludes with ways in which future policies could benefit by addressing adolescent stress as a means of reducing adolescent nicotine abuse.

Keywords

Nicotine; adolescence; stress; learning and memory; affect; addiction

1. Introduction

Tobacco use is a leading cause of preventable death and despite the known risks associated with smoking, 18.1% of Americans are every day smokers (Mitka, 2014). According to the Center for Disease Control (CDC), 70% of current smokers want to quit (Mitka, 2014) and 40% of smokers have reported attempts to quit but have failed in the previous year (CDC, 2011). The prevalence of everyday smoking has leveled off at 18.1% of the population after dramatically declining over the last several decades. Thus, it is important to identify

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individual factors that contribute to nicotine addiction, such as stress, and at-risk populations, such as adolescents, in order to continue reducing smoking prevalence rates.

Preclinical research in the last 10 years has established that adults and adolescents respond to nicotine quite differently and implicates adolescence as a critical period for developing enduring effects caused by nicotine exposure (Torres et al., 2008; Slotkin et al., 2008). Examining the effect of nicotine in adolescence is especially important because 90% of adult smokers initiate smoking prior to turning 20 (United States Department of Health and Human Services, 1994) and the younger the age of smoking initiation, the more likely an individual will become dependent on tobacco in adulthood. Younger initiation of smoking is also associated with greater severity of nicotine dependence, which in turn, decreases the likelihood of quitting (Chassin et al. 1990; Colby et al. 2000). Furthermore, the CDC has recently reported that the use of e-cigarettes among adolescents nearly tripled from 2013 to 2014 after nearly doubling from 2011 to 2012 (CDC, 2016). This is incredibly alarming since 75% of those reporting e-cigarette use also smoked conventional cigarettes (CDC, 2016) and indicates adolescent nicotine abuse remains a problem.

Identifying at-risk factors for nicotine and tobacco use during adolescence is essential for the continued reduction of tobacco-related health care costs and tobacco-related deaths in future generations. The 2012 Surgeon General's report stated that if youth smoking prevention efforts had been sustained between 1997 and 2003, we could have nearly 3 million less young smokers. This review will explore the contributions of stress to nicotine dependence and examine neurobiological factors that make adolescence such a vulnerable time for smoking initiation. In addition, the long-term consequences of adolescent nicotine exposure will be explored. This review will also focus on the effects of adolescent stress on affect and cognition and how this may contribute to smoking prevalence rates. The review will conclude with suggestions to improve the current approach to youth tobacco use prevention based on findings from the discussed preclinical research.

1.1 Stress Overview

A brief review of the stress response system, including the effects of glucocorticoids on learning and memory, is necessary before discussing the relationship between stress and nicotine addiction. Stress can be defined as any threat to homeostasis and the subsequent stress response refers to changes in the body's hormone signaling cascade in an effort to restore homeostasis after exposure to noxious stimuli (McEwen, 2005; Selye, 1976). The response relies on the activation of the hypothalamus-pituitary-adrenal (HPA) axis. The cells of the paraventricular nucleus of the hypothalamus are activated during stressful situations and send projections to the median eminence of the hypothalamus to secrete corticotropin-releasing factor (CRF) and vasopressin (de Kloet et al., 2005). In turn, CRF activates the anterior pituitary gland by binding to CRF receptors (Bale, 2005; Van Den Eede et al., 2005). Once CRF receptors are activated, the pituitary gland then secretes adrenocorticotropic hormone (ACTH) into the bloodstream. When ACTH reaches the adrenal cortex, it facilitates the production and release of glucocorticoid hormones into systemic circulation (Romero, Levine, & Sapolsky, 1995). Glucocorticoids (GCs) can also pass through the blood-brain-barrier and cease the activity of the HPA axis once they bind to

either glucocorticoid receptors (GRs) or mineralcorticoid receptors (MRs) in what is known as a negative feedback mechanism (Reviewed by Finsterwald & Albertini, 2013). For example, binding of GCs within the hippocampus results in the inhibition of CRF production within the hypothalamus (Radley & Sawchenko, 2011). This implicates the hippocampus as both a modulator of the stress response and an area vulnerable to excessive GC signaling. Thus, the brain regulates the initial production of stress hormones as well as the termination of the stress response.

1.2 Nicotine Overview

A brief review on nicotine's mechanism of action, including the effects of nicotine on learning and memory and the involvement of different receptor configurations, is necessary before discussing the relationship between stress and nicotine. Nicotine acts by binding to nicotinic acetylcholine receptors (nAChRs), which are pentamaric ligand-gated receptors, and located throughout the central and peripheral nervous system (Rosencrans & Karan, 1993). The nicotinic receptor configuration consists of 5 subunits that can either be αs or βs. Differences in nicotine binding allows classification of receptors into high affinity and low affinity nAChRs, which have differential impacts on learning and memory (Marks et al., 1986; Davis & Gould, 2009).

Acute nicotine has been shown to enhance hippocampal-dependent learning (Gould & Higgins, 2003; Gould & Wehner, 1999), such as contextual fear conditioning, where an intact hippocampus is necessary to learn the association between a context paired with an aversive stimuli such as a mild foot shock (Kim & Fanselow; 1992; Logue et al., 1997). Further, withdrawal from chronic nicotine impairs contextual fear conditioning (André et al., 2008; Davis et al., 2005; Davis & Gould, 2009). Nicotinic receptors that bind nicotine with a high affinity, which include the α4β2 nAChRs and make up 99% of high affinity receptors in the hippocampus (Perry et al., 2002), are required for nicotine enhancement of learning. Infusions of dihydro-beta-erythoidine (DHβE), an α4β2 nAChR antagonist, into the hippocampus blocked the enhancement of systemic nicotine (Davis & Gould, 2006). On the other hand, α7 nAChRs bind nicotine with low affinity and quickly desensitize (Marks et al., 1986), but do not contribute to acute cognitive enhancing effects of nicotine. Infusions of the α7 antagonist methyllycaconitine (MLA) did not block the acute nicotine enhancement of contextual fear conditioning (Davis & Gould, 2006). Further, withdrawal from chronic nicotine leads to impairments of hippocampal-dependent learning tasks. This is likely due to an upregulation in α4β2 nAChRs, as cognitive deficits abate over time but the duration of deficits parallels the upregulation of α4β2 nAChRs (Gould et al., 2014). Thus, the ability of nicotine to alter cognition is likely mediated through high-affinity α4β2 nAChRs. It is important to keep these distinctions in mind when discussing adolescent nicotine exposure. Nicotine treatment during adolescence, but not adulthood, leads to long-lasting upregulation of α4β2 nAChRs throughout the brain (Trauth et al., 1999). This indicates that adolescence may be a particularly vulnerable time to produce long-lasting alterations in cognition as a result of nicotine exposure, as reviewed in depth in later sections.

2. STRESS AND NICOTINE

Stress and nicotine share a very tumultuous relationship. Stress reduction is often cited as a reason for continuing to smoke and the action of nicotine on the stress response system is quite complex (Metcalfe, et al., 2003). Acute nicotine injections elevate CORT, much like elevations observed after acute stress (Balfour, Khullar, & Longden, 1975). In addition, repeated administration of nicotine leads to an altered stress response, such that chronic nicotine treatment alters the ability of CORT levels to habituate following chronic restraint stress. Habituation is an attenuation of expected elevations in CORT levels in response to repeated presentations of a stressor and is considered an adaptive response to chronic stress (Benwell and Balfour, 1982). Repeated nicotine also augments both behavioral responses to stress (Faraday et al., 1999) and CORT concentrations following an acute stressor (Chen et al., 2008). Thus, although chronic nicotine administration creates a hyper-responsiveness in the stress system, the ramifications of this remain unclear. In summary, acute nicotine increases CORT concentrations while chronic nicotine disrupts the stress response by both altering acute stress response and abolishing the adaptive response to chronic stress. The following section reviews both clinical and preclinical studies on the interactive effects of stress and nicotine on behavior.

2.1 Clinical studies

In humans, stress is often a factor in smoking prevalence, with smokers reporting more cigarettes consumed when they feel stressed (Metcalfe et al., 2003). When faced with an acute stressor in a laboratory setting, smokers were less likely to resist smoking, smoked more intensely, and also reported greater satisfaction from smoking compared to smokers in a non-stressed situation (Mckee et al., 2011). Additionally, individuals who experience a disproportionate amount of stress compared to the general population have higher rates of smoking. For example, unemployed laborers in Italy, a group that faces more daily stressors than the general population, have 3 times the odds of smoking compared to employed professionals and those in upper management positions (Vogli & Santinello, 2005). In US military personnel deployed to Kuwait, nearly 46% of 402 military service members reported daily use of tobacco products. This is over double the rate of smoking in the general population and stress remained one of the often cited reasons for engaging in smoking (Dinicola et al., 2013). Given these results, it is clear that experiencing stress compounds the issue of eliminating smoking behaviors as many smokers report stress and anxiety reduction as one of the main reasons for engaging in smoking behavior. Thus, a higher level of stress may reduce successful tobacco cessation by increasing the odds of smoking and increasing the amount of tobacco consumed.

2.2 Preclinical studies

One way stress can impact smoking prevalence is by facilitating reinstatement of nicotine seeking behaviors that were previously extinguished. For example, Long-Evans rats were trained to self-administer nicotine and subsequently underwent extinction of that learned response. Once rats successfully completed extinction training, they were subjected to intermittent foot shock stress and then tested for reinstatement of nicotine-seeking measured by increased lever pressing behaviors. Rats subjected to foot shock stress had higher rates of

lever pressing on the bar previously associated with nicotine administration compared to non-stressed controls (Buczek et al, 1999; Zislis et al., 2007). Interestingly, foot shock stress did not induce reinstatement of sucrose intake, indicating stress reinstatement is not a universal effect on rewarding stimuli, but specific to drugs of abuse, or at least nicotine. Further, this effect was attenuated when Wistar rats were administered a CRF antagonist 15 minutes prior to the foot shock, effectively blocking the activation of the stress system (Zislis et al, 2007). Thus, stress reinstates nicotine-seeking behaviors through direct activation of the stress response system. The mechanism by which stress facilitates nicotine reinstatement has not been fully explored but could be due to the interaction of stress and nicotine on the mesolimbic cortical system.

Aside from stress facilitating nicotine-seeking behavior and thereby increasing the likelihood of continued tobacco use, another possibility is that stress alters the physiological and behavioral responses to nicotine, thereby increasing nicotine's addictive liability. One way to assess the interaction of stress and nicotine on behavior is by observing cross-sensitization of stress to nicotine (Robinson & Berridge, 2001). Cross-sensitization can occur with stress and nicotine, where prior stress augments nicotine-induced locomotor activity during a nicotine challenge (Kita et al., 1999). In studies examining behavioral sensitization after repeated nicotine injections, it was found that stress hormones are necessary for the expression of nicotine sensitization. Sprague-Dawley rats that underwent an adrenalectomy did not display the expected increases in locomotor activity after repeated nicotine injections and this effect was reversed by administering corticosterone to adrenalectomized rats (Johnson et al., 1995). Therefore, stress can augment the behavioral responses to nicotine thereby increasing the vulnerability for developing addiction. In contrast, stress attenuated the rewarding properties of nicotine and this effect was reversed upon the administration of a CORT synthesis inhibitor and a glucocorticoid receptor (GR) antagonist indicating that the attenuated DA response is mediated through CORT (Enrico et al., 2013). This may explain why stress elevates smoking in humans, as increased smoking may reflect reduced reward and satisfaction, despite self-reported elevations in smoking satisfaction following stress. Thus, the alterations caused by stress likely increase the probability of continued tobacco use by simultaneously increasing behavioral responses associated with the neural underpinnings of sensitization while also attenuating the rewarding properties of nicotine.

3. ADOLESCENT NICOTINE

Despite the connection between stress and initiation and continuation of nicotine use during adolescence there is a paucity of research examining the impact of both nicotine and stress exposure during adolescence on cognition and mental health. Therefore, the next sections are devoted to age-dependent effects of nicotine exposure on brain and behavior, the interactive effects of stress and nicotine exposure during adolescence on these processes, and how this interaction may contribute to smoking initiation and maintenance.

3.1 Adolescent Overview and Clinical Studies

Within the last 100 years, adolescence has emerged as a focal point in psychological research. Adolescence was first described as a period of storm and stress in 1904 by Granville Stanley Hall, widely regarded as the founder of adolescent psychology. Thus, adolescence was identified as a period of dynamic transition and unique turmoil that was previously unstudied (Alderman, Rieder, & Cohen, 2003). Whereas research in the mid-20th century highlighted adolescent rebellion as a normal and pervasive behavior, research in the last 25 years has emphasized a neurobiological approach and noted differences in brain structure and function between adolescents and adults. Regardless of focus on behavior or physiology, a common theme emerges suggesting adolescence is a period of development that transitions an individual from childhood to adulthood.

While adolescence has no discrete start and end points, these age ranges encompass gradual changes in brain development that occur and may contribute to adolescent-typical behaviors (Spear, 2000; Willoughby, 2013). There is some debate on the age range that defines adolescence, researchers studying this period have often defined it in humans as being between 12–20 years, occasionally including ages up to 25 years of age, and in rodent models as between post-natal days 21 and 60 (P21–60) (for in depth review see Spear, 2000 and Laviola et al., 2003). This range of post-natal days can further be divided into early adolescence (P21–34), middle adolescence or periadolescence, (P34–46), and late adolescence (P46–59) that also reflect shifts in brain development, sexual maturity, and behavior throughout the adolescent period (Laviola et al., 2003; Spear and Brake, 1983). Of note, rodents in middle adolescence, or periadolescence, which includes the days leading up to puberty (around P40) and a few days following (Spear and Brake, 1983), have demonstrated increased impulsivity (Adriani & Laviola, 2003; Dormeus-Fitzwater et al., 2012) and increased risk-taking (Macri et al., 2002) which correspond to behaviors among human adolescents that make this period of development especially vulnerable to drug initiation and a good candidate to study the long-term effects of adolescent drug use (see Laviola et al., 2003 for in depth review).

A consistent finding in adolescent clinical research regarding brain development is a decrease in gray matter followed by an increase in white matter, particularly in the frontal and parietal cortices (Blakemore, 2012; Giedd, 1999; Gogtay, 2006; Perrin et al., 2008; Casey, Getz, & Galvan, 2008). These changes, including neural restructuring and maturation of cognitive control, may underlie some of the age-related behaviors commonly reported in adolescents. For example, adolescence is a time of increased risk taking, impulsivity, sensation seeking, and increased reward sensitivity (Spear, 2000; Steinberg, 2010; Willoughby et al., 2013). One of the prevailing developmental theories posits that risky behavior in adolescents is due to a maturing limbic system, responsible for emotional and reward processing, coupled with an immature prefrontal cortex, the area of the brain responsible for executive function and inhibitory control (Casey et al., 2008; Ernst, Pine, Hardin, 2006). While these behaviors may seem detrimental, they are well-known characteristics of adolescence and can be observed in both clinical and animal models. However, the characteristic increase in these domains underlies the vulnerability to drug initiation during adolescence.

Global changes in gray and white matter cannot account for all common traits of adolescents. While functional imaging studies have elaborated on the maturation of the adolescent brain, and are consistent with behavioral studies in both humans and animals, it is also important to note the changes that occur at the molecular level. These behavioral differences may be related to continued maturation of several neurotransmitter systems during the adolescent period. Two of these systems are the dopaminergic and cholinergic systems. Respectively, these systems play a role in reward processing (Wise & Rompre, 1989) and learning and memory (Gold, 2003). Given the wide-scale brain and behavior changes exhibited throughout adolescence, examining the effect of nicotine in adolescence is especially important because 90% of adult smokers initiate smoking in adolescence, and the younger an individual is when they begin smoking, the greater the increased risk for tobacco dependence later in life (Chen & Millar, 1998).

3.2 Preclinical studies

Preclinical research in the last 10 years has established that adults and adolescents respond to acute nicotine and chronic nicotine quite differently. The ongoing maturation of the dopaminergic and cholinergic systems likely contributes to the commonly reported increase in nicotine reward and augmented pro-cognitive effects that occur during adolescence. For example, acute nicotine during adolescence results in a larger release of dopamine in the limbic system (Azam et al., 2007; Shearman et al., 2008) and acute nicotine also enhances contextual fear learning at lower doses in adolescent C57BL/6J mice compared to adult mice (Portugal et al., 2012). In addition, adolescent rodents show differences in anxiety-like behaviors and also demonstrated enhanced reward to nicotine when compared to adults (Elliot et al., 2004; Spear, 2000; Torres et al., 2008). The increased sensitivity to nicotine's positive effects, coupled with increased risk taking and impulsivity, partly explains why adolescence is a vulnerable time for smoking initiation. Additionally, adolescence represents a critical period for the enduring effects caused by nicotine exposure, as adolescent nicotine exposure disrupts adult learning but similar nicotine treatments in adults do not produce long-lasting impairments in learning and memory later in adulthood (Smith et al., 2006; Portugal et al., 2012). Thus, an examination of the differences between adolescents and adults in response to nicotine, particularly on measures associated with nicotine addiction and mental health (i.e. affect and cognition), is crucial to develop effective policies regarding youth smoking prevention and reduction of smoking.

3.2.1 Nicotine and anxiety—Elevated anxiety increases the risk for nicotine dependence and smokers often cite alleviated anxiety as a reason to continue smoking (Breslau, Kilbey, & Andreski, 1991; McCabe et al., 2004; Watson et al., 2012). Studies examining the effects of nicotine in adult rodents on anxiety-like behaviors have reported inconsistent findings. Some studies report that nicotine is anxiolytic while others indicate nicotine is anxiogenic. Brioni et al. (1993) reported that low doses of nicotine increased time spent in the open arms of the elevated-plus maze (EPM), an assessment of anxiety-like behaviors in rodents (Wall & Messier, 2001), in adult male CD-1 mice; suggesting an anxiolytic effect. In another study using adult Swiss mice, acute administration of nicotine resulted in anxiogenic effects in the EPM at 5 minutes and 30 minutes afterwards (Biala & Budzynska, 2006). Furthermore, when assessing anxiety in adult Lister rats in the social interaction test, where rodents

approach an unfamiliar conspecific, nicotine had a bimodal effect (File, Kenny, Ouagazzal, 1998). Low doses of nicotine (0.01, 0.1 mg/kg) facilitated social interaction whereas high doses decreased social interaction (0.5, 1.0mg/kg). Given these disparate findings, it is important to consider the dose of nicotine when analyzing nicotine's effect on anxiety-like behavior, as low doses may be anxyiolitic and high doses may be anxiogenic. Furthermore, that nicotine may cause both an anxyiolitic and an anxiogenic effect in rodent models is consistent with the human literature (Brown et al., 2001).

Like in adults, adolescent nicotine exposure can result in anxiogenic or anxyiolitic effects. For example, Kupferschmidt et al. (2010) showed that mid-adolescent Long-Evans rats (P33–37) treated with acute nicotine spent less time in the open arms of the EPM, compared to adult rats (P65–69) treated with acute nicotine. However, in the same study, there were no differences between nicotine treated adolescent and adult rats when comparing behaviors in a light-dark box assay. In another study, there were no differences in anxiety-like behaviors using time spent in the center of an open field arena as the dependent measure (Prut & Belzung, 2003) following a single nicotine injection when comparing early adolescent (p28), late adolescent (p45) and adult (p80) Long-Evans rats (Falco et al., 2014). In contrast, Elliot and colleagues (2004) demonstrated that repeated injections of nicotine in adolescent Sprague-Dawley rats (P25–30) and adult rats (P55–60) resulted in an age- and sex-dependent effect on anxiety. Adolescent males showed anxiolytic behaviors, with increased percentages of time in the open arms, whereas adolescent females, and adult males and females, showed anxiogenic effects. Although it should be noted that the adult range used by Elliot in colleagues could correspond to late adolescence and perhaps there would be a difference among the female rats if an older age was used. When the social interaction test was used as measure of anxiety in Lister hooded rats, adolescent females displayed more time interacting with a novel conspecific after nicotine administration compared to males, indicating anxiolytic effects in females but not males (Cheeta et al., 2001). It appears that adolescent rodents have differential effects of anxiety based on the age when nicotine is administered and this effect can also be moderated by both sex hormones and type of anxiety task used. For example, in the study conducted by Kupferschmidt et al. (2010), rats that received acute nicotine during mid to late adolescence displayed more anxiogenic effects compared to adults, whereas Elliot et al. (2004) administered repeated nicotine at early adolescence and found anxiolytic effects in males but not females in the EPM. Further, differences in anxiety were found when using the EPM and social interaction tasks but not light-dark box or open field assays which may suggest these tasks probe different types of anxiety. Regardless of sex or task, the timing of nicotine administration in adolescence (i.e. early versus late), as well as acute versus repeated administration, can have a profound effect on the emergence of anxiety-like behavior. These effects could also explain why smoking initiation occurs at younger ages, as nicotine exposure during early adolescence results in anxiety reduction (File et al., 1998) but could foster dependence later in life.

3.2.2 Nicotine Reward and Aversion—Adolescents also have a propensity to self-administer more nicotine compared to adults, indicating they may find the drug more rewarding. For example, adolescent female Lewis rats (P40–42) were given 23-hour access to nicotine for a period of 10 days and, compared to adult females, adolescent females

acquired self-administration at a much faster rate and also had higher total number of infusions (Chen, Matta, & Sharp, 2007). Additionally, Levin and colleagues demonstrated similar findings, in male and female adolescent Sprague-Dawley rats (Levin et al., 2007; Levin et al., 2003). In both studies, adolescent rodents (p32) demonstrated higher levels of nicotine self-administration compared to adult animals (p60). Adriani et al. (2002) compared self-administration via oral consumption in CD-1 mice across early adolescence (p24-p35), middle adolescence (p37-p48) and late adolescence (p50–61). Early adolescent mice showed greater oral consumption compared to late adolescents and adults over a 10 day period and also showed greater compensatory intake when the dose of nicotine was lowered on days 11 and 12. On the other hand, late adolescence showed a slight aversion to oral nicotine consumption, suggesting adolescents find nicotine less aversive. Further, the differences observed by Adriani et al. were not due to nicotine metabolism, as cotinine levels were consistent across the age groups (Adriani et al., 2002). Taken together, these findings suggest that early adolescents are particularly sensitive to the reinforcing properties of nicotine compared to adults. This also suggests at least one way that adolescent nicotine exposure increases the risk of dependency, as adolescents show increased sensitivity to reinforcement and reduced aversive symptoms of nicotine treatment.

As mentioned before, adolescents find nicotine more rewarding than their adult counterparts. One way to assess drug reward is through conditioned place preference (CPP) where animals are conditioned to prefer a drug-paired side of a 2- or 3-compartment chamber. No drugs are administered on testing days and time spent in the prior drug-paired side indicates higher rewarding properties of the drug (Tzschentke, 1998). Kota et al. (2011) examined differences between adolescent (P28–36) and adult (P70) ICR mice using three drug pairings at 5 different doses. It was found that adolescent mice conditioned with nicotine acquired CPP at 0.05mg/kg, 0.1mg/kg, and 0.5 mg/kg compared to saline controls. On the other hand, adult animals demonstrated CPP at only the 0.5mg/kg dose. These findings indicate that adolescent animals are more sensitive to the rewarding properties of nicotine at lower doses compared to adults. In addition, Belluzzi et al. (2004) found that early adolescent Sprague-Dawley rats (p28) would acquire CPP after a single injection of nicotine (0.5mg/kg, s.c.). Late adolescent (p38) and adult (p90) rats did not develop CPP after a single injection, and also failed to establish CPP after 4 drug pairings. This also suggests that early adolescence is a period of increased sensitivity to nicotine reward. Although another interpretation could be that nicotine reduced anxiety, which could make the nicotine paired side preferred. Additionally, Torres et al. (2008) showed similar age-dependent shifts in nicotine CPP dose-response. Specifically, adolescent Wistar rats displayed CPP at a wider range of doses and displayed more robust difference scores compared to adult animals. Interestingly, acute administration of nicotine in adolescent rats (p35) increased *c-fos* expression in the nucleus accumbens and VTA compared to both age-matched saline controls and nicotine-treated adults (Shram, Funk, Li, and Le, 2007). Since *c-fos* is a marker of neuronal activity, increases in activity in areas associated with reward likely represent an increase in sensitivity to nicotine reward. Due to the fact that adolescents show CPP at lower doses and across a wider range of doses than adults, and display more robust nicotine preference, it suggests that adolescence is a period of enhanced sensitivity to nicotine's rewarding properties, and

this could contribute to the increased vulnerability for initiation of nicotine use at this time period.

Decreased aversive symptoms during nicotine withdrawal in adolescence may further contribute to nicotine addiction. For example, administering nicotine to adolescent Sprague-Dawley rats (p28) and adult rats (p60) via osmotic mini pump for seven days and then precipitating withdrawal via mecamylamine, a non-selective and non-competitive antagonist of nAChRs (Bacher et al., 2009), resulted in age-dependent differences in withdrawal-induced anxiogenesis (Wilmouth and Spear, 2006). While adult animals showed increases in startle amplitude, an indicator of increased anxiety, and decreased time spent in the open arms during EPM, adolescents did not. Thus, the anxiogenic effect of nicotine withdrawal was absent in adolescence. Further, somatic signs of withdrawal were greatly reduced in Wistar adolescent rats compared to adults (O'Dell et al., 2004). In a follow up study, O'Dell et al. (2007) found that adolescents showed no conditioned place aversion during precipitated withdrawal, whereas adults did. This was not attributed to age-dependent differences in aversion learning, as lithium chloride produced conditioned place aversion in both adult and adolescent rats (O'Dell et al., 2007). In summary, adolescents display reduced withdrawal-related symptoms compared to adults and this may contribute to increased vulnerability for nicotine dependence during adolescence, as nicotine reward is augmented and aversion is reduced.

3.2.3 Nicotine and Cognition—Adolescents also demonstrate enhanced sensitivity to the acute effects of nicotine on cognition and lesser impact of nicotine withdrawal on cognition. Early adolescent (p23), late adolescent (p38), and adult (p54) C57BL/6J mice were given a range of acute doses during training and testing for contextual fear conditioning (Portugal et al., 2012). Early adolescent mice showed enhanced learning at all doses of nicotine (0.045, 0.09, 0.18 mg/kg), late adolescent mice showed enhancement at the two highest doses and adults showed enhancement at the two lowest doses. This suggests that early adolescent animals are especially sensitive to the acute cognitive enhancing properties of nicotine while the dose response is shifted in late adolescence compared to adult mice receiving the same doses of nicotine. The finding that the effects of acute nicotine are not only different between adolescents and adult mice but also between different aged adolescent mice suggest that there are multiple stages of cholinergic system development and that adolescence is not a homogenous developmental period. Further, when early adolescent, late adolescent, and adult mice were given varying doses of chronic nicotine (3, 6.3, 12 mg/kg/day) and trained and tested in fear conditioning, it was apparent that the early adolescent brain was affected differently by chronic nicotine. Specifically, while late adolescent and adult animals developed tolerance for the effects of chronic nicotine on learning early adolescent mice showed enhanced learning with the highest chronic dose. This effect was not due to increases in anxiety or changes in locomotion as freezing behaviors during baseline measures were unaffected (Portugal et al., 2012) and in another study early adolescent Sprague-Dawley rats were particularly resistant to the hypolocomotor effects of nicotine (Belluzzi et al., 2004). Finally, withdrawal from chronic nicotine produced deficits in adult mice at the two highest doses, in late adolescence at all doses, and only in the highest dose for early adolescence. It is possible that this may be due to differences in the nicotinic

acetylcholine receptor system across the developmental span (Portugal et al., 2012; Doura et al., 2008). Thus, it appears that early adolescence is associated with enhanced sensitivity to the acute pro-cognitive effects of nicotine and decreased aversive symptoms during withdrawal from nicotine compared to adults. On the other hand, withdrawal-related deficits begin to emerge in late adolescence at doses that did not elicit withdrawal deficits in younger rats and mice. Taken together, it is possible that continued nicotine use during the transition from early adolescence to late adolescence represents the ontogeny of developing nicotine dependence, as cognitive impairments, which were observed at all doses in mid-adolescent rodents, are often cited as a reason to continue smoking (Parrott & Roberts, 1991; Cole et al., 2010).

Overall, adolescence is a vulnerable time for the initiation of tobacco use and also represents a critical window for developing nicotine dependence later in life, as well as enhancing drug cue-related learning in adulthood (Mojica, Belluzzi, & Leslie, 2014). Early adolescence seems to be an especially vulnerable time as adolescent animals display anxiolytic responses to acute nicotine, acquire nicotine-CPP after a single administration of nicotine, and show reduced withdrawal symptoms compared to adults. Thus, nicotine reward is enhanced and aversion is attenuated, which could provide a basis for continued tobacco use throughout adolescence. This is problematic because this could lead to the emergence of dependence on nicotine and continued use during adulthood. Future research should focus on ways to attenuate nicotine reward in adolescence. This should also be coupled with developing cessation treatment programs geared toward adolescents that may not emphasize symptoms of nicotine withdrawal, as the previous preclinical research suggests withdrawal symptoms may not be a motivator in continued tobacco use for adolescence as it is in adults (O'Dell, 2009), and instead focus on redirecting and eliminating smoking related behaviors to reduce the likelihood of tobacco use in adulthood.

3.2.4 Enduring Effects of Adolescent Nicotine Exposure—Adolescence represents a time of enhanced vulnerability to nicotine use and addiction. Part of this enhanced vulnerability can be explained by increased sensitivity to nicotine's rewarding properties coupled with a decreased sensitivity to the aversive effects of nicotine. However, it is important to examine other factors that can contribute to the increased addiction liability of nicotine when given during adolescence. Thus, the next section will review long-lasting changes as a result of adolescent nicotine exposure including effects on adult anxiety, persistent changes in cognition, and long-term changes in structures that support reward processing and learning and memory,

3.2.4.1 Enduring effects: Anxiety: Adolescent nicotine treatment can induce anxiogenesis in adulthood. This indicates that nicotine during adolescence leads to changes in behavior that can be observed well after drug administration ends. Smith et al. (2006) examined the effect of chronic nicotine administration during adolescence and found increased anxiety in Long-Evans rats tested in an open field assay in adulthood. The increases in anxiety in adult rats were due to nicotine exposure during adolescence, as nicotine was not administered during testing in adulthood. Thus, nicotine exposure during adolescence caused persistent increases in adult anxiety. Further, when adolescent (p31–36) Sprague-Dawley rats were

treated chronically with nicotine they demonstrated increased anxiety-like behaviors in an open field test, indicated by less time spent in the center and also decreased food intake in a modified version of the open field (Slawecki et al., 2003). While the biological mechanism of this remains unstudied, increases in adult anxiety could contribute to the enhanced risk of nicotine dependence following nicotine use in adolescence, as increased anxiety levels are a risk factor for nicotine abuse (McCabe et al., 2004).

3.2.4.2 Enduring effects: Reward: Adolescent nicotine alters the reinforcing efficacy of nicotine in adulthood, which could also contribute to increased risk of dependence later in life. Specifically, adolescent nicotine exposure enhances nicotine intake in adulthood and alters adult reward processing. For example, Sprague-Dawley rats that began self-administering nicotine in adolescence self-administered higher amounts of nicotine in adulthood compared to animals that began the self-administration paradigm in adulthood (Levin et al., 2003). Higher self-administration rates indicate either a reduced efficacy of the drug or increased reward value, but this was not directly tested. Other published work suggests increased nicotine self-administration during adulthood following adolescent nicotine pretreatment, but not post-adolescent pretreatment, reflects more sensitivity to the reinforcing and motivational properties of nicotine (Adriani et al., 2003). Repeated nicotine injections over the course of 10 days in adolescent (P34–43) and adult (P60–69) Sprague Dawley rats resulted in increased drug intake during self-administration acquisition and a higher rate of responding across a wider range of rations in a progressive-ratio (PR) schedule of reinforcement in adult rats pretreated with nicotine during adolescence compared to rats pretreated during post-adolescence. In self-administration models, a progressive-ratio schedule increases the number of responses needed to receive a drug infusion and this method provides a way to examine the motivational aspects of a drug (Arnold & Roberts, 1997; Piazza et al., 2000). Thus, while Levin et al. (2003) used a fixed-ratio (FR) schedule where each response resulted in an infusion of nicotine, Adriani et al. (2003) used a PR schedule of reinforcement which was able to parse out changes in nicotine reinforcement efficacy in adulthood following adolescent nicotine pretreatment. Further, Adriani et al. (2003) also reported increased expression in α5, α6, and β2 subunits of the nAChRs. This is an important finding as α5 and α6 subunits are found exclusively in DA containing neurons and facilitate dopaminergic signaling (Exley et al., 2012; Klink et al., 2001) and β2 subunits facilitates dopaminergic release following nicotine exposure (Exley et al., 2012). These studies demonstrate that nicotine exposure during adolescence, but not later in development, either through self-administration (Levin et al., 2003) or repeated injections (Adriani et al., 2003), caused higher levels of self-administration in adulthood that were driven by increased sensitivity to the reinforcing properties of nicotine and are likely due to changes in altered dopaminergic signaling. It is clear that nicotine self-administration that started in adolescence led to a greater amount of the drug consumed, which could translate into increased risk for nicotine dependence.

Adolescent nicotine exposure can also alter reward saliency of subsequent nicotine administration in adulthood (Adriani et al., 2006). Adolescent Sprague-Dawley rats (P34–43) pre-exposed to 10 days of nicotine injections were more sensitive to the rewarding properties of nicotine in adulthood. When the rats were tested 5 weeks later, both a low dose

(0.3mg/kg) and a high dose (0.6mg/kg) of nicotine led to the establishment of nicotine-CPP. Conversely, animals that were pretreated with nicotine in adulthood (P60–69) failed to develop CPP at the low dose of nicotine but were able to establish CPP with the higher dose. Further, adult rats pretreated with saline established CPP with the low dose and high dose of nicotine, suggesting that pre-exposure to nicotine in adulthood actually diminishes the rewarding properties of subsequent nicotine. It appears that nicotine pretreatment during adolescence versus after adolescence results in different reward responses to nicotine in adulthood. Interestingly, it has been reported that low-dose adolescent nicotine treatment increased the reward of subsequent cocaine administered during adulthood, indicating the reward altering effects of adolescent nicotine extend to other psychostimulants (McQuown, Belluzzi, & Leslie, 2007). This suggests that adolescent pre-exposure to nicotine can increase the addictive properties of subsequent nicotine and other drugs of abuse.

3.2.4.3 Enduring effects: Cognition: Adolescent nicotine exposure produces long-term changes in cognitive processes. For instance, adolescent nicotine exposure altered both the acquisition and extinction of cued learning and the underlying neural structures. Briefly, acquisition refers to the ability to form an association between an auditory cue and a mild foot shock, measured by higher levels of freezing when the cue is presented in the absence of the shock, and extinction refers to reductions in freezing behaviors after several presentations of the cue in the absence of the shock (Maren, 2011; Quirk & Mueller, 2007). Smith et al. (2006) administered chronic nicotine (1mg/kg or 2mg/kg) for 15 days in adolescent (P28–42) or adult (P85–99) Long-Evans rats and then 1 month following nicotine cessation tested them in cued fear conditioning. Rats treated with 1mg/kg of nicotine in adolescence showed enhanced acquisition of the cue-shock association compared to controls and failed to extinguish this learned response. The superior acquisition in conjunction with the failure to extinguish may be related to increased apical dendrites in the basolateral amygdala, a structure necessary for cued fear learning, observed twenty days following chronic nicotine exposure in adolescent Sprague-Dawley rats (Bergstrom et al., 2010). Failure to extinguish previously learned memories as a result of adolescent nicotine exposure suggests that adolescent nicotine treatments can interfere with normal learning and memory.

Changes in cue acquisition and extinction are not the only long-term behavioral effects that arise following adolescent nicotine treatment. Chronic administration of nicotine during adolescence leads to lasting changes in hippocampus-dependent learning tasks in adulthood. Specifically, adult Sprague-Dawley rats that were administered chronic nicotine (3.0mg/kg) during adolescence (P28–42) showed deficits in lick suppression in a context paired with a shock (Spaeth et al., 2010). Unfortunately, it is difficult to determine if this effect was age-dependent as adult rats treated with nicotine were not used as controls. However, when examining contextual fear conditioning in C57BL/6J mice, it is apparent that adult mice treated chronically with nicotine during adolescence displayed learning deficits that were not seen when chronic nicotine treatment began in adulthood (Portugal et al., 2012). Early adolescent mice (p23), late adolescent mice (p38), and adult (p54) mice were administered nicotine (8.8 and 12 mg/kg) for a period of 12 days. Once nicotine administration terminated, all mice underwent a thirty-day washout period and were then trained and tested

in contextual fear conditioning. While adult mice that received nicotine during early and late adolescence displayed deficits in contextual fear, adult mice that received nicotine during adulthood and were trained 30 days later did not show learning deficits. Further, cued learning was unaffected in all age conditions. As contextual fear conditioning is hippocampus-dependent (Logue et al., 1997; Kim and Fanselow 1992; Phillips & LeDoux, 1992), this suggests that hippocampal function is especially vulnerable to adolescent nicotine exposure.

3.2.4.4 Enduring effects: Molecular changes: In addition to enduring effects on behavioral measures of learning and memory, adolescent nicotine treatment leads to persistent cellular and molecular changes in the hippocampus and medial prefrontal cortex (mPFC). Of particular importance, chronic adolescent nicotine treatment resulted in an upregulation of nAChRs that lasted 4 weeks after cessation of nicotine treatment (Trauth et al., 1999). Adolescent (p30) and adult Sprague-Dawley rats were treated chronically with nicotine and at the end of the treatment adolescents showed global upregulation of nAChRs while adult upregulation was limited to the cortex and hippocampus. However, only rats treated as adolescents showed upregulation 4 weeks after the end of nicotine treatment. Interestingly, this long-term effect was limited to the cortex and hippocampus rather than the same global pattern of upregulation seen at the end of adolescent nicotine treatment. This further suggests that areas that support learning and memory are particularly vulnerable to the effects of adolescent nicotine treatment. In another study by Trauth and colleagues, the same treatment protocol in adolescent rats resulted in reductions in ChAT activity in the midbrain and reductions in the high-affinity choline transporter in the hippocampus, suggesting a decrease in acetylcholinergic activity following adolescent nicotine treatment (Trauth et al., 2000). Adolescent nicotine treatment also leads to long-lasting alterations in the mPFC such that metabolic glutamate receptors-2 (mGluR2) were reduced 5 weeks following the cessation of adolescent nicotine treatment in Wistar rats; this corresponded with worse performance in a sustained attention task (Counotte et al., 2009; Counotte et al., 2011). Thus, adolescent nicotine treatment leads to enduring alterations in the hippocampus and mPFC that parallel the long-lasting deficits in learning and memory.

3.3 Summary and conclusion

Because adolescent nicotine exposure increases drug intake as adults as well as changing reward processes during adulthood, interventions should be specifically tailored to address differences between individuals that initiate smoking during adolescence versus adulthood. In addition, adolescent nicotine exposure leads to changes in structure and function of the hippocampus and mPFC that may underlie persistent cognitive impairments, with earlier age of initiation leading to greater deficits later in life. Since cognitive impairments are often reported as a reason for maintaining tobacco use (Patterson et al., 2010), nicotine use during adolescence creates a worrisome combination as increased reward coupled with decreased aversion likely increases both the initiation and continued use of nicotine. Furthermore, adolescent nicotine use could contribute to long-lasting changes in cognition that could contribute to maintaining nicotine dependence in adulthood. Clinical work also supports the correlation between adolescent nicotine use and poor cognitive performance (Jacobsen et al., 2005; Fried et al., 2006). These changes in cognition are associated with greater

compensatory activation in circuits crucial for verbal working memory during nicotine abstinence compared to non-smoking controls (Jacobsen et al., 2007). This offers some insight into the maintenance of nicotine use as continued use may counteract cognitive deficits caused by dysregulated brain activity. Sadly, negative effects on mental health and attention were noted even after passive youth exposure to nicotine through secondhand smoke (Bandiera et al., 2011). Finally, these results indicate that future policy and practice should focus efforts not only on minimizing adolescent tobacco use but also on finding effective ways to minimize, eliminate, or reverse long-term alterations caused by adolescent nicotine exposure.

4. ADOLESCENCE, STRESS, AND NICOTINE

4.1 Clinical Studies

Alleviation of stress is often cited as a reason to continue to engage in smoking in clinical populations (Carmody, 1989). Additionally, stress during adolescence has been identified as a risk factor for the initiation of tobacco use and is a mediator in the decision to start smoking in previously non-smoking adolescents (Byrne et al., 1995). In clinical studies, it has been shown that daily stressful events occur more frequently and are perceived more negatively in adolescent humans compared to adults and children (Rahdar & Galvan, 2014). This, of course, is problematic, because other research has established that a buildup of daily stressors, such as homework and interpersonal conflict with peers, has been linked to behavioral problems and risk for development of psychopathologies (Dumont & Provost, 1999). Stress experienced during the adolescent period is positively correlated with the risk of developing anxiety disorders and depression later in life (Compas, Orosan, & Grant, 1993; Brook et al., 2004). When comparing adults and adolescents on response inhibition in a go-no go task, daily stress accumulation impaired inhibitory responses in both age groups but the impairment was greater in adolescents (Rahdar & Galvan, 2014). In addition, when engaging in response inhibition there was decreased activation of the dorso-lateral PFC (DLPFC), part of the brain responsible for controlling inhibition of responses during decision making (Fassbender et al., 2006). This may also contribute to the association between stress and substance abuse, as DLPFC activation is seen in risky-decision making and is disrupted in drug users (Yamamoto et al., 2015). Not only do adolescents experience different stressors, they respond quite differently than other age groups to stressors. For example, when blood pressure is used to measure response to a stressful situation, adolescent have higher levels of blood pressure than children undergoing the same stressor (Allen & Matthews, 1997). Taken together, adolescence represents a time of increased vulnerability to stressors that is confounded by the ongoing maturation of the HPA axis resulting in exaggerated stress reactivity.

Stress during adolescence has been identified as a risk factor for the initiation of tobacco use. Stress is a mediator in the decision to engage in smoking behavior in previously non-smoking adolescents (Byrne, Byrne, & Reinhart, 1995). For example, intentions to smoke and smoking behaviors are also associated with negative school-related events and negative peer interactions across a multi-ethnic sample (Booker et al., 2004). Recent research has also shown that higher perceived stress during adolescence is associated with increased risk for

the initiation of smoking and continuation of smoking when controlling for social status (Finkelstein et al., 2006). Sex differences in the motivation to smoke emerge during adolescence, where adolescent females report higher incidences of smoking with higher perceived family and social stressors while adolescent males report general stressors as a motivator to continue smoking (Byrne & Mazanov, 1999; Byrne & Mazanov, 2003). Additionally, early life stress increases the risk of smoking in adolescent girls but not in adolescent boys (Iakunchykova et al., 2015). These clinical studies suggest that stress is an important moderator of smoking behaviors in adolescents and sex differences may further contribute to this relationship.

4.2 Preclinical studies

Stress during adolescence may further augment the rewarding properties of nicotine and alter behavioral responses to nicotine later in life. Brielmaier et al. (2012) demonstrated that stress during adolescence augments the rewarding properties of the initial exposure to nicotine. Adolescent (p28) Sprague-Dawley rats were exposed to a single trial of unpredictable foot shocks and twenty-four hours later were trained in a nicotine CPP paradigm. Exposure to foot shocks increased the time spent in the nicotine-paired side compared to non-stressed adolescent animals trained with nicotine. Further, this effect was blocked by systemic administration of CP-154,526, a CRF-R1 antagonist. This suggests that the enhancement of nicotine CPP following acute stress is caused by activation of the stress system. It is possible that the elevation of glucocorticoids following the acute stress and subsequent nicotine treatment enhanced the associative learning rather than the rewarding properties of nicotine. Considering it took only a single conditioning trial to establish nicotine CPP, one interpretation is that the reward is more salient and this strengthened learning. This presents a unique problem- if an adolescent is stressed and turns to smoking to alleviate their negative affect, they may find it far more rewarding than in a non-stressed situation, thereby increasing their risk of continued tobacco use.

Only relatively recently has adolescence been viewed as a critical period of development that programs adult behaviors (Steinberg et al., 2010; Spear, 2000) and since then studies have suggested that exposure to stress and nicotine could alter normal developmental trajectories. The first study to examine the long-term effects of stress on later responses to nicotine reported that social stress experienced during adolescence affected locomotor responses to nicotine in adulthood, but the effect was limited to females (McCormick et al., 2004). Male and female adolescent (p33–48) Long-Evans rats were exposed to daily isolation and changing of cage-mates in a social instability stress paradigm. Three weeks later animals were tested for their locomotor responses to nicotine and female adults who experienced stress during adolescence had higher locomotor activity scores during a single nicotine challenge and during repeated nicotine injections compared to non-stressed controls and stressed males. This suggests that stress during the adolescent period makes females more sensitive to the immediate and repeated effects of nicotine administration. Thus, stressed adolescent females may be more susceptible to nicotine addiction at later time points.

4.3 Conclusions and Summary

The lack of research focusing on the interactions of stress and nicotine exposure during adolescence is alarming given that both stress and nicotine independently cause long-term changes in brain and behavior when experienced during adolescence. It is also important to note that nicotine by itself can cause an elevation in glucocorticoids and a synergistic elevation in corticosterone caused by the combination of stress and nicotine may have more deleterious effects than either stress or nicotine alone. This is especially important when considering that both glucocorticoids and nicotine exposure during adolescence alter the adult brain and behavior and thus stress reduction should be taken into consideration when developing interventions targeted at adolescent smoking.

5. IMPLICATIONS FOR TREATMENT

Currently, the CDC has reported that the most effective form of reducing adolescent nicotine use is limiting marketing by tobacco companies along with aggressive counter advertising campaigns to encourage staying tobacco free. This has led to a marked reduction in adolescent smoking (CDC, 2015). Additionally, the recommendation from the Association of American Family Physicians (AAFP) to reduce adolescent tobacco use in adolescents who already smoke is to engage in aggressive interventions including pharmacotherapies, nicotine replacement therapies, and counseling (Pbert et al., 2003). While these are important strategies for reducing adolescent nicotine use, other factors should also be considered. First, adolescents are more prone to risk-taking, making them more likely to initiate tobacco use during this time. Thus, strategies to reduce impulsivity should be considered. Second, alternatives to nicotine replacement should be considered. There are long-term changes in brain and behavior resulting from nicotine administration during adolescence, regardless of the source of nicotine, making nicotine replacement therapies a less than ideal nicotine cessation treatment in this population as nicotine replacement therapies may perpetuate the negative consequences of adolescent nicotine use discussed earlier (also reviewed in detail by Slotkin, 2008). In fact, the AAFP even notes that nicotine replacement therapies in the form of gum or patches lead to lower abstinence rates in adolescents compared to adults (Larzelere & Williams, 2012). Finally, attention needs to be paid to the effect of stress on moderating the initiation and maintenance of tobacco use during adolescence.

Taken together, in order to effectively combat nicotine addiction and continue to reduce the prevalence of every day smokers the following should be considered:

1. Target preventing adolescents from initiating tobacco use, as nicotine during adolescence can lead to long-term alterations in behavior and deficits in cognition. The long-term behavior changes may work against an individual maintaining abstinence. However, this is especially tenuous as adolescence is a period of increased impulsivity and a vulnerable time for initiating drug use. Any initiative that addresses the elimination of tobacco use in adolescence should take this into account.

2. Create and implement effective stress management programs that are age appropriate. Since stress is often cited as a reason to engage in smoking, and preclinical models indicate that stress during adolescence makes nicotine more rewarding, it is important to manage stress in the quest for eliminating adolescent tobacco use.

3. Future preclinical work must investigate the underlying mechanisms of long-term deficits caused by nicotine and/or stress during adolescence. Doing so could lead to effective interventions that reduce, or even eliminate, the long-lasting impacts of adolescent nicotine use. In turn, this could also help develop specific interventions that would increase the chances for successful nicotine abstinence, and, hopefully, reduce the number of tobacco-related illnesses and deaths overall.

6. IMPLICATIONS FOR RESEARCH

This review discussed the independent effects of stress and nicotine (Balfour et al., 1975; Buczek et al., 1999; Chen et al., 2008) as well as the unique contributions of adolescent nicotine on cognition and affect (Brielmaier et al., 2012; Elliot et al., 2004; Portugal et al., 2012; Spaeth et al., 2010). Further, this review covered studies examining the association between adolescent stress and the initiation and continuation of tobacco use during adolescence (Byrne et al., 1995; Byrne & Mazanov 1999; Finkelstein et al., 2006; Iakunchykova et al., 2015). Given the strong association in clinical research suggesting a link between stress and adolescent smoking behaviors it is imperative that future preclinical work elucidate the underlying biological and neural processes that contribute to adolescent stress increasing the propensity for adolescent nicotine abuse. However, as this review emphasized, there is a dearth of preclinical research that examines the interactions of stress and nicotine during the adolescent period on both short-term and long-term effects as it relates to affect and learning. In conclusion, this review highlights a need for future preclinical work to examine the interactive effects of stress and nicotine during adolescence in addition to their independent contributions to short-term and long-term consequences on behavior and in the brain.

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REFERENCES

1. Adriani W, Deroche-Gamonet V, Moal M, Laviola G, Piazza P. Preexposure during or following adolescence differently affects nicotine-rewarding properties in adult rats. 2006; 184(3–4):382–390. [PubMed: 16163527]
2. Adriani W, Deroche-Gamonet V, Moal ML, Laviola G, Piazza PVV. Preexposure during or following adolescence differently affects nicotine-rewarding properties in adult rats. Psychopharmacology. 2005; 184(3–4):382–390. [PubMed: 16163527]
3. Adriani W, Laviola G. Elevated levels of impulsivity and reduced place conditioning with d-amphetamine: two behavioral features of adolescence in mice. Behav Neurosci. 2003; 117(4):695–703. [PubMed: 12931955]

4. Adriani W, Macrì S, Pacifici R, Laviola G. Peculiar vulnerability to nicotine oral self-administration in mice during early adolescence. Neuropsychopharmacology. 2002; 27(2):212–224. [PubMed: 12093595]
5. Adriani W, Spijker S, Deroche-Gamonet V, et al. Evidence for enhanced neurobehavioral vulnerability to nicotine during periadolescence in rats. J Neurosci. 2003; 23(11):4712–4716. [PubMed: 12805310]
6. Alderman EM, Rieder J, Cohen MI. The History of Adolescent Medicine. Pediatr Res. 2003; 54(1): 137–147. [PubMed: 12672903]
7. Allen MT, Matthews KA. Hemodynamic responses to laboratory stressors in children and adolescents: the influences of age, race, and gender. Psychophysiology. 1997; 34(3):329–339. [PubMed: 9175447]
8. André JM, Gulick D, Portugal GS, Gould TJ. Nicotine withdrawal disrupts both foreground and background contextual fear conditioning but not pre-pulse inhibition of the acoustic startle response in C57BL/6 mice. Behav Brain Res. 2008; 190(2):174–181. [PubMed: 18367257]
9. Arnold JM, Roberts DCS. A Critique of Fixed and Progressive Ratio Schedules Used to Examine the Neural Substrates of Drug Reinforcement. Pharmacology Biochemistry and Behavior. 1997; 57(3):441–447.
10. Azam L, Chen Y, Leslie FM. Developmental regulation of nicotinic acetylcholine receptors within midbrain dopamine neurons. Neuroscience. 2007; 144(4):1347–1360. [PubMed: 17197101]
11. Bacher I, Wu B, Shytle DR, George TP. Mecamylamine - a nicotinic acetylcholine receptor antagonist with potential for the treatment of neuropsychiatric disorders. Expert Opinion on Pharmacotherapy. 2009; 10(16):2709–2721. [PubMed: 19874251]
12. Bale TL. Sensitivity to stress: dysregulation of CRF pathways and disease development. Horm Behav. 2005; 48(1):1–10. [PubMed: 15919381]
13. Balfour DJ, Khullar AK, Longden A. Effects of nicotine on plasma corticosterone and brain amines in stressed and unstressed rats. Pharmacol Biochem Behav. 1975; 3(2):179–184. [PubMed: 1170575]
14. Bandiera FC, Richardson AK, Lee DJ, He J-P, Merikangas KR. Secondhand Smoke Exposure and Mental Health Among Children and Adolescents. Arch Pediatr Adolesc Med. 2011; 165(4):1–14.
15. Belluzzi J, Lee A, Oliff H, Leslie F. Age-dependent effects of nicotine on locomotor activity and conditioned place preference in rats. Psychopharmacology (Berl). 2004; 174(3):1–7.
16. Benwell ME, Balfour DJ. Effects of chronic nicotine administration on the response and adaptation to stress. Psychopharmacology (Berl). 1982; 76(2):160–162. [PubMed: 6805027]
17. Bergstrom H, Smith R, Mollinedo N, McDonald C. Chronic nicotine exposure produces lateralized, age-dependent dendritic remodeling in the rodent basolateral amygdala. Synapse. 2010; 64(10):754–764. [PubMed: 20336623]
18. Biala G, Budzynska B. Effects of acute and chronic nicotine on elevated plus maze in mice: involvement of calcium channels. Life Sci. 2006; 79(1):81–88. [PubMed: 16458932]
19. Blakemore S-J. Imaging brain development: The adolescent brain. NeuroImage. 2012; 61(2):397–406. [PubMed: 22178817]
20. Breslau N, Kilbey M, Andreski P. Nicotine dependence, major depression, and anxiety in young adults. Arch Gen Psychiatry. 1991; 48(12):1069–1074. [PubMed: 1845224]
21. Brielmaier J, McDonald CG, Smith RF. Effects of acute stress on acquisition of nicotine conditioned place preference in adolescent rats: a role for corticotropin-releasing factor 1 receptors. Psychopharmacology (Berl). 2012; 219(1):73–82. [PubMed: 21720754]
22. Brielmaier JM, McDonald CG, Smith RF. Immediate and long-term behavioral effects of a single nicotine injection in adolescent and adult rats. Neurotoxicol Teratol. 2007; 29(1):74–80. [PubMed: 17095188]
23. Brioni JD, O'Neill AB, Kim DJ, Decker MW. Nicotinic receptor agonists exhibit anxiolytic-like effects on the elevated plus-maze test. European journal of pharmacology. 1993; 238(1):1–8. [PubMed: 8405072]
24. Brook JS, Schuster E, Zhang C. Cigarette smoking and depressive symptoms: a longitudinal study of adolescents and young adults. Psychol Rep. 2004; 95(1):159–166. [PubMed: 15460371]

25. Brown RA, Kahler CW, Zvolensky MJ, Lejuez CW, Ramsey SE. Anxiety sensitivity: relationship to negative affect smoking and smoking cessation in smokers with past major depressive disorder. Addictive Behaviors. 2001; 26(6):887–899. [PubMed: 11768550]
26. Buczek Y, Lê AD, Wang A, Stewart J, Shaham Y. Stress reinstates nicotine seeking but not sucrose solution seeking in rats. Psychopharmacology (Berl). 1999; 144(2):183–188. [PubMed: 10395000]
27. Byrne DG, Byrne AE, Reinhart MI. Personality, stress and the decision to commence cigarette smoking in adolescence. J Psychosom Res. 1995; 39(1):53–62. [PubMed: 7760303]
28. Byrne DG, Mazanov J. Sources of adolescent stress, smoking and the use of other drugs. Stress and Health. 1999; 15(4):215–227.
29. Byrne DG, Mazanov J. Adolescent stress and future smoking behaviour: A prospective investigation. Journal of Psychosomatic Research. 2003; 54(4):313–321. [PubMed: 12670608]
30. Carmody TP. Affect regulation, nicotine addiction, and smoking cessation. J Psychoactive Drugs. 1989; 21(3):331–342. [PubMed: 2681631]
31. Casey BJ, Getz S, Galvan A. The adolescent brain. Dev Rev. 2008; 28(1):62–77. [PubMed: 18688292]
32. Center for Disease Control. [Accessed February 23, 2016] Smoking and Tobacco Use. Surgeon General's Report. Smoking and Tobacco Use. 2012. http://www.cdc.gov/tobacco/data_statistics/sgr/2012/. Published 2012
33. Center for Disease Control. [Accessed February 23, 2016] Smoking and Tobacco Use; Fact Sheet; Adult Cigarette Smoking in the United States; Smoking and Tobacco Use. http://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/. Published 2015
34. Center for Disease Control. [Accessed February 23, 2016] E-cigarette use by youth is dangerous. Centers for Disease Control and Prevention. http://www.cdc.gov/vitalsigns/ecigarette-ads/index.html Published January 5, 2016
35. Center for Disease Control and Prevention (CDC). Quitting smoking among adults--United States, 2001–2010. MMWR Morb Mortal Wkly Rep. 2011; 60(44):1513–1519. [PubMed: 22071589]
36. Chassin L, Presson CC, Sherman SJ, Edwards DA. The natural history of cigarette smoking: predicting young-adult smoking outcomes from adolescent smoking patterns. Health Psychol. 1990; 9(6):701–716. [PubMed: 2286181]
37. Cheeta S, Irvine EE, Tucci S, Sandhu J, File SE. In adolescence, female rats are more sensitive to the anxiolytic effect of nicotine than are male rats. Neuropsychopharmacology. 2001; 25(4):601–607. [PubMed: 11557173]
38. Chen H, Fu Y, Sharp BM. Chronic nicotine self-administration augments hypothalamic-pituitary-adrenal responses to mild acute stress. Neuropsychopharmacology. 2008; 33(4):721–730. [PubMed: 17551542]
39. Chen H, Matta SG, Sharp BM. Acquisition of Nicotine Self-Administration in Adolescent Rats Given Prolonged Access to the Drug. Neuropsychopharmacology. 2007; 32(3):700–709. [PubMed: 16794562]
40. Chen J, Millar WJ. Age of smoking initiation: implications for quitting. Health Rep. 1998; 9(4): 39–46. [PubMed: 9836879]
41. Chen YI, Choi J-K, Xu H, Ren J, Andersen SL, Jenkins BG. Pharmacologic Neuroimaging of the Ontogeny of Dopamine Receptor Function. Dev Neurosci. 2010; 32(2):125–138. [PubMed: 20523024]
42. Colby SM, Tiffany ST, Shiffman S, Niaura RS. Are adolescent smokers dependent on nicotine? A review of the evidence. Drug and Alcohol Dependence. 2000; (59 Suppl 1):S83–S95. [PubMed: 10773439]
43. Cole DM, Beckmann CF, Long CJ, Matthews PM, Durcan MJ, Beaver JD. Nicotine replacement in abstinent smokers improves cognitive withdrawal symptoms with modulation of resting brain network dynamics. NeuroImage. 2010; 52(2):590–599. [PubMed: 20441798]
44. Compas BE, Orosan PG, Grant KE. Adolescent stress and coping: implications for psychopathology during adolescence. J Adolesc. 1993; 16(3):331–349. [PubMed: 8282901]
45. Counotte DS, Goriounova NA, Li KW, et al. Lasting synaptic changes underlie attention deficits caused by nicotine exposure during adolescence. Nat Neurosci. 2011; 14(4):417–419. [PubMed: 21336271]

46. Counotte DS, Spijker S, de Burgwal LHV, et al. Long-lasting cognitive deficits resulting from adolescent nicotine exposure in rats. Neuropsychopharmacology. 2009; 34(2):299–306. [PubMed: 18580873]
47. Davis JA, Gould TJ. The effects of DHBE and MLA on nicotine-induced enhancement of contextual fear conditioning in C57BL/6 mice. Psychopharmacology (Berl). 2006; 184(3–4):345–352. [PubMed: 15988571]
48. Davis JA, Gould TJ. Hippocampal nAChRs mediate nicotine withdrawal-related learning deficits. Eur Neuropsychopharmacol. 2009; 19(8):551–561. [PubMed: 19278836]
49. Davis JA, James JR, Siegel SJ, Gould TJ. Withdrawal from chronic nicotine administration impairs contextual fear conditioning in C57BL/6 mice. Journal of Neuroscience. 2005; 25(38):8708–8713. [PubMed: 16177040]
50. de Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease. Nat Rev Neurosci. 2005; 6(6):463–475. [PubMed: 15891777]
51. Dinicola AF, Scott NC, Mcclain AM, Bell MP. Tobacco Product Usage Among Deployed Male and Female Military Personnel in Kuwait. Military Medicine. 2013; 178(1):3–3. [PubMed: 23356110]
52. Doremus-Fitzwater TL, Barreto M, Spear LP. Age-related differences in impulsivity among adolescent and adult Sprague-Dawley rats. Behav Neurosci. 2012; 126(5):735–741. [PubMed: 22889309]
53. Doura MB, Gold AB, Keller AB, Perry DC. Adult and periadolescent rats differ in expression of nicotinic cholinergic receptor subtypes and in the response of these subtypes to chronic nicotine exposure. Brain Res. 2008; 1215:40–52. [PubMed: 18474362]
54. Dumont M, Provost MA. Resilience in adolescents: Protective role of social support, coping strategies, self-esteem, and social activities on experience of stress and depression. Journal of Youth and Adolescence. 1999; 28(3) http://link.springer.com/article/10.1023/A:1021637011732.
55. Eede FVD, Broeckhoven CV, Claes SJ. Corticotropin-releasing factor-binding protein, stress and major depression. Ageing Res Rev. 2005; 4(2):213–239. [PubMed: 15996902]
56. Elliott BM, Faraday MM, Phillips JM, Grunberg NE. Effects of nicotine on elevated plus maze and locomotor activity in male and female adolescent and adult rats. Pharmacol Biochem Behav. 2004; 77(1):21–28. [PubMed: 14724038]
57. Enrico P, Sirca D, Mereu M, Peana AT, Mercante B, Diana M. Acute restraint stress prevents nicotine-induced mesolimbic dopaminergic activation via a corticosterone-mediated mechanism: A microdialysis study in the rat. Drug and Alcohol Dependence. 2013; 127(1–3):8–14. [PubMed: 22809896]
58. Ernst M, Pine DS, Hardin M. Triadic model of the neurobiology of motivated behavior in adolescence. Psychol Med. 2006; 36(3):299–312. [PubMed: 16472412]
59. Exley R, McIntosh JM, Marks MJ, Maskos U, Cragg SJ. Striatal α5 Nicotinic Receptor Subunit Regulates Dopamine Transmission in Dorsal Striatum. J Neurosci. 2012; 32(7):2352–2356. [PubMed: 22396410]
60. Exley R, McIntosh JM, Marks MJ, Maskos U, Cragg SJ. Striatal α5 Nicotinic Receptor Subunit Regulates Dopamine Transmission in Dorsal Striatum. J Neurosci. 2012; 32(7):2352–2356. [PubMed: 22396410]
61. Falco AM, McDonald CG, Bachus SE, Smith RF. Developmental alterations in locomotor and anxiety-like behavior as a function of D1 and D2 mRNA expression. Behavioural Brain Research. 2014; 260:25–33. [PubMed: 24239691]
62. Faraday MM, O'Donoghue VA, Grunberg NE. Effects of nicotine and stress on startle amplitude and sensory gating depend on rat strain and sex. Pharmacol Biochem Behav. 1999; 62(2):273–284. [PubMed: 9972694]
63. Fassbender C, Simoes-Franklin C, Murphy K, et al. The Role of a Right Fronto-Parietal Network in Cognitive Control. Journal of Psychophysiology. 2006; 20(4):286–296.
64. File SE, Kenny PJ, Ouagazzal AM. Bimodal modulation by nicotine of anxiety in the social interaction test: role of the dorsal hippocampus. Behav Neurosci. 1998; 112(6):1423–1429. [PubMed: 9926824]
65. Finkelstein DM, Kubzansky LD, Goodman E. Social Status, Stress, and Adolescent Smoking. Journal of Adolescent Health. 2006; 39(5):678–685. [PubMed: 17046504]

66. Finsterwald C, Alberini CM. Stress and glucocorticoid receptor-dependent mechanisms in long-term memory: From adaptive responses to psychopathologies. Neurobiology of Learning and Memory. 2013 Oct.:1–13.

67. Fried PA, Watkinson B, Gray R. Neurocognitive consequences of cigarette smoking in young adults- a comparison with pre-drug performance. Neurotoxicol Teratol. 2006; 28(4):517–525. [PubMed: 16904287]

68. Giedd JN, Blumenthal J, Jeffries NO, et al. Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci. 1999; 2(10):861–863. [PubMed: 10491603]

69. Gogtay N, Nugent TF, Herman DH, et al. Dynamic mapping of normal human hippocampal development. Hippocampus. 2006; 16(8):664–672. [PubMed: 16826559]

70. Gold PE. Acetylcholine modulation of neural systems involved in learning and memory. Neurobiol Learn Mem. 2003; 80(3):194–210. [PubMed: 14521863]

71. Gould TJ, Higgins JS. Nicotine enhances contextual fear conditioning in C57BL/6J mice at 1 and 7 days post-training. Neurobiology of Learning and Memory. 2003; 80(2):147–157. [PubMed: 12932430]

72. Gould TJ, Wilkinson DS, Yildirim E, Blendy JA, Adoff MD. Dissociation of tolerance and nicotine withdrawal-associated deficits in contextual fear. Brain Res. 2014; 1559(C):1–10. [PubMed: 24594018]

73. Gould TJ, Wehner JM. Nicotine enhancement of contextual fear conditioning. Behav Brain Res. 1999; 102(1–2):31–39. [PubMed: 10403013]

74. Iakunchykova OP, Andreeva TI, Nordstrom DL, et al. The impact of early life stress on risk of tobacco smoking initiation by adolescents. Addictive Behaviors. 2015; 50:222–228. [PubMed: 26164763]

75. Jacobsen LK, Krystal JH, Mencl WE, Westerveld M, Frost SJ, Pugh KR. Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. Biol Psychiatry. 2005; 57(1):56–66. [PubMed: 15607301]

76. Jacobsen LK, Picciotto MR, Heath CJ, et al. Prenatal and Adolescent Exposure to Tobacco Smoke Modulates the Development of White Matter Microstructure. Journal of Neuroscience. 2007; 27(49):13491–13498. [PubMed: 18057207]

77. Johnson DH, Svensson AI, Engel JA, Söderpalm B. Induction but not expression of behavioural sensitization to nicotine in the rat is dependent on glucocorticoids. European journal of pharmacology. 1995; 276(1–2):155–164. [PubMed: 7781685]

78. Kim JJ, Fanselow MS. Modality-specific retrograde amnesia of fear. Science. 1992; 256(5057): 675–677. [PubMed: 1585183]

79. Kita T, Okamoto M, Kubo K, Tanaka T, Nakashima T. Enhancement of sensitization to nicotine-induced ambulatory stimulation by psychological stress in rats. Prog Neuropsychopharmacol Biol Psychiatry. 1999; 23(5):893–903. [PubMed: 10509382]

80. Klink R, d'Exaerde A de K, Zoli M, Changeux J-P. Molecular and Physiological Diversity of Nicotinic Acetylcholine Receptors in the Midbrain Dopaminergic Nuclei. J Neurosci. 2001; 21(5): 1452–1463. [PubMed: 11222635]

81. Kota D, Sanjakdar S, Marks MJ, Khabour O, Alzoubi K, Damaj MI. Exploring behavioral and molecular mechanisms of nicotine reward in adolescent mice. Biochem Pharmacol. 2011; 82(8): 1008–1014. [PubMed: 21708139]

82. Kupferschmidt DA, Funk D, Erb S, Lê AD. Age-related effects of acute nicotine on behavioural and neuronal measures of anxiety. Behav Brain Res. 2010; 213(2):288–292. [PubMed: 20546793]

83. Larzelere MM, Williams DE. Promoting smoking cessation. Am Fam Physician. 2012; 85(6):591–598. [PubMed: 22534270]

84. Laviola G, Macrı S, Morley-Fletcher S, Adriani W. Risk-taking behavior in adolescent mice: psychobiological determinants and early epigenetic influence. Neuroscience & Biobehavioral Reviews. 2003; 27(1–2):19–31. [PubMed: 12732220]

85. Levin ED, Lawrence SS, Petro A, Adolescent vs, et al. adult-onset nicotine self-administration in male rats: duration of effect and differential nicotinic receptor correlates. Neurotoxicol Teratol. 2007; 29(4):458–465. [PubMed: 17433619]

86. Levin ED, Rezvani AH, Montoya D, Rose JE, Swartzwelder HS. Adolescent-onset nicotine self-administration modeled in female rats. Psychopharmacology (Berl). 2003; 169(2):141–149. [PubMed: 12764575]

87. Logue SF, Paylor R, Wehner JM. Hippocampal lesions cause learning deficits in inbred mice in the Morris water maze and conditioned-fear task. Behav Neurosci. 1997; 111(1):104–113. [PubMed: 9109628]

88. Macrì S, Adriani W, Chiarotti F, Laviola G. Risk taking during exploration of a plus-maze is greater in adolescent than in juvenile or adult mice. Animal Behaviour. 2002; 64(4):541–546.

89. Maren S. Seeking a Spotless Mind: Extinction, Deconsolidation, and Erasure of Fear Memory. Neuron. 2011; 70(5):830–845. [PubMed: 21658578]

90. Marks MJ, Stitzel JA, Romm E, Wehner JM, Collins AC. Nicotinic binding sites in rat and mouse brain: comparison of acetylcholine, nicotine, and alpha-bungarotoxin. Mol Pharmacol. 1986; 30(5):427–436. [PubMed: 3534542]

91. McCabe RE, Chudzik SM, Antony MM, Young L, Swinson RP, Zolvensky MJ. Smoking behaviors across anxiety disorders. J Anxiety Disord. 2004; 18(1):7–18. [PubMed: 14725865]

92. McCormick CM, Robarts D, Gleason E, Kelsey JE. Stress during adolescence enhances locomotor sensitization to nicotine in adulthood in female, but not male, rats. Horm Behav. 2004; 46(4):458–466. [PubMed: 15465532]

93. Mcewen BS. Stressed or stressed out: what is the difference? J Psychiatry Neurosci. 2005; 30(5): 315–318. [PubMed: 16151535]

94. Mckee SA, Sinha R, Weinberger AH, et al. Stress decreases the ability to resist smoking and potentiates smoking intensity and reward. Journal of Psychopharmacology. 2011; 25(4):490–502. [PubMed: 20817750]

95. McQuown SC, Belluzzi JD, Leslie FM. Low dose nicotine treatment during early adolescence increases subsequent cocaine reward. Neurotoxicol Teratol. 2007; 29(1):66–73. [PubMed: 17174067]

96. Metcalfe C, Smith GD, Wadsworth E, et al. A contemporary validation of the Reeder Stress Inventory. Br J Health Psychol. 2003; 8(Pt 1):83–94. [PubMed: 12643818]

97. Miczek KA, Covington HE, Nikulina EM, Hammer RP. Aggression and defeat: persistent effects on cocaine self-administration and gene expression in peptidergic and aminergic mesocorticolimbic circuits. Neurosci Biobehav Rev. 2004; 27(8):787–802. [PubMed: 15019428]

98. Mojica CY, Belluzzi JD, Leslie FM. Age-dependent alterations in reward-seeking behavior after brief nicotine exposure. Psychopharmacology (Berl). 2014; 231(8):1763–1773. [PubMed: 24030468]

99. O'Dell LE, Bruijnzeel AW, Ghozland S, Markou A, Koob GF. Nicotine withdrawal in adolescent and adult rats. Ann N Y Acad Sci. 2004; 1021:167–174. [PubMed: 15251887]

100. O'Dell LE, Torres OV, Natividad LA, Tejeda HA. Adolescent nicotine exposure produces less affective measures of withdrawal relative to adult nicotine exposure in male rats. Neurotoxicol Teratol. 2007; 29(1):17–22. [PubMed: 17184972]

101. O'Dell LE. A psychobiological framework of the substrates that mediate nicotine use during adolescence. Neuropharmacology. 2009; 56:263–278. [PubMed: 18723034]

102. Parrott AC, Roberts G. Smoking deprivation and cigarette reinstatement: effects upon visual attention. Journal of Psychopharmacology. 1991; 5(4):404–409. [PubMed: 22282850]

103. Patterson F, Jepson C, Loughead J, et al. Working memory deficits predict short-term smoking resumption following brief abstinence. Drug and Alcohol Dependence. 2010; 106(1):61–64. [PubMed: 19733449]

104. Pbert L, Moolchan ET, Muramoto M, et al. The State of Office-Based Interventions for Youth Tobacco Use. Pediatrics. 2003; 111(6):e650–e660. [PubMed: 12777581]

105. Perrin JS, Herve P-Y, Leonard G, et al. Growth of White Matter in the Adolescent Brain: Role of Testosterone and Androgen Receptor. Journal of Neuroscience. 2008; 28(38):9519–9524. [PubMed: 18799683]

106. Perry DC, Xiao Y, Nguyen HN, Musachio JL, Dávila-García MI, Kellar KJ. Measuring nicotinic receptors with characteristics of alpha4beta2, alpha3beta2 and alpha3beta4 subtypes in rat tissues by autoradiography. J Neurochem. 2002; 82(3):468–481. [PubMed: 12153472]

107. Philbert J, Pichat P, Palme R, Belzung C, Griebel G. The CRF1 receptor antagonist SSR125543 attenuates long-term cognitive deficit induced by acute inescapable stress in mice, independently from the hypothalamic pituitary adrenal axis. Pharmacol Biochem Behav. 2012; 102(3):415–422. [PubMed: 22659580]
108. Phillips RG, LeDoux JE. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci. 1992; 106(2):274–285. [PubMed: 1590953]
109. Piazza PV, Deroche-Gamonent V, Rouge-Pont F, Moal ML. Vertical Shifts in Self-Administration Dose-Response Functions Predict a Drug-Vulnerable Phenotype Predisposed to Addiction. J Neurosci. 2000; 20(11):4226–4232. [PubMed: 10818158]
110. Portugal GS, Wilkinson DS, Turner JR, Blendy JA, Gould TJ. Developmental effects of acute, chronic, and withdrawal from chronic nicotine on fear conditioning. Neurobiology of Learning and Memory. 2012; 97(4):482–494. [PubMed: 22521799]
111. Prut L, Belzung C. The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: a review. European journal of pharmacology. 2003; 463(1–3):3–33. [PubMed: 12600700]
112. Quirk GJ, Mueller D. Neural Mechanisms of Extinction Learning and Retrieval. Neuropsychopharmacology. 2007; 33(1):56–72. [PubMed: 17882236]
113. Radley JJ, Sawchenko PE. A Common Substrate for Prefrontal and Hippocampal Inhibition of the Neuroendocrine Stress Response. Journal of Neuroscience. 2011; 31(26):9683–9695. [PubMed: 21715634]
114. Rahdar A, Galván A. The cognitive and neurobiological effects of daily stress in adolescents. NeuroImage. 2014; 92:267–273. [PubMed: 24553284]
115. Robinson TE, Berridge KC. Incentive-sensitization and addiction. Addiction. 2001; 96(1):103–114. [PubMed: 11177523]
116. Romero LM, Levine S, Sapolsky RM. Patterns of adrenocorticotropin secretagog release in response to social interactions and various degrees of novelty. Psychoneuroendocrinology. 1995; 20(2):183–191. [PubMed: 7899537]
117. Rosecrans JA, Karan LD. Neurobehavioral mechanisms of nicotine action: role in the initiation and maintenance of tobacco dependence. J Subst Abuse Treat. 1993; 10(2):161–170. [PubMed: 8510190]
118. Schmidt MV, Sterlemann V, Ganea K, et al. Persistent neuroendocrine and behavioral effects of a novel, etiologically relevant mouse paradigm for chronic social stress during adolescence. Psychoneuroendocrinology. 2007; 32(5):417–429. [PubMed: 17449187]
119. Selye H. Forty Years of Stress Research: Principal Remaining Problems and Misconceptions. Canadian Medical Association journal. 1976; 115(1):53–56. [PubMed: 1277062]
120. Shearman E, Fallon S, Sershen H, Lajtha A. Nicotine-induced monoamine neurotransmitter changes in the brain of young rats. Brain Res Bull. 2008; 76(6):626–639. [PubMed: 18598854]
121. Shram MJ, Funk D, Li Z, Lê AD. Acute nicotine enhances c-fos mRNA expression differentially in reward-related substrates of adolescent and adult rat brain. Neuroscience Letters. 2007; 418(3):286–291. [PubMed: 17420096]
122. Slawecki CJ, Gilder A, Roth J, Ehlers CL. Increased anxiety-like behavior in adult rats exposed to nicotine as adolescents. Pharmacology Biochemistry and Behavior. 2003; 75(2):355–361.
123. Slotkin TA, Bodwell BE, Ryde IT, Seidler FJ. Adolescent nicotine treatment changes the response of acetylcholine systems to subsequent nicotine administration in adulthood. Brain Res Bull. 2008; 76(1–2):152–165. [PubMed: 18395624]
124. Slotkin TA. If nicotine is a developmental neurotoxicant in animal studies, dare we recommend nicotine replacement therapy in pregnant women and adolescents? Neurotoxicology and Teratology. 2008; 30(1):1–19. [PubMed: 18380035]
125. Smith LN, McDonald CG, Bergstrom HC, et al. Long-term changes in fear conditioning and anxiety-like behavior following nicotine exposure in adult versus adolescent rats. Pharmacol Biochem Behav. 2006; 85(1):91–97. [PubMed: 16919320]
126. Spaeth AM, Barnet RC, Hunt PS, Burk JA. Adolescent nicotine exposure disrupts context conditioning in adulthood in rats. Pharmacol Biochem Behav. 2010; 96(4):501–506. [PubMed: 20655941]

127. Spear LP, Brake SC. Periadolescence: Age-dependent behavior and psychopharmacological responsivity in rats. Dev Psychobiol. 1983; 16(2):83–109. [PubMed: 6339302]

128. Spear LP. The adolescent brain and age-related behavioral manifestations. Neurosci Biobehav Rev. 2000; 24(4):417–463. [PubMed: 10817843]

129. Steinberg L. A behavioral scientist looks at the science of adolescent brain development. Brain and Cognition. 2010; 72(1):160–164. [PubMed: 19963311]

130. Torres OV, Tejeda HA, Natividad LA, O'Dell LE. Enhanced vulnerability to the rewarding effects of nicotine during the adolescent period of development. Pharmacol Biochem Behav. 2008; 90(4):658–663. [PubMed: 18571223]

131. Trauth JA, Seidler FJ, McCook EC, Slotkin TA. Adolescent nicotine exposure causes persistent upregulation of nicotinic cholinergic receptors in rat brain regions. Brain Res. 1999; 851(1–2):9–19. [PubMed: 10642823]

132. Trauth JA, Seidler FJ, Slotkin TA. An animal model of adolescent nicotine exposure: effects on gene expression and macromolecular constituents in rat brain regions. Brain Res. 2000; 867(1–2):29–39. [PubMed: 10837795]

133. Tzschentke TM. Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues. Progress in neurobiology. 1998; 56(6):613–672. [PubMed: 9871940]

134. United States Department of Health. [Accessed February 23, 2016] Smoking and Tobacco Use; Surgeon General's Reports. Smoking and Tobacco Use. 1994. http://www.cdc.gov/tobacco/data_statistics/sgr/1994/. Published 1994

135. Vogli RD, Santinello M. Unemployment and smoking: does psychosocial stress matter? Tob Control. 2005; 14(6):389–395. [PubMed: 16319362]

136. Wall PM, Messier C. Methodological and conceptual issues in the use of the elevated plus-maze as a psychological measurement instrument of animal anxiety-like behavior. Neurosci Biobehav Rev. 2001; 25(3):275–286. [PubMed: 11378181]

137. Watson NL, Vanderveen JW, Cohen LM, Demarree KG, Morrell HER. Examining the interrelationships between social anxiety, smoking to cope, and cigarette craving. Addictive Behaviors. 2012; 37(8):986–989. [PubMed: 22507303]

138. Willoughby T, Good M, Adachi PJC, Hamza C, Tavernier R. Examining the link between adolescent brain development and risk taking from a socialâ€"developmental perspective. Brain and Cognition. 2013; 83(3):315–323. [PubMed: 24128659]

139. Wilmouth CE, Spear LP. Withdrawal from chronic nicotine in adolescent and adult rats. Pharmacol Biochem Behav. 2006; 85(3):648–657. [PubMed: 17173961]

140. Wise RA, Rompre PP. Brain dopamine and reward. Annu Rev Psychol. 1989; 40:191–225. [PubMed: 2648975]

141. Yamamoto DJ, Woo C-W, Wager TD, Regner MF, Tanabe J. Influence of dorsolateral prefrontal cortex and ventral striatum on risk avoidance in addiction: A mediation analysis. Drug and Alcohol Dependence. 2015; 149:10–17. [PubMed: 25736619]

142. Zislis G, Desai TV, Prado M, Shah HP, Bruijnzeel AW. Effects of the CRF receptor antagonist D-Phe CRF(12-41) and the alpha2-adrenergic receptor agonist clonidine on stress-induced reinstatement of nicotine-seeking behavior in rats. Neuropharmacology. 2007; 53(8):958–966. [PubMed: 17976662]

HIGHLIGHTS

- Identifying the differences between adolescents and adults in response to nicotine, particularly on measures associated with nicotine addiction and mental health (i.e. affect and cognition), is crucial to develop effective policies regarding youth smoking prevention and reduction.
- Stress during adolescence has been identified as a risk factor for the initiation of tobacco use and is a mediator in the decision to start smoking in previously nonsmoking adolescents.
- Stress during adolescence may further augment the rewarding properties of nicotine and alters behavioral responses to nicotine later in life.
- In order to continue to reduce the prevalence of everyday smokers it is important to consider ways to for adolescents to manage stress to minimize the possibility of smoking initiation which could lead to nicotine dependence in adulthood.