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Nicotine and the developing brain: Insights from preclinical models

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Abstract

Use of tobacco products during pregnancy is associated with increased risk for neurodevelopmental disorders in the offspring. Preclinical models of developmental nicotine exposure have offered valuable insights into the neurobiology of nicotine's effects on the developing brain and demonstrated lasting effects of developmental nicotine exposure on brain structure, neurotransmitter signaling and behavior. These models have facilitated discovery of novel compounds as candidate treatments for attention deficit hyperactivity disorder, a neurodevelopmental disorder associated with prenatal nicotine exposure. Using these models the significance of heritability of behavioral phenotypes from the nicotine-exposed pregnant female or adult male to multiple generations of descendants has been demonstrated. Finally, research using the preclinical models has demonstrated synergistic interactions between developmental nicotine exposure and repetitive mild traumatic brain injury that contribute to "worse" outcomes from the injury in individuals with attention deficit hyperactivity disorder associated with developmental nicotine exposure.

Keywords

Nicotine; Mouse; Attention; Memory; Kappa opioid receptor; Traumatic brain injury; Transgenerational transmission

1. Introduction

Nicotine use continues to be a significant public health concern throughout the world, despite compelling evidence for its harmful health effects. In the late 20th century public health and legislative efforts led to a significant downturn in cigarette smoking in the United

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States (Centers for Disease, 1999, 2021). However, the 21st century saw the introduction of electronic nicotine delivery systems such as e-cigarettes, and an accompanying resurgence in nicotine use (Jaber et al., 2018; U.S. Surgeon General's Report, 2016). As a result, nicotine use is once again becoming a public health concern.

Electronic cigarettes (e-cigarettes) are marketed as "safer" alternatives for traditional, combustible cigarettes. However, e-cigarettes contain nicotine, in some cases at levels higher than those in combustible cigarettes. In fact, all forms of tobacco products whether combustible cigarettes, e-cigarettes or chewing tobacco are marketed and used precisely because of their nicotine content. Nicotine is the neuro-active, addictive constituent in all of these products (Dwyer et al., 2008; Dwyer et al., 2009; Harvey et al., 2004; Rose, 2006; Slotkin, 2004). Therefore, the assumptions of e-cigarette "safety" may be misplaced (D'Angelo et al., 2019; Kandra et al., 2014; Ma et al., 2021; Saw et al., 2013; Tong et al., 2013; Whittington et al., 2018).

Independent of the harmful effects of nicotine, the delivery systems also can contribute to health effects of tobacco products, including neurobehavioral effects, because the chemical additives contained in the delivery vehicle can be harmful. For example, combustible cigarettes are notorious for the thousands of chemicals such as aldehydes, arsenic, creosols, cyanide and polycyclic hydrocarbons that they contain either as additives or as natural constituents of the tobacco leaf itself (Centers for Disease Control and Prevention et al., 2010). E-cigarettes contain a delivery vehicle called e-liquid or e-juice consisting of a cocktail of harmful chemicals including propylene glycol (Muthumalage et al., 2017; Rubinstein et al., 2018; Sassano et al., 2018). Thus, all tobacco products contain harmful chemicals in addition to nicotine, and as the technology for nicotine delivery has evolved over the centuries from tobacco leaves to electronic cigarettes, one characteristic has remained invariant: A cocktail of chemicals that can harm human health.

More men use tobacco products than women (Gowing et al., 2015; Makadia et al., 2017; U.S. Surgeon General's Report, 2014). However, women show unique vulnerabilities to nicotine's harmful effects. Women are more susceptible to nicotine dependence, withdrawal symptoms and smoking-related health effects such as cancer and coronary artery disease compared to men (Allen et al., 2014; Cross et al., 2017; O'Dell and Torres, 2014; Perkins, 2001). Nicotine use by women warrants additional considerations because nicotine use by pregnant and nursing women not only places their own health at risk but also the health of their children.

It is well known that use of tobacco products during pregnancy increases the risk for pulmonary, metabolic, immunological, and neurodevelopmental disorders in the children (McEvoy and Spindel, 2017; Zacharasiewicz, 2016). Clinical and preclinical studies offer compelling evidence that developmental nicotine exposure increases the risk for attention deficit hyperactivity disorder, conduct disorder, aggression, developmental delays, working memory deficits, as well as novelty-seeking, risk-taking and drug addiction in the offspring (Biederman et al., 2012; Faraone et al., 2018; Jacobsen et al., 2009; Martin et al., 2020; Pagani, 2014; Polli et al., 2020b; Wickstrom, 2007; Zhang et al., 2021c; Zhang et al., 2018; Zhu et al., 2017; Zhu et al., 2014a; Zhu et al., 2012).

There is yet another, perhaps more serious and less well appreciated consequence of nicotine use by pregnant women. It is the risk of transmission of the adverse effects from the pregnant mother who uses nicotine or the children who are exposed to nicotine in utero, to their descendants in multiple generations (Buck et al., 2019a; Buck et al., 2019b; Golding et al., 2017; Golding et al., 2020; Miller et al., 2014a; Miller et al., 2014b; Williams et al., 2019; Zhu et al., 2014a). Such "transgenerational transmission" likely increases the population at risk for neurodevelopmental disorders 2–3-fold above current estimates and produces public health and socioeconomic impacts that may last for at least 3 generations or 90 years.

Nicotine use by men also can influence the mental health of their offspring (McCarthy and Bhide, 2021), suggesting that nicotine use by either parent (i.e., father or mother) can produce adverse effects on offspring health. Nicotine use by the father around the time of conception of the child increases the child's risk for cancer, disorders of the immune and metabolic systems as well as cognitive deficits (Biederman et al., 2020; Marczylo et al., 2012; Northstone et al., 2014; Soubry, 2018; Zhu et al., 2014b).

Turning to the consequences of nicotine use by pregnant women for their offspring, preclinical models of prenatal and early postnatal nicotine exposure have offered significant mechanistic and phenomenological insights into the neurobiology underlying nicotine's effects on the developing brain as well as the link between developmental nicotine exposure and neurodevelopmental disorders. Preclinical models are valuable tools to extend and verify clinical data because cause-effect associations can be analyzed more rigorously in pre-clinical models than in human subjects. Preclinical models also permit a detailed analysis of the effects of dose, route and duration of nicotine exposure, as well as delineation of independent effects of each substance in a multiple exposure paradigm.

We review here nearly two decades of work from our laboratory using mouse models of developmental nicotine exposure, and the relevance of the findings to ADHD and related neurodevelopmental disorders. Specifically, we discuss the validity of the mouse models as preclinical models of ADHD and illustrate the use of the mouse models to facilitate drug discovery, investigation of heritability of behaviors arising from nicotine exposure and examination of potential synergistic interactions between ADHD and concussions. We also discuss studies showing that paternal nicotine exposure can produce significant adverse effects on offspring behaviors.

2. Mouse models of developmental nicotine exposure

Preclinical research on developmental nicotine exposure has relied principally on rodent models. Pioneering work by Slotkin, Levin, Pauly and colleagues established rodent models of developmental nicotine exposure as reliable and valuable preclinical models of human developmental nicotine exposure (England et al., 2017; Levin et al., 1993; Matta et al., 2007; Navarro et al., 1989; Navarro et al., 1988; Pauly and Slotkin, 2008; Pauly et al., 2004; Rosenthal and Slotkin, 1977; Roy et al., 2002; Slotkin, 1998, 2002; Slotkin et al., 1987a; Slotkin et al., 1987c; Trauth et al., 2000). These foundational studies showed that developmental nicotine exposure produces lasting changes in brain neuro-chemistry,

receptor signaling mechanisms and behavior. The timing, route and dose of nicotine administration established by these investigators has served as a model for subsequent studies, including our own.

2.1. Developmental nicotine exposure paradigm

We used mouse models of prenatal and early postnatal nicotine exposures (Fig. 1). Female C57BL/6 or Swiss Webster mice were exposed to nicotine (100–200 μg/ml) in drinking water beginning 3-weeks prior to mating so that the mice could attain some tolerance to drinking nicotine-containing water by the time they were bred. The daily nicotine exposure continued throughout pregnancy and ceased at the time of parturition [prenatal-only exposure (Zhu et al., 2017; Zhu et al., 2012)] or continued until the offspring were weaned [prenatal and postnatal exposures; (Martin et al., 2020; Zhang et al., 2021c; Zhang et al., 2018)]. On average, the mice consumed 600–1200 μg (i.e., 20–40 mg/kg bodyweight) nicotine per day. The prenatal-only exposure represents human exposures during the first and second trimesters of pregnancy, whereas the pre- and postnatal exposures represent exposure throughout the 3 trimesters of the human pregnancy (Clancy, 2007; Clancy et al., 2001; Clancy et al., 2007; Semple et al., 2013).

For consistency with previous reports, in some studies we included the artificial sweetener saccharin as a vehicle to mask nicotine's bitter taste in the drinking water (Zhang et al., 2021c; Zhu et al., 2014a; Zhu et al., 2012). We included two groups of controls in these studies: Mice that were exposed to saccharin alone and mice that were exposed to plain drinking water without additives. These controls facilitated analysis of the independent effects of saccharin. We found that prenatal and early postnatal exposures to saccharin did not produce significant effects on behavioral, neuroanatomical, or neurochemical features. In other studies (Martin et al., 2020) we excluded the use of saccharin as a sweetener upon discovering that the consumption of nicotine-containing drinking water by mice was not significantly affected by the addition of saccharin (Martin et al., 2020; McCarthy et al., 2018). We point out that in other studies, in which male mice were exposed to saccharin, behavioral changes were observed in the offspring derived from (i.e., sired by) the saccharin-exposed male mice (McCarthy et al., 2020). The behavioral changes produced by the paternal saccharin exposure are described under the heading "Transgenerational Transmission".

Our nicotine exposure paradigm produced plasma cotinine levels (cotinine is a relatively stable metabolite of nicotine and its plasma content is used as a reliable indicator of nicotine exposure) of approximately 130 ng/ml (Martin et al., 2020), which is comparable to the plasma cotinine levels reported in other mouse models of developmental nicotine exposure (Pauly et al., 2004) and in cigarette smokers (Matta et al., 2007; Nagano et al., 2010).

We used the oral nicotine delivery method because it does not involve exposing the mice to the stress associated with daily systemic nicotine administrations (subcutaneous, intraperitoneal, or intravenous) or the stress of subcutaneous implantation of osmotic pumps for nicotine delivery. We recognize that nicotine delivery via the drinking water may not produce the "peaks and valleys" in maternal plasma nicotine content associated with inhalation of cigarette smoke (Benowitz et al., 1982), and in that sense it does not

mimic cigarette smoking during pregnancy. However, peaks and valleys in fetal nicotine concentrations following maternal cigarette smoking are unlikely because of the differences in nicotine pharmacokinetics between adults and fetuses (Wickstrom, 2007). Another significant difference between cigarette smoking and nicotine delivery via drinking water is that nearly 70% of the orally delivered nicotine is catabolized in the liver. Thus, the route and dose of nicotine are among the most significant variables affecting the pharmacokinetics of nicotine and the outcome measures in preclinical models [Reviews in (Centner et al., 2020; Matta et al., 2007; Polli and Kohlmeier, 2020)].

Our prenatal-only nicotine exposure paradigm required us to cross-foster offspring from all prenatal exposure conditions (nicotine + saccharin, saccharin-only and plain drinking water) within 1–2 days of birth, to drug naïve foster dams [Fig. 1, (Zhu et al., 2017; Zhu et al., 2014a; Zhu et al., 2012)]. The cross-fostering was used to restrict nicotine exposure to the prenatal period. To account for potential independent effects of cross-fostering, we cross-fostered offspring from all three groups: nicotine + saccharin, saccharin only and plain drinking water. Cross-fostering could introduce at least two technical artifacts: 1) Effects of sudden withdrawal from nicotine upon cross fostering to a non-nicotine exposed nursing dam, and 2) effects of stress associated with cross-fostering (Muhammad and Kolb, 2011). Sudden nicotine withdrawal occurs in virtually every preclinical model of developmental nicotine exposure. It occurs soon after birth in the prenatal-only models and around the time of weaning in the pre- and postnatal models. A gradual step-up or step-down method of nicotine exposure can avoid abrupt nicotine withdrawal (Paz et al., 2007). However, we did not take such measures in our mouse models. The stress associated with cross-fostering was controlled in our studies by cross-fostering offspring from all prenatal exposure groups.

2.2. Breeding success, pregnancy, and litter metrics

Major adverse outcomes of cigarette smoking during pregnancy in humans include preterm delivery and low birth weight (Froggatt et al., 2020; Inoue et al., 2017; Ko et al., 2014). However, we did not observe statistically significant effects on the length of the pregnancy, the number of pups born, offspring sex ratio at birth, or offspring birth-weight. Breeding success (i.e., fertility) was not affected. In addition, the nicotine exposure did not affect offspring developmental milestones such as the time of eye opening or the time of appearance of fur in the offspring. Thus, our nicotine exposure paradigms did not replicate all the effects on pregnancy or pregnancy outcomes reported in humans. A higher dose of nicotine than the dose used here may be necessary to produce those effects. In fact, other studies using higher nicotine dose report effects on litter size as well as birth weight in rodent models (Newman et al., 1999; Santiago and Huffman, 2012; Slotkin et al., 1993).

2.3. Behavior

When the offspring in the nicotine exposed and control groups reached 2–3 months of age, we examined spontaneous locomotor activity (home cage activity monitoring for 24 h.), attention (object based attention), spatial working memory (Y-maze), motor impulsivity (cliff avoidance reflex) and novelty-seeking/risk-taking behavior (elevated plus maze). These behaviors were chosen for analysis to evaluate the possibility that the nicotine exposure contributed to behavioral changes consistent with ADHD. Attention deficit, hyperactivity

and impulsivity are core symptoms of ADHD whereas working memory deficit and risk-taking behavior are co-morbidities (Antshel et al., 2010; Biederman, 2007; Biederman et al., 2004; Faraone et al., 2018; Fried et al., 2016; Silverstein et al., 2020).

We observed locomotor hyperactivity, attention deficit, spatial working memory deficit, motor impulsivity and novelty-seeking/risk-taking behavior in the offspring [Fig. 1 (Martin et al., 2020; Zhang et al., 2021c; Zhang et al., 2018; Zhu et al., 2017; Zhu et al., 2012)]. There were differences in the behavioral outcomes between prenatal-only and pre- and postnatal nicotine exposure models as well as between the C57BL/6 and SW strains. The locomotor hyperactivity and motor impulsivity were observed in the prenatal-only model but not in the pre-and postnatal exposure model. Attention deficit and spatial working memory deficit were observed in the C57BL/6 strain in the prenatal only as well as the pre- and postnatal exposure models. However, these deficits were not present in the pre- and postnatal exposure paradigm using the Swiss Webster strain. The novelty-seeking/risk-taking behavior was observed in the Swiss Webster in the pre- and postnatal exposures paradigm but not the C57BL/6 strain in either paradigm. Finally, many of the behavioral changes were observed in male but not female mice, consistent with the differences in the behavioral manifestations of ADHD between boys and girls (Biederman et al., 2002; Gaub and Carlson, 1997). Thus, the duration of the nicotine exposure, the strain of the mouse, and sex of the offspring influenced the behavioral outcomes.

Multiple reports in the literature suggest that differences in the timing of the nicotine exposure can introduce variability in the outcomes. For example, two studies examined the effects of nicotine exposure occurring at each one of six different windows of prenatal and postnatal development from conception to postnatal day 7 on cognitive and emotional behaviors (Alkam et al., 2013a; Alkam et al., 2013b). Nicotine exposure occurring from the 12th day of gestation until birth produced significant effects on these behaviors compared to exposures that began prior to or after the 12th day of gestation.

A plausible explanation for the differences in behavioral outcomes due to the differences in the timing of the exposure is that peak occurrence of the different developmental events (such as neurogenesis, gliogenesis, programmed cell death and synaptic reorganization) is at different times during the pre- and postnatal development. Therefore, a developmental event may be impacted particularly severely if the nicotine exposure overlapped with its peak. Another possibility is that with longer nicotine exposure (Martin et al., 2020; Zhang et al., 2021c; Zhang et al., 2018) the potential for adaptation to occur within the neural systems may be proportionately greater, and these adaptations may influence the behavioral outcomes (Zhang et al., 2018).

The differences in the novelty-seeking/risk-taking behavior between the SW and C57BL/6 strains of mice are supported by other reports of strain differences in the effects of nicotine [Review in (Zhang et al., 2018) (Marks et al., 1986a; Marks et al., 1986b)]. However, at the present time, detailed insights into the precise mechanisms that may contribute to the strain differences are not available.

Sex-dependent changes in behaviors such as hyperactivity, nicotine preference and pre-pulse inhibition have been reported in rodent models of developmental nicotine exposure (Klein et al., 2003; Pauly et al., 2004; Polli et al., 2020b; Popke et al., 1997; Romero and Chen, 2004; Shacka et al., 1997). Differences in hypothalamic-pituitary axis signaling, estrogen receptor signaling, neurotransmitter receptor signaling have been proposed as potential mechanisms for these sex differences (Andersen and Teicher, 2000; Pauly, 2008; Torres and O'Dell, 2016).

Thus, the findings from preclinical studies can be influenced significantly by technical and biological variables. These variables include timing of the nicotine exposure, use of vehicles such as sweeteners, type of nicotine exposure (aerosol, smoke or nicotine per se) the dose, frequency and route of nicotine administration, the strain and sex of the animal and the age at which the outcome measures are evaluated. Whereas the design of each study is justified by its specific goals and the specific hypotheses being tested, the influence of each variable should be considered while comparing outcomes from different studies and drawing conclusions about translational relevance.

2.4. Monoamine neurotransmitter content and synaptic release in the frontal cortex

We examined changes in monoamine neurotransmitter content and synaptic release in the frontal cortex in male C56BL/6 mice in our mouse models (Fig. 1). We focused on monoamines because of the association of these neurotransmitters with the symptoms as well as pharmacological treatment of ADHD (Berridge et al., 2006; Kuczenski et al., 1997; Kuczenski and Segal, 1997, 2005; Spencer et al., 2006; Spencer et al., 2013; Spencer et al., 2005; Volkow et al., 2012). We examined male mice because most of the behavioral changes were present in male but not female mice.

We found significant reductions in dopamine tissue content in the frontal cortex in our C57BL/6 prenatal nicotine exposure model (Zhu et al., 2014a; Zhu et al., 2012). In addition, in vivo microdialysis studies in the C57BL/6 pre- and postnatal nicotine exposure model showed significant reductions in dopamine and noradrenaline but not serotonin release in the frontal cortex (Zhang et al., 2021c). These findings are supported by another report that examined monoamine levels in the frontal cortex following pre- and postnatal nicotine exposure (Alkam et al., 2017).

The changes were not limited to dopamine and noradrenaline. In another study using transgenic SW mice in which the GFP reporter is under the control of the GAD67 promoter (McCarthy and Bhide, 2012; McCarthy et al., 2011; Tamamaki et al., 2003), we found that developmental nicotine exposure produced significant reductions in the GABA to non-GABA neuron ratio in the frontal cortex (Martin et al., 2020), suggesting a dampening of the frontal cortical inhibitory tone. Other studies have reported changes in glutamate and acetylcholine receptor signaling following developmental nicotine exposure (Aoyama et al., 2016; Baumann and Koch, 2017; Gavini et al., 2021; Parameshwaran et al., 2012; Polli et al., 2020a; Polli et al., 2020b; Slotkin et al., 2004; Vaglenova et al., 2008).

Nicotine's effects on the developing brain are mediated via nicotinic acetylcholine receptors, which are expressed in the fetal brain by a variety of neurons including those that

contain neurotransmitters such as dopamine or GABA (Navarro et al., 1989; Slotkin et al., 1987a; Slotkin et al., 1986; Slotkin et al., 1987b; Slotkin et al., 1987c). Therefore, it is not surprising that effects of developmental nicotine exposure are not limited to the cholinergic system but are manifested by dopamine, noradrenaline, GABA and glutamate neurotransmitter systems as well.

2.5. Structural changes in the brain

We performed a pilot diffusion tensor imaging study in C57BL/6 male mice from the developmental nicotine + saccharin, saccharin alone or plain drinking water exposure groups (Zhang et al., 2021c; Zhang et al., 2018). We used an ex-vivo scanning protocol that was consistent with our prior work (Caffall et al., 2021). Only 3 brains from each developmental exposure group were imaged. Regions of interest (ROI) were identified by performing whole-brain voxel-wise independent-samples *t*-tests between the nicotine + saccharin, saccharin-only and plain drinking water using Analysis of Functional Neuroimages (AFNI) software. A voxel-wise threshold of $p < 0.10$ was used to identify ROIs for further analyses. Although preliminary and although based on a small sample, data from this analysis supported the hypothesis that the medial prefrontal cortex and dorsal striatum showed reduced microstructural integrity (i.e., reduced fractional anisotropy) in the developmentally nicotine exposed group (Fig. 2). These are the same two brain regions that were implicated by our behavioral and neurotransmitter data in this mouse model (Martin et al., 2020; Zhang et al., 2021c; Zhang et al., 2018; Zhu et al., 2017; Zhu et al., 2012). In an earlier study we had showed that the volume of the medial prefrontal cortex was significantly reduced in the prenatal nicotine exposure mouse model (Zhu et al., 2012). The imaging analysis also highlighted the ansiform lobule (Crus 1) of the cerebellum as a third region with reduced microstructural integrity in the developmentally nicotine exposed group (Fig. 2). This part of the lateral cerebellum or cerebro-cerebellum is implicated in ADHD and other cognitive disorders (Makris et al., 2015; Stoodley et al., 2010, 2012).

Changes identified by diffusion tensor imaging are reported to reflect histological changes in the gray matter regions in neurological disorders and during normal development (Kim et al., 2019; Mori and Zhang, 2006). Therefore, developmental nicotine exposure may produce changes in neuronal, glial, and synaptic numbers and organization. Neuroimaging of network function in ADHD has identified structural and functional deficits associated with the medial prefrontal cortex, dorsal striatum, and the cerebellum (Makris et al., 2009; Makris et al., 2015; Monuteaux et al., 2008; Seidman et al., 2006; Shaw et al., 2006; Shaw et al., 2012; Valera et al., 2010). Thus, our neuroimaging data represent a first step toward identification and characterization of network-wide structural and functional changes in the brain following developmental nicotine exposure and relating the changes to those reported in ADHD and other neurodevelopmental disorders.

2.6. Summary of findings

Our findings offer insights into the effects of developmental nicotine exposure on behavioral, neurochemical, and neuroanatomical parameters. These data facilitate an integrated, system-wide view of nicotine's effects on the developing brain. A major theme that emerges is that developmental nicotine exposure may target neural networks

involving the frontal cortex, striatum and the cerebellum and dopamine, noradrenaline, and GABA neurotransmission in the frontal cortex. Frontal cortex plays a critical role in the regulation of attention, working memory, impulsivity, and risk-taking behaviors (Arnsten et al., 1994; Arnsten and Jin, 2014; Arnsten and Pliszka, 2011; Robbins and Arnsten, 2009). Our data suggest that changes in frontal cortical network function, likely via changes in monoamine and GABA neurotransmission may be a key functional outcome of the effects of developmental nicotine exposure. The unique trajectory of the structural and functional development of the frontal cortical regions (Kolk and Rakic, 2021; Mills et al., 2014; Shaw et al., 2006; Shaw et al., 2012; Tsujimoto, 2008), which results in a characteristic maturational "delay" compared to the other brain regions may render these regions particularly vulnerable to the effects of nicotine, and other risk factors for neurodevelopmental disorders.

3. Developmental nicotine exposure mouse models as preclinical models of ADHD

Translational value of preclinical models of neuro-psychiatric conditions such as ADHD can be significant, because these models can offer novel insights into the neurobiological mechanisms of the disorder and facilitate discovery of novel therapeutics. Here we discuss how we have used our mouse models as preclinical models of ADHD as a first step toward these objectives.

3.1. Construct, face and predictive validities

We developed our mouse models based on evidence from the clinical literature that maternal cigarette smoking during pregnancy increased the risk for ADHD in the offspring (Altink et al., 2009; Biederman et al., 2012; Mick et al., 2002; Milberger et al., 1996; Milberger et al., 1998; Schmitz et al., 2006; Torabi et al., 2021). We had shown that the clinical presentations of ADHD due to maternal cigarette smoking during pregnancy are the same as the presentations of ADHD due to other causes (Biederman et al., 2012). Our findings (described in the previous sections) show that the mouse models replicate behavioral and neurochemical phenotypes that are consistent with ADHD. Therefore, our mouse models carry significant construct validity and face validity. Other reports in the literature support the notion that rodent models of developmental nicotine exposure are valid models of ADHD (Bryden et al., 2016; Buck et al., 2019b; Polli et al., 2020b; Russell, 2011; Yochum et al., 2014).

Next, we examined whether the mouse models carried predictive validity. In these studies, we examined the effects of methylphenidate, a classic stimulant drug with decades-long record of safety and efficacy in the treatment of ADHD in children and adults. In our prenatal nicotine exposure mouse model, a single administration of methylphenidate [0.75 mg/kg; intraperitoneal, which is equivalent to therapeutic dose administered to ADHD patients (Balcioglu et al., 2009)] reduced hyperactivity (Zhu et al., 2014a; Zhu et al., 2012), motor impulsivity, and improved attention as well as spatial working memory (Zhu et al., 2017). Methylphenidate improved attention and working memory in our pre- and postnatal nicotine exposure mouse model as well (Zhang et al., 2021c). In another study using in

vivo microdialysis in awake, behaving mice in our pre- and postnatal nicotine exposure mouse model a single methylphenidate administration significantly increased dopamine and noradrenaline release in the frontal cortex (Zhang et al., 2021c). The increase in monoamine release (compared to the baseline level) was statistically significant between 30 min and 4 h. following the methylphenidate administration (Zhang et al., 2021c). The methylphenidate-induced improvement in attention and working memory was evident at 0.5 h. but not at 2.5 h., suggesting that the behavioral improvement occurred during the period of increased monoamine release (Zhang et al., 2021c). The behavioral responses to methylphenidate are consistent with the therapeutic effects of this drug in ADHD suggesting that our mouse models carry significant predictive validity as preclinical models of ADHD.

3.2. Evaluation of efficacy of candidate therapeutic compounds using the mouse model

One of the advantages of a well-characterized mouse model of a human disorder is the opportunity it offers to test the efficacy of novel therapeutic compounds. Since our developmental nicotine exposure mouse model fulfils the criteria for construct, face, and predictive validity, we used this model to test a candidate non-stimulant compound as a potential therapeutic for ADHD.

Discovery and development of non-stimulant drugs for the treatment of ADHD remains a high priority for the field. Stimulant drugs such as methylphenidate and amphetamines are mainstays of ADHD treatment because of their proven efficacy and safety. However, stimulants carry significant abuse potential (Spencer et al., 2018; Wilens et al., 2008). In fact, prescription stimulants are among the most frequently misused medications (Butler et al., 2021; Vosburg et al., 2021; Vosburg et al., 2020). As a result, there are significant concerns about the safety of stimulants among patients, prescribers and families of patients, and these concerns represent significant barriers to successful treatment of ADHD. Thus, there is an urgent need for a non-stimulant compound with the efficacy of stimulants but without the abuse potential. Here we show that the developmental nicotine exposure mouse model can be used successfully for evaluation of potential, novel non-stimulant candidates for the treatment of ADHD,

The non-stimulant compound that was examined was norbinaltorphimine, a selective kappa opioid receptor (KOR) antagonist. KORs are widely distributed throughout the central nervous system and are activated by the endogenous ligand dynorphin (DePaoli et al., 1994; Liu-Chen, 2004). KOR signaling plays a role in stress response, affective disorders and pain sensation. KOR antagonists show significant “beneficial” effects in animal models of depression, anxiety, and drug addiction (Bruchas et al., 2010; Carlezon and Krystal, 2016; Carlezon et al., 1998; Chavkin and Koob, 2016; Knoll and Carlezon, 2010; Van’t Veer et al., 2013). KORs are expressed by midbrain/brainstem monoamine neurons, and KORs serve as negative feedback regulators of dopamine and noradrenaline release at the synapse in the frontal cortex (Fuentealba et al., 2006; Margolis et al., 2003; Margolis et al., 2006). Therefore, KOR antagonists have the potential to increase frontal cortical dopamine and noradrenaline release by inhibiting the KOR-mediated negative feedback for neurotransmitter release.

We found that norbinaltorphimine dose-dependently increased dopamine and noradrenaline release in the frontal cortex of mice (Zhang et al., 2021c). In our pre- and postnatal nicotine exposure mouse model (C57BL/6 mice), a single administration of norbinaltorphimine (20 mg/kg; intraperitoneal) produced significant increases in the release of both the neurotransmitters beginning at 2.5 h. and lasting until 6.0 h. (Zhang et al., 2021c). As discussed previously, the mice in the pre- and postnatal nicotine exposure group have significant deficits in object based attention and working memory. The norbinaltorphimine administration produced significant improvements in both these behaviors at 2.5 h and 5.5 h., but not at 24 h. following the single administration. Thus, the increase in frontal cortical monoamine neurotransmitter release and the behavioral improvement showed temporal overlap following the norbinaltorphimine administration.

In a head-to-head comparison, the effects of norbinaltorphimine and methylphenidate on frontal cortical monoamine neurotransmitter release, attention and working memory were comparable in direction as well as magnitude. However, the effects of norbinaltorphimine lasted much longer than those of methylphenidate. Norbinaltorphimine's CNS actions are known to be longer lasting compared to the action of other KOR antagonists. One of the intracellular mechanisms of norbinaltorphimine's actions is phosphorylation of c-Jun N-terminal kinase (Bruchas et al., 2007; Chavkin et al., 2019; Melief et al., 2010; Melief et al., 2011; Munro et al., 2012). We found that norbinaltorphimine produced significant increases in phosphorylated c-Jun N-terminal kinase in the frontal cortex in our mouse model, and that the phosphorylation lasted for 24 h., coinciding with the neurotransmitter and behavioral changes (Zhang et al., 2021c). Thus, the developmental nicotine exposure mouse model proved to be a valuable tool for examining the efficacy of a KOR antagonist as a potential non-stimulant treatment for ADHD.

4. Transgenerational transmission

Heritability of environment-induced phenotypes from one generation to the next is gaining acceptability as a phenomenon with significant scientific and public health relevance. A growing list of environmental factors including stress, hormones and chemicals such as nicotine, cocaine, alcohol, pesticides are implicated in producing heritable effects (Crews et al., 2012; McCarthy and Bhide, 2021; McCarthy et al., 2020; McCarthy et al., 2018; Skinner, 2011a, 2011b; Skinner et al., 2011; Vassoler et al., 2014; Vassoler et al., 2013; Wimmer et al., 2019).

We examined whether the locomotor hyperactivity in the prenatally nicotine exposed mice was heritable from one generation to the next. We bred the prenatally nicotine exposed mice (F1 generation; the nicotine exposed dams are the F0 generation) with drug naïve partners to produce the next generation of offspring (F2 generation; Fig. 3). We found that locomotor hyperactivity, which was present in male and female mice in the F1 generation (Zhu et al., 2014a; Zhu et al., 2012) was also present in the F2 generation, demonstrating intergenerational transmission of hyperactivity. The transmission from F1 to F2 generation is intergenerational (rather than transgenerational) because the germline of the F1 generation was directly exposed to nicotine in utero as well as in the pre-weaning period. For the

transmission to be transgenerational, the founder in the preceding generation should not be exposed to the environmental factor at any time.

To examine if the effects were transmitted transgenerationally, we bred the F2 female mice (F2 males were not bred because they did not show hyperactivity) with drug naïve partners to produce the F3 generation (Fig. 3). We found significant hyperactivity in the F3 generation as well (Zhu et al., 2014a). Thus, hyperactivity produced by developmental nicotine exposure shows transgenerational transmission, via the maternal line of descent.

Around the time of publication of our study and since then, several preclinical (Buck et al., 2019a; Buck et al., 2019b) and clinical (Golding et al., 2017; Golding et al., 2020; Miller et al., 2014a; Miller et al., 2014b; Williams et al., 2019) studies have reported transgenerational transmission of multiple phenotypes produced by the developmental nicotine exposure.

Heritable consequences of nicotine use by fathers has received significant attention in recent years and some of the behavioral phenotypes transmitted from the nicotine-exposed father to his offspring are consistent with the symptoms associated with ADHD and other neurodevelopmental disorders [Review in (McCarthy and Bhide, 2021)]. For example, locomotor hyperactivity was observed in the first generation offspring derived from nicotine-exposed male mice (Dai et al., 2017; Hawkey et al., 2019; McCarthy et al., 2018; Zhang et al., 2020), suggesting that hyperactivity may be a heritable phenotype common to developmental (i.e., maternal) and paternal nicotine exposure. However, hyperactivity was not observed in the second generation derived from the nicotine-exposed males. Paternal nicotine exposure also decreased nicotine self-administration and increased contextual and cued fear responses in the first generation of descendants (Goldberg and Gould, 2019; Goldberg et al., 2019). Significant reversal learning deficits were observed in both the first and second generations derived from nicotine-exposed males suggesting that cognitive inflexibility, a symptom shared by developmental disorders such as autism spectrum disorder, schizophrenia and ADHD (Dajani and Uddin, 2015; Izquierdo et al., 2016; Klanker et al., 2013; Ozsivadjian et al., 2021) may be a heritable phenotype following paternal nicotine exposure (McCarthy et al., 2018).

Although prenatal and early postnatal (i.e., developmental or maternal) exposure to the artificial sweetener saccharin did not produce locomotor hyperactivity in the descendants in the mouse model (Zhu et al., 2014a), exposure of male mice to saccharin produced locomotor hyperactivity and motor impulsivity in the first generation of descendants (McCarthy et al., 2020). Co-exposure of male mice to nicotine and saccharin, which occurs when humans consume certain forms of smokeless tobacco (Miao et al., 2016) produced hyperactivity and working memory deficits in the first generation (McCarthy et al., 2020).

Thus, intergenerational and transgenerational transmission of multiple behavioral phenotypes was observed following paternal exposure to nicotine, saccharin or co-exposure to nicotine and saccharin.

4.1. Molecular mechanisms of transgenerational transmission

The transgenerational inheritance of nicotine-induced phenotypes whether following developmental (i.e., maternal) or paternal exposure does not follow the classic Mendelian pattern of heritability across generations, pointing toward epigenetic modification of germ cells as a plausible mechanism of heritability rather than genetic mutations in the germline (McCarthy et al., 2018). However, the ability of cigarette smoke and nicotine to produce germ line mutations is well-known (Beal et al., 2017; Marchetti et al., 2011; Yauk et al., 2007).

Epigenetic modification occurs by chemical modification of the DNA or histones as well as by the action of non-coding RNAs such as miRNAs (Brunner et al., 2014; Carrell, 2012; Hamatani, 2012). The effects of nicotine on epigenetic modification of germ cells have been studied in the spermatozoa more widely than in the oocyte, perhaps due to the ease of access to the male germ cells compared to the female germ cells. Studies in human subjects and preclinical models show that exposure to cigarette smoke, e-cigarette aerosol or direct exposure to nicotine (in preclinical models) produces significant changes in DNA methylation and miRNA expression in the spermatozoa (Altintas et al., 2021; Beal et al., 2017; Bline et al., 2020; Dai et al., 2017; Jenkins et al., 2017; Liu et al., 2022; Marczylo et al., 2012; McCarthy and Bhide, 2021; McCarthy et al., 2020; McCarthy et al., 2018; Murphy et al., 2020; Soubry, 2018; Zhang et al., 2020) supporting the possibility that epigenetic changes in the germ cells can mediate transgenerational transmission of nicotine-induced phenotypes. However, multiple epigenetic reprogramming events involving erasure and re-acquisition of epigenetic marks occur throughout embryonic and postnatal development. Therefore, how exactly epigenetic changes in the germ cells of one generation can produce changes in somatic cells and behaviors in multiple generations of descendants remains an area of intensive research (Spadafora, 2020).

5. Synergistic interaction between ADHD and repetitive mild traumatic brain injury

Recent evidence suggests a potentially concerning association between ADHD and concussions [also known as repetitive mild traumatic brain injury (mTBI)]. Individuals with untreated ADHD are more likely to engage in activities that carry a higher risk of concussions (Alosco et al., 2014; Biederman et al., 2015; Chasle et al., 2016; Cook et al., 2020; Iverson et al., 2016; Nelson et al., 2016). Moreover, concussions in individuals with untreated ADHD result in significant deficits in visual and verbal memory, and visual motor processing speed that are not observed in individuals without ADHD who suffer concussions (Cook et al., 2017; Kaye et al., 2019; Nowak et al., 2020). Student athletes with ADHD report increased incidence of symptoms such as fatigue and poor concentration following concussions (Biederman et al., 2015). Paradoxically, participation in sports and other organized physical activities is often recommended as part of ADHD management programs.

Since our mouse models of developmental nicotine exposure carry validity as preclinical models of ADHD, we examined whether we could gain further insights into potential

link between ADHD and repetitive mTBI using our mouse model. We subjected C57BL/6 male mice that were exposed to nicotine during the pre- and postnatal periods (as well as mice in the control groups) to repetitive mTBI or sham procedure. In one study we used isoflurane anesthesia during the repetitive mTBI or sham procedure (Zhang et al., 2021b) whereas in another we used unanesthetized mice (Zhang et al., 2021a). Anesthetic agents can exert "neuroprotective" effects on the injured brain (Bailes et al., 2014; Petraglia et al., 2014a; Petraglia et al., 2014b). Moreover, using unanesthetized mice mimics "real-life" concussions in humans more closely. Collectively, our studies showed that the combination of developmental nicotine exposure and repetitive mTBI produced transient depression-like behavior and novelty-seeking/risk-taking behavior. These behaviors were not produced by either factor alone, but emerged only when the two factors were combined, demonstrating synergistic interactions between developmental nicotine exposure and repetitive mTBI.

In the non-nicotine exposed control group of mice, the repetitive mTBI produced transient deficits in object based attention, consistent with findings from human studies showing poor attention following concussion (Ling et al., 2015). In the developmentally nicotine exposed mice, deficits in object based attention were present at baseline (i.e., prior to repetitive mTBI), and those deficits persisted following the repetitive mTBI. It is possible that the repetitive mTBI had an "additive" effect on attention deficits in the developmentally nicotine exposed group that were not detectable by our method.

We could not evaluate the contribution of anesthesia to the behavioral outcomes fully because of the differences in the mTBI protocols (5 versus 7 mTBI episodes) between the two studies. However, depression-like behavior in the nicotine exposed mice and attention deficit in the non-nicotine exposed mice following the repetitive mTBI were observed in anesthetized as well as unanesthetized mice. Novelty-seeking/risk-taking behavior was analyzed only in the unanesthetized mice.

Our findings are consistent with findings from human studies that concussions produce "worse" outcomes in individuals with untreated ADHD, once again illustrating the translational value of the mouse models. We recognize that ADHD is a complex disorder to which multiple etiological and risk factors contribute. Therefore, it is possible that our findings apply to ADHD associated with developmental nicotine exposure only rather than to ADHD associated with other etiological factors.

6. Synopsis and prospective

The nicotine exposure mouse models offer a valuable experimental framework for examination of the effects of nicotine on the developing brain. Our research has identified neural networks involving the frontal cortex, striatum and the cerebellum and signaling via the neurotransmitters dopamine, noradrenaline and GABA in the frontal cortex as modulators of behavioral consequences of developmental nicotine exposure. The mouse models have facilitated identification of the selective kappa opioid receptor antagonist norbinaltorphimine as a candidate non-stimulant treatment for ADHD, analysis of transgenerational transmission of the effects of developmental nicotine exposure, and synergistic interactions between ADHD associated with developmental nicotine exposure

and concussions. With the emergence of e-cigarette use during pregnancy as a major public health concern preclinical research is beginning to incorporate rodent models of e-cigarette or e-liquid exposures. These models have shown that developmental exposure to e-cigarette aerosol produces behavioral changes that overlap with the behavioral changes produced by developmental exposure to nicotine (Church et al., 2020; Lauterstein et al., 2016; Nguyen et al., 2018; Ponzoni et al., 2015; Smith et al., 2015). The public health implications of e-cigarette use during pregnancy are enormous. These implications, especially the potential for transgenerational transmission of the effects of developmental e-cigarette or e-liquid exposure, are beginning to be recognized. Research using preclinical models offers our best chance to build a sound scientific understanding of the consequences of nicotine use during pregnancy and to facilitate formulation of rational public education and public policy efforts.

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Declaration of competing interest

Deirdre McCarthy has financial interest in Avekshan, LLC, which is disclosed to and is managed by the Florida State University Research Foundation. She is an inventor of following intellectual property through Florida State University: US Patent (#10,245,271 B2) and a pending US patent application 16/369,748.

Lin Zhang, Bradley Wilkes and David Vaillancourt: No conflict of interest to declare.

Joseph Biederman is currently receiving research support from the following sources: AACAP, Feinstein Institute for Medical Research, Genentech, Headspace Inc., NIDA, Pfizer Pharmaceuticals, Roche TCRC Inc., Sunovion Pharmaceuticals Inc., Takeda/Shire Pharmaceuticals Inc., Tris, and NIH. He receives honoraria from the Medlearning Inc. and MGH Psychiatry Academy for tuition-funded CME courses. Through MGH corporate licensing, Dr. Biederman has a US Patent (#14/027,676) for a non-stimulant treatment for ADHD, a US Patent (#10,245,271 B2) on a treatment of impaired cognitive flexibility, and a US patent (11,045,465 B2) on a method to prevent stimulant abuse. Dr. Biederman and his program have received royalties from a copyrighted rating scale used for ADHD diagnoses, paid by Biomarin, Bracket Global, Cogstate, Ingenix, Medavent Prophase, Shire, Sunovion, and Theravance; these royalties were paid to the Department of Psychiatry at MGH. In 2020: Dr. Biederman received an honorarium for a scientific presentation from Tris, and research support from the Food & Drug Administration. In 2019, Dr. Biederman was a consultant for Akili, Avekshan, Jazz Pharma, and Shire/Takeda. He received research support from Lundbeck AS and Neurocentria Inc. Through MGH CTNI, he participated in a scientific advisory board for Supernus. In 2018, Dr. Biederman was a consultant for Akili and Shire.

Pradeep Bhide has financial interest in Avekshan, LLC, which is disclosed to and is managed by the Florida State University Research Foundation. He is an inventor of following intellectual property through Florida State University: US patents 14/027,676, 10,245,271 B2, 11,045,465 B2 and a pending application 16/369,748.

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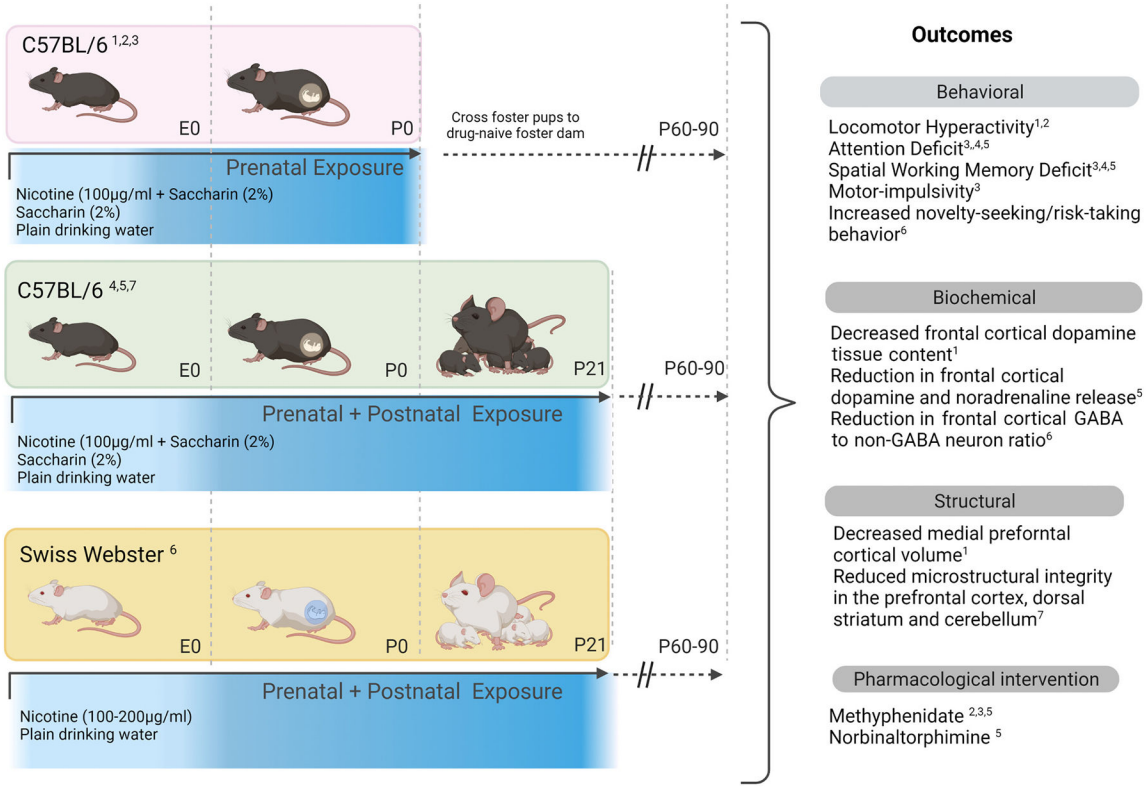

Fig. 1.

Mouse models of developmental nicotine exposure showing the experimental design and a summary of the outcomes. Three mouse models were used: A) Prenatal exposure in C57BL/6 strain, B) Prenatal + postnatal exposure in C57BL/6 strain, and C) Prenatal + postnatal exposure in Swiss Webster strain. Nicotine was supplied in drinking water (100–200 ng/ml) sweetened with 2% saccharin. Control groups included mice exposed to 2% saccharin in drinking water and plain drinking water. The prenatal period corresponded approximately to the first two trimesters of human pregnancy whereas the prenatal + postnatal periods to all three trimesters. The offspring from in the prenatal exposure paradigm (from all three exposure groups) were cross-fostered to drug naïve nursing dams within 1–2 days of birth. The offspring in the prenatal + postnatal exposure paradigm were raised by biological mothers. In all three paradigms, the offspring were subjected to behavioral, biochemical, structural and pharmacological assays around 60–90 days age. Citations: 1 Zhu et al., 2012; 2 Zhu et al., 2014a, 2014b; 3 Zhu et al., 2017; 4 Zhang et al., 2018; 5 Zhang et al., 2021c; 6 Martin et al., 2020; 7 Present data.

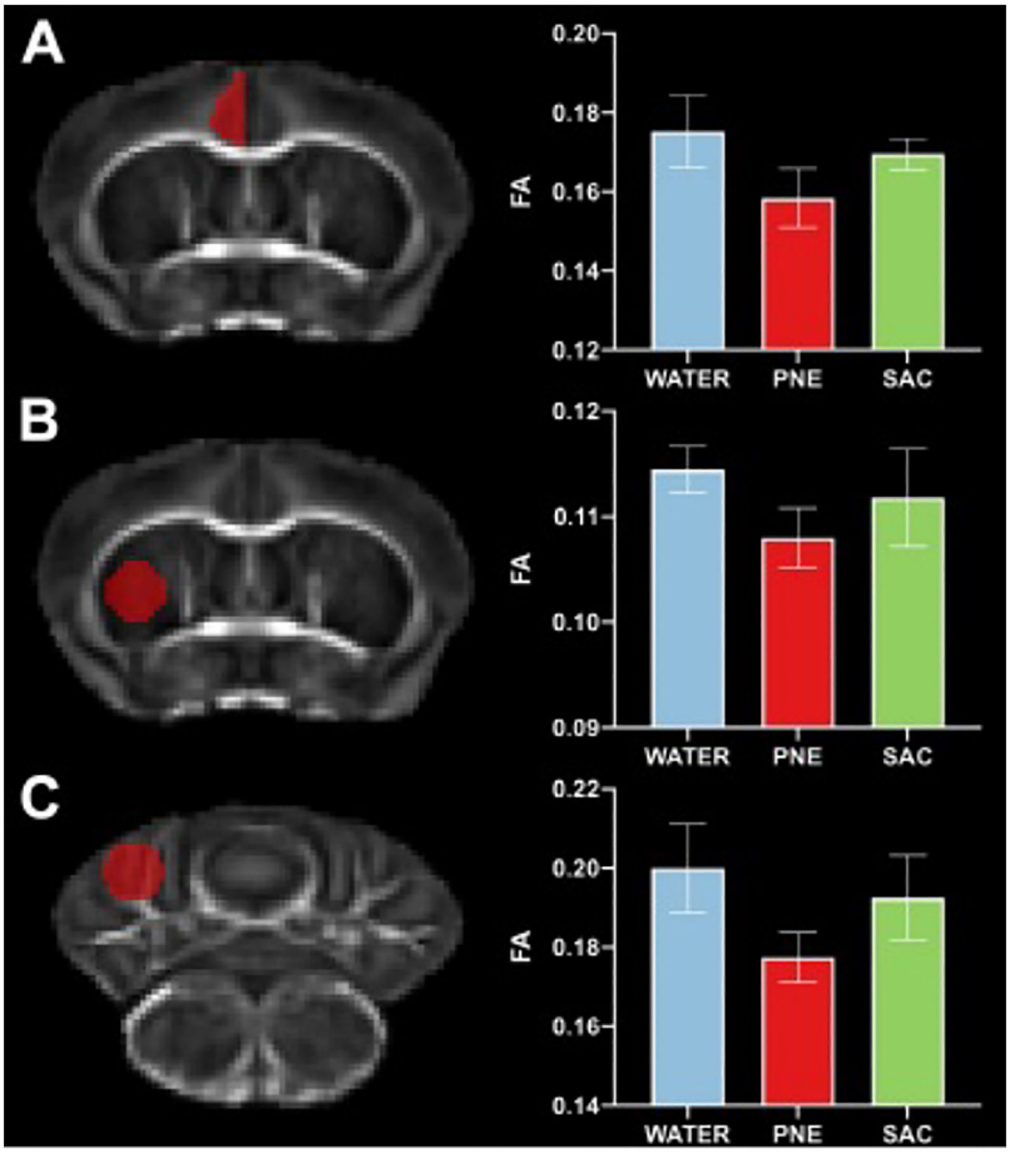

Fig. 2.

Summary of findings from the pilot neuroimaging study. Region of interest (ROI) analysis of fractional anisotropy (FA) in the diffusion tensor imaging study. Left column shows ROI, right column shows FA (mean ± SEM) by group. (A) medial prefrontal cortex; (B) dorsal striatum (C), ansiform lobule of the cerebellum. There is a significant decrease ($p < 0.1$) in FA values in the medial prefrontal cortex (A), dorso-lateral striatum (B) and the ansiform lobule of the cerebellum (C) in the pre- and postnatal nicotine exposure (PNE) group compared to the plain drinking water (WATER) or saccharin-only (SAC) exposure groups.

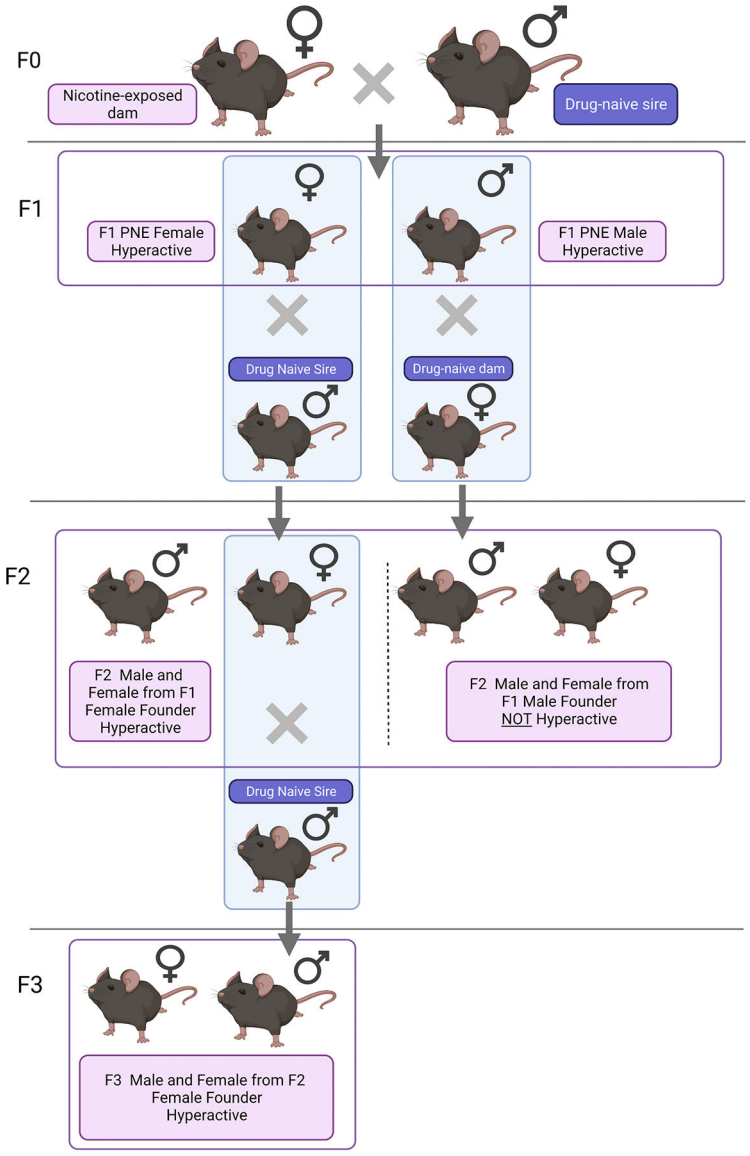

Fig. 3.

Experimental design for the transgenerational transmission study. Female C57BL/6 mice (F0 generation) were exposed to nicotine in drinking water beginning 3 weeks before breeding with a drug naïve sire. The nicotine exposure of the females continued throughout pregnancy. On the day of birth, the offspring (F1 generation) were cross-fostered to drug naïve nursing dams. Both the male and female F1 mice were hyperactive. They were crossed with drug naïve partners to produce the F2 generation. F2 male and female mice from an F1 female founder but not F1 male founder were hyperactive. F2 female mice produced by F1 female founder were crossed with drug naïve males to produce the F3 genaration. The F2 male mice produced by an F1 female were not used for further breeding. Similarly, F2 male or female mice produced by an F1 male founder were not bred further. An identical breeding plan was used to generate F1, F2 and F3 mice from the saccharin-only exposed F0 females (not shown).