12-2017

EFFECTS OF NICOTINE EXPOSURE ON METHAMPHETAMINE ORAL SELF-ADMINISTRATION, EXTINCTION, AND REINSTATEMENT IN ADOLESCENT RATS

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A Thesis

Presented to the

Faculty of

California State University,

San Bernardino

In Partial Fulfillment

of the Requirements for the Degree

Master of Arts

in

General/Experimental

Psychology

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by

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ABSTRACT

Adolescence is a vulnerable developmental period in regards to drug initiation and use. The gateway hypothesis suggests that adolescent cigarette smoking may result in a heightened risk for methamphetamine use. However, little is understood about the role of nicotine on adolescent methamphetamine addiction. The aim of the present study was to determine whether early, late, or continuous adolescent nicotine exposure would alter oral methamphetamine self-administration, extinction, or reinstatement. A total of 164 male and female Sprague-Dawley rats were pretreated with saline or nicotine (0.16, or 0.64 mg/kg, sc) beginning on postnatal day (PD) 25 for 10 consecutive days. On PD 35, rats in the 0.16 and 0.64 mg/kg pretreatment groups were evenly divided and assigned to a group that either continued to receive the same nicotine dose they received as adolescents or saline. Rats that had received saline as adolescents were divided into three equal groups, where they received 0.16 or 0.64 mg/kg nicotine or continued to receive saline injections. Drug treatments starting on PD 35 continued until the end of the experiment. Thus, there were a total of 7 groups: SAL–SAL, 0.16–0.16, 0.16–SAL, SAL-0.16, 0.64–0.64, 0.64–SAL, SAL-0.64. On PD 35, all rats began nose poke training. Rats were exposed to a methamphetamine fade in, sucrose fade out procedure across 5 different methamphetamine-sucrose combinations. This procedure resulted in exposure to a 40 mg/l methamphetamine solution for 3 consecutive days on a FR2 schedule. Following the last day of methamphetamine self-administration, rats were

exposed to extinction training. Once the extinction criteria were met, rats were given a priming injection of methamphetamine (1.0 mg/kg, ip). Data from the present investigation revealed two main important findings: a) acquisition of oral methamphetamine self-administration can be attained in adolescent rats; and b) adolescent nicotine exposure differentially alters oral methamphetamine self-administration. Exposure to a low dose of nicotine (0.16 mg/kg), but not a high dose of nicotine (0.64 mg/kg), attenuated consumption and responding for methamphetamine during self-administration. During the extinction and reinstatement periods, we found that nicotine (0.16 or 0.64 mg/kg) exposure did not alter consumption or responding for methamphetamine. Female rats showed augmented total active nose pokes and active nose pokes within the reinforcement period compared to male rats. Conversely, male rats showed augmented sucrose and methamphetamine solution consumption across methamphetamine acquisition sessions 1–6. These data suggest that for adolescents who already present moderate cigarette smoking behavior at the time of methamphetamine cessation treatment, total abstinence from both nicotine and methamphetamine may be a less effective form of treatment. It may be clinically beneficial to first treat the methamphetamine addiction, and subsequently treat the nicotine addiction. Regardless of the method of treatment for adolescent methamphetamine addiction, nicotine exposure should be closely monitored.

ACKNOWLEDGMENTS

A special thank you and great appreciation for my advisor, Dr. Cynthia Crawford, for her patience and guidance throughout my collegiate career at California State University, San Bernardino. I would like to acknowledge Drs. Sanders McDougall and Matt Riggs for their guidance, feedback, and time put into perfecting my thesis.

I would also like to thank my mother Jenny, father Robert, brothers Josh and Nate, sisters-in-law Jenna and Kristin, mother-in-law Mariah Williams, and father-in-law Steve Williams. It was with their love and support that made this possible. Lastly, I would like to take the time to especially thank my wife Amanda Harmony for her patience, love, and support.

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CHAPTER ONE

DRUG ADDICTION

Introduction

Drug addiction is a progressive, complex, and multidimensional disease (Baler & Volkow, 2006; Everitt & Robbins, 2005; Koob & Le Moal, 1997). The National Institute of Drug Addiction (NIDA) defines drug addiction as a "chronic, relapsing brain disease, which is characterized by compulsive drug seeking and use, despite harmful consequences" (NIDA, National Institute of Health [NIH], & US Department of Health and Human Services [UDHHS], 2010). Initial voluntary stages of drug use are typically characterized by reward and feelings of euphoria (Everitt, 2014; Wise & Koob, 2014). However, prolonged drug use leads to a loss of control over drug taking and can eventually result in addiction (Everitt, 2014; Wise & Koob, 2014). A variety of potential factors influence the transition from recreational drug use to drug addiction, including route of administration, genetics, history of drug use, stress, and life events (Koob & Le Moal, 1997). Drug addiction ultimately leaves addicted individuals with detrimental physiological, psychological, behavioral, and sociocultural changes (Everitt, 2014; Everitt & Robbins, 2005; Volkow & Morales, 2015).

The stages of drug addiction are depicted in some theories as a complex, downward spiraling model (Everitt, 2014; Koob, 2000; Koob & Le Moal, 1997). These theories suggest that individuals who possess characteristic behavioral traits (e.g., impulsivity, novelty-seeking, or anxiety) may be more vulnerable to

drug initiation (Everitt, 2014; Koob & Le Moal, 1997). These behavioral traits may lead to acquisition of drug self-administration, wherein drug-cued learning and drug-induced cognitive impairments occur (Everitt, 2014; Koob & Le Moal, 1997). Consequently, continued drug use and habitual drug-taking patterns take form via conditioned reinforcement (Everitt, 2014; Koob & Le Moal, 1997). Initially, addictive drugs act as positive reinforcers, in which positive associations from the drug-taking experience increase the probability of later drug-seeking behavior (Gilpin & Koob, 2008; Wise & Koob, 2014). Continued drug use results in a transition where the user becomes physiologically dependent on the drug (Wise & Koob, 2014). With drug tolerance (i.e., increased reward thresholds) in place, addictive drugs become negatively reinforcing when the probability of drug seeking increases in order to alleviate aversive withdrawal symptoms (Gilpin & Koob, 2008). Following binges and heavy intoxication, compulsive drug use (i.e., addiction) takes hold, resulting in failures in executive control (Everitt, 2014; Koob & Le Moal, 1997). After repeated drug withdrawals, the user is likely to experience relapse (Baler & Volkow, 2006).

Relapse is one of the major problems associated with the treatment of drug addiction (Koob, 2013; Marchant, Li, & Shaham, 2013; Robinson & Berridge, 2008). Drug addiction relapse rates (e.g. 40-60%) are substantial and compare to relapse rates of other major chronic illnesses (McLellan, Lewis, O'Brien, & Kleber, 2000). Prolonged drug use results in repeated drug-associated pairings, such as with social, physical, or emotional contexts (McLellan et al.,

2000). Following periods of abstinence, a drug user may encounter many of these previously drug-paired contexts, which can generate profound psychological reactions (McLellan et al., 2000). Thus, relapse is often driven by the subjective desires or cravings for a drug triggered by previous drug-paired contexts (O'Brien, 2005). In addition, relapse may result from acute re-exposure to the drug or stress (Koob & Le Moal, 1997).

Adolescent drug use is of major concern because of the increased level of detrimental effects associated with early drug exposure (Odgers et al., 2008). For example, exposure to illicit drugs during adolescence is linked to sexually transmitted diseases, teen pregnancy, low educational attainment, and crime (Odgers et al., 2008). Further, illicit drug and alcohol exposure prior to the age of 15 is a robust indicator of substance use disorders in adulthood (Grant & Dawson, 1997).

Cigarette smoking during adolescence is particularly problematic because it leads to a number of adverse consequences. Of specific interest, is the relationship between early onset of cigarette smoking and later use of illicit drugs (Lewinsohn, Rohde, & Brown, 1999). For example, early onset of nicotine use has been associated with early stimulant and marijuana use (Rubinstein, Rait, & Prochaska, 2014; Weinberger & Sofuoglu, 2009). Indeed, approximately 97% of methamphetamine users are regular users of tobacco (Brecht et al., 2004; Brecht, Greenwell, & Anglin, 2007). Moreover, preclinical studies show that early exposure to nicotine can increase the reinforcing effects and reduce the aversive

effects of drugs (e.g., Neugebauer, Harrod, & Bardo, 2010; Pipkin et al., 2014). Importantly, psychostimulant users who also smoke tobacco experience increased stimulant dependence and health problems, as well as poorer treatment outcomes (Weinberger & Sofuoglu, 2009).

In the current proposal, we aim to investigate the effects of nicotine exposure on the reinforcing properties of methamphetamine in adolescent rats. To this end, we will assess adolescent nicotine exposure on acquisition of methamphetamine oral self-administration, extinction, and reinstatement. The following chapters discuss the importance of the adolescent period, relevant neurotransmitter systems, nicotine, methamphetamine, self-administration paradigm, and the rationale for the proposed study.

CHAPTER TWO

ADOLESCENCE

Introduction

Adolescence is a pivotal transitional period during development that bridges the gap between childhood and adulthood. The adolescent period is typically regarded as roughly 10 to 19 years of age and characterized by many different hormonal, physical, psychological, and social changes (Sacks, 2003). Specifically, early adolescence (i.e., ~10-14 years) is characterized by the onset of physical (e.g., onset of puberty), cognitive (e.g., abstract thought), social (e.g., sense of identity), and emotional (e.g., mood swings) development (Blakemore, 2012; Dumontheil, 2014; Marcia, 1980; Sawyer et al., 2012; Zeman, Cassano, Perry-Parrish, & Stegall, 2006). In late adolescence (i.e., ~15-19 years), physical changes begin to subside, while the ability for abstract thought, cognitive control, drive for independence, and emotional regulation continues to develop (Blakemore, 2012; Dumontheil, 2014; Marcia, 1980; Sawyer et al., 2012; Zeman et al., 2006).

The complex changes experienced during adolescence promote increased risk-taking behavior (e.g., substance use, unsafe sex, illegal activities, and dangerous driving) (Bond, Carlin, Thomas, & Patton, 2001; Herrenkohl et al., 2000). Social development in adolescents is characterized by a need for independence, in which less time is spent with parents or family and more time is spent with peer groups (Gorrese & Ruggieri, 2012). Increases in peer-influence

may potentially lead to risky behavior, such as substance use (Berndt, 1979; Spear, 2000). Risk-taking behavior may also result from the positive association with the novelty, complexity, or intensity of a new experience, which often is the reason for adolescent drug initiation (Arnett, 1992).

Throughout adolescence there are many changes in the development of brain areas that responsible for response inhibition, risk, reward, and emotion (Steinberg, 2005). Specifically, subcortical areas (e.g., ventral striatum, nucleus accumbens, hippocampus, and amygdala) involved in emotion, motivation, and reward, develop in early adolescence (Crews, He, & Hodge, 2007; Wetherill & Tapert, 2012). Cortical brain areas such as the prefrontal cortex, which is important in executive functioning (e.g., inhibitory control), do not finalize connections until early adulthood, suggesting that adolescents may lack impulse control and effective decision-making processes, while maintaining increases in motivation, emotion, and reward sensitivity (Casey & Jones, 2010; Luciana, 2013; Steinberg, 2010; Wetherill & Tapert, 2012). Given the weak top-down cognitive control and heightened emotional reactivity evident during normal adolescent brain development, adolescents are susceptible to difficulties with affect, risk-taking, inhibitory control, and reward-related behaviors, all of which play a role in substance initiation and use (Casey & Jones, 2010).

Depending on the brain area and period of development, many neurons in the brain undergo synaptic pruning, in which the number of neural connections are reduced (Giedd et al., 1999; Gogtay et al., 2004). This synaptic pruning leads

to decreased cortical volume and thickness (Giedd et al., 1999; Gogtay et al., 2004). For example, during adolescence, pruning takes place in the amygdala, nucleus accumbens, and prefrontal cortex (Andersen, Thompson, Rutstein, Hostetter, & Teicher, 2000; Teicher, Andersen, & Hostetter, 1995; Zehr, Todd, Schulz, McCarthy, & Sisk, 2006). Although this pruning process is not entirely understood, the neuronal remodeling that occurs during adolescence maybe an essential stage to facilitate developmental plasticity that helps prepare for more mature behavior in adulthood (Crews et al., 2007). However, this period of neuronal change results in adolescents being more vulnerable to alterations in the neuronal environment brought about by psychopharmacological agents (Geier, 2013).

Adolescence and Drug Addiction

Adolescence is a period of increased illicit drug initiation because adolescents often display impulsivity in decision-making (Kalivas & Volkow, 2005). Many adult smokers begin smoking within their teenage years, which often leads to health complications (UDHHS, 2012). Based on a self-report measure of adults with substance use disorders, the median age for illicit drug initiation was 16, and initiation after age 20 was rare (Good & Radcliffe, 2011). Cessation of smoking is more difficult for individuals who begin smoking at an earlier age when compared to those who initiate smoking later in life (Stanton & Grimshaw, 2013). Additionally, nicotine addiction in adolescence develops rapidly, creating difficulty for smoking cessation in this age group (DiFranza &

Richmond, 2008). The use of nicotine in adolescence produces a more sensitive response to the positive rewarding and reinforcing effects of nicotine (Torres, Tejeda, Natividad, & O'Dell, 2008; Kota, Martin, Robinson, & Damaj, 2007).

Similar to nicotine, methamphetamine is a highly addictive psychoactive drug that poses enormous problems for society (Panenka et al., 2013). Due to the relatively easy synthesis and production, as well as the highly addictive nature of methamphetamine, the drug has become one of the most widely used and distributed psychostimulants in the world (United Nations Office on Drugs and Crime [UNODC], 2010). In a 2010 Monitoring the Future study, it was found that adolescent methamphetamine use among high school students was 1.6% (Panenka et al., 2013). Although methamphetamine use in adolescence declined in 2010, the prevalence rates for methamphetamine use have fluctuated substantially throughout past decades (Johnston, O'Malley, Bachman, & Schulenberg, 2012). Evidence from animal models suggest that adolescents may be more vulnerable to the effects of methamphetamine and other drugs of abuse, because they are less sensitive to withdrawal and can develop robust drug sensitization when drug use initiates in early to mid-adolescence (Schramm-Sapyta, Walker, Caster, Levin, Kuhn, 2009).

Given the many neurological changes during adolescence, the effects of psychostimulants like nicotine and methamphetamine on the vulnerable adolescent brain need to be considered in more detail. In order to study the effects of these addictive psychostimulants on the adolescent brain and resulting

behavior, it is imperative to understand changes in relevant neurotransmitter systems across the period of adolescence. Therefore, the following two chapters will give an overview of the cholinergic and monoamine neurotransmitter systems.

CHAPTER THREE

ACETYLCHOLINE

Introduction

Acetylcholine (ACh) was the first neurotransmitter to be identified and is found in both the central and peripheral nervous systems (Sofuoglu & Mooney, 2009; Stjärne, 1999). Peripheral action of ACh at the neuromuscular junction is vital for skeletal and cardiac muscle contraction (Brown, Wetzel, & Dunlap, 1982; Fambrough, 1979). Within the central nervous system (CNS), ACh is involved in numerous psychological processes, including addiction, attention, arousal, motivation, mood, reward, learning, memory, and stress (Acquas, Wilson, & Fibiger, 1996; Mansvelder & McGehee, 2002; Pepeu & Blandina, 1998; Poorthuis & Mansvelder, 2013; Robbins, 1997; Thiel, Huston, & Schwarting, 1998; Warner-Schmidt et al., 2012). Neurological and psychiatric disorders that are due to cholinergic dysfunction include, Parkinson's, Alzheimer's, bipolar disorder, schizophrenia, and substance use disorders (Lester, Rogers, & Blaha, 2010; Levin, 2012; Maskos, 2008; McEvoy & Allen, 2002).

Acetylcholine Synthesis, Release, and Catabolism

The synthesis of ACh is initiated in the presynaptic terminals of cholinergic neurons. Within these cholinergic neurons, ACh is formed from the two compounds choline and acetyl-CoA in the presence of the enzyme choline acetyltransferase (ChaT) (Parsons, Prior, & Marshall, 1993; Prado et al., 2002;

Scremin & Jenden 1993). In addition to producing ACh, ChaT levels are often used as a marker to determine if a neuron is cholinergic (Kimura, McGeer, Peng, & McGeer, 1980). Intracellular choline concentrations are determined by the uptake of choline into the presynaptic axon terminal by the high-affinity choline transporter (CHT1) (Bellier & Kimura, 2011; Simon, Atweh, & Kuhar, 1976). In the process of ACh synthesis, choline serves as the rate-limiting step (Bellier & Kimura, 2011; Simon et al., 1976). After formation, ACh is then accumulated in synaptic vesicles by the actions of the vesicular acetylcholine transporter (VAChT) (Parsons et al., 1993; Prado et al., 2002; Scremin & Jenden, 1993).

In response to an action potential reaching the axon terminal, an influx of extracellular calcium (Ca^{2+}) enters the neuron through voltage-gated Ca^{2+} channels. ACh containing vesicles then bind to the cytosolic neuronal membrane, allowing for the subsequent release of ACh into the synaptic cleft (Dunant & Israel, 2000; Langley & Grant, 1997; Lima, Prado, Prado, & Kushmerick, 2010). The action of ACh containing vesicles fusing to the neuronal membrane is promoted by the binding of vesicle soluble N-ethylmaleimide-sensitive-factor attachment-protein receptor, or v-SNARE to a corresponding target SNARE (t-SNARE) on the active zone of the cytoplasmic membrane (Dunant & Israel, 2000; Israel & Dunant, 1998).

The release of ACh by the presynaptic neuron into the synaptic cleft results in diffusion of ACh to the post-synaptic neuron, where ACh either binds to cholinergic receptors and/or is subjected to enzymatic degradation by

acetylcholinesterase (AChE) into choline and acetic acid (Prado, Roy, Kolisnyk, Gros, & Prado, 2013; Silman & Sussman, 2005). The choline is then recycled back into the terminal of the presynaptic neuron by uptake, predominately carried out by CHT1 (Matsuo et al., 2011).

Acetylcholine Receptors and Subtypes

ACh receptors are divided into two major classes: muscarinic (mAChRs) and nicotinic (nAChRs) receptors (Picciotto, Higley, & Mineur, 2012). The receptors were named based on the drugs that bound to them. Specifically, the stimulant nicotine binds to nAChRs, whereas the psychoactive ingredient in certain mushrooms, muscarine, binds to mAChRs (Haga, 2013; Papke, 2014). The mAChRs are metabotropic receptors, which promote the initiation of second messenger systems and indirectly open ion channels on the post-synaptic neuron (Wess, 2003). The five subtypes of mAChRs (i.e., $M_{1\text{-}5}$) are all classified as G-protein-coupled receptors, of which the M_1, M_3, and M_5 type belong to the G_q family, whereas M_2 and M_4 belong to the $G_{i/o}$ family (Caulfield & Birdsall, 1998; Haga, 2013; Picciotto et al., 2012; Wess, 1996). The action of mAChRs is initiated when ACh binds to the metabotropic receptor that is attached to intercellular G-proteins (Ishii & Kurachi, 2006). Following this initial binding, mAChRs belonging to the G_q family (i.e., M_1, M_3, and M_5) begin an information cascade (Haga, 2013; Ishii & Kurachi, 2006). This signaling pathway starts with the activation of phospholipase C (PLC), which initiates the phosphatidylinositol 4,5-bisphosphate (PIP_2) cascade by hydrolyzing PIP_2 into diacylglycerol (DAG)

and inositol 1,4,5-triphosphate (IP_3). Intracellular Ca^{2+} is mobilized by IP_3 and protein kinase C (PKC) is activated by DAG and Ca^{2+} (Berridge, & Irvine, 1984; Haga, 2013; Ishii & Kurachi, 2006). The second messenger signaling of mAChRs belonging to the $G_{i/o}$ family (i.e., M_2 and M_4) differs from receptors of the G_q family, in that they inhibit adenylyl cyclase from converting ATP into cyclic AMP, which decreases cAMP production and protein kinase A activity (Haga, 2013; Ishii & Kurachi, 2006; Nathanson, 2000; Onali & Olianas, 1995; Wess, 1996). In addition to decreasing cAMP, mAChRs of the $G_{i/o}$ type also act on G protein-coupled potassium (K^+) channels, which allows for the efflux of K^+ and the hyperpolarization of the neuronal membrane, ultimately inhibiting action potentials (Haga, 2013; Ishii & Kurachi, 2006).

In contrast to mAChRs, nAChRs function as ionotropic receptors that act as non-selective cation channels (Picciotto, Caldarone, King, & Zachariou, 2000). The 11 different neuronal nAChR subtypes are homomeric or heteromeric and are composed of five different α or β subunits (Picciotto et al., 2000; Picciotto et al., 2012). After the direct binding of ACh to the two α or β subunits, the nAChRs open and allow for the influx of Ca^{2+} and sodium (Na^+) into the cytoplasm, leading to the depolarization of the post-synaptic neuron (Beker, Weber, Fink, & Adams, 2003; Picciotto et al., 2000). nAChRs are dispersed along the post-synaptic terminal and are also found on the presynaptic terminal, whereas nAChRs at the neuromuscular junction are found directly opposite from ACh release sites, thus facilitating rapid muscle movement (McGehee, Heath, Gelbert,

Devay, & Role, 1995; Pires-Oliveira, Moen, & Akaaboune, 2013; Vidal & Changeux, 1993).

Acetylcholine Innervation

There is extensive cholinergic innervation because of the essential action of ACh at synapses in both the CNS and at the neuromuscular junction of the peripheral nervous system (PNS) (Picciotto et al., 2012; Pires-Oliveira et al., 2013; Ren et al., 2011; Zaborszky et al., 2008). Within the CNS, cholinergic neurons are found in various brain nuclei, including the pedunculopontine and laterodorsal tegmental areas, the medial habenula, and the basal forebrain complex, with widespread projections all over the brain (Picciotto et al., 2012). The widespread effects of ACh on behavior are largely due to the diffuse nature of the cholinergic system. Interestingly, ACh can function as a neuromodulator in the mesolimbic dopamine (DA) system, which is important for reward and addiction (Fagen, Mansvelder, Keath, & McGehee, 2003); Mansvelder, De Rover, McGehee, & Brussaard, 2003).

Nicotinic Acetylcholine Receptor Development

Due to the large number of adolescents who smoke cigarettes (World Health Organization [WHO], 2001), it is important to examine the development of nicotinic acetylcholine receptors (nAChRs). The expression and functional properties of nAChRs often vary across childhood, adolescence, and adulthood (Slotkin, 2002), which the expression of some nAChR subunits (e.g., α_2 and α_3 in

the thalamus; α_4 in the cortex, thalamus, and brainstem; α_7 in the thalamus and brainstem; β_2 in most brain areas besides the striatum) are constant across development (Zhang, Liu, Miao, Gong, & Nordberg, 1998). The widely dispersed nAChR $\alpha_4\beta_2$ that is involved in learning processes, is expressed more in early adolescence than adulthood within 33 different brain areas (Doura, Gold, Keller, & Perry, 2008). Another nAChR involved in long-term memory, α_7 is also expressed more in early adolescence than adulthood within 12 different brain regions (Doura et al., 2008). DA release via nAChR stimulation in midbrain (i.e., ventral striatal) DA neurons is heightened during adolescence when compared to adulthood (Azam, Chen, & Leslie, 2007). The latter finding is important because, the addictive and reinforcing properties of nicotine involves ventral striatal DA release (Corrigall, Franklin, Coen, & Clarke, 1992; Imperato, Mulas, & Di Chiara, 1986; Nisell, Nomikos, & Svensson, 1995).

Therefore, many changes in the cholinergic system relating to nAChRs are evident in early postnatal development, which some receptor changes occur during the adolescent period (Dwyer, McQuown, & Leslie, 2009). Pivotal changes in the development of the adolescent cholinergic system may leave this system vulnerable to pharmacological insult via certain drugs of abuse (i.e., nicotine). Thus, early postnatal and adolescent nicotine exposure may alter brain structure and function later on in life (Dwyer et al., 2009).

CHAPTER FOUR

MONOAMINE NEUROTRANSMITTERS

Introduction

Monoamine neurotransmitters are characterized as containing one amino group attached to an aromatic ring via a two-carbon chain. Specifically, catecholamine neurotransmitters are a type of monoamine neurotransmitter that contain a catechol and side chain amine (Fernstrorn & Fernstrom, 2007). There are three different catecholamine neurotransmitters that are derived from the amino acid tyrosine: dopamine (DA), norepinephrine (NE), and epinephrine (Fernstrorn & Fernstrom, 2007). An important indolamine synthesized from tryptophan is the neurotransmitter serotonin (5-HT) (Fidalgo, Ivanov, & Wood, 2012). Due to the relevance of these neurotransmitter systems to the present study, the catecholamine neurotransmitters DA and NE, as well as the indolamine 5-HT, will be discussed in the following sections.

Dopamine

The dopaminergic system is known to mediate a number of behaviors, including motivation, sleep and wake cycle, learning, mood, cognition, movement, addiction, and reward (Alcaro, Huber, & Panksepp, 2007; Dzirasaet al., 2006; Gorwood et al., 2012; Plowman & Kleim, 2011; Salamone & Correa, 2012; Schultz, 2010; Yacubian & Buechel, 2009). Psychological and neurological diseases or disorders stemming from dopaminergic dysfunction include

Parkinson's, schizophrenia, Tourette's syndrome, anxiety, depression, attention-deficit hyperactivity disorder (ADHD), and substance use disorders (Bisaglia, Greggio, Beltramini, & Bubacco, 2013; Buse, Schoenefeld, Münchau, & Roessner, 2013; de la Mora, Gallegos-Cari, Arizmendi-García, Marcellino, & Fuxe, 2010; del Campo, Chamberlain, Sahakian, & Robbins, 2011; El Mansari et al., 2010; Grace, 2010; Schmitt & Reith, 2010).

Dopamine Synthesis, Release, and Catabolism

The synthesis of DA begins in the terminal of the presynaptic neuron, where the amino acid tyrosine is converted into L-dihydroxyphenylalanine (L-DOPA) in the presence of tyrosine hydroxylase (Elsworth & Roth, 1997; Feve, 2012; Haavik & Toska, 1998; Icard-Liepkalns et al., 1993). L-DOPA is then converted into DA in the presence of aromatic amino acid decarboxylase (DOPA decarboxylase) (Bertoldi, 2014; Elsworth & Roth, 1997; Feve, 2012). Tyrosine hydroxylase is the rate-limiting step in the process of DA synthesis and production (Elsworth & Roth, 1997; Haavik & Toska, 1998). Vesicular monoamine transporters (VMAT), which are found at both dendrites and the axon terminals of dopaminergic neurons, store DA in synaptic vesicles (Elsworth & Roth, 1997; Henry et al., 1994; Pifl et al., 2014).

Similar to ACh release, the release of DA and other classical monoamine neurotransmitters (e.g., NE and 5-HT) occurs through Ca^{2+}−dependent exocytosis into the synaptic cleft (Jaffe, 1998; Sofuoglu & Sewell, 2009; Suedhof, 2012). Following release from the presynaptic terminal, DA either diffuses into

the synaptic cleft to bind with DA receptors on the presynaptic or post-synaptic terminal, or undergoes reuptake into the presynaptic terminal by DA transporters (DAT) (Elsworth & Roth, 1997).

The process of reuptake by DAT is critical in maintaining consistent intra- and extracellular DA levels through the recycling of DA (Elsworth & Roth, 1997; Schmitt, Rothman, & Reith, 2013; Vaughan & Foster, 2013). DAT also serves as a marker to distinguish dopaminergic neurons through use of ligands and antibodies. DAT functions as the site of action for some psychostimulants, such as methamphetamine (Elsworth & Roth, 1997; Schmitt et al., 2013; Vaughan & Foster, 2013). Once DA is transported into the presynaptic neuron, it is either repackaged into vesicles for reuse or is enzymatically degraded into a number of different metabolites (Elsworth & Roth, 1997). Catabolism of DA depends on the cell type, brain region, and species (Elsworth & Roth, 1997). In the striatum, monoamine oxidase (MAO) located on the outer membrane of mitochondria is the enzyme that converts DA into 3,4-dihydroxyphenylacetic acid (DOPAC), which is then converted into homovanillic acid (HVA) by the enzyme catechol O-methyltransferase (COMT) located in the cytoplasm (Elsworth & Roth, 1997; Goldstein & Lieberman, 1992; Napolitano, Cesura, & Da Prada, 1995). In rodents, the main end product of DA degradation is DOPAC, whereas HVA is the main DA metabolite in humans (Elsworth & Roth, 1997).

Dopamine Receptors and Subtypes

There are five subtypes of dopamine receptors (i.e., D_1-D_5), all of which are heterotrimeric G protein-coupled receptors (Ares-Santos, Granado, & Moratalla, 2013; Beaulieu & Gainetdinov, 2011; Elsworth & Roth, 1997). There are two major families of DA receptors, with D_1 and D_5 receptors belonging to the D_1-like family, and D_2, D_3, and D_4 receptors belonging to the D_2-like family (Ares-Santos et al., 2013; Beaulieu & Gainetdinov, 2011; Elsworth & Roth, 1997).

When DA binds to receptors of the D_1-like family on the post-synaptic membrane, it causes the $G_{\alpha s/olf}$ proteins to activate adenylyl cyclase, which then activates the second messenger molecule cAMP that increases the enzyme PKA. Increases in PKA leads to the phosphorylation of neuronal proteins, regulation of ion channel functioning, and depolarization of the post-synaptic neuron (Ares-Santos et al., 2013; Beaulieu & Gainetdinov, 2011; Vallone, Picetti, & Borrelli, 2000).

When DA binds to receptors of the D_2-like family on either the pre- or post-synaptic membrane, it causes the $G_{\alpha i/o}$ proteins to inhibit activation of adenylyl cyclase. Inhibition of adenylyl cyclase leads to the inhibition of cAMP and PKA activity, inducing hyperpolarization of the receptor bound neuron (Ares-Santos et al., 2013; Beaulieu & Gainetdinov, 2011; Missale et al., 1998; Vallone et al., 2000). D_1 and D_2 receptor subtypes are diffuse within the brain and exist in all known dopaminergic projections, with high concentrations in the striatum,

nucleus accumbens, olfactory bulb, amygdala, frontal cortex, substantia nigra, and at lower levels in the hippocampus and ventral tegmental area (Ares-Santos et al., 2013; Beaulieu & Gainetdinov, 2011; Gangarossa et al., 2012).

Dopamine Innervation

The primary production of DA occurs in the neurons of the substantia nigra and ventral tegmental area (Baik, 2013). The neuronal projections from these brain areas make up three major dopaminergic pathways: mesolimbic, mesocortical, and nigrostriatal (Maharajan, Maharajan, Ravagnan, & Paino, 2001). The nigrostriatal pathway consists of dopaminergic neurons projecting from the substantia nigra to the striatum (Dahlstrom & Fuxe, 1964; Janhunen & Ahtee, 2007). The mesocortical pathway consists of dopaminergic neurons projecting from the ventral tegmental area to the frontal cortex (Sogabe, Yagasaki, Onozawa, & Kawakami, 2013). The mesolimbic pathway is comprised of dopaminergic neurons from the ventral tegmental area projecting to the nucleus accumbens (Ikemoto, 2007; Koob, 1992; Wise, 1996). The mesolimbic pathway, involved in the regulation of reward, motivation, and emotion, is subject to physiological changes following repeated exposure to addictive substances (Baik, 2013; Nestler & Carlezon, 2006). The changes to the mesolimbic system produced by certain addictive drugs are thought to be responsible for drug dependence (Thomas, Kalivas, & Shaham, 2008).

Dopaminergic System Development

Development of the dopaminergic system is important to examine because stimulants like methamphetamine bind to vesicular DA transporters, causing the release of DA into the synaptic cleft (Courtney & Ray, 2014). The expression of DA receptor subtypes varies across developmental periods (Spear, 2010). At birth, D_1 and D_2 receptors are present in the striatum, but by PD 15 D_1 receptors begin to increase in density (Gelbard, Teicher, Faedda, & Baldessarini, 1989). By adulthood, there is a three-fold increase in D_1 receptors, compared to D_2 receptors in the striatum (Gelbard et al., 1989). D_1 receptor expression peaks in the striatum around PD 40 and then stabilizes to adult levels around PD 60 (Gelbard et al., 1989; Teicher et al., 1995). This increase in D_1 receptor expression may be important for the early development of the basal ganglia (Meng, Ozawa, Itoh, & Takashima, 1999).

D_2 receptors also increase in density across early development and adolescence, peaking around PD 21-28, followed by a reduction in receptor density going into adulthood (Demotes-Mainard, Henry, Jeantet, Arsaut, & Arnauld, 1996; Murrin & Zeng, 1986; Tarazi, Tomasini, & Baldessarini, 1998). Within the striatum, D_2 receptors develop at the same rate, but with less density than D_1 receptors (Andersen et al., 2000; Teicher et al., 1995). Within the limbic system, D_3 receptor expression is observed as early as PD_3 and increases in receptor density occur through adulthood (Demotes-Mainard et al., 1996; Fallon, Riley, Sipe, & Moore, 1978). Further, DAT levels are increased during

adolescence when compared to adulthood (Meng et al., 1999). Innervation of DA neurons from the striatum and midbrain to the prefrontal cortex peaks during adolescence (Benes, Taylor & Cunningham, 2000). Thus, alterations in the dopaminergic system may cause adolescents to express heightened reward sensitivity compared to adults, which leaves this group particularly vulnerable to substance use (Geier, 2013).

Norepinephrine

Within the CNS, NE is involved in a variety of behavioral outcomes, including attention, arousal, cognition, impulsivity, memory, emotion, stress, drug seeking, and reward (Flavin & Winder, 2013; Goddard et al., 2010; Hamon & Blier, 2013; Howells, Stein, & Russell, 2012; Logue & Gould, 2014; Pattij & Vanderschuren, 2008; Sofuoglu & Sewell, 2009; Tully & Bolshakov, 2010). Dysfunction of the noradrenergic system results in various disorders and diseases, ranging from ADHD, major depressive disorder, anxiety disorders, bipolar disorder, to addiction and substance use disorders (Belujon & Grace, 2011; El Mansari et al., 2010; Fitzgerald, 2013; Goddard et al., 2010; Park, Caballero, & Omidian, 2014; Pervanidou, 2008; Sofuoglu & Sewell, 2009; Swan, 2010).

Norepinephrine Synthesis, Release, and Catabolism

NE is synthesized from DA in the presence of dopamine-β-hydroxylase (Ressler & Nemeroff, 1999; Sofuoglu & Sewell, 2009). The synthesis of NE can

occur in either DA containing vesicles or NE is transferred from the cytoplasm into synaptic vesicles by VMAT and is stored in the axon terminal (Ressler & Nemeroff, 1999; Sofuoglu & Sewell, 2009).

Following Ca^{2+}−dependent exocytosis, NE undergoes reuptake by the NE transporter (NET) and is reused, or MAO enzymatically destroys NE (Bönisch, & Brüss, 2006; Ressler & Nemeroff, 1999; Sofuoglu & Sewell, 2009). MAO converts NE into aldehyde, which is then converted into either 3,4-dihydroxyphenylglycol (DHPG) or 3,4-dihydroxymandelic acid (DHMA) by dehydrogenase or reductase enzymes (Ressler & Nemeroff, 1999). COMT continues to catabolize these compounds, especially when NE levels are high (Huotari et al., 2002; Ressler & Nemeroff, 1999).

Norepinephrine Receptors and Subtypes

Noradrenergic receptors can be activated by both NE and epinephrine, and are G protein-coupled receptors that exist in two major family types, α or β receptors (Bylund et al., 1994). The α receptors are divided into α_1 and α_2 adrenergic families (Bylund et al., 1994). The α_1 receptor family is divided into α_{1A}, α_{1B}, and α_{1D} subtypes, whereas the α_2 adrenergic family is divided into α_{2A}, α_{2B}, and α_{2C} subtypes (Bylund et al., 1994; Oh et al., 2013; Segura et al, 2010). The α_1 family is mostly comprised of post-synaptic excitatory G_q protein coupled receptors, which activates PLC (Sofuoglu & Sewell, 2009). The α_2 adrenoreceptors are located on pre- and post-synaptic terminals and are coupled

to the $G_{i/o}$ protein, which inhibits adenylyl cyclase (Sofuoglu & Sewell, 2009). The inhibition of adenylyl cyclase results in a reduction of cAMP production, causing hyperpolarization of the neuronal membrane and reduced neuronal firing (Stojilkovic, 2012).

The β adrenoreceptors are divided into β_1, β_2, and β_3 subtypes and are coupled to the G_s protein, which activates adenylyl cyclase (Sofuoglu & Sewell, 2009). Activation of adenylyl cyclase results in the conversion of ATP into cAMP, leading to changes in ion channels and subsequent depolarization of the neuronal membrane (Stojilkovic, 2012).

Norepinephrine Innervation

Noradrenergic nuclei are primarily found in the locus coeruleus of the brain stem and project to nearly every area of the brain (Szabadi, 2013). In comparison to the dopaminergic system, the DA projections from the ventral tegmental area and substantia nigra are relatively limited when compared to NE neuronal projections extending from the locus coeruleus (Ressler & Nemeroff, 1999).

Noradrenergic System Development

Like other neurotransmitter systems, the NE system experiences changes in NE release and receptor expression throughout development. For example, social stress occurring during early adolescence (i.e., PD 28), but not mid-adolescence (i.e., PD 42) produces heightened spontaneous locus coeruleus

discharge, and attenuates responsiveness to sensory stimuli (Bingham et al., 2011). Cerebral β-adrenoreceptor expression rapidly increases between PD 10 and PD 21, after which receptor expression remains fairly constant up to mid-adolescence (i.e., PD 42), but then quickly attenuates thereafter (Pittman, Minneman, & Molinoff, 1980). In contrast, cerebellar β-adrenoreceptor expression rises slowly from PD 5 to PD 42, where receptor levels are constant up to at least 6 months of age (Pittman et al., 1980). Due to the remodeling that the noradrenergic system undergoes during development and adolescence, in particular, it is possible that adolescent stimulant exposure produces fundamental changes in the NE system during this vulnerable time period (Trauth, Seidler, Ali, & Slotkin, 2001). Adolescent stimulant exposure to nicotine or methamphetamine may fundamentally alter noradrenergic and dopaminergic systems, potentially resulting in heightened reward sensitivity and susceptibility to drug abuse (Trauth et al., 2001).

Serotonin

5-HT is a monoamine found in both the PNS and CNS (Fidalgo et al., 2012). In the PNS, roughly 95% of the 5-HT is produced within enterochromaffin cells of the digestive tract (Gershon, 2004). In the CNS, 5-HT is readily produced from neurons originating in the raphe nuclei of the brain stem (Adell, Celada, Abellán, & Artigas, 2002). 5-HT is involved in a wide variety of neuropsychological processes, including cognition, decision-making, learning,

memory, appetite, sleep, sexual desire, social behavior, mood, and emotion (Cowen & Sherwood, 2013; Homberg, 2012; Lam, Garfield, Marston, Shaw, & Heisler, 2010; Kiser, Steemers, Branchi, & Homberg, 2012; Menese & Liy-Salmeron, 2012; Montgomery, Baldwin, & Riley, 2002; Monti, 2011). Dysfunction of the serotonergic system is related to a number of disorders, such as Parkinson's disease, Alzheimer's disease, schizophrenia, depression, anxiety, phobias, panic attacks, post-traumatic stress disorder, antisocial behavior, drug abuse, addiction, and substance use (Eggers, 2013; Fernandez & Gaspar, 2012; Huot & Fox, 2013; Kirby, Zeeb, & Winstanley, 2011; Meltzer, 1989; Nordquist, & Oreland, 2010; Rodríguez, Noristani, & Verkhratsky, 2012).

Serotonin Synthesis, Release, and Catabolism

The synthesis of 5-HT can occur in either the soma or axon terminal of serotonergic neurons (Daszuta, Hery, & Faudon, 1984; Daszuta, Faudon, & Hery, 1984). 5-HT is derived from tryptophan, which is obtained from the diet (Leathwood, 1987). Tryptophan is converted into 5-hydroxy-l-tryptophan (5-HTP) by the enzyme l-tryptophan-5-monooxygenase hydroxylase (tryptophan hydroxylase), which serves as the rate-limiting step in the biosynthesis of serotonin (Boadle-Biber, 1993; Fidalgo, et al., 2012; Leathwood, 1987; Tyce, 1990). 5-HTP is then converted into 5-HT by the enzyme aromatic-l-amino-acid decarboxylase (DOPA decarboxylase) (Boadle-Biber, 1993; Fidalgo, et al., 2012; Leathwood, 1987; Tyce, 1990). Newly formed 5-HT is then packaged into secretory synaptic vesicles for protection against degradation by MAO and to

await release into the synaptic cleft via Ca^{2+}−dependent exocytosis (Jorgensen, Christensen, & Gether, 2014; Tamir, & Gershon, 1990).

Following release into the synaptic cleft, 5-HT either binds to pre- or post-synaptic 5-HT receptors and/or is removed from the synaptic cleft by the 5-HT transporter (SERT) through active reuptake into the presynaptic terminal (Fuller, 1986; Ni & Watts, 2006; Südhof, 2008). After reuptake, 5-HT is either repackaged or undergoes enzymatic degradation (Duncan, Johnson, & Xiao-Ming, 2012). The removal of 5-HT from the synaptic cleft is essential to avoid potentially deadly levels of extracellular 5-HT (i.e., serotonin syndrome) (Squires, Talbot, Rubakhin, & Sweedler, 2007). 5-HT catabolism within the CNS begins when MAO converts 5-HT into 5-hydroxy-3-indole acetaldehyde (5-HAIL), which is further broken down into 5-hydroxy-3-indoleacetic acid (5-HIAA) by aldehyde dehydrogenase (Squires et al., 2006).

Serotonin Receptors and Subtypes

5-HT receptors are classified into seven major types: 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7 (Berger, Gray, & Roth, 2009; Hoyer, Hannon, & Martin, 2002). All seven types, with the exception of the 5-HT_3 ligand-gated ion channel, are G-protein-coupled receptors (Hoyer et al., 1994; Nichols & Nichols, 2008). Specifically, the 5-HT_1 family (i.e., 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_{5A}, and 5-HT_{5B}) are $G_{i/o}$ coupled receptors that, when activated, cause the inhibition of adenylyl cyclase and decrease the production of cAMP (Hamel, 1999; Hartig, Branchek, & Weinshank, 1992; Kobilka et al., 1987; Lovenberg et

al., 1993; Noda, Higashida, Aoki, & Wada, 2004; Wacker et al., 2013; Watts & Neve, 2005; Wisden et al., 1993). The 5-HT_2 family (i.e., 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}) are $G_{q/11}$ coupled receptors that cause the hydrolysis of membrane phosphoinositides into DAG and inositol phosphates (Belmer et al., 2014; Chambers & Nichols, 2002; Facchinetti, & Russo de Boland, 2001; Huidobro-Toro, Valenzuela, & Harris, 1996). DAG and inositol phosphates then work as signaling molecules that ultimately lead to PKC activation or elevation of intracellular calcium, respectively (Nichols & Nichols, 2008). The 5-HT_4, 5-HT_6, and 5-HT_7 families are G_s coupled receptors that, when bound to lead to adenylyl cyclase activation, result in the conversion of ATP into cAMP (Hamblin, Guthrie, Kohen, & Heidmann, 1998; Kang et al., 2005; Nedi, White, Coupar, & Irving, 2011). The 5-HT_3 receptor is a ligand-gated ion channel composed of five subtypes (i.e., 5-HT_{3A}, 5-HT_{3B}, 5-HT_{3C}, 5-HT_{3D}, and 5-HT_{3E}) (Massoura, Dover, Newman, & Barnes, 2011; Takimoto et al., 2014). When 5-HT binds to the 5-HT_3 receptor, an excitatory post-synaptic potential occurs on the neuronal membrane (Barnes, Hales, Lummis, & Peters, 2009; Connolly & Wafford, 2004).

Serotonin Innervation

The brain is innervated by serotonergic neurons that primarily arise from raphe nuclei of the brain stem, and a smaller amount of neurons from the lateral reticular formation (Hornung, 2003). Serotonergic neurons extending from the raphe nuclei can be divided into a rostral group, which projects to areas of the mesencephalon, rostral pons, and forebrain, and a caudal group, which projects

to the caudal pons, caudal medulla oblongata, brain stem, and spinal cord (Hornung, 2003; Moore, Halaris, & Jones, 1978). The rostral projections account for 85% of 5-HT within the brain, most of which project to the ventral tegmental area and interpeduncular nucleus (Halliday & Tork, 1986; Hornung, 2003).

Serotonergic System Development

In the rodent brain, 5-HT levels peak in early development (i.e., PD 21-30) and gradually decline to adult levels (Hedner, Lundell, Breese, Mueller, & Hedner, 1986; Murrin, Sanders, & Bylund, 2007; Toth & Fekete, 1985). The number of 5-HT synapses within the basal forebrain increases from birth to PD 14, followed by a rapid decline during early adolescence (Dinopoulos, Dori, & Parnavelas, 1997; Dori, Dinopoulos, & Parnavelas, 1998). 5-HT receptor subtypes are also expressed in different time periods and brain regions, with peaks either at birth or just before adolescence (Bar-Peled et al., 1991; Morilak & Ciaranello, 1993; Vizuete et al., 1997). For example, cortical 5-HT_{2A} receptors (Morilak & Ciaranello, 1993), as well as striatal and hippocampal 5-HT_{7} receptors (Vizuete et al., 1997) are in greatest numbers immediately before adolescence and steadily decline to adult levels, whereas 5-HT_{1A} receptors reach peak expression at birth, but rapidly decline across adolescence and into adulthood (Bar-Peled et al., 1991; Burnet, Eastwood, & Harrison, 1994; Daval, Vergé, Basbaum, Bourgoin, & Hamon, 1987). 5-HT turnover in the nucleus accumbens also shows ontogenetic differences, as 5-HT turnover is 4 times less during adolescence than during the preweanling period or adulthood (Spear, 2000). It is

possible that decreased serotonergic activity across adolescence contributes to heightened anxiety and hypersensitivity to mild stressors (Depue & Spoont, 1986). It is clear the 5-HT system undergoes many changes beginning at birth, through childhood, adolescence, and into adulthood. Thus, the adolescent serotonergic system remains increasingly vulnerable to pharmacological induced neuronal changes (Chambers, Taylor, & Potenza, 2003).

CHAPTER FIVE

NICOTINE

Introduction

Nicotine is a psychostimulant drug with strong addictive properties. Nicotine is used in a variety of products, such as cigarettes, chewing tobacco, snuff, nicotine gum or patches, and most recently electronic cigarettes (Fagerstrom, Schneider, & Lunell, 1993; Farsalinos & Polosa, 2014; Hoffmann & Hoffmann, 1997; Puri, Chaudhary, Srivastava, Tiwari, 2013). Of the various nicotine products, cigarettes are the most popular, with worldwide cigarette smoking resulting in about 6 million deaths a year, and is predicted to be the cause of nearly 1 billion deaths within the 21st century (Farsalinos & Polosa, 2014; Yach, 2014). Lung cancer remains the leading cause of cancer related deaths, in which 80-90% of lung cancer deaths are attributed to cigarette smoking (Centers for Disease Control and Prevention [CDC], 2008; Henley et al., 2014). In addition, cigarette smoking remains one of the most difficult stimulant addictions to treat, with a relapse rate of around 90-95% in unaided quit attempts within one year of the cessation date (Bancej, O'Loughlin, Platt, Paradis, & Gervais, 2007; Hughes, Keely, & Naud, 2004; Lydon, Wilson, Child, & Geier, 2014; Van Zundert, Ferguson, Shiffman, & Engels, 2012).

Mechanism of Action and Pharmacokinetics

When smoke particles containing nicotine are inhaled, nicotine is rapidly absorbed through the lungs and into the bloodstream, where it quickly moves to the brain (Benowitz, 2010; Weinberger & Sofuoglu, 2009). After crossing the blood-brain barrier, nicotine binds to nAChRs (Clader & Yuguang, 2005; Dajas-Bailador & Wonnacott, 2004; Dani & Bertrand, 2007). Increased ACh release results in augmented release of other neurotransmitters, such as DA (Benowitz, 2010). Nicotine-induced DA release from ventral tegmental area neurons projecting to the nucleus accumbens are a pivotal component in nicotine-induced pleasure and reward (Dani & De Biasi, 2001; Nestler, 2005; Picciotto & Corrigall, 2002).

Nicotine augments the release of glutamate in the VTA, which promotes the release of DA in the nucleus accmubens (Mansvelder & McGehee, 2000; 2002). Conversely, *γ*-aminobutyric acid (GABA) release in the VTA inhibits DA release in the nucleus accmubens (Mansvelder & McGehee, 2000; 2002). Continual binding of nicotine causes some of the nicotinic ACh receptors to become desensitized (Mansvelder & McGehee, 2000; 2002). This desensitization results in a diminished inhibition of DA release, while glutamate continues to augment DA release (Benowitz, 2010; Mansvelder & McGehee, 2000; 2002).

Behavioral and Physiological Effects

Following cigarette smoking, a smoker will typically feel sensations of stimulation and pleasure, as well as a reduction in stress and anxiety (Benowitz,

2009). Additional behavioral effects of nicotine include augmented finger tapping, focused and sustained attention, as well as improved reaction time, recognition memory, and reasoning (Heishman, 1999). Physiological effects of nicotine include decreases in body weight, as well as increases in heart rate and blood pressure (Heishman, 1999; Omvik, 1996). When a smoker stops smoking, they will often experience aversive withdrawal symptoms, such as anxiety, difficulty concentrating, irritability, and restlessness (Benowitz, 2010; Heishman, 1999). Therefore, smokers need nicotine to relieve aversive symptoms during withdrawal (Jarvik, 1991). It is believed that chronic cigarette use is partly due to this negative reinforcement (Jarvik, 1991).

Adolescent Cigarette Smoking

Cigarette smoking is most likely to begin during adolescence (Chen & Kandel, 1995; Lantz, 2003). Among adult smokers within the United States, nearly 90% of them began smoking before the age of 18 (CDC, 2013). The prevalence rates for tobacco product use among middle school and high school students are 6.7% and 23.3%, respectively (CDC, 2013). Additionally, the rate of increase in cigarette smoking among adolescents is striking, with 3,000 American children under the age of 18 beginning to smoke each day (Slotkin, 2002). This is particularly concerning given that smoking is the main causal factor in nearly 30% of all cancer-related deaths (CDC, 2008; Henley et al., 2014).

Nicotine as a Gateway Drug

Gateway theories of drug addiction propose that psychological and neurobiological mechanisms of less deleterious drugs (e.g., nicotine or alcohol) function as a gateway to more dangerous hard drugs of abuse (e.g., methamphetamine or cocaine) (Kandel & Faust, 1975; Lindsay & Rainey, 1997; Nolley & Kelley, 2007; Weinberger & Sofuoglu, 2009). Indeed, among U.S. adults (i.e., ages 18 to 34) who used cocaine in their lifetime, 87.9% smoked cigarettes before their cocaine use (Kandel & Kandel, 2014). In contrast, 5.7% of adults used cocaine and cigarettes at the same time, 3.5% of adults used cocaine first, and 2.9% of cocaine users never smoked cigarettes (Kandel & Kandel, 2014). With the recent rise in electronic cigarette use, especially among adolescents, some researchers are suggesting the possibility of electronic cigarettes functioning as a gateway for more traditional tobacco cigarettes (Bell & Keane, 2014).

Although the gateway theory of drug addiction is mostly accepted in popular culture, it still remains debated within academic literature and researchers in this field are careful not to express causal relationships between the progressions from soft drugs to hard drugs (Bell & Keane, 2014). Rather, the correlational relationship between this progression is typically expressed as being strongly statistically linked (Lindsay & Rainey, 1997). In terms of the gateway hypothesis, epidemiological studies are important for establishing the sequence in which certain drugs may be used; however, it is imperative to

employ animal models of addiction to make causal assertions about the progression of one drug to another (Kandel & Kandel, 2014).

Adolescent Animal Studies

Adolescent animal models of smoking are essential to determine how nicotine exposure can alter adolescent brain structure, functioning, and resulting behavior. For example, adolescent nicotine exposure alters brain neurochemistry when compared to adults (Shearman, Fallon, Sershen, & Lajtha, 2008). Specifically, adolescent nicotine exposure induces greater extracellular levels of dopamine and 5-HT in the nucleus accumbens (Shearman et al., 2008). Comparing nicotine withdrawal in adolescent and adult rodents, adolescent rodents show significantly less mecamylamine-induced withdrawal signs than adults (Kota, Martin, & Damaj, 2008; O'Dell, Bruijnzeel, Ghozland, Markrou, & Koob, 2004). These results suggest that adolescents display decreased sensitivity to nicotine withdrawal, which by minimizing the aversive effects of nicotine abstinence may maximize the reinforcing effects of nicotine during the adolescent period (Kota et al., 2008; O'Dell et al., 2004). Further comparing adolescent and adult nicotine-pretreated rodents, adolescent-pretreated rodents display heightened nicotine reward sensitivity in adulthood, as compared to adult-pretreated rodents tested on conditioned place preference (CPP) task (Adriani, Deroche-Gamonet, Le Moal, Laviola, & Piazza, 2006; Kota et al., 2008). Additionally, a single nicotine conditioning trial can elicit a CPP response in adolescents, but not adults, suggesting that adolescents form associations more

readily (Belluzzi, Lee, Oliff, & Leslie, 2004; Brielmaier, McDonald, & Smith, 2007). The results from these CPP experiments indicate that adolescent smokers may be at a greater risk for nicotine addiction than individuals who start smoking later in life (Adriani et al., 2006; Belluzzi et al., 2004; Brielmaier et al., 2007; Kota et al., 2008). Similarly, comparing the self-administration of nicotine between adolescent and adult rats, adolescent rats acquire more quickly and take higher amounts of nicotine than adult rats, suggesting that nicotine is more reinforcing in adolescent compared to adult rats (Chen, Matta, & Sharp, 2007; Levin, Rezvani, Montoya, Rose, & Swartzwelder, 2003; but see Shram, Funk, Li, & Lê, 2008). Lastly, adolescent mice have a greater preference for a nicotine and sucrose solution than adults, further suggesting a heightened vulnerability to nicotine (Adriani, Macrì, Pacifici, & Laviola, 2002).

CHAPTER SIX

METHAMPHETAMINE

Introduction

Methamphetamine hydrochloride is a highly addictive and abused psychostimulant classified as a schedule II controlled substance within the United States (Calcaterra & Binswanger, 2013; Drug Enforcement Administration [DEA], U.S. Department of Justice, 2003). methamphetamine is often sold illicitly and used recreationally, with estimates of approximately 25 million methamphetamine abusers worldwide (Panenka et al., 2013). This prevalence rate is greater for both cocaine (i.e., ~14 million) and heroin (i.e., ~11 million) abusers (Panenka et al., 2013).

Mechanism of Action and Pharmacokinetics

Methamphetamine enters the body typically through the lungs via inhalation of smoke particles, although methamphetamine can be taken by a number of routes, including sublingual, rectal, intranasal, intravenous injection, subcutaneous injection, or solubilized and consumed orally as a liquid, but the latter routes are not as common (Courtney & Ray, 2014; Novak & Kral, 2011; Rusyniak, 2013). Once in the blood stream, methamphetamine travels to the brain where it readily crosses the blood-brain barrier, due to its lipophilic structure (Courtney & Ray, 2014; Rusyniak, 2013; Vearrier, Greenberg, Miller, Okaneku, Haggerty, 2012).

Within the CNS, methamphetamine functions as an indirect agonist, which acts on DA, NE, 5-HT, and to a lesser extent glutamate neurotransmitter systems in the nucleus accumbens (Cruickshank & Dyer, 2009; Nordahl, Salo, & Leamon, 2003). The impact of methamphetamine on reward occurs through an increase of DA in the nucleus accumbens (Wise & Bozarth, 1984). Due to a similar molecular structure, methamphetamine substitutes for the monoamine neurotransmitters DA, NE, and 5-HT at their respective transporter sites (i.e., DAT, NET, and SERT) (Cruickshank & Dyer, 2009; Rothman et al., 2001). Once in the cell, methamphetamine induces changes in pH levels and the vesicle proton gradient, so that newly synthesized monoamine neurotransmitter accumulates in the cytosol of the presynaptic neuron (Courtney & Ray, 2014; Cruickshank & Dyer, 2009; Sulzer, Sonders, Poulsen, & Galli, 2005). Additionally, methamphetamine alters the functioning of VMAT, aiding in the cytoplasmic accumulation of monoamine neurotransmitters (Halpin, Collins, & Yamamoto, 2014). Accumulation of excess monoamine neurotransmitters in the cytosol causes DAT, NET, and SERT to actively pump DA, NE, or 5-HT into the synaptic cleft, thus methamphetamine reverses the endogenous roles of these monoamine transporters (Courtney & Ray, 2014; Cruickshank & Dyer, 2009; Rusyniak, 2013; Sulzer et al., 2005; Vearrier et al., 2012).

In addition to increasing the release of monoamine neurotransmitters, methamphetamine also attenuates the metabolism of DA, NE, and 5-HT by inhibiting the enzyme MAO (Cruickshank & Dyer, 2009; Sulzer et al., 2005). This

action produces a rapid accumulation of monoamine neurotransmitters in the brain because MAO is inhibited from catabolizing DA, NE, and 5-HT (Meredith, Jaffe, Ang-Lee, & Saxon, 2005; Rusyniak, 2013). Methamphetamine has longer half-life of about 12 h, whereas cocaine has a shorter half-life (i.e., 90 min) (Rawson et al., 2000).

Behavioral and Physiological Effects

Acute effects of methamphetamine are generally linked with feelings of euphoria, invincibility, increased energy, wakefulness, and heightened sexual experiences (Cruickshank & Dyer, 2009; Russell et al., 2008; Vearrier et al., 2012). However, continued methamphetamine use can become harmful and typically effects physical and psychological processes, causing confusion, tremors, convulsions, anxiety, aggressiveness, hallucinations, and paranoia (Russell et al., 2008; Vearrier et al., 2012). Prolonged methamphetamine use results in increased cravings leading to chronic use (Russell et al., 2008; Vearrier et al., 2012). The effects of chronic methamphetamine use are characterized by neurotoxicity and major depressive disorder, with the potential for suicidal ideation and action (Russell et al., 2008; Vearrier et al., 2012).

Methamphetamine abuse may result in a wide range of complications, such as cardiovascular, dermatological, hematological, gastrointestinal, genitourinary, musculoskeletal, neurological, psychiatric, and pulmonary problems, as well as renal failure, perinatal maternal death, and premature death (Russell et al., 2008; Vearrier et al., 2012). In addition to these complications,

methamphetamine addiction also serves as a serious public health problem because of the crime and violence associated with methamphetamine abuse (Vearrier et al., 2012). Due to the highly addictive nature of methamphetamine, negative treatment outcomes and relapse are often expected for methamphetamine addictions (Vearrier et al., 2012). Many of the psychosocial interventions for methamphetamine dependence are riddled with poor entrance and retention rates (Shearer, 2007). There currently are no psychopharmacological treatments approved by the U.S Food and Drug Administration for methamphetamine dependence, although several medications are currently under study (Courtney & Ray, 2014).

Adolescent Methamphetamine Use

In terms of the United States, a 2012 report from the Substance Abuse and Mental Health Services Administration (SAMHSA) found that approximately 12 million (~ 4.7 %) Americans aged 12 and older have tried methamphetamine in their lifetime (Courtney & Ray, 2014; SAMHSA, 2013). Additionally, about 1.2 million have reported using methamphetamine in the last year, and around 440,000 have used methamphetamine in the last month (Courtney & Ray, 2014; SAMHSA, 2013). Among high school students, a Monitoring the Future survey found that 1.6% had used methamphetamine in 2010 (Panenka et al., 2013). Additionally, adolescent methamphetamine use is particularly common in the western regions of the United States and Canada (Gruenewald, Johnson, Ponicki, Remer, & Lascala, 2010; Rawson, Anglin, & Ling, 2002).

Methamphetamine and Nicotine

Simultaneous psychostimulant and nicotine use is highly prevalent (Brecht et al., 2004). Indeed, cocaine users reported increased rates of cigarette use (70-80%) and nicotine dependence (50%) compared to the general population (22% and 13%, respectively) (Grant, Hasin, Chou, Stinson, & Dawson, 2004; Kalman, Morissette, & George, 2005; Patkar et al., 2006). The co-morbidity rates of methamphetamine use and cigarette smoking are even higher (87-92%) (Baker et al., 2004; Grant et al., 2007).

In regards to cigarette smoking and treatment of other stimulant addictions (e.g., cocaine or methamphetamine), it is clear users are motivated to quit; however, smoking cessation rates are low (~12 %) (Campbell, Wander, Stark, & Holbert, 1995; Weinberger & Sofuoglu, 2009). Due to mixed reports, it is unclear whether concurrent cigarette smoking and other stimulant use is detrimental to drug treatment outcomes (Weinberger & Sofuoglu, 2009). Some clinical reports suggest that use of nicotine-containing products may facilitate the onset of methamphetamine relapse in addicts, thus the management of nicotine intake should be considered in clinical settings (Berry et al., 2012). Similarly, self-report studies show that cocaine-dependent individuals report stronger cocaine cravings following nicotine treatment (Reid, Mickalian, Delucchi, Hall, & Berger, 1998), whereas the nicotine antagonist, mecamylamine, reduces cocaine craving in cocaine-dependent individuals (Reid, Mickalian, Delucchi, & Berger, 1999). In contrast, other clinical reports suggest concern that cessation of nicotine-

containing products may increase the risk of relapse to other stimulants, such as methamphetamine or cocaine (Weinberger & Sofuoglu, 2009). The potential for cigarette smoking to produce neurological changes that facilitate the initiation and augmentation of methamphetamine or cocaine use is concerning. In order to further investigate this relationship, it is necessary to turn to animal models of addiction.

Psychostimulant and Nicotine Animal Studies

Periadolescent rats pretreated with nicotine for 7 days and subsequently challenged with cocaine or amphetamine on the following day, display heightened locomotor activity when compared to adult rats (Collins & Izenwasser, 2004; Collins, Montano, & Izenwasser, 2004). These results suggest that adolescent nicotine exposure creates a greater risk for cocaine or amphetamine abuse in adolescence as compared to adulthood (Collins & Izenwasser, 2004; Collins et al., 2004). Relatedly, adolescent nicotine pretreatment enhances the acquisition of cocaine self-administration when compared to adults, further indicating the susceptibility of the adolescent brain to the effects of nicotine on subsequent stimulant use (McQuown, Belluzzi, & Leslie, 2007). Rats treated with nicotine for 10 days during adolescence engaged in more cocaine seeking following cocaine-induced reinstatement in adulthood, suggesting that nicotine exposure in adolescence may alter the vulnerability for cocaine relapse in adulthood (Anker, & Carroll, 2011).

When considering the role of nicotine treatment on methamphetamine self-administration, rats that received nicotine treatment in adolescence through adulthood received more methamphetamine infusions when compared to rats treated with saline (Pipkin et al., 2014). Thus, continuous nicotine exposure beginning in adolescence through adulthood enhances the reinforcing effects of methamphetamine. In addition, nicotine-pretreated adolescent rats received more methamphetamine intake in adulthood than saline-pretreated adolescent rats (Pipkin et al., 2014). Thus, adolescent nicotine pre-exposure increases the reward potential of methamphetamine in adulthood.

In regards to the role of nicotine on methamphetamine relapse, nicotine treatment in adolescent rats does not alter methamphetamine-induced reinstatement in adults (Pipkin et al., 2014). Thus, adolescent nicotine exposure does not affect methamphetamine seeking and relapse in adulthood. In contrast, 5 days of nicotine treatment during extinction attenuates methamphetamine reinstatement in adult rats, suggesting that in certain experimental conditions, nicotine treatment reduces methamphetamine seeking and attenuate the risks associated with relapse (Hiranita, Anggadiredja, Fujisaki, Wantanabe, & Yamamoto, 2004; Hiranita, Nawata, Sakimura, Anggadiredja, & Yamamoto, 2006; Hiranita, Nawata, Sakimura, & Yamamoto, 2008). The difference in methamphetamine reinstatement findings may be due to age and/or duration of nicotine treatment. Despite opposing directions between nicotine and

methamphetamine self-administration and reinstatement data, it is clear that a relationship between the two drugs exists.

CHAPTER SEVEN

SELF-ADMINISTRATION

Introduction

The drug self-administration paradigm has been widely used since the 1960's and functions as an operant conditioning procedure used to study reward and addiction behavior (Deneau, Yangita, & Seevers, 1969; Thompson & Schuster, 1964; Weeks, 1962). Self-administration examines whether the effects of a drug will reinforce a certain behavior, such as pressing a lever for a drug injection (Balster & Schuster, 1973; Stoops, 2008).

Self-administration can be used on animal or human subjects and can utilize different routes of administration, such as insufflation, oral ingestion, inhalation, or intragastric infusion, as well as intramuscular, intravenous, intraperitoneal, or intracerebral injections (Gardner, 2000; Panlilio & Goldberg, 2007). Intravenous injections and oral ingestion are the most typically used routes of administration (Gardner, 2000; Panlilio & Goldberg, 2007); however, intravenous injections and inhalation are the faster routes of delivery and, therefore, produce stronger reinforced behaviors (Gardner, 2000; Panlilio & Goldberg, 2007).

The drug self-administration paradigm relies on operant conditioning principles, with the main assumption that drugs serve as reinforcers, thus increasing the likelihood of a certain behavior that is paired with the effects of a drug (Edwards & Koob, 2013; Panlilio & Goldberg, 2007). The response and

reinforcement relationship (i.e. pushing a lever for a drug injection) can be further manipulated by using different schedules of reinforcement, such as requiring a certain number of responses or amount of time to pass before the subject receives the reinforcing effects of the drug (Haney & Spealman, 2008; Spealman & Goldberg, 1978; Stoops, 2008). One of the most simple and extensively used schedules of reinforcement is continuous reinforcement, where the subject is reinforced for every response given (Domjan, 2005; Gál & Gyertyán, 2003; Minhas & Len, 2014; Panlilio & Goldberg, 2007). This schedule is results in a dose-dependent manner; with higher doses resulting in less frequent responses (Panlilio & Goldberg, 2007). Continuous reinforcement does not typically correspond to behavior in a natural context, because an oragnism must often work for a reward, or wait a given amount of time to receive a reinforcing stimulus (Domjan, 2005; Panlilio & Goldberg, 2007).

Ratio schedules require that a certain number of responses to pass before the subject receives the reinforcer (Domjan, 2005; Haney & Spealman, 2008; Panlilio & Goldberg, 2007; Spealman & Goldberg, 1978). In fixed-ratio (FR) scheduling, the subject receives the reinforcer after a certain number of responses. FR schedules typically produce high, steady rates of responding, with a brief pause in responding after the reinforcer is given (Domjan, 2005; Panlilio & Goldberg, 2007; Spealman & Goldberg, 1978). FR scheduling is often used to determine the reinforcing effects of long-lasting drugs that may result in an infrequent self-administration rate over time (Panlilio & Goldberg, 2007).

Typically, an FR 1 schedule (i.e., continuous reinforcement) is used for initial self-administration training (Panlilio & Goldberg, 2007). When an animal has established consistent responding for reinforced drug delivery, the ratio can be increased sequentially (i.e., FR 2, FR 5, etc.) (Panlilio & Goldberg, 2007).

FR schedules of reinforcement are utilized in drug self-administration with laboratory animals, including cocaine, amphetamine, methamphetamine, caffeine, opiates, ethanol, and other addictive compounds (Balster, Kilbey, & Ellinwood, 1976; Deneau et al., 1969; Goldberg, 1973; Winger & Woods, 1973). When animals are given unlimited access to stimulants, such as cocaine, amphetamine, methamphetamine, methylphenidate, or caffeine, it produces increased periods of alternating consumption and abstinence (Deneau et al., 1969; Johanson, Balster, & Bonese, 1976; Pickens & Harris, 1968; Yokel & Pickens, 1973). This is similar to what is observed in the human condition, with periods of binging and abstinence (Kramer, Vitezslav, & Littlefield, 1967). When given a reinforcement schedule that allows limited drug access, stimulant self-administration produces smaller binges at the beginning of the session, and consistent drug intake throughout the remainder of the session (Gardner, 2000).

Reinstatement and Relapse

Reinstatement of a drug is used to model drug relapse after a period of abstinence (Bossert, Marchant, Calu, & Shaham, 2013; Sanchis-Segura & Spanagel, 2006). After multiple extinction sessions, the subject is then either re-exposed to the original or different reinforcing drug, presented with drug-

associated cues, or given foot shock stress within the self-administration chamber (Bossert et al., 2013; Sanchis-Segura & Spanagel, 2006). These types of treatments are meant to model triggers associated with relapse in humans (Bossert et al., 2013; Sanchis-Segura & Spanagel, 2006).

Advantages and Disadvantages of Intravenous Self-Administration

Given the various schedules and manipulations used in the drug self-administration paradigm, it is clear that self-administration models many aspects of human addiction. When compared to other behavioral paradigms, self-administration represents the highest point-to-point correspondence with addictive behaviors observed in the natural environment (Panlilio & Goldberg, 2002). Therefore, self-administration procedures maintain a very high level of face validity, reliability, and species generality (Haney & Spealman, 2008). In regards to predictive validity, drug self-administration in animals predicts the abuse potential of new compounds in humans (Balster, 1991; Lile & Nader, 2003). Self-administration procedures are often conducted via nose-poke holes or levers (Gardner, 2000). One advantage to using nose-pokes is that they are an innate behavior for rodents, whereas lever pressing is a learned behavior that can be time consuming.

A limitation for the drug self-administration paradigm is expense in both time and other resources (Panlilio & Goldberg, 2002). Due to its complexity, the self-administration procedure may, in some cases, be less productive than simpler behavioral paradigms when screening for novel drugs or relating

addiction-like behaviors to neural circuitry (Panlilio & Goldberg, 2002). An additional limitation of intravenous self-administration is unique to ontogeny. Specifically, adolescent rats can quickly outgrow the implanted cannulas because of the normal growth that occurs during this developmental period. More importantly, because of the recovery time required after surgery, it is difficult to complete intravenous self-administration procedures during the short time span of adolescence. One way to avoid these problems is to change the route of drug administration.

Oral Self-Administration

Oral self-administration can be established in many different animals with a number of abused drugs (e.g., alcohol, opiates, and psychostimulants) (Meisch, 2001). Following a response (i.e., nose-poke or lever press), rats are presented with a spigot, to which they can lick a drug solution (Gardner, 2000). An automated device then measures individual licks taken by the rat (Gardner, 2000). Another form of oral self-administration that does not make use of operant reinforcement procedures involves giving rats free access to two water bottles for a specified period of time, one containing vehicle and the other containing a solution of the drug of interest (Collins, Pogun, Nesil, & Kanit, 2012). The water bottles are then weighed and the preferred solution is determined (Collins et al., 2012).

Advantages and Disadvantages of Oral Self-Administration

The main advantage of the oral route of self-administration is that surgery is not necessary and there is no need for catheters, which avoids infection, obstruction, and incorrect placement (Macenski & Meisch, 1994). Additionally, the surgical procedures limit the amount of time an animal can be used in a given experiment (Macenski & Meisch, 1994).

The main disadvantages of the oral route of self-administration include the lack of drug absorption resulting from chemical polarity, as well as the degradation of drugs via digestive enzymes and alternating pH levels (Turner, Brabb, Pekow, & Vasbinder, 2011). Other limitations include first pass effects by the liver, delayed time for drugs to reach the CNS and produce behavioral effects, the aversive taste of many drugs, and the small amounts of drug volume consumed per drinking episode (Macenski & Meisch, 1994; Meisch, 2001; Turner et al., 2011). Regardless of the possible limitations, laboratory animals have learned to orally self-administer using alcohol, cocaine, amphetamine, methamphetamine, and other psychoactive drugs (Meisch, 2001; Shabani et al., 2013).

CHAPTER EIGHT

THESIS PROPOSAL AND HYPOTHESES

Adolescence is a vulnerable period in development, especially in regards to pharmacologically-induced changes in neurochemistry and resulting behavior (Stanis & Andersen, 2014). Cigarette smoking is most likely to begin during adolescence and can often serve as a gateway to other drugs of abuse (Lewinsohn et al., 1999). Adolescent methamphetamine use is also common, with about 1.6% of high school students having used methamphetamine in 2010 (Panenka et al., 2013). Simultaneous nicotine and methamphetamine use is very prevalent, with an estimate that 97% of methamphetamine users also use nicotine (Brecht et al., 2004). Nicotine and methamphetamine have comparable effects on neural reward pathways, such as increasing DA in the nucleus accumbens (Dani & De Biasi, 2001; Nestler, 2005; Picciotto & Corrigall, 2002; Wise & Bozarth, 1984). When administered together, nicotine and methamphetamine display variable effects on reward-related behaviors (Hiranita et al., 2004; Neugebauer et al., 2010; Pipkin et al., 2014). The effects of nicotine and methamphetamine co-treatment have been seldom investigated, with little known about how these drugs interact in adolescent populations.

Animal studies have shown a potential connection between nicotine and methamphetamine. For example, nicotine can be substituted for

methamphetamine in a discrimination procedure, which suggests that the two drugs possess similar properties (Gatch, Flores, & Forster, 2008). In mice, repeated nicotine treatment produces locomotor cross-sensitization when given a methamphetamine challenge (Kuribara, 1999). Thus, repeated cigarette smoking may increase the rewarding potential of initial methamphetamine use. Interestingly, the same study found that coadministration of methamphetamine and a high dose of nicotine reduced the induction of methamphetamine sensitization, suggesting that nicotine, in some cases, may contain protective properties against methamphetamine abuse potential (Kuribara, 1999).

In contrast to findings of nicotine and methamphetamine cross-sensitization, prior nicotine exposure does not have an effect on methamphetamine CPP, extinction, or reinstatement, indicating that nicotine may not be responsible for an enhancement of the rewarding effects of methamphetamine (Berry et al., 2012). Although CPP and self-administration can both model the rewarding effects of certain drugs, it is evident that neuropharmacological mechanisms underlying the paradigms are dissociable (Bardo & Bevins, 2000). Thus, in rats previously trained to self-administer methamphetamine, nicotine exposure produces methamphetamine reinstatement (Neugebauer et al., 2010), suggesting that nicotine exposure during a withdrawal period may facilitate the onset of methamphetamine relapse. Methamphetamine pretreatment increases nicotine self-administration (Rauhut, Neugebauer, Dwoskin, & Bardo, 2003), further connecting the rewarding properties of the two

psychostimulants. Prenatal nicotine exposure produces heightened methamphetamine infusions in adulthood, which is congruent with the notion that early developmental nicotine exposure can enhance methamphetamine reward later in life (Lacy, Morgan, & Harrod, 2014). Thus, preclinical evidence suggests that nicotine exposure can augment the rewarding and abuse potential of methamphetamine in certain experimental conditions (e.g., self-administration, behavioral-sensitization); however, this effect is not observed in others (e.g., CPP).

As for adolescent nicotine exposure on methamphetamine self-administration in early adulthood, a low dose of nicotine treatment beginning in adolescence through adulthood augmented methamphetamine infusions (Pipkin et al., 2014), suggesting that a moderate amount of smoking during adolescence through adulthood may enhance the reinforcing effects of methamphetamine. In addition, nicotine-pretreated adolescent rats received more methamphetamine intake in adulthood than saline-pretreated adolescent rats (Pipkin et al., 2014). Thus, adolescent cigarette smoking may increase the reward potential of methamphetamine in adulthood.

In regards to methamphetamine withdrawal and relapse, adolescent nicotine exposure had no effect on methamphetamine extinction or reinstatement in adult rats (Pipkin et al., 2014). Therefore, adolescent cigarette smoking may not alter methamphetamine seeking and relapse in adulthood. Alternatively, a high dose of nicotine exposure during a 5-day methamphetamine withdrawal

period attenuated lever-responding in adult rats following a single methamphetamine priming injection (Hiranita et al., 2004; 2006), suggesting that nicotine exposure, under certain experimental conditions, can reduce methamphetamine seeking and risk associated with relapse. It is evident that the effects of adolescent or adult nicotine exposure on methamphetamine self-administration, extinction, and reinstatement vary widely based on various experimental procedures and design (i.e., age of animal, dose, and behavioral paradigm).

Lastly, there is clear pre-clinical evidence suggesting sex differences exist in regards to the reinforcing properties of nicotine or methamphetamine. During nicotine self-administration, female rats maintain a higher motivation to obtain nicotine than male rats, while no sex differences are observed during nicotine-induced reinstatement (Donny et al., 2000; Feltenstein, Ghee, & See, 2012). Similar to the sex differences observed within nicotine self-administration, female rats are more susceptible to the reinforcing properties of methamphetamine than male rats. Specifically, female rats acquire methamphetamine self-administration more readily than male rats (Kucerova, Vrskova, & Sulcova, 2009; Reichel, Chan, Ghee, & See, 2012; Roth & Carroll, 2004; Ruda-Kucerova et al., 2015). During methamphetamine reinstatement, female rats respond more for access to methamphetamine than male rats (Ruda-Kucerova et al., 2015). Given the distinct differences between male and female rats observed within nicotine or methamphetamine reinforcement procedures, it is possible that sex may alter

adolescent nicotine exposure-induced changes on methamphetamine self-administration, extinction, and reinstatement.

The aim of the present investigation was to gain a further understanding about the effects of nicotine exposure on the reinforcing properties of methamphetamine during adolescence. To this end, we assessed methamphetamine acquisition, extinction, and reinstatement in adolescent male and female rats. Employing an oral self-administration procedure allowed us to test rats during this pivotal developmental period. Moreover, this method shortened training time and omitted surgical procedures, which allowed for the testing of a large number of subjects and a more complicated research design.

The PD 25 to PD 65 age range was selected to approximate adolescence (Spear, 2000), which the oral self-administration paradigm was used to model human addiction. A total of seven treatment groups were used in order to precisely determine whether nicotine exposure enhances or diminishes the reinforcing effects of methamphetamine during the adolescent period. On PD 25, adolescent male and female rats were injected with saline or nicotine (0.16 or 0.64 mg/kg, sc) once a day for 10 days until PD 34. Subsequently, half of the nicotine-pretreated rats continued to receive nicotine at the same doses, while the other half received saline for the remainder of the experiment. In addition, one third of the saline pretreated rats continued to receive saline, while two thirds received nicotine (0.16 or 0.64 mg/kg) for the remainder of the experiment (see Figure 1). On PD 35, rats underwent training to nose poke for a 10% sucrose

solution. After reaching sucrose-training criteria, methamphetamine acquisition occurred across seven different 2 h sessions. When criteria were met, rats began extinction training, where nose poke responses were not reinforced. Once extinction criteria were met, all rats were given a priming injection of methamphetamine (1.0 mg/kg) in order to induce reinstatement of methamphetamine responding.

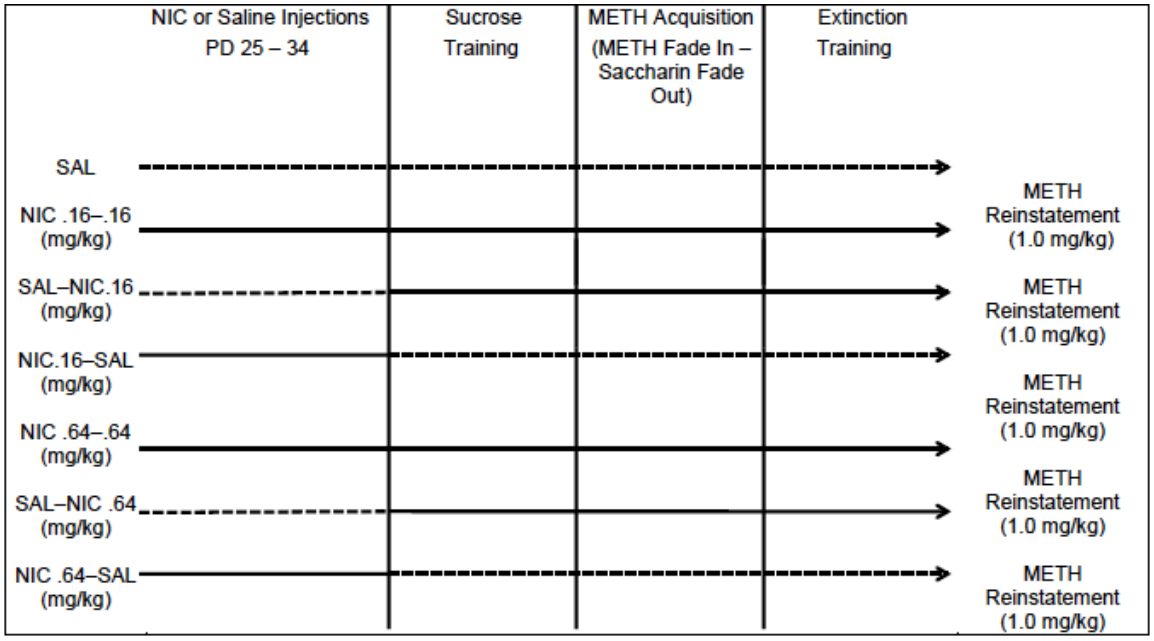

Figure 1. Project design and timeline.

Overall, we had two primary hypotheses about how nicotine and sex would affect oral methamphetamine self-administration:

First, we predicted that nicotine exposure would alter consumption and responding for methamphetamine. We hypothesized that exposure to a low dose of nicotine (0.16 mg/kg) would enhance consumption and responding for methamphetamine. In contrast, we hypothesized that exposure to a high dose of

nicotine (0.64 mg/kg) would attenuate consumption and responding for methamphetamine. These hypotheses were founded in past research showing that exposure to low doses of nicotine potentiates the rewarding properties of methamphetamine or cocaine (McQuown et al., 2007; Pipkin et al., 2014), whereas exposure to higher doses of nicotine attenuates methamphetamine self-administration and reinstatement (Hiranita et al., 2004; 2006; Neugebauer et al., 2010).

Second, we predicted that sex would also alter consumption and responding for methamphetamine. We hypothesized that female rats would have enhanced consumption and responding for methamphetamine. These hypotheses were founded in past research showing that female rats acquire methamphetamine self-administration more readily (Kucerova, Vrskova, & Sulcova, 2009), as well as respond more for access to methamphetamine during reinstatement than male rats (Ruda-Kucerova et al., 2015). Moreover, we hypothesized that female rats would show larger changes in responding for methamphetamine and consumption at both doses of nicotine.

Table 1. Hypothesized Main Effects and Interactions for Nicotine (0.16 or 0.64 mg/kg) Treatment and Sex (Male or Female) Across Methamphetamine Self-Administration, Extinction, and Reinstatement.

Low Dose (0.16 mg/kg)	
Sex Main Effect	Female > Male
Pre- or Post-Treatment Main Effect	Nicotine (0.16 mg/kg) > Saline
Sex × Pre- or Post-Treatment Interaction	Female (0.16 mg/kg) > Female Saline Female (0.16 mg/kg) > Male (0.16 mg/kg) or Saline
Pre- × Post-Treatment Interaction	0.16-0.16 > SAL-SAL, 0.16-SAL, SAL-0.16
Sex × Pre- and Post-Treatment Interaction	Female (0.16-0.16) > Female (SAL–SAL; 0.16–SAL; SAL–0.16) Female (0.16-0.16) > Male (SAL–SAL; 0.16–SAL; SAL–0.16;0.16-0.16)
High Dose (0.64 mg/kg)	
Sex Main Effect	Female > Male
Pre- or Post-Treatment Main Effect	Saline > Nicotine (0.64 mg/kg)
Sex × Pre- or Post-Treatment Interaction	Male (0.64 mg/kg) < Male Saline Male (0.64 mg/kg) < Female (0.64 mg/kg) or Saline
Pre- × Post-Treatment Interaction	SAL-SAL > 0.64-0.64, 0.64-SAL, SAL-0.64
Sex × Pre- and Post-Treatment Interaction	Male (0.64-0.64) < Male (SAL–SAL; 0.64–SAL; SAL–0.64) Male (0.64-0.64) < Female (SAL–SAL; 0.64–SAL; SAL–0.64; 0.64-0.64)

CHAPTER NINE

MATERIALS AND METHODS

Subjects

Subjects were 164 young male and female rats (n = 9–11) of Sprague-Dawley descent (Charles River, Hollister, CA). Four subjects were found to be statistical outliers and removed from data analyses. Rats were housed with the dam until being weaned on PD 23, after which they were housed with same-sex littermates in large maternity cages. Food and water were provided ad-libitum, except as noted below. The colony room was maintained at 21–23 °C and kept under a 12 L:12 D cycle. Rats were tested in a quiet, separate room during the light phase of the cycle. Subjects were cared for according to the “Guide for the Care and Use of Mammals in Neuroscience and Behavioral Research” (National Research Council, 2010) under a research protocol approved by the Institutional Animal Care and Use Committee of CSUSB.

Apparatus

Behavioral testing occurred in standard operant chambers (Coulbourn Instruments, Whitehall, PA). Each chamber contained two nose poke operandums (2 cm from the floor), an optical lickometer, a house light, a stimulus light, and a sound cue (500 Hz, 10 dB above background). The two nose poke operandums were positioned on the front wall of the chamber, with the optical lickometer positioned between the two nose poke operandums. The stimulus

light and sound cue were located directly above the active nose poke hole. The location of the active nose poke hole was counterbalanced across all self-administration chambers on either the left or right side of the optical lickometer. Nose pokes in the active nose poke hole resulted in rats receiving access to a reinforcer (e.g., sucrose or methamphetamine) for 30 s. Nose pokes in the inactive nose poke hole resulted in no scheduled consequences. The house light was located on the rear wall of the chamber and remained on while rats were inside the operant chambers, except during timeout periods, wherein the house light was turned off for 20 s. Each chamber was housed in a soundproof isolation cubicle and controlled by an IBM compatible computer interfaced with a data collection program (Graphic State, Coulbourn Instruments).

Drugs

(−)-Nicotine hydrogen tartrate and (±)-methamphetamine hydrochloride (Sigma-Aldrich, St. Louis, MO) was dissolved in saline. Nicotine injections were administered subcutaneously (SC), whereas methamphetamine injections were administered intraperitoneally (IP). Methamphetamine and sucrose were dissolved in distilled water for drinking solutions.

Procedures

In Vivo Drug Treatment

Starting on PD 25, rats were weighed and then injected with nicotine (0.16 or 0.64 mg/kg) or saline for 10 consecutive days until PD 34 (see Figure 2). This

injection period (PD 25−PD 34) is developmentally comparable to early adolescence in humans (Anderson, 2003). On PD 35, rats in the 0.16 and 0.64 mg/kg pretreatment groups were evenly divided and assigned to a group that either continued to receive the same nicotine dose they received as adolescents or saline. Rats that had received saline as adolescents were divided into three equal groups, where they received 0.16 or 0.64 mg/kg nicotine or continued to receive saline injections. Drug treatments starting on PD 35 continued until the end of the experiment. In total, there were 7 drug groups: SAL–SAL, 0.16–0.16, 0.16–SAL, SAL–0.16, 0.64–0.64, 0.64–SAL, SAL–0.64.

Nose Poke Training

Starting on PD 33, rats were pre-exposed to a 10% sucrose solution for 32 h in their home cage. On PD 35, rats were placed in a self-administration chamber and allowed to nose poke for access to a 10% sucrose (w/v) solution on an FR1 schedule for 60 min each day until a criterion of ≥ 10 presentations for 2 consecutive days was met. Following each session, rats were treated with nicotine (0.16 or 0.64 mg/kg) or saline in their home cage. Nose poke responses in the active hole resulted in the simultaneous presentation of a stimulus light, sound cue (500 Hz, 10 dB above background), and a 30 s presentation of a liquid dropper (i.e., reinforcement period). After each liquid dropper presentation, the active nose poke hole became inactive for 20 s, which was indicated by the absence of the house light (i.e., timeout period). On training days, water availability was restricted for 16 hr/day to accelerate acquisition of operant

responding. Following nose poke training, rats were food restricted to 90% of their free-feeding weight for the remainder of the experiment, while water was made available ad-libitum. Rats that failed to meet training criterion were excluded from the study.

Methamphetamine Self-Administration

Once the sucrose-training criterion was met, methamphetamine fade-in and sucrose fade-out began across seven (2 h) sessions (adopted from Shabani et al., 2013; see Figure 2). Each nose poke response in the active hole resulted in the simultaneous presentation of a stimulus light, sound cue (500 Hz, 10 dB above background), and a 30 s presentation of a liquid dropper that delivered either a sucrose, methamphetamine, or sucrose and methamphetamine solution (i.e., reinforcement period). After each liquid dropper presentation, the active nose poke hole became inactive for 20 s, which was indicated by the absence of the house light (i.e., timeout period). During sessions 1–2 liquid solutions were presented on an FR1 schedule; during sessions 3–7 liquid solutions were presented on an FR2 schedule. The criterion for sessions 1–6 was ≥ 10 presentations for each 2 hr session. Sessions 1 and 3 required a criterion of ≥ 10 presentations for 2 consecutive days. Rats were exposed to session 7 for three consecutive days. If rats did not meet criteria for a particular session, then rats remained on that session at least 4 days, after which they were advanced to the next session.

Session 1 served as a baseline, in which a 10% sucrose solution was presented alone. On session 2, methamphetamine fade-in and sucrose fade-out began. Specifically, a low dose of methamphetamine (20 mg/l) was introduced into an 8.5% sucrose solution. On sessions 3–6, a high dose of methamphetamine (40 mg/l) was introduced into the sucrose solutions (i.e., 6.5% for session 3, 4.5% for session 4, 2.5% for session 5, and 0.5% for session 6). On session 7, no sucrose was present in the methamphetamine (40 mg/l) liquid solution (see Figure 2).

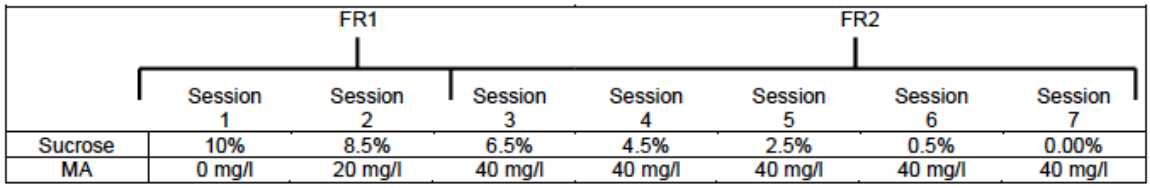

Figure 2. Methamphetamine acquisition

Extinction Training

Extinction training began following methamphetamine (40 mg/l) acquisition (see Figure 1). During extinction, rats underwent 2 h training sessions, in which nose poke behavior resulted in no scheduled consequences, but responses were recorded. Rats remained in extinction for 7 consecutive days or until active nose poke responses were < 10% of the last day of FR2 methamphetamine (40 mg/l) acquisition for two consecutive days.

Drug Prime Reinstatement

Once extinction criteria were met, all rats were given a priming injection of methamphetamine (1.0 mg/kg, IP) 5 min before being placed in the self-

administration chambers (see Figure 1). Reinstatement sessions lasted 2 h, during which nose pokes resulted in no consequences.

Data Analysis

Data for acquisition, extinction, and reinstatement sessions were collected using Graphic State program software (Coulbourn Instruments). Total active and inactive nose pokes, active and inactive nose pokes during the timeout period, active nose pokes during the reinforcement period, and amount of volume consumed (i.e., sucrose and/or methamphetamine) were recorded and calculated for all acquisition and self-administration sessions. Total active and inactive nose pokes were recorded and calculated for all extinction and reinstatement sessions. Data from rats exposed to a low dose of nicotine (0.16 mg/kg) or a high dose of nicotine (0.64 mg/kg) were analyzed separately. Thus, all data from methamphetamine self-administration and reinstatement sessions were analyzed by 2×2×2 ANOVAs (sex × pre-treatment × post-treatment). Acquisition training data (sucrose training – session 6) were analyzed with mixed between-within ANOVAs, with session as the within subjects variable and sex, pre-treatment, and post-treatment as the between subjects variables (session × sex × pre-treatment × post-treatment). Extinction data were analyzed with mixed between-within ANOVAs, with day as the within subjects variable and sex, pre-treatment, and post-treatment as the between subjects variables (day × sex × pre-treatment × post-treatment). If needed, data were further analyzed with one-way ANOVAs. In addition, body weight data were analyzed with mixed between-

within ANOVAs, with day as the within subjects variable and sex, pre-treatment, and post-treatment as the between subjects variables (day × sex × pre-treatment × post-treatment). If the assumption of sphericity was violated, then the Greenhouse-Geisser correction was used. Post hoc comparisons were made with Tukey tests, $p < .05$.

CHAPTER TEN

RESULTS

Effects of Nicotine (0.16 mg/kg) Exposure on Oral Methamphetamine Self-Administration, Extinction, and Reinstatement

Effect of Nicotine (0.16 mg/kg) Exposure on Bodyweight

Adolescent nicotine (0.16 mg/kg) exposure across the pre- (PD 25−PD 34) and post-treatment (PD 35−54) phases did not alter bodyweights of either male or female rats. Bodyweights of all rats progressively increased across the pre- (PD 25−PD 34) and post-treatment (PD 35−54) periods [day main effect, $F(1.99,1.63.96) = 696.69$, $p > .001$] (see Figure 3). Male rats ($M = 175.80$, $SEM = 2.70$) weighed more than female rats ($M = 143.75$, $SEM = 2.81$) across the pre- and post-treatment periods [sex main effect, $F(1,75) = 67.64$, $p > .001$] (see Figure 3).

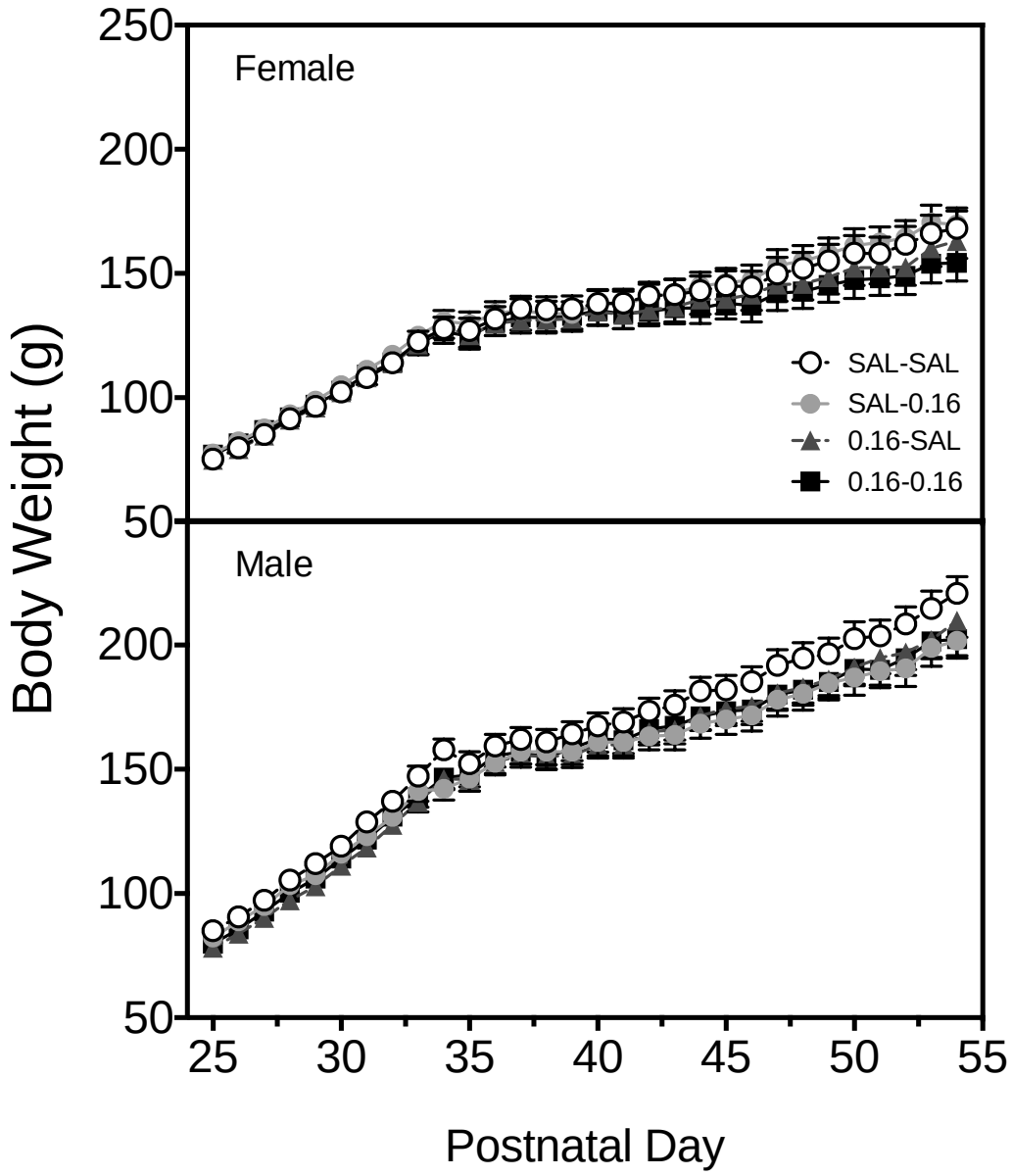

Figure 3. Mean body weight (± SEM) of male and female rats exposed to saline (SAL) or nicotine (0.16 mg/kg) during the pre- (PD 25–34) or post-treatment (PD 35–~60) phases.

Acquisition of Methamphetamine Self-Administration

Oral methamphetamine self-administration was acquired over six training sessions, in which sucrose was phased out and methamphetamine was introduced. On session 7, rats responded for methamphetamine alone. In general, neither pre- nor post-treatment with nicotine (0.16 mg/kg) altered consumption or responding for methamphetamine (see Figure 4). However, rats exposed to saline during the pre-treatment period had more inactive nose pokes within the timeout period than rats exposed to nicotine (0.16 mg/kg) during the pre-treatment period [pre-treatment main effect, $F(1,75) = 7.02$, $p < .01$] (see Figure 5D).

Sex did not alter consumption or responding for methamphetamine during the first six sessions (see Figure 4); however, female rats had more active nose pokes during the timeout period than male rats across methamphetamine acquisition training [sex main effect, $F(1,75) = 5.12$, $p < .05$] (see Figure 5B & 6A). In addition, female rats had more total inactive nose pokes than male rats across methamphetamine acquisition training [sex main effect, $F(1,75) = 12.70$, $p < .001$] (see Figures 5C & 6B). Lastly, female rats had more inactive nose pokes during the timeout period than male rats [sex main effect, $F(1,75) = 7.95$, $p < .01$] (see Figures 5D & 6C).

None of the remaining dependent measures (i.e., total active nose pokes) were altered by nicotine (0.16 mg/kg) or sex (see Figure 5).

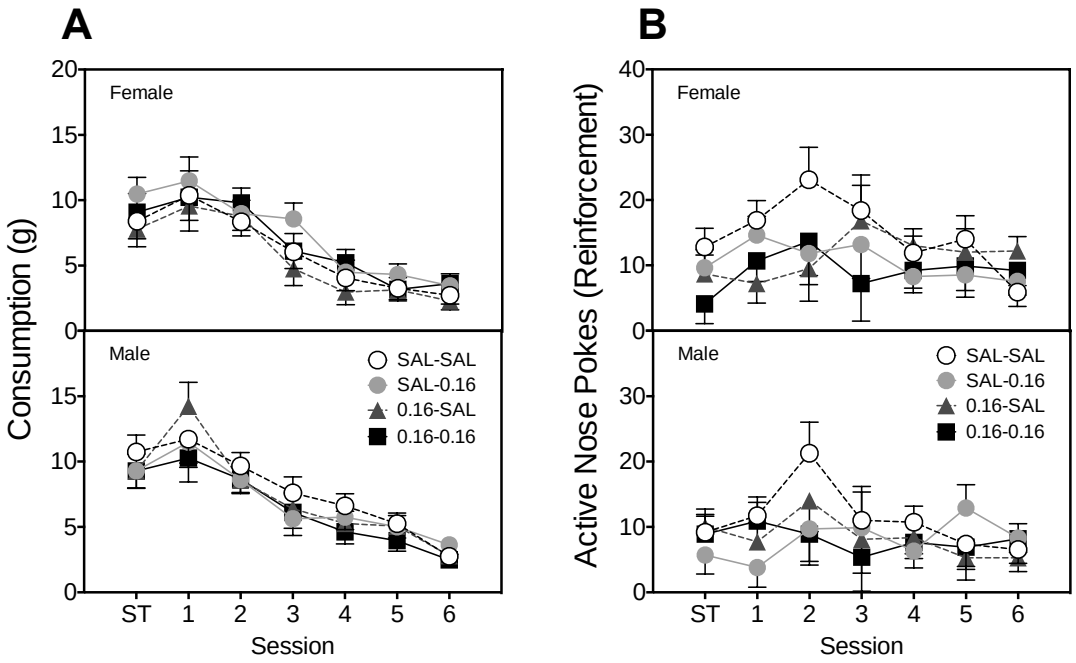

Figure 4. A) Mean sucrose and methamphetamine consumption; and B) mean number of active nose pokes (reinforcement) (± SEM) for male and female rats on the last day of behavioral responding across methamphetamine acquisition training sessions (sucrose training–session 6). Rats were exposed to saline (SAL) or nicotine (0.16 mg/kg) during the pre- (PD 25–34) or post-treatment (PD 35–~60) periods.

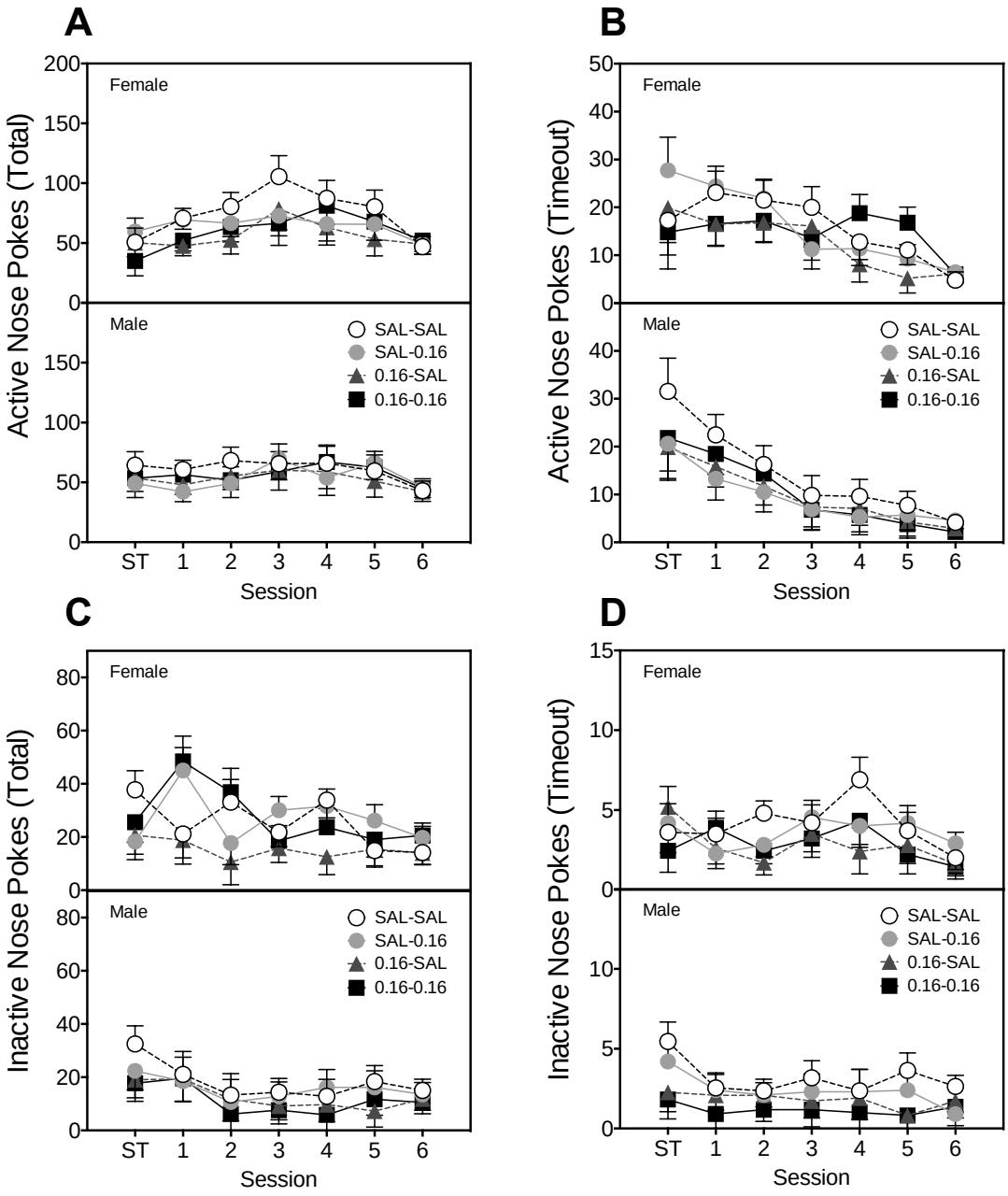

Figure 5. A) Mean number of active nose pokes (total); B) mean number of active nose pokes (timeout); C) mean number of inactive nose pokes (total); and D) mean number of inactive nose pokes (timeout) (± SEM) for male and female rats on the last day of behavioral responding across methamphetamine acquisition training sessions (sucrose training–session 6). Rats were exposed to saline (SAL) or nicotine (0.16 mg/kg) during the pre- (PD 25–34) or post-treatment (PD 35–~60) periods.

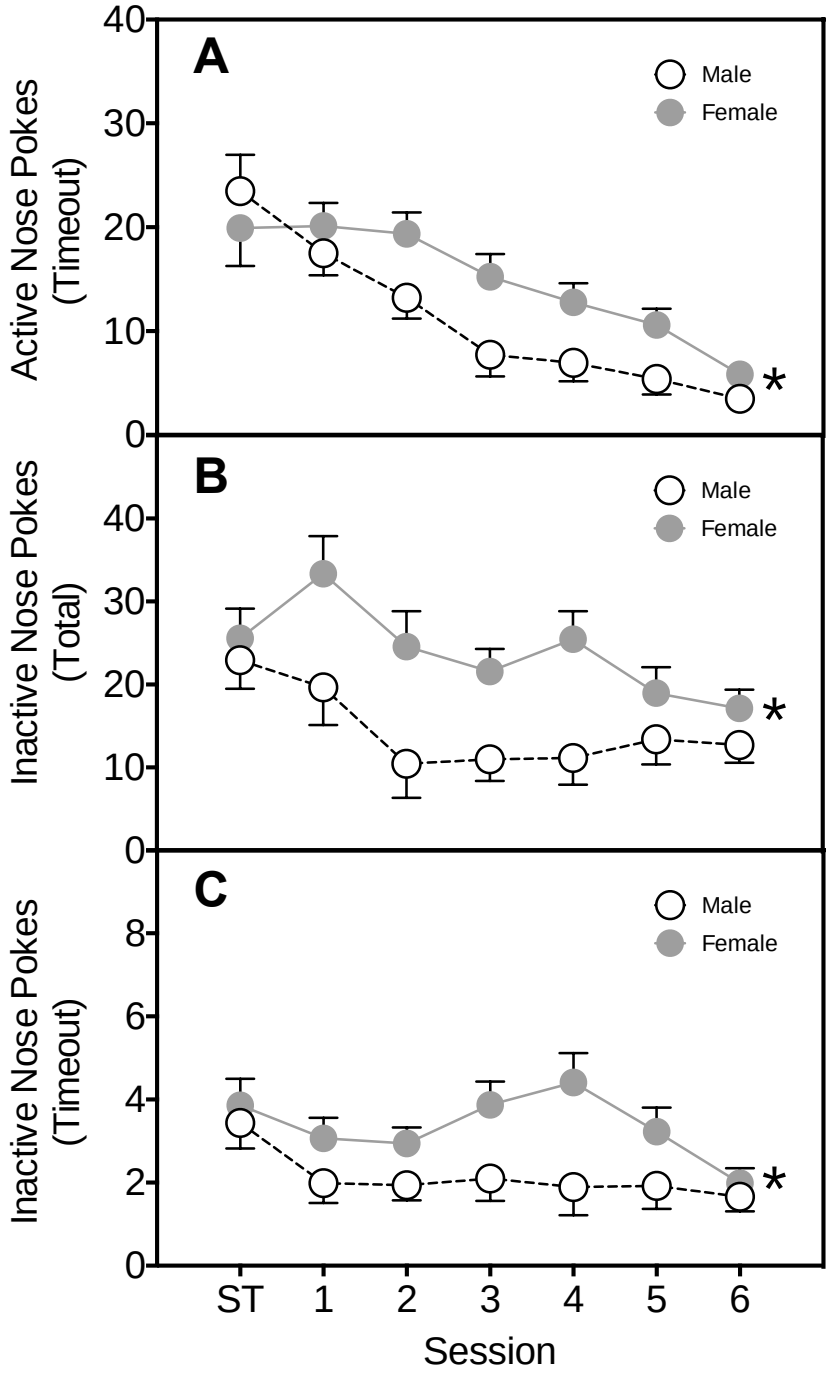

Figure 6. A) Mean number of active nose pokes (timeout); B) mean number of inactive nose pokes (total); and C) mean number of inactive nose pokes (timeout) (± SEM) for male and female rats on the last day of behavioral responding across methamphetamine acquisition training sessions (sucrose training–session 6). * Indicates a significant difference from male rats ($p < .05$).

Post-treatment with nicotine (0.16 mg/kg) altered consumption and responding for methamphetamine on session 7. Specifically, rats exposed to saline during the post-treatment period had more active nose pokes within the reinforcement period, and greater methamphetamine consumption (40 mg/l methamphetamine solution), than rats exposed to a low dose of nicotine (0.16 mg/kg) during the post-treatment period [post-treatment main effect, $F(1,75) = 4.09$, $p > .05$; $F(1,75) = 5.22$, $p > .05$, respectively] (see Figures 7A & 7B). Pre-treatment with nicotine (0.16 mg/kg) did not alter consumption or responding for methamphetamine on session 7; however, rats exposed to saline during the pre-treatment period had more total inactive nose pokes compared to rats exposed to a low dose of nicotine (0.16 mg/kg) during the pre-treatment period [pre-treatment main effect, $F(1,75) = 5.17$, $p > .05$] (see Figures 7E).

Sex also altered responding for methamphetamine on session 7, because female rats had more total active nose pokes and active nose pokes within the reinforcement period than male rats [sex main effect, $F(1,75) = 4.53$, $p < .05$; $F(1,75) = 5.56$, $p < .05$, respectively] (see Figures 7B, 7C, 8A, & 8B). Female rats also had more active nose pokes within the timeout period and more total inactive nose pokes than male rats [sex main effect, $F(1,75) = 11.13$, $p < .01$; $F(1,75) = 4.98$, $p < .05$, respectively] (see Figures 7D, 7E, 8C, & 8D).

None of the remaining dependent measures (i.e., inactive nose pokes during the timeout period) were altered by nicotine (0.16 mg/kg) treatment or sex (see Figure 7).

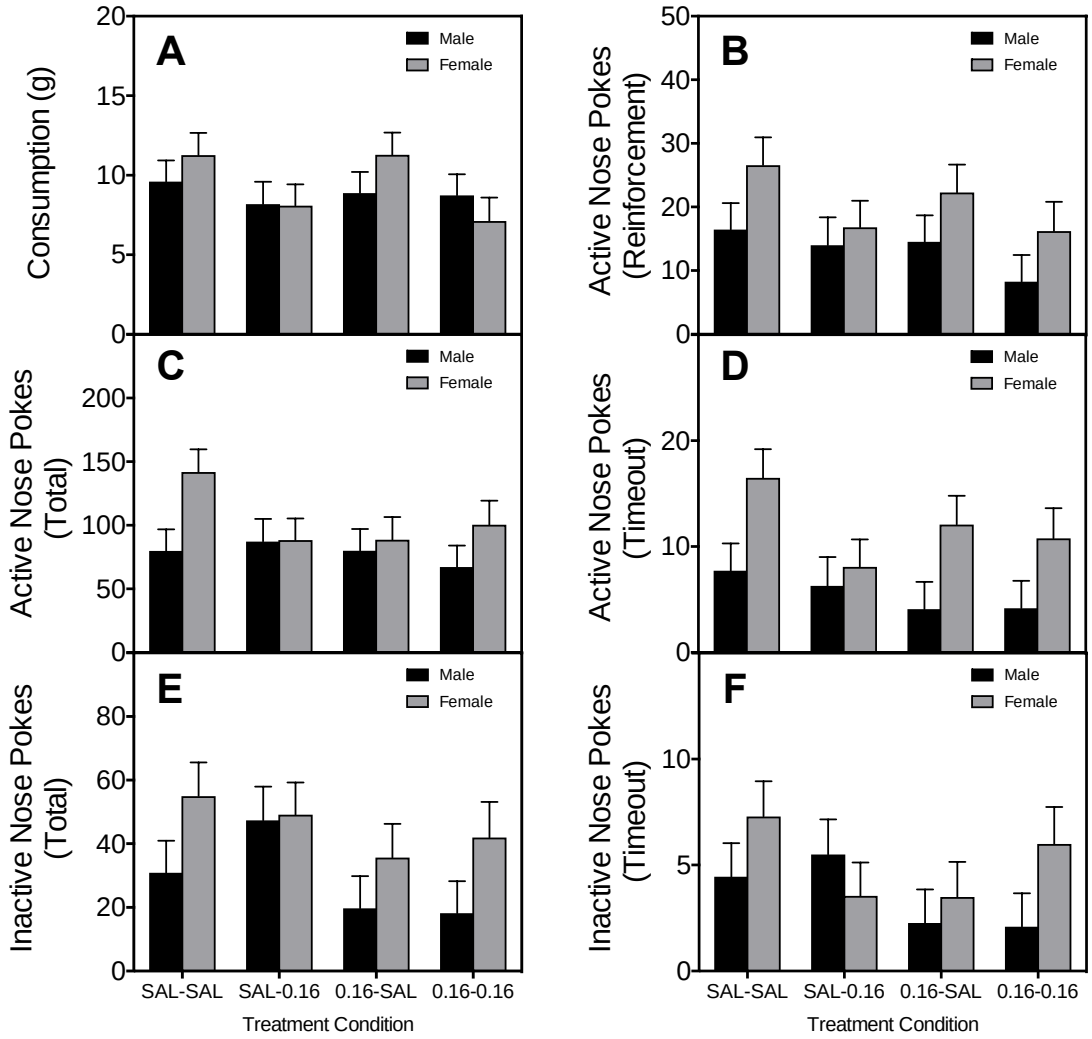

Figure 7. A) Mean methamphetamine (40 mg/l) consumption; B) mean number of active nose pokes (reinforcement); C) mean number of active nose pokes (total); D) mean number of active nose pokes (timeout); E) mean number or inactive nose pokes (total); and F) mean number of inactive nose pokes (timeout) (± SEM) made by adolescent male and female rats during methamphetamine acquisition on session 7 (FR 2). Rats were exposed to saline (SAL) or nicotine (0.16 mg/kg) during the pre-treatment (PD 25–34) or post-treatment (PD 35–~60) phases.

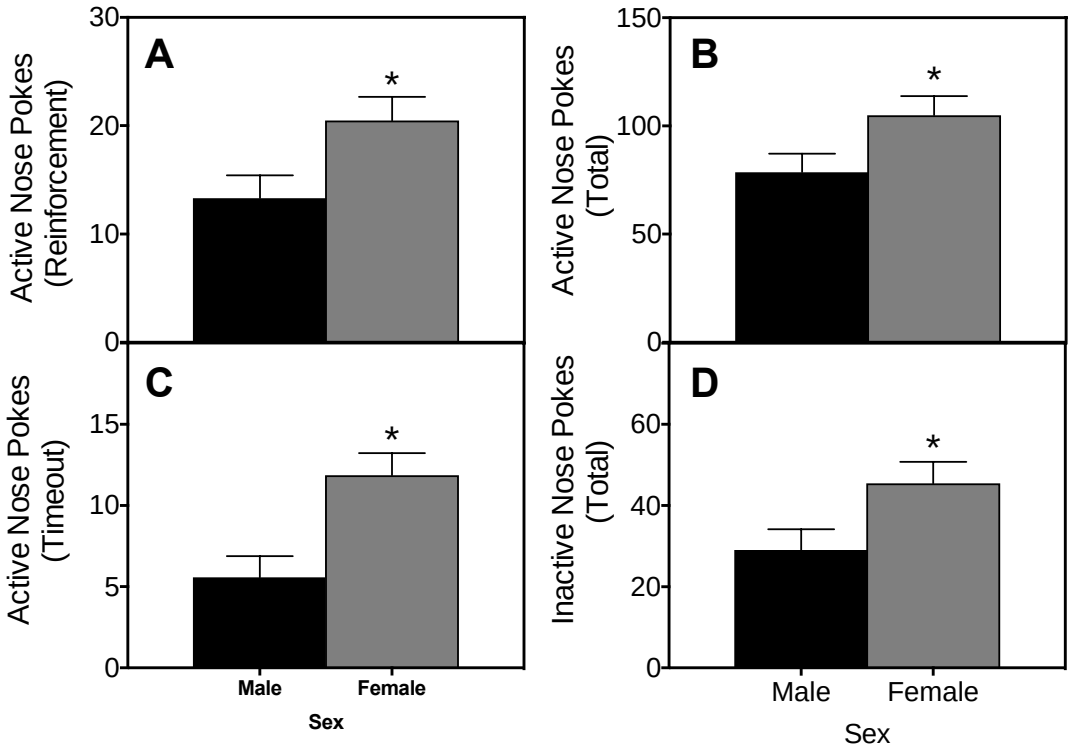

Figure 8. A) Mean number of active nose pokes (reinforcement); B) mean number of active nose pokes (total); C) mean number of active nose pokes (timeout); and D) mean number of inactive nose pokes (total) (± SEM) made by male and female rats during methamphetamine (40 mg/l) acquisition on session 7 (FR 2). * Indicates a significant difference from male rats ($p < .05$).

Extinction Training and Drug-Primed Reinstatement

Active nose pokes decreased across the seven extinction days [active, $F(4.04,326.99) = 8.69$, $p < .001$] (see Figure 9A). In contrast, inactive nose pokes remained relatively constant across extinction days [inactive, $F(6,486) = .741$, $p = .617$] (see Figure 9B).

Total active nose pokes were not altered by nicotine (0.16 mg/kg) pre- or post-treatment during extinction (see Figure 9A). Rats exposed to saline during the pre-treatment period had more total inactive nose pokes across extinction days than rats exposed to nicotine (0.16 mg/kg) during the pre-treatment period [pre-treatment main effect, $F(1,74) = 8.42$, $p < .01$] (see Figure 9B).

Sex altered responding for methamphetamine during extinction. Specifically, female rats had more total active nose pokes across extinction days than male rats [sex main effect, $F(1,74) = 8.42$, $p < .01$] (see Figures 9A & 9C). Total inactive nose pokes did not differ by sex during extinction (see Figure 9B).

Total active nose pokes were not altered by nicotine (0.16 mg/kg) pre- or post-treatment during reinstatement (see Figure 10A). Rats exposed to saline during the pre-treatment period had more total inactive nose pokes than rats exposed to a low dose of nicotine (0.16 mg/kg) during the pre-treatment period [pre-treatment main effect, $F(1,75) = 4.43$, $p < .05$] (see Figures 10B & 11).

Lastly, sex did not alter total active and inactive nose pokes during reinstatement (see Figure 10).

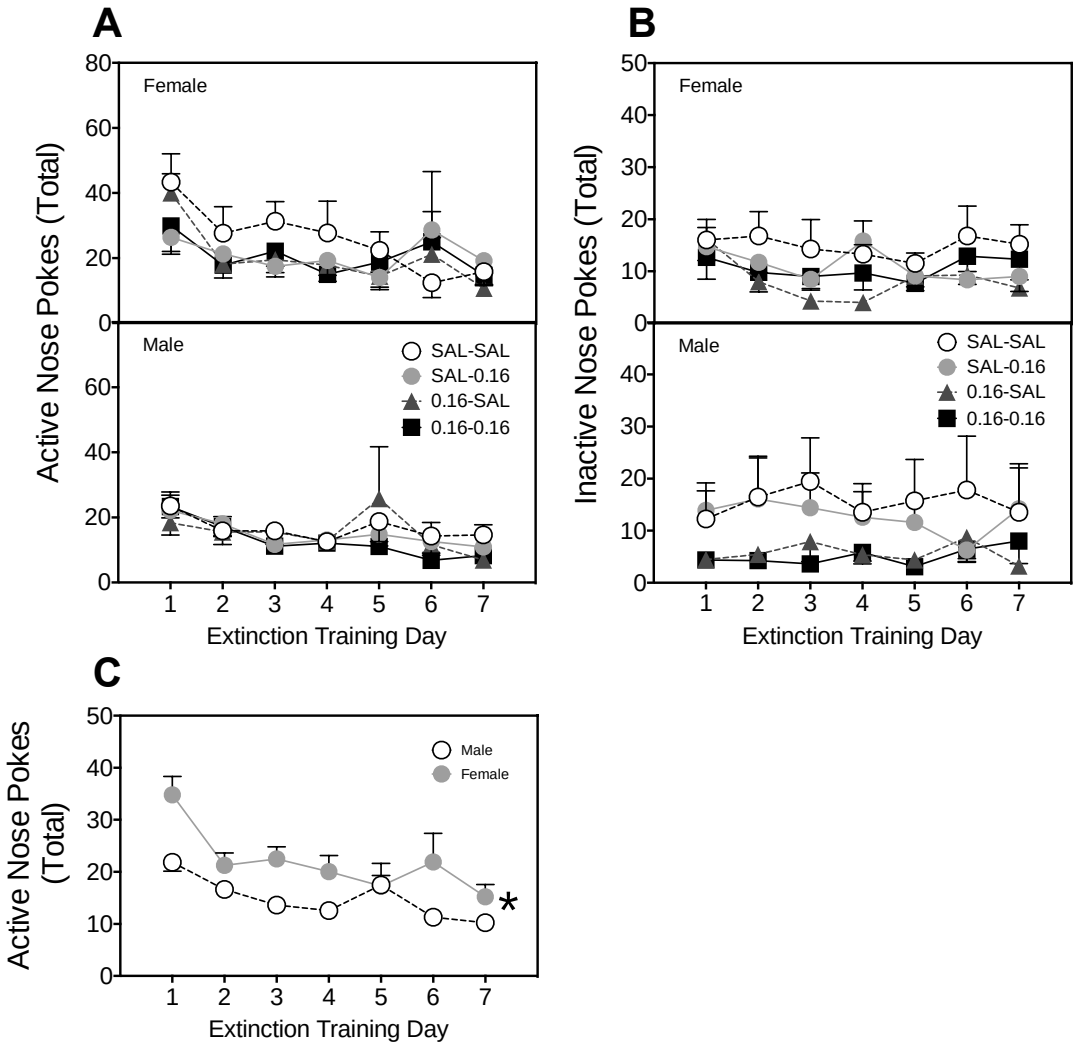

Figure 9. A) Mean number of active nose pokes (total); B) mean number of inactive nose pokes (total); and C) mean number of active nose pokes (total) (± SEM) made by male and female rats during extinction training days 1 – 7. Rats were exposed to saline (SAL) or nicotine (0.16 mg/kg) during the pre-treatment (PD 25–34) or post-treatment (PD 35–~60) phases. * Indicates a significant difference from male rats ($p < .05$).

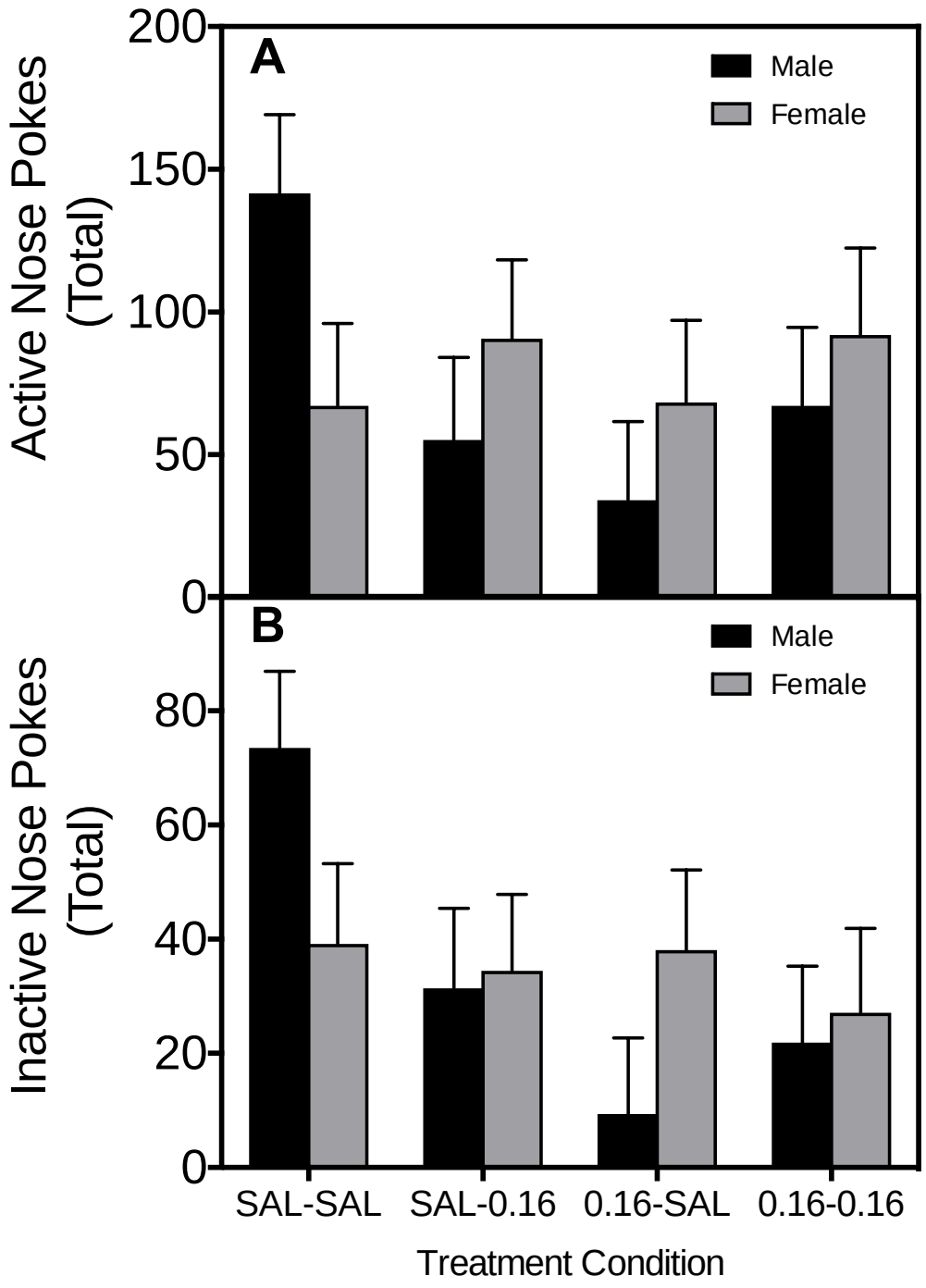

Figure 10. A) Mean number of active nose pokes (total); and B) mean number of inactive nose pokes (total) (± SEM) made by male and female rats during the reinstatement period. Rats were exposed to saline (SAL) or nicotine (0.16 mg/kg) during the pre-treatment (PD 25–34) or post-treatment (PD 35–~60) phases.

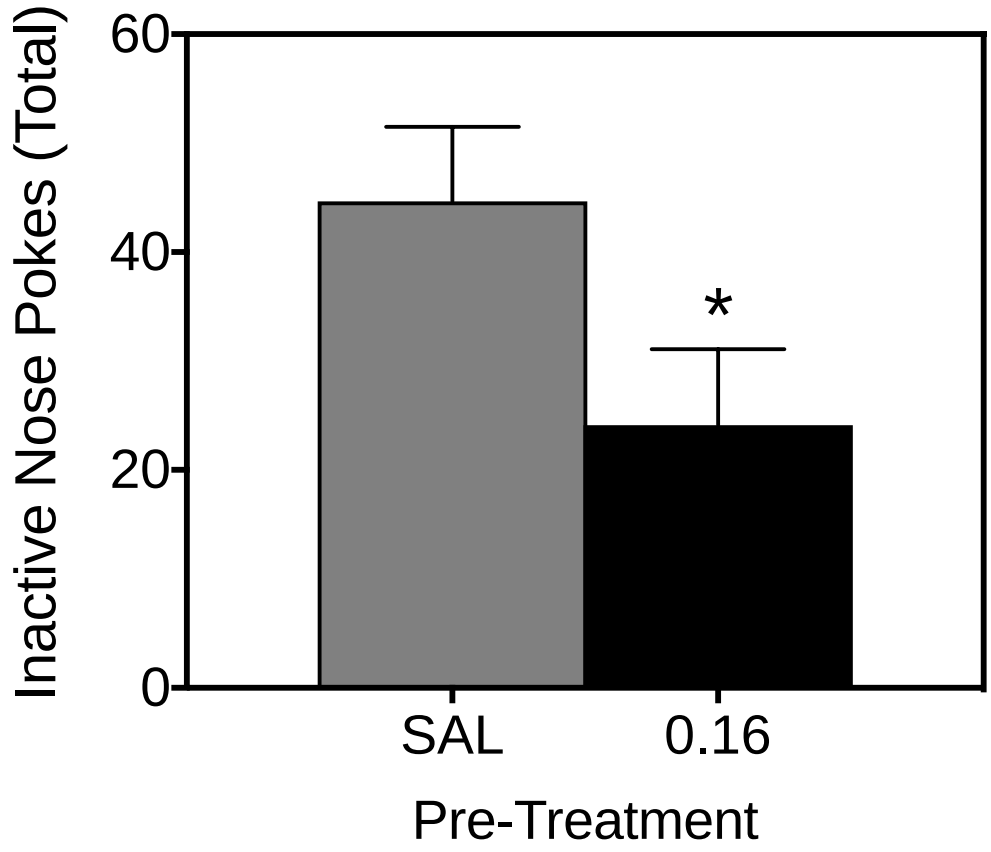

Figure 11. Mean number of inactive nose pokes (total) (± SEM) made by adolescent rats during methamphetamine reinstatement. Rats were exposed to saline (SAL) or nicotine (0.16 mg/kg) during the pre-treatment phase. * Indicates a significant different from saline treated rats ($p < .05$).

Effects of Nicotine (0.64 mg/kg) Exposure on Oral Methamphetamine Self-Administration, Extinction, and Reinstatement

Effect of Nicotine (0.64 mg/kg) Exposure on Bodyweight

Adolescent nicotine (0.64 mg/kg) exposure across the pre- (PD 25−PD 34) and post-treatment (PD 35−54) phases did not alter bodyweights of either male or female rats. Bodyweights of all rats progressively increased across the pre- (PD 25−PD 34) and post-treatment (PD 35−54) periods [day main effect, $F(1.83,146.32) = 542.52$, $p > .001$] (see Figure 12). Male rats ($M = 157.57$, $SEM = 2.34$) weighed more than female rats ($M = 129.47$, $SEM = 2.36$) across the pre- and post-treatment periods [sex main effect, $F(1,73) = 71.64$, $p > .001$] (see Figure 12).

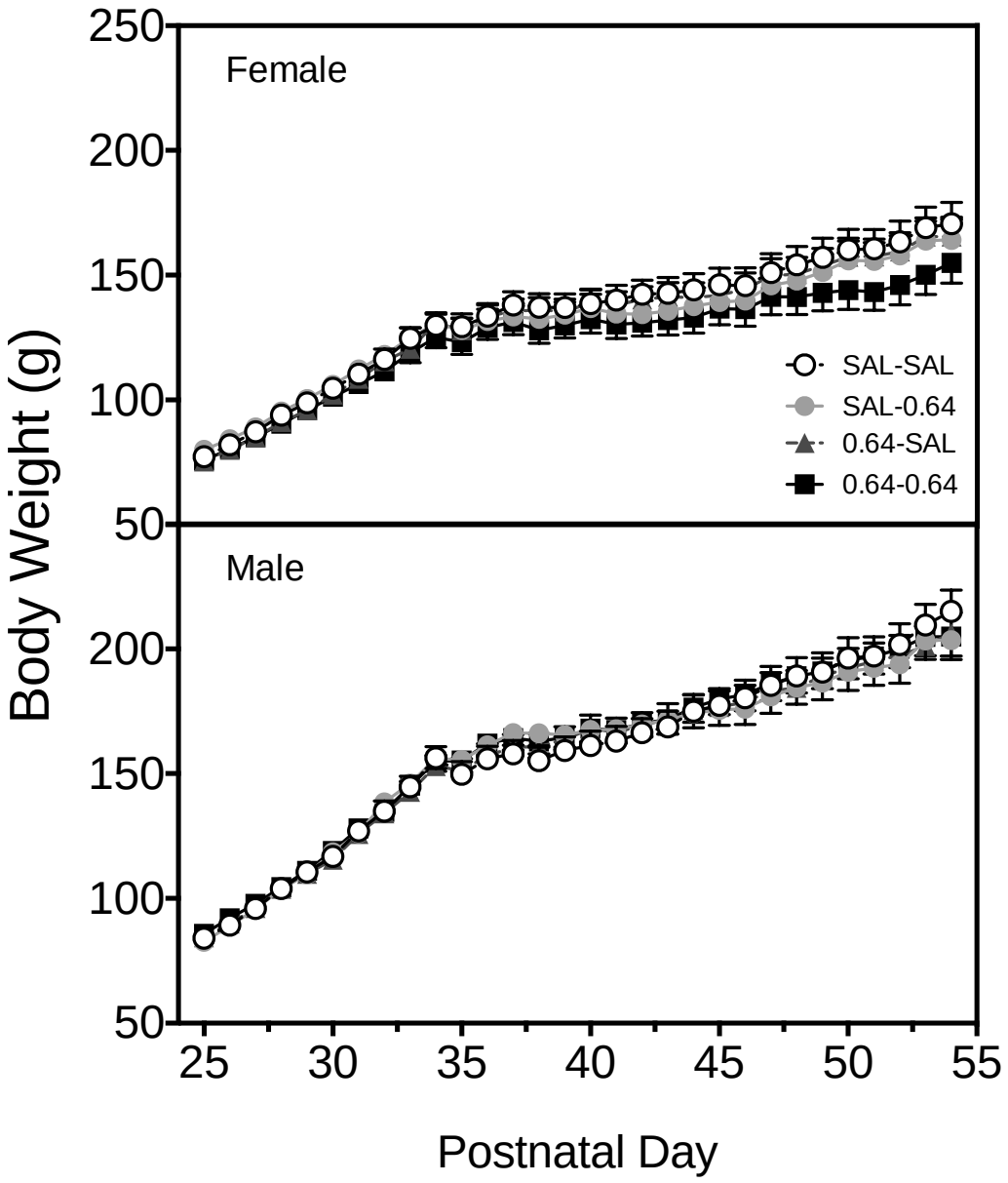

Figure 12. Mean body weight (± SEM) of male and female rats exposed to saline (SAL) or nicotine (0.64 mg/kg) across the pre- (PD 25–34) or post-treatment (PD 35–~60) phases.

Acquisition of Methamphetamine Self-Administration

Oral methamphetamine self-administration was acquired over six training sessions, in which sucrose was phased out and methamphetamine was introduced. On session 7, rats responded for methamphetamine alone. Neither pre- nor post-treatment with nicotine (0.64 mg/kg) altered consumption or responding for methamphetamine (see Figure 13). Male rats (M = 7.92, SEM = .36) consumed more sucrose and methamphetamine than female rats (M = 6.17, SEM = .37) [sex main effect, $F(1,73) = 11.46$, $p < .01$] (see Figure 13A).

None of the remaining dependent measures (i.e., total active and inactive nose pokes, active and inactive nose pokes during the timeout period) were altered by nicotine (0.64 mg/kg) or sex (see Figure 14).

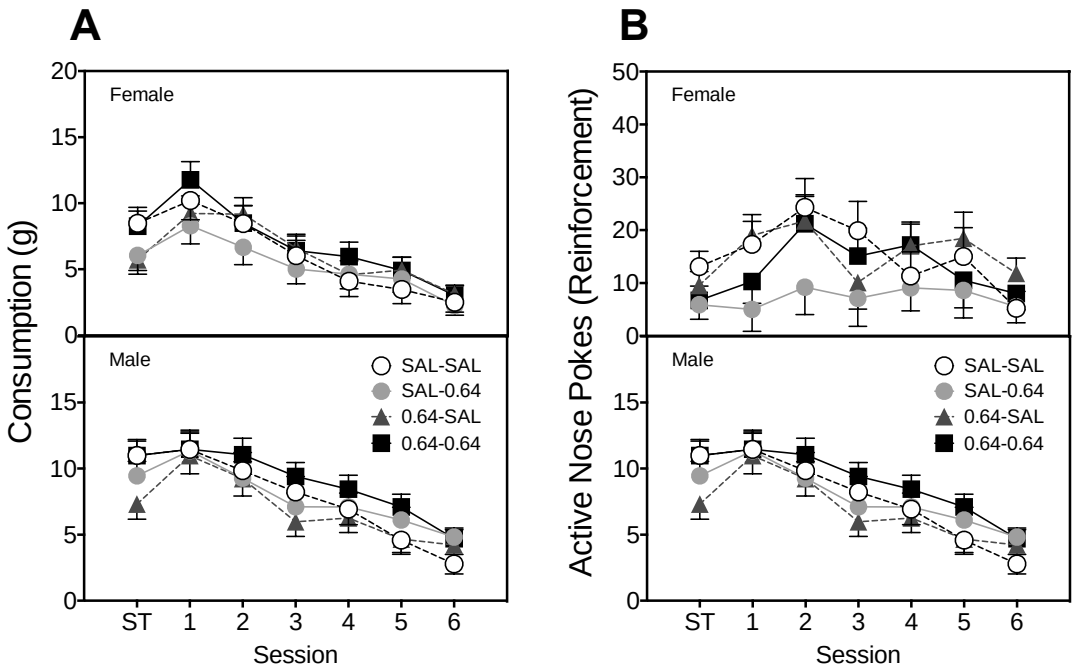

Figure 13. A) Mean sucrose and methamphetamine consumption; and B) mean number of active nose pokes (reinforcement) (± SEM) made by male and female rats exposed to saline (SAL) or nicotine (0.64 mg/kg) across the pre- (PD 25–34) or post-treatment (PD 35–~60) phases during methamphetamine acquisition training sessions (sucrose training–session 6).

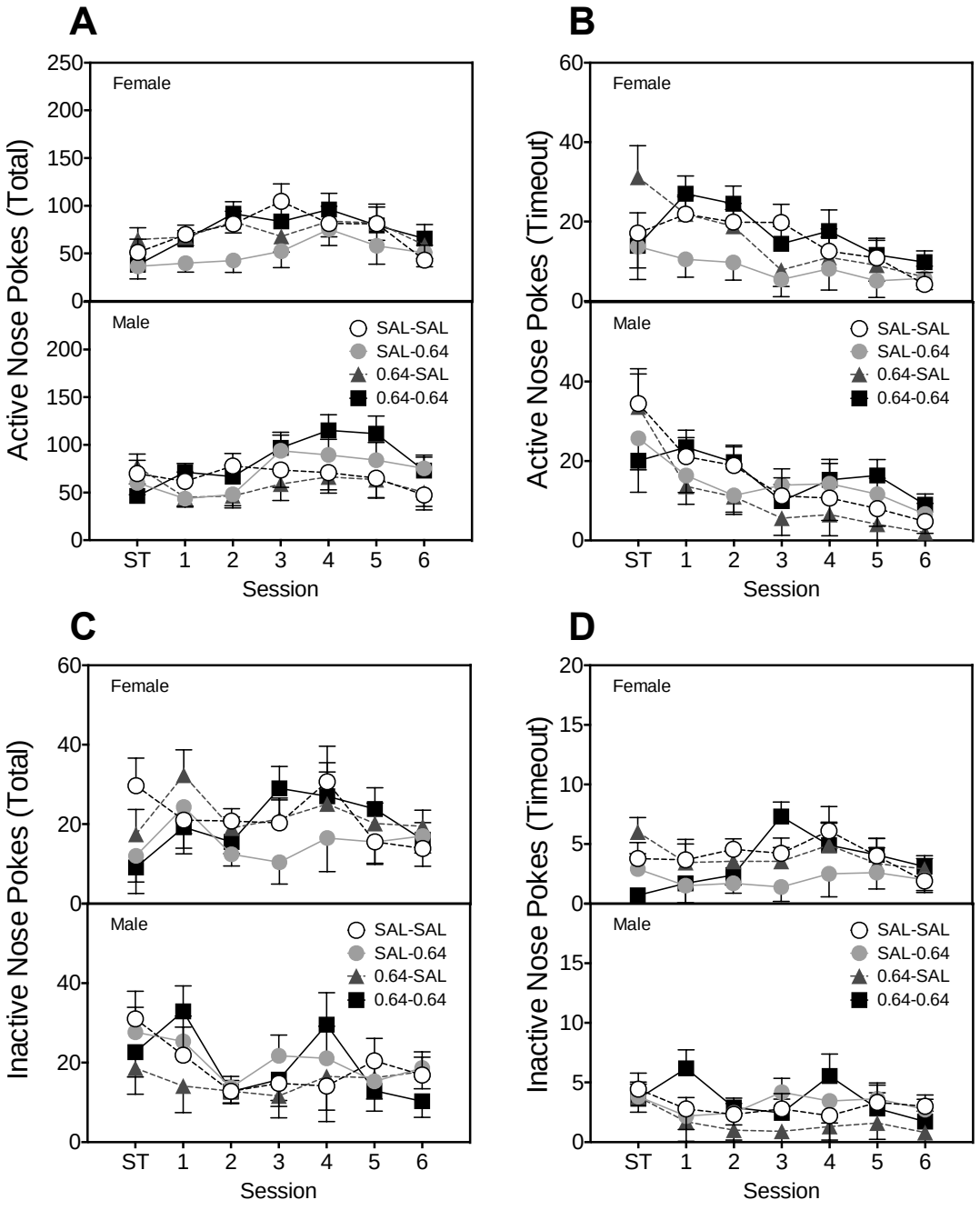

Figure 14. A) Mean number of active nose pokes (total); B) mean number of active nose pokes (timeout); C) mean number of inactive nose pokes (total); and D) mean number of inactive nose pokes (timeout) (± SEM) made by male and female rats exposed to saline (SAL) or nicotine (0.64 mg/kg) across the pre- (PD 25–34) or post-treatment (PD 35–~60) phases during methamphetamine acquisition training sessions (sucrose training–session 6).

Neither pre- nor post-treatment with nicotine (0.64 mg/kg) altered consumption or responding for methamphetamine on session 7 (see Figure 15).

Sex altered responding for methamphetamine on session 7 because female rats had more total active nose pokes and more active nose pokes within the reinforcement period than male rats [sex main effect, $F(1,73) = 3.97$, $p < .05$; $F(1,73) = 6.36$, $p < .05$, respectively] (see Figures 15B, 15C, 16A & 16B). Female rats also had more total inactive nose pokes and more inactive nose pokes within the timeout period than male rats [sex main effect, $F(1,73) = 4.08$, $p < .05$; $F(1,73) = 4.57$, $p < .05$, respectively] (see Figures 15E, 15F, 16C & 16D).

None of the remaining dependent measures (i.e., active nose pokes during the timeout period) were altered by nicotine (0.64 mg/kg) or sex (see Figure 15).

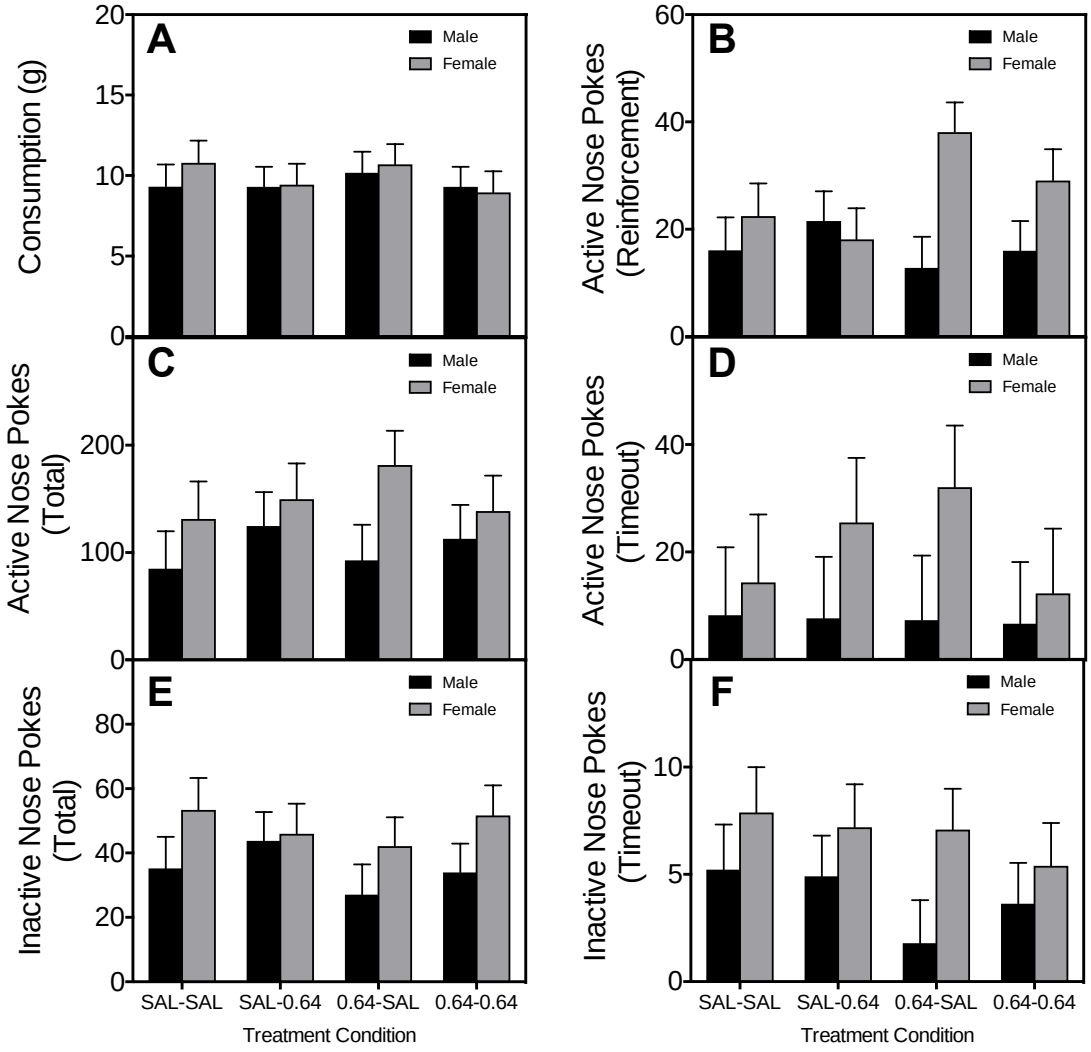

Figure 15. A) Mean methamphetamine (40 mg/l) consumption; B) mean active nose pokes (reinforcement); C) mean active nose pokes (total); D) mean active nose pokes (timeout); E) mean inactive nose pokes (total); and F) mean inactive nose pokes (timeout) (± SEM) made by adolescent male and female rats during methamphetamine acquisition on session 7 (FR 2). Rats were exposed to saline (SAL) or nicotine (0.64 mg/kg) during the pre-treatment (PD 25–34) or post-treatment (PD 35–~60) phases.

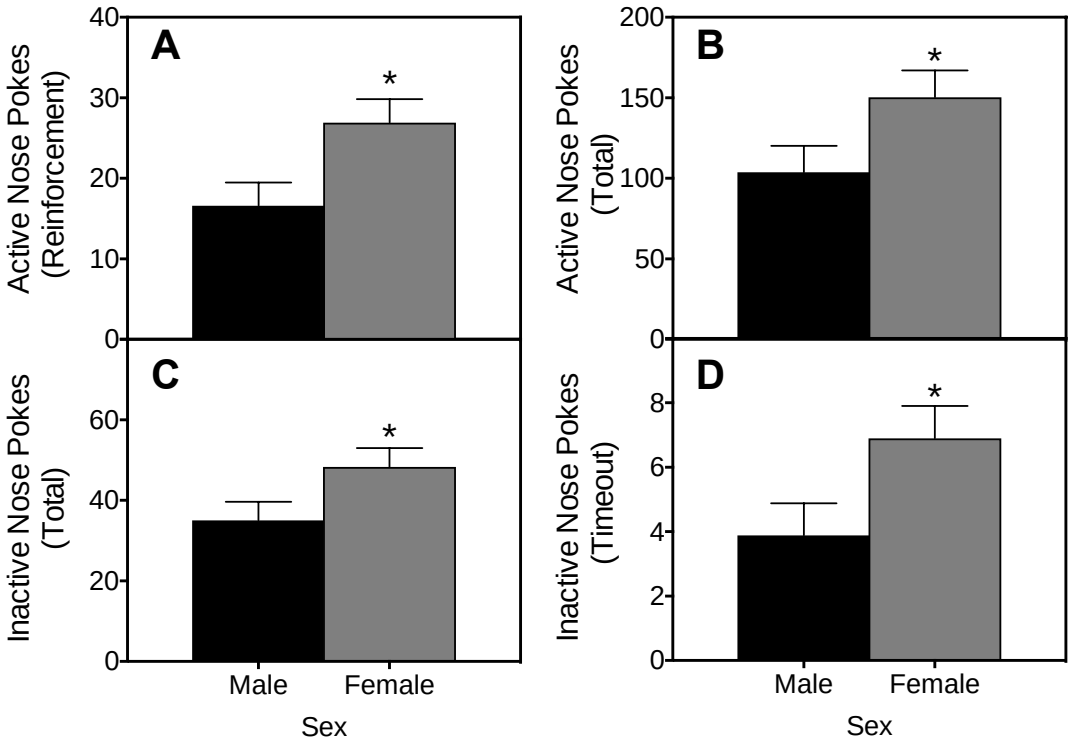

Figure 16. A) Mean number of active nose pokes (reinforcement); B) mean active nose pokes (total); C) mean number of inactive nose pokes (total); and D) mean number of inactive nose pokes (timeout) (± SEM) made by adolescent male and female rats during methamphetamine (40 mg/l) acquisition session 7 (FR 2). * Indicates a significant difference from male rats ($p < .05$).

Extinction Training and Drug-Primed Reinstatement

Active nose pokes decreased across extinction days [active, $F(2.91,232.4) = 6.73$, $p < .001$] (see Figure 17A). This decrease in active lever presses was not altered by sex or nicotine (0.64 mg/kg) exposure. Inactive nose pokes did not significantly change across extinction days [inactive, $F(3.98,318.00) = 1.26$, $p = .274$] (see Figure 17B). Inactive lever presses were not altered by sex or nicotine (0.64 mg/kg) exposure.

Neither nicotine (0.64 mg/kg) exposure nor sex altered total active or inactive nose pokes during extinction training (see Figure 17A & 17B). Similarly, neither nicotine (0.64 mg/kg) exposure nor sex altered total active or inactive nose pokes during methamphetamine-primed reinstatement (see Figure 18A & 18B).

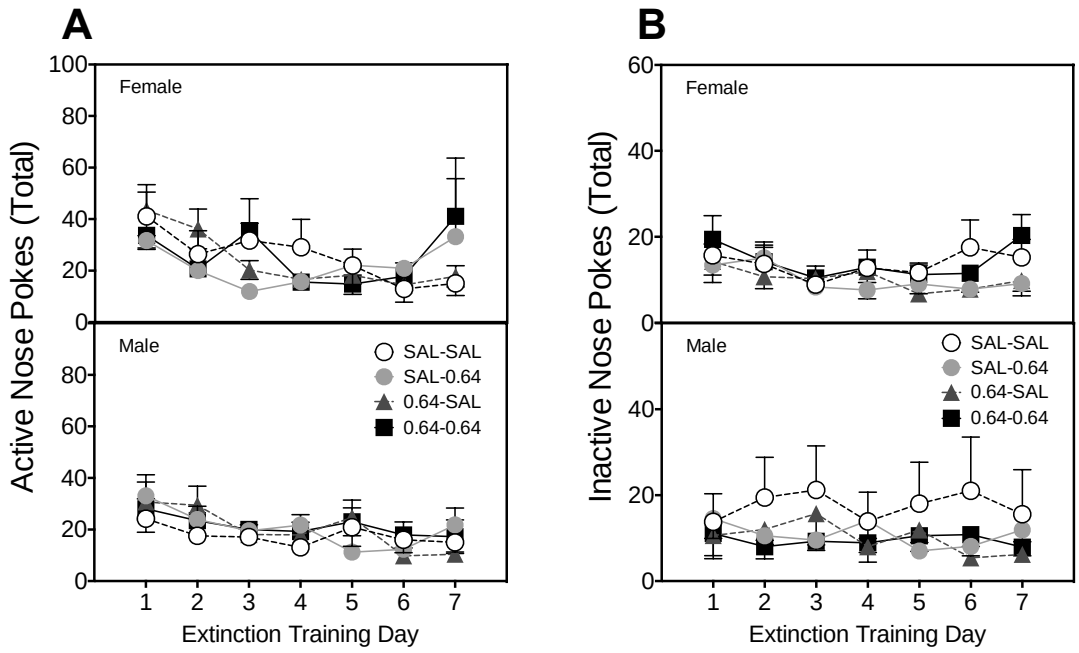

Figure 17. A) Mean number of active nose pokes (total); and B) mean number of inactive nose pokes (total) (± SEM) made by adolescent male and female rats during methamphetamine extinction. Rats were exposed to saline (SAL) or nicotine (0.64 mg/kg) during the pre-treatment (PD 25–34) or post-treatment (PD 35–~60) phases.

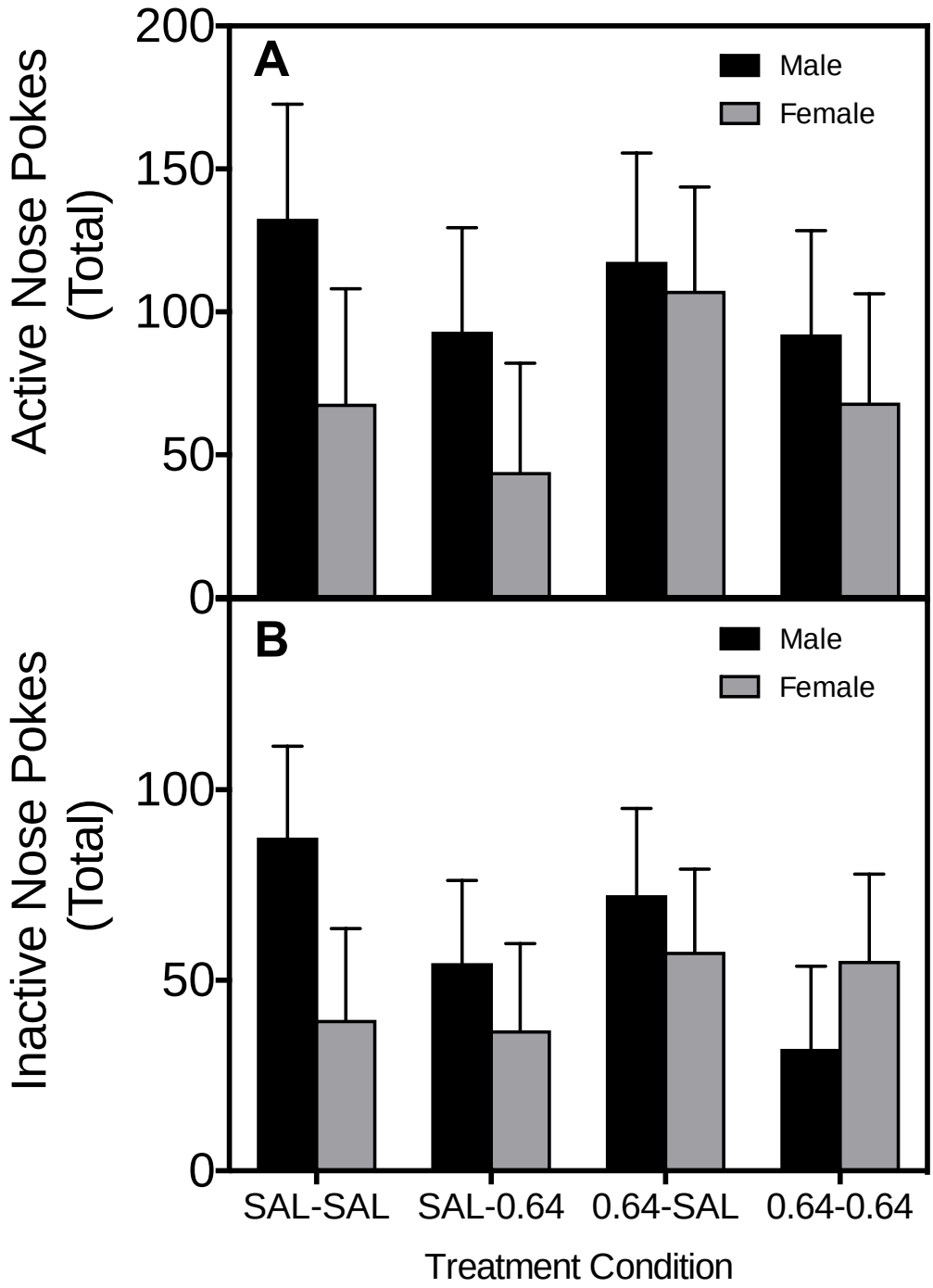

Figure 18. A) Mean number of active nose pokes (total); and B) mean number of inactive nose pokes (total) (± SEM) made by rats during reinstatement. Rats were exposed to saline (SAL) or nicotine (0.64 mg/kg) during the pre-treatment (PD 25–34) or post-treatment (PD 35–~60) phases.

CHAPTER ELEVEN

DISCUSSION

Introduction

Cigarette smoking is most likely to begin during the adolescent period, and often functions as a gateway to other drugs of abuse, such as methamphetamine (Lewinsohn et al., 1999). Methamphetamine use during adolescence is particularly troublesome given the severe psychological and physiological consequences of methamphetamine abuse (Russell et al., 2008; Vearrier et al., 2012). Given that adolescence is a vulnerable period in development, in which cigarette smoking can lead to the onset of methamphetamine use and addiction, it is imperative to investigate the neurobiological relationship between these highly addictive drugs during the adolescent period (Yuan, Cross, Loughlin, & Leslie, 2015). Therefore, the aim of the present thesis was to determine the role of adolescent nicotine exposure on the reinforcing properties of methamphetamine, as well as drug seeking behavior, through the use of an oral methamphetamine self-administration procedure.

We had two primary hypotheses. First, we hypothesized that nicotine exposure would alter methamphetamine self-administration and methamphetamine drug seeking behavior. Specifically, we predicted that exposure to a low dose of nicotine (0.16 mg/kg) would enhance the reinforcing effects of methamphetamine (i.e., increased consumption and more active nose pokes) compared to rats exposed to saline. Conversely, we predicted that

exposure to a high dose of nicotine (0.64 mg/kg) would attenuate the reinforcing effects of methamphetamine (i.e., decreased consumption and a reduced number of active nose pokes) compared to rats exposed to saline. These hypotheses were founded in past research showing that exposure to low doses of nicotine potentiates the rewarding properties of methamphetamine and cocaine (McQuown et al., 2007; Pipkin et al., 2014), whereas exposure to higher doses of nicotine attenuates methamphetamine self-administration and reinstatement (Hiranita et al., 2004; 2006; Neugebauer et al., 2010).

Second, we hypothesized that sex would alter methamphetamine self-administration and methamphetamine drug seeking behavior. Specifically, we predicted that female rats would display behavior indicating an enhancement of the reinforcing effects of methamphetamine (i.e., increased consumption and more active nose pokes) compared to male rats. These hypotheses were founded in past research showing that female rats acquire methamphetamine self-administration more readily (Kucerova, Vrskova, & Sulcova, 2009), as well as respond more for access to methamphetamine during reinstatement, than male rats (Ruda-Kucerova et al., 2015).

During methamphetamine acquisition training sessions (i.e., sucrose training – session 6), nicotine (0.16 or 0.64 mg/kg) exposure did not alter consumption or responding for methamphetamine; however, rats exposed to saline had more inactive nose pokes within the timeout period than rats exposed to a low dose of nicotine (0.16 mg/kg).

During methamphetamine self-administration (i.e., session 7), nicotine (0.16 mg/kg) exposure altered consumption and responding for methamphetamine. In contrast to our hypotheses, rats exposed to saline during the post-treatment period had more active nose pokes during the reinforcement period and more methamphetamine consumption than rats exposed to a low dose of nicotine (0.16 mg/kg) during the post-treatment period. Nicotine (0.16 mg/kg) exposure during the pre-treatment period did not alter consumption or responding for methamphetamine. Rats exposed to saline during the pre-treatment period had more total inactive nose pokes compared to rats exposed to a low dose of nicotine (0.16 mg/kg) during the pre-treatment period. Neither pre- nor post-treatment with a high dose of nicotine (0.64 mg/kg) altered consumption or responding for methamphetamine during self-administration.

During the extinction and reinstatement periods, nicotine (0.16 or 0.64 mg/kg) exposure did not alter consumption or responding for methamphetamine; however, rats exposed to saline during the pre-treatment period had more total inactive nose pokes across extinction days than rats exposed to nicotine (0.16 mg/kg) during the pre-treatment period. During the reinstatement period, rats exposed to saline during the pre-treatment period had more total inactive nose pokes than rats exposed to a low dose of nicotine (0.16 mg/kg) during the pre-treatment period.

The present results also demonstrated that oral methamphetamine self-administration differed by sex. Consistent with our hypotheses, female rats had

augmented total active nose pokes and a greater number of active nose pokes within the reinforcement period compared to male rats. Conversely, male rats showed augmented sucrose and methamphetamine solution consumption across methamphetamine acquisition training sessions (i.e., sucrose training – session 6). Female rats had augmented total inactive nose pokes, as well as more active and inactive nose pokes, within the timeout period compared to male rats. During extinction, female rats had an augmented number of total inactive nose pokes compared to male rats; however, no sex differences were observed during methamphetamine reinstatement.

From a methodological perspective, the present thesis highlights that oral methamphetamine self-administration can be achieved in adolescent rats. Specifically, all groups, regardless of sex or drug treatment, exhibited consumption and operant responding for methamphetamine through the oral route of administration. To our knowledge, very few studies have utilized oral methamphetamine self-administration in mice (Shabani et al., 2013), with no published research demonstrating this effect in rats. As a genetic animal model of methamphetamine addiction, Shabani et al. (2013) utilized selectively bred mice to consume methamphetamine at either high or low rates. These researchers found that high methamphetamine-drinking mice have augmented intake, but a similar number of active lever presses when compared to low methamphetamine-drinking mice in the oral self-administration procedure. In

addition, they found comparable results utilizing an intracerebroventricular route of methamphetamine self-administration.

The present thesis and Shabani et al. (2013) utilized similar acquisition training, in which sucrose faded-out and methamphetamine faded-in across seven different sessions. This type of acquisition is frequently used in oral ethanol self-administration studies (Ford et al., 2009). One difference between acquisition in the present thesis and Shabani et al. (2013) includes the use of sucrose or saccharin, respectively. In addition, mice in Shabani et al. (2013) underwent five, 1 hr operant trials for every change in solution or fixed ratio scheduling, resulting in a total of 35 operant trials. In the present thesis, rats underwent 2 hr operant trials, in which advancement to the next session was dependent on meeting specific criteria (e.g., 10 or more presentations). Due to the short adolescent period in rats (~30 days), it was necessary to utilize the more abbreviated acquisition schedule to allow additional time for nicotine pre-treatment (i.e., 10 days). It is unclear whether these methodological differences affect the acquisition of oral methamphetamine self-administration; however, Shabani et al., 2013 suggest that increasing the number of operant trials per session facilitates the stabilization of behavior associated with each solution type.

Taken together, findings from the present thesis and past research demonstrate that oral methamphetamine self-administration is attainable in both rats and mice. It is important to determine whether this effect in rats is age-specific. Future research may consider testing oral methamphetamine self-

administration in adult rats, as evidence suggests that drugs of abuse, such as methamphetamine, have a heightened reward value in adolescent rats, and this age group has a diminished sensitivity for the aversive effects of the drug (Schramm-Sapyta, Morris, & Kuhn, 2006; Schramm-Sapyta et al., 2009).

The present data supports previous findings that nicotine exposure attenuates behavioral responding for methamphetamine during self-administration and reinstatement (Hiranita et al., 2004; 2006; Neugebauer et al., 2010). Specifically, adolescent male and female rats exposed to a low dose of nicotine (0.16 mg/kg) during the post-treatment (PD 35–~60) period had attenuated active nose pokes and reduced methamphetamine consumption across methamphetamine (40 mg/l) self-administration. Similarly, adolescent male and female rats exposed to a low dose of nicotine (0.16 mg/kg) during the pre-treatment (PD 25–34) period had attenuated total inactive nose pokes during the methamphetamine (40 mg/l) self-administration, extinction, and reinstatement phases. Neugebauer et al. (2010) found that adult male rats exposed to a higher dose of nicotine (0.40 mg/kg) showed a reduction in responding for methamphetamine access during self-administration, while a lower dose of nicotine (0.20 mg/kg) had no effect. This nicotine-induced attenuation of responding for methamphetamine was only observed at a higher fixed ratio schedule (i.e., FR 5) and was not observed at lower fixed ratio scheduling (i.e., FR 1) (Neugebauer et al., 2010). The authors attribute this finding to the susceptibility of nicotine to disrupt higher, but not lower rates of responding;

however, data from the present thesis suggests that a low dose of nicotine can also attenuate responding for methamphetamine at low rates of responding (i.e., FR 2).

The present findings also show that nicotine exposure reduces responding for methamphetamine access during extinction and methamphetamine-primed reinstatement. Hiranita et al. (2004) found that adult male rats showed a reduction in methamphetamine seeking behavior during primed reinstatement following a repeated or single nicotine (0.30 mg/kg) exposure during a methamphetamine-withdrawal period. In addition, the nicotine-induced attenuation of methamphetamine seeking behavior was blocked by exposure to the nicotinic antagonist mecamylamine, thus demonstrating that the cholinergic system may be important in methamphetamine relapse (Hiranita et al., 2004; 2006). Hiranita et al. (2006) found the attenuating effects of nicotine on methamphetamine seeking behavior was not altered by the muscarinic antagonist scopolamine, indicating that the inactivation of nicotinic ACh receptors is important for methamphetamine seeking behavior.

Despite the clear methodological differences, the present findings and Hiranita et al. (2004; 2006) demonstrate a relationship between the nicotinic ACh system and methamphetamine seeking behavior. Within the CNS, the $\alpha_4\beta_2$ and α_7 nAChRs are the main receptor subtypes, with each receptor thought to play a different role in drug-seeking behavior (Grottick, Wyler, & Higgins, 2000). Compared to adults, adolescent $\alpha_4\beta_2$ and α_7 nAChRs expression and binding are

augmented in many different brain areas (Yuan et al., 2015). When exposed to the selective $\alpha_4\beta_2$ nAChR antagonist DhβE in the nucleus accumbens core and prelimbic cortex, the AM251-induced (i.e., cannabinoid receptor 1 antagonist) attenuation of methamphetamine seeking behavior is blocked (Hiranita et al., 2008). However, exposure to the selective α_7 nAChR antagonist MLA does not alter the AM251-induced attenuation of methamphetamine seeking behavior, suggesting that normal functioning of the $\alpha_4\beta_2$ nAChR plays an important role in methamphetamine seeking behavior (Hiranita et al., 2008). In addition, nicotine and ACh have a greater affinity for the $\alpha_4\beta_2$ nAChR compared to α_7, further indicating the importance of the $\alpha_4\beta_2$ nAChR (Decker, Brioni, Bannon, & Arneric, 1995; Gotti, Zoli, & Clementi, 2006). Taken together, it is possible that the nicotine-induced attenuation of methamphetamine seeking behavior observed in the present thesis may be due, in part, to the activation of the $\alpha_4\beta_2$ nAChR.

The present findings contrast with previous work showing that daily nicotine (0.16 mg/kg) treatment beginning in adolescence increases methamphetamine infusions, as well as active, inactive, and timeout lever presses in adult male rats (Pipkin et al., 2014). A potential explanation for the differing results is the self-administration procedures being used. Specifically, Pipkin et al. (2014) utilized intravenous self-administration of methamphetamine and found that nicotine exposure augmented responding for methamphetamine, whereas the present study used an oral method of methamphetamine self-administration. The oral self-administration procedures used in the present study

were adopted from oral ethanol self-administration studies, wherein the drug is introduced in a sweetened solution and faded out across acquisition training (Ford et al., 2009). The drug is orally consumed and must first pass through the gastrointestinal lining and subsequently enters the blood stream. In contrast, the intravenous self-administration method requires surgery and the insertion of a catheter into the jugular vein, wherein the drug is directly infused into the bloodstream. Despite the disadvantages of oral self-administration procedures (e.g., delay in onset of the psychoactive effects of methamphetamine or the degradation of the drug via digestive enzymes and alternating pH levels), it is apparent that our rats did readily oral self-administer methamphetamine in the present thesis. It is not clear as to the extent this methodological difference played a role in the differing results found in the present thesis and Pipkin et al. (2014), but future direct comparisons of the two methamphetamine self-administration procedures are warranted and may provide further clarity on this issue.

Another explanation for the inconsistent results found in the present study and results from Pipkin et al. (2014) may be due to the age that rats were exposed to nicotine and tested on the methamphetamine self-administration procedures. Maturational changes in ACh and related neurotransmitter systems occur across early ontogeny and into adulthood (Yuan et al., 2015). For example, nAChR stimulation causes augmented ventral striatal DA release during adolescence when compared to adulthood (Azam et al., 2007). Nicotine

exposure leads to an increase of DA release via the mesolimbic reward pathway, in which consistently heightened DA levels results in the desensitization of these neurons (Pidoplichko, DeBiasi, Williams, & Dani, 1997). In addition, methamphetamine exposure leads to heightened DA release in the mesolimbic reward pathway (Dobbs & Mark, 2012). Age-related effects of nicotine exposure may be due, in part, to the protective mechanisms of nicotine against methamphetamine-induced dopaminergic deficits (Vieira-Brock et al., 2015).

Stimulation of the $\alpha_4\beta_2$ nAChR via nicotine exposure may act as a neuroprotective mechanism against methamphetamine-induced DA deficits (Baladi, Nielsen, McIntosh, Hanson, & Fleckenstein, 2016; Vieira-Brock et al., 2015). Specifically, adolescent nicotine exposure (PD 41−61) attenuates methamphetamine-induced striatal dopaminergic deficits through $\alpha_4\beta_2$ nAChR stimulation; however, this nicotine-induced neuroprotection was more pronounced in rats chronically treated with nicotine beginning in adolescence and ending in adulthood (Vieira-Brock et al., 2015). In contrast, nicotine exposure beginning in adulthood did not result in the same neuroprotection as adolescent nicotine administration, suggesting that the neuroprotective effects of nicotine against methamphetamine-induced DA deficits are age-related (Vieira-Brock et al., 2015). Taken together, these findings and data from the present thesis support the notion that nicotine exposure during the adolescent period acts to protect against methamphetamine-induced DA deficits and decreases the robust reinforcing properties of methamphetamine (Vieira-Brock et al., 2015). Moreover,

the nicotine-induced attenuation of responding for methamphetamine during self-administration may be due to the age-related differences in the neuroprotective effects of $\alpha_4\beta_2$ nAChR stimulation. Future research should consider investigating the specific neural mechanisms surrounding the nicotine-induced attenuation of responding for methamphetamine in adolescent rats.

In the present thesis, female rats consistently responded for access to methamphetamine more than male rats during self-administration. Clinical reports show that females account for approximately 50% of adolescent methamphetamine users (Chen et al., 2014). Females report methamphetamine initiation at a younger age, a greater psychological burden and severity of methamphetamine use, and a more rapid increase in the frequency of methamphetamine use when compared to male users (Dluzen & Liu, 2008; Liu, Wang, Chu, & Chen, 2013; Rawson, Gonzales, Obert, McCann, & Brethen, 2005; Simpson et al., 2016). Men show a significant correlation between methamphetamine cravings and depression or anxiety while females do not show the same correlation, thus indicating that females do not share some of the same side effects from methamphetamine use as men (Hartwell, Moallem, Courtney, Glasner-Edwards, & Ray, 2016). Similar to clinical reports, pre-clinical findings indicate that female rats acquire methamphetamine self-administration more rapidly and exhibit a more robust reinstatement than male rats (Kucerova, et al., 2009; Reichel et al., 2012; Roth & Carroll, 2004; Ruda-Kucerova et al., 2015). Thus, the present data support and extend previous clinical and pre-

clinical findings, in which female rats consistently respond more for access to methamphetamine than male rats during an oral self-administration procedure.

In contrast to data from adolescent rats exposed to a low dose of nicotine (0.16 mg/kg), data from adolescent rats exposed to a high dose of nicotine (0.64 mg/kg) suggests that nicotine exposure does not alter responding for access to methamphetamine during adolescence. The reason for this dose-dependent effect is unknown; however, higher doses of nicotine (e.g., > 0.60 mg/kg) can be averse (Torres et al., 2008). Given that a low dose of nicotine (0.16 mg/kg) in the present thesis altered responding for methamphetamine and a high dose of nicotine (0.64 mg/kg) did not, the aforementioned explanation is unlikely. Previous preclinical work is mixed in regard to the disruption of methamphetamine self-administration by a high dose of nicotine. Specifically, Neugebauer et al. (2010) found a reduction in responding for methamphetamine following exposure to a higher dose of nicotine (0.40 mg/kg), while a lower dose of nicotine (0.20 mg/kg) had no effect. Consistent with the present thesis, Pipkin et al. (2014) found that a high dose of nicotine (0.64 mg/kg) did not alter responding for methamphetamine. Pipkin et al. (2014) suggest these findings maybe due to response competition (i.e., high nicotine doses induce stereotyped behavior that interferes with responding for methamphetamine). Again, this explanation is also unlikely, as we found that a low dose of nicotine, but not a high dose, attenuated responding for methamphetamine.

Interestingly, we consistently found that inactive nose pokes were attenuated in rats treated with a low dose of nicotine (0.16 mg/kg) across methamphetamine self-administration, extinction, and reinstatement. This finding suggests that nicotine exposure reduced activity and impulsivity levels of rats during these periods. Prior clinical research suggests that impulsivity and drug dependence are positively correlated, with impulsivity being a strong predictor of nicotine and methamphetamine dependence (Balevich, Wein, & Flory, 2013; Ryan, MacKillop, & Carpenter, 2013; Tziortzis, Mahoney, Kalechstein, Newton, & De La Garza, 2011). Impulsivity also enhances an individual's vulnerability to relapse (Kreek, Nielsen, Butelman, & LaForge, 2005). Therefore, the present study contrasts with previous clinical work and suggests that exposure to a low dose of nicotine (0.16 mg/kg) reduces impulsivity of rats during methamphetamine self-administration, extinction, and reinstatement.

In addition, we found that female rats had heightened inactive nose pokes compared to male rats during methamphetamine self-administration and extinction. This finding suggests that female rats exposed to methamphetamine were more active and impulsive than similarly treated male rats. Previous clinical work suggests there are no sex differences in the impulsivity of methamphetamine users (Kogachi, Chang, Alicata, Cunningham, & Ernst, 2017). However, sex differences in methamphetamine users may be a function of age, as younger female methamphetamine users tend to have higher impulsivity scores (Kogachi et al., 2017; Semple, Zians, Grant, & Patterson, 2005).

Preclinical research suggests that sex differences in activity and impulsivity levels also occur in methamphetamine-treated rats. Consistent with the present study, female rats exposed to methamphetamine had more inactive lever presses than similarly-treated male rats (Reichel et al., 2012).

The present results suggest that adolescents are exceedingly sensitive to nicotine doses. Adolescents who undergo treatment for methamphetamine addiction may benefit from the nueroprotective effects of exposure to a low dose of nicotine, while exposure to higher doses of nicotine may be counter productive. Thus, for adolescents who already present cigarette smoking behavior at the time of methamphetamine addiction treatment, total abstinence from both nicotine and methamphetamine may be a less effective form of treatment. It may be clinically beneficial to first treat the methamphetamine addiction, and subsequently treat the nicotine addiction. Regardless of the method of treatment for adolescent methamphetamine addiction, nicotine exposure should be closely monitored.

Taken together, data resulting from exposure to a low dose of nicotine (0.16 mg/kg) and a high dose of nicotine (0.64 mg/kg) differentially supports the gateway theory of drug addiction, which suggests that using legal drugs, such as nicotine, increases the propensity for subsequent use of illicit drugs, such as methamphetamine (Lewinsohn et al., 1999). Within a strictly social context, it is likely that nicotine use may indeed lead to subsequent methamphetamine use, as approximately 97% of methamphetamine users also smoke cigarettes (Brecht

et al., 2004). From a purely pharmacological perspective, it is also apparent that moderate adolescent nicotine exposure can be protective against the robust reinforcing properties of methamphetamine; whereas, heightened adolescent nicotine exposure does not alter the reinforcing properties of methamphetamine.

Conclusion

The major findings from the present thesis are threefold: a) oral methamphetamine self-administration, extinction, and reinstatement are attainable in adolescent rats; b) exposure to a low dose of nicotine (0.16 mg/kg) attenuates the reinforcing properties of methamphetamine; c) exposure to a high dose of nicotine (0.64 mg/kg) does not alter the reinforcing properties of methamphetamine. The present research extends previous results showing: 1) oral methamphetamine self-administration is possible in mice (Shabani et al., 2013); 2) exposure to nicotine has neuroprotective effects, resulting in the attenuation of methamphetamine seeking during methamphetamine self-administration, extinction, and primed reinstatement (Baladi et al., 2016; Hiranita et al., 2004; 2006; Neugebauer et al., 2010; Vieira-Brock et al., 2015); and 3) exposure to a high dose of nicotine does not alter acquisition of methamphetamine self-administration (Pipkin et al., 2014).

Future research may consider investigating oral methamphetamine self-administration in adult rats, as adolescent rats exhibit heightened reward and diminished sensitivity to the aversive effects of drugs of abuse, such as methamphetamine (Schramm-Sapyta et al., 2006, 2009). Future research should

also consider investigating the specific neural mechanisms surrounding the nicotine-induced attenuation of responding for methamphetamine during self-administration, extinction, and reinstatement in adolescent rats.

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