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COCAINE-INDUCED BEHAVIORAL SENSITIZATION AND CONDITIONED PLACE PREFERENCE IN JAPANESE QUAIL (*COTURNIX JAPONICA*): A FOCUS ON SEX DIFFERENCES AND DOPAMINERGIC MECHANISMS

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COCAINE-INDUCED BEHAVIORAL SENSITIZATION AND CONDITIONED PLACE PREFERENCE IN JAPANESE QUAIL (*COTURNIX JAPONICA*): A FOCUS ON SEX DIFFERENCES AND DOPAMINERGIC MECHANISMS

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Arts and Sciences
at the University of Kentucky

By

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Lexington, Kentucky

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2015

ABSTRACT OF DISSERTATION

COCAINE-INDUCED BEHAVIORAL SENSITIZATION AND CONDITIONED PLACE PREFERENCE IN JAPANESE QUAIL (*COTURNIX JAPONICA*): A FOCUS ON SEX DIFFERENCES AND DOPAMINERGIC MECHANISMS

Research has indicated that gonadal hormones may mediate behavioral and biological responses to cocaine. Estrogen, in particular, has been shown to increase behavioral responding to cocaine in female rats relative to male rats. The use of Japanese quail may add to our knowledge of sex differences in drug abuse because of their advanced visual system and the ability to control their gonadal hormones via alterations in photoperiod. In three experiments, cocaine-induced behaviors were examined using this avian model.

In Experiment 1, I investigated the potential sex differences in cocaine-induced locomotor activity between male and female Japanese quail and I examined the potential role of gonadal hormones in these effects. Results from Experiment 1 indicated that cocaine-induced locomotor activity correlates with testosterone in male quail. Surprisingly, cocaine-induced activity did not correlate with estradiol in female quail, nor did female quail respond to cocaine as expected. Due to these results, Experiment 2 was designed to determine whether D2 receptors are involved in the psychomotor activating effects of cocaine in female quail. Results from Experiment 2 showed that D2 blockade enhances acute cocaine-induced locomotor activity in female quail. This result suggests that D2 receptors play an important role in cocaine-induced locomotor activity in female quail.

Cocaine's psychomotor and rewarding properties are typically attributed to different neural mechanisms and are thought to represent different aspects of drug abuse. In Experiment 3, the rewarding properties of cocaine were examined in female quail using a CPP procedure. Additionally, Experiment 3 examined the potential role of estradiol in those effects. Results from Experiment 3 revealed that cocaine is dose-dependently rewarding and estradiol may enhance the rewarding properties of cocaine in female quail.

Taken together, the present work suggests that gonadal hormones may play an important role in both the psychomotor activating effects and rewarding properties of cocaine in Japanese quail. Additionally, the collective results add to our understanding of the underlying hormonal and neurobiological mechanisms that may mediate sex differences in cocaine-induced behaviors.

KEYWORDS: Cocaine, Japanese quail, hormones, dopamine, conditioned place preference, locomotor activity

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April 27, 2015
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COCAINE-INDUCED BEHAVIORAL SENSITIZATION AND CONDITIONED PLACE PREFERENCE IN JAPANESE QUAIL (*COTURNIX JAPONICA*): A FOCUS ON SEX DIFFERENCES AND DOPAMINERGIC MECHANISMS

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Dedicated to my daughter, Josie

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CHAPTER 1

INTRODUCTION

Background & Significance

Cocaine is a powerfully addictive central nervous system stimulant that is a naturally occurring alkaloid found in the leaves of the coca plant indigenous to South America (NIDA, 2013). Prior to the Harrison Act of 1914, cocaine was believed to elevate mood, suppress appetite, aid in digestion, and was used to treat a variety of illnesses including fatigue, sinus infections, headaches, and to sustain performance. Today, cocaine is classified as a Schedule II drug which indicates that it has a high potential for abuse, but also maintains limited medicinal value as a local anesthetic and vasoconstrictor (NIDA, 2009).

The cost to society of illicit drug use accounts for $181 billion in health care, productivity loss, crime, incarceration, and drug enforcement each year with cocaine being the second most commonly used illicit drug (following marijuana) in the United States (NIDA, 2009). In 2012, an estimated 1.7 million Americans aged 12 and older were current cocaine users, a decline from a reported 2.1 million in 2007 (NSDUH, 2012). The 2013 Monitoring the Future (MTF) survey indicated that, while continuing a steady decline, 2.6% of 12th graders still report past year use of cocaine (SAMHSA, 2013). Cocaine remains the most frequently mentioned illicit drug in emergency department (ED) visits according to the Drug Abuse Warning Network report, involved in nearly half of ED visits involving illicit drugs in 2009 (DAWN, 2009). The National Survey on Drug Use and Health (SAMHSA, 2008) reported that roughly 1.4 million

Americans met criteria for abuse or dependence of cocaine in accordance with the Diagnostic and Statistical Manual of Mental Disorders. After decades of research, no FDA-approved medications are available to treat cocaine addiction. The current treatment regime, therefore, is restricted to behavior therapy for cocaine dependent individuals (NIDA, 2009). Despite needing treatment for cocaine dependence, only 8.1% of crack-cocaine users and 3.2% of powdered cocaine users were admitted into treatment facilities in 2008 (SAMHSA, 2008).

Overall, men report higher rates of current cocaine use; however the number of women cocaine users has increased and the gender gap continues to narrow (SAMHSA, 2013). The increased use among men is believed to be due to an increased opportunity to use (Kasperski et al., 2011; Van Etten, Neumark, & Anthony, 1999, Wagner & Anthony, 2007). When given the opportunity to use cocaine, men and women are equally likely to try the drug (Kasperski et al., 2011; Van Etten & Anthony, 1999, Wagner & Anthony, 2007). Recently, a four-year longitudinal study on college students at one large public university revealed that of 243 cocaine users, women (n=113) reported a higher frequency of use and had more serious use patterns than men (Kasperski et al., 2011). Additionally, the women in the study had a greater likelihood of meeting criteria for cocaine dependence than men (9.3% vs. 2.5%) particularly being more likely to give up important activities, spending a lot of time drug seeking, and continuing use despite having issues with physical and mental health (Kasperski et al., 2011).

Several studies have suggested that men and women differ in their subjective experience and biological response to cocaine (Evans & Foltin, 2006a). When shown drug-related cues, cocaine-dependent women report higher levels of craving compared to

cocaine-dependent men (Robbins, Ehrman, Childress, & O'Brien, 1999). Additionally, women report having shorter periods of abstinence from cocaine and enter into treatment at younger ages compared to men (Kosten, Gawin, Kosten, & Rounsaville, 1993). When women are admitted into treatment for cocaine dependence, their use is often more severe than men (Du, Huang, Zhao, & Hser, 2013; Kosten et al., 1993). The tendency for women to progress through the stages of initiation of use to dependence at a faster rate than men is known as "telescoping" (Brady & Randall, 1999). This phenomenon has been observed among women for several drug categories including alcohol, opiates, and stimulants (Brady & Randall, 1999; Kosten, Rounsaville, & Kleber, 1985). Collectively, these studies indicate that females may be more vulnerable to certain aspects of drug addiction than males (Becker & Hu, 2008; Lynch, Roth, & Carroll, 2002).

Japanese quail: A Potential Model for Sex Differences in Cocaine Addiction.

Japanese quail are a viable alternative to rodents for the study of sex differences and drug abuse. Exposure to long photoperiods of daylight stimulate gonadal growth and increase plasma sex steroids in male and female quail, whereas short daylight photoperiods eliminate sexual behavior and cause less activity overall (Guyomarc'h & Guyomarc'h, 1992; Mills et al., 1997; Robinson & Follett, 1982). Previous research has shown that female quail housed in photoperiods of 8 hours of light a day or less have significant decreases in plasma concentrations of estradiol compared to age-matched females exposed to 14 or more hours of light a day (Adkins & Adler, 1972; Brain, Onagbesan, Peddie, & Taylor, 1988; Delville, Sulon, & Balthazart, 1986; Delville & Balthazart, 1987; Doi, Takai, Nakamura, & Tanabe, 1980; Noble, 1972). Similarly, male quail housed in short-light conditions display decreased plasma concentrations of

testosterone compared to birds housed in long-light conditions (Balthazart, Massa, & Negri-Cesi, 1979; Balthazart, Schumacher, & Ottinger, 1983; Domjan, 1987; Guyomarc'h & Guyomarc'h, 1994). In addition, Adkins & Nock (1976) demonstrated that exposure to short-light conditions was a comparable experimental procedure to surgical gonadectomy for both male and female quail. Given that sex hormones can be altered without surgical methods, quail may be an ideal model to study sex differences in behavioral effects of cocaine.

In addition to the benefits stated above, Japanese quail have color vision and high visual acuity similar to humans (Fidura & Gray, 1966); unlike rodents that tend to rely, primarily on olfactory information. Since behavioral sensitization and drug reward appear to be heavily influenced by environmental visual cues (see Robinson & Berridge, 1993 for review), Japanese quail may add further understanding to the study of human drug abuse.

Cocaine: Mechanisms of Action

Cocaine belongs to a class of drugs known as psychomotor stimulants, classified in part because of the classic "upper" effects that the drug has on the central and peripheral nervous systems (NIDA, 2009). At low doses, cocaine increases energy, alertness, euphoria, athletic performance, and feelings of well-being, as well as enhances the pleasures derived from various activities (WHO, 2004). Acute, low-level experiences with cocaine have relatively few negative consequences, which can rapidly progress to repeated administrations (Das, 1993a). In long-term abuse and dependency, cocaine can cause several medical consequences mostly involving cardiovascular, central nervous and

reproductive systems, as well as cause financial, personal, and moral devastation (Das, 1993a, b; NIDA, 2013).

Pharmacokinetics. Cocaine can be absorbed through mucus membranes as well as the gastrointestinal tract which lends itself to having multiple routes of administration including injecting, smoking, and oral routes (Das, 1993a). Cocaine hydrochloride (a mixture of 89% cocaine alkaloid and hydrochloric acid) is the most typical form of cocaine and, in powdered form, is most commonly administered intranasally by "snorting" (Das, 1993a). Plasma half-life of cocaine ranges between 0.5 – 1.5 hours, depending on the route of administration (Inaba, 1989).

Regardless of administration route, cocaine is absorbed, metabolized, and excreted rapidly, with metabolites being detected as soon as 2 hours after administration (Huestis et al., 2007). Metabolism occurs primarily in the liver via hydrolytic ester cleavage by at least two liver carboxylesterases (hCE-1 & hCE-2) (Kamendulis, Brzezinski, Pindel, Bosron, & Dean, 1996). Benzoylecgonine (BE) is the major metabolite excreted in the urine with ecgonine methyl ester (EME) and ecgonine also excreted in significant amounts (Kolbrich et al., 2006). When alcohol is combined with cocaine in the liver, cocaethylene is produced which is believed to have higher cardiovascular toxicity than cocaine alone (Hayase, Yamamoto, & Yamamoto, 1999; Pan & Hedaya, 1999). Additionally, cocaine is demethylated by the cytochrome P450 enzyme to form the active metabolite norcocaine (Hawks, Kopin, Colburn, & Thoa, 1974; Kolbrich et al., 2006). Cytochrome P450 (CYP) enzymes are found in most human tissues and, in addition to drug metabolism, play important roles in the synthesis and breakdown of steroid hormones such as estrogen and testosterone (Bandiera &

Dworschak, 1992; Guengerich, 2008; Villablanca, Tetali, Altman, Ng, & Rutledge, 2013).

Studies indicate that behavioral sex differences observed in cocaine administration may be, in part, explained by sex-specific pharmacokinetic differences. Bowman and colleagues (1999) found that male and female rats had similar levels of cocaine in the brain and serum; however female rats had higher levels of EME than those of male rats (Bowman et al., 1999). Additionally, Bowman et al. (1999) found that norcocaine levels in female rats were higher in the brain and serum than those of male rats, while male rats had greater serum BE levels than those of female rats. Norcocaine is self-administered by monkeys (Spealman & Kelleher, 1981) and been shown to be increase locomotor activity comparative to cocaine in male rats (Schuelke, Konkol, Terry, & Madden, 1996).

Pharmacodynamics. Cocaine is a weak base with a pKa of ~ 8.7 enabling it to be quickly converted into a unionized form to easily cross the blood-brain barrier via passive diffusion (Schwartz-Bloom & Halpin, 2003). Once in the brain, cocaine is a potent inhibitor to the transporters of dopamine (DA), serotonin (5-HT), and norepinephrine (NE) (Iversen, Iversen, Bloom, & Roth, 2009). By blocking these monoamine transporters, cocaine indirectly increases synaptic concentrations of these neurotransmitters (Ritz, Cone, & Kuhar, 1990). In peripheral tissue, blockade of the norepinephrine transporter in sympathetic neurons appears to account for the autonomic effects of cocaine, while the binding of the dopamine transporter (DAT) appears to account for the majority of central nervous system effects (Iversen et al., 2009; Ritz, Lamb, Goldberg, & Kuhar, 1987). In fact, nearly all of cocaine's psychostimulant effects

may be explained by the increase in extracellular monoamines, especially by the increase of extracellular dopamine (Iversen et al., 2009).

In the CNS, cocaine interacts with the nigrostriatal system and the mesocorticolimbic pathway, also known as "the reward pathway" (Iversen et al., 2009; Wise & Bozarth, 1982). The reward pathway is rich in monoamines, such as dopamine (DA), norepinephrine (NE), and serotonin (5-HT), and involves key brain structures such as the ventral tegmental area (VTA), nucleus accumbens (NAc), amygdala, hippocampus, and the medial prefrontal cortex (mPFC) (Iverson et al., 2009). The nigrostriatal system connects the substantia nigra (a component of the basal ganglia) to the striatum, consists mostly of dopaminergic neurons, and is particularly involved in movement (Iversen et al., 2009).

Dopamine. In a normally functioning brain, dopamine plays important roles in motivation, reward, cognition, arousal, and motor control. Natural reinforcers such as food (Church, Justice, & Neill, 1987; Yoshida et al., 1992) and sex (Bitran & Hull, 1987; Blackburn, Pfaus, & Phillips, 1992; Hull, Du, Lorrain, & Matuszewich, 1995; Hull et. al., 1986) are known to increase the level of DA. Once stimulated, a dopaminergic neuron will release DA into the synaptic cleft where it can bind to receptors of nearby neurons. Extra DA that remains in the synapse is then recycled (taken back up into the neuron) and repackaged for later use in a process known as "reuptake" (Iversen et al., 2009). Cocaine binds to the dopamine transporter (DAT) of the neuron which inhibits this reuptake, leaving DA in the synapse to continue and intensify the activation of cellular responses. The role of DA in cocaine reinforcement was discovered after various DA-selective 6-hydroxydopamine lesions of the NAc produced extinction of cocaine self-administration

(Roberts, Koob, Klonoff, & Fibiger, 1980). Additionally, low doses of dopamine antagonists were shown to reliably decrease cocaine reinforcement to further implicate DA in cocaine addiction (Ettenberg, Pettit, Bloom, & Koob, 1982; Yokel & Wise, 1975).

Currently, dopamine is known to have 5 receptor types in mammals that fall into two categories, the D1-like family (D1, D5) and the D2-like family (D2, D3, D4). The D1-like and D2-like receptor families are both G-coupled to produce second messenger signaling, but have opposite effects on adenylate cyclase (cAMP) activity; with D1 increasing and D2 decreasing cAMP (Monsma Jr., Mahan, McVittie, Gerfen, & Sibley, 1990; Senogles, Spiegel, Padrell, Lyengar, & Caron, 1990). Both families of DA receptors can be found post-synaptically, but the D2 receptor specifically is also found pre-synaptically as an autoreceptor (Iverson et al., 2009). An experiment by Wachtel, Hu, Galloway, and White (1989) suggested that occupation of the D1 receptor was essential for the expression of post-synaptic D2 receptor effects, but not for D2 autoreceptor function. Additionally, D2 autoreceptors appear to be more sensitive than D2 post-synaptic receptors (Iversen et al., 2009).

Generally speaking, both D1-like and D2-like receptor agonists have been shown to have reinforcing effects (Self & Stein, 1992; Weed & Woolverton, 1995; Woolverton & Randali, 2002); while antagonists for both receptor families attenuate the behavioral effects of cocaine (see Mello & Negus, 1996 for review). Despite this, D1-like and D2-like receptors have been shown to play very different, and sometimes opposite, roles in the brain. These differences in DA receptor function have also been found in cocaine addiction (see Clark & White, 1987 for review). Khroyan, Barrett-Larimore, Rowlett, and Spealman (2000) investigated D1-like and D2-like receptor mechanisms in cocaine-

seeking and relapse behaviors in cocaine-dependent squirrel monkeys. After stable cocaine self-administration was established, subjects were extinguished before being administered a priming dose of cocaine (Khroyan et al., 2000). Both D1-like and D2-like antagonists inhibited reinstatement of cocaine-seeking, however, D1-like and D2-like agonists had opposite effects (Khroyan et al., 2000). D2-like agonists mimicked the effects of cocaine priming, but D1-like agonists inhibited cocaine's priming effects (Khroyan et al., 2000). Cervo & Samanin (1995) examined D1 and D2 receptor mechanisms in the rewarding properties of cocaine in rats. The researchers administered either a D1 antagonist or a D2 antagonist prior to an injection of 10 mg/kg cocaine or saline before each conditioning trial in a conditioned place preference (CPP) paradigm (Cervo & Samanin, 1995). The results showed that the D2 antagonist had no effect on cocaine-induced CPP. However, the D1 antagonist blocked the establishment of CPP (Cervo & Samanin, 1995). Additionally, both D1 (Fontana, Post, Weiss, & Pert, 1993) and D2 (White & Kalivas, 1998) antagonists have been shown to block the development of behavioral sensitization. However, only D1 antagonists (Cabib, Castellano, Cestari, Filibeck, & Puglisi-Allegra, 1991; Le, Tomkins, Higgins, Quan, & Sellers, 1997) have been shown to attenuate the expression of behavioral sensitization while D2 antagonists have not (Kalivas & Duffy, 1990). Collectively, these studies suggest that D1-like and D2-like receptor families may play different roles in cocaine addiction depending on the paradigm and behavior of interest.

Information on the pharmacological properties of dopamine receptors in the avian brain resembles the rodent brain (Kubikova, Vyboh, & Kostal, 2009). Kubikova and colleagues (Kubikova et al., 2009) reported that the dissociation and association rate

constants for [3H]SCH 23390 and [3H]spiperone in Japanese quail were within the range of values reported in rats. Additionally, Kubikova et al. (2009) reported that the Kd value of [3H]SCH 23390 and [3H]spiperone binding in slide-mounted Japanese quail brain-mash sections were in agreement with reports for rat brain slide-mounted sections. While the general organization and pharmacological profile of the DA system appears to be similar between birds and mammals, the distribution and density of D1 and D2 receptors may be different (Kleitz, Cornil, Balthazart, & Ball, 2009; Kubikova et al., 2009; Smeets & Reiner, 1994). In an autoradiography labeling study, Kleitz and colleagues (Kleitz et al., 2009) found a species difference in the D2:D1 ratio in target sites for DA between Japanese quail and rats (see figures 1.1 and 1.2). Specifically, quail have a higher D2:D1 receptor ratio in the striatal regions of the brain compared to rats (Kleitz et al., 2009; see figures 1.1 and 1.2). Despite this ratio disparity, the role of DA receptor subtypes in cocaine addiction has been shown to be similar between birds and mammals. Levens and Akins (2001) found that the D2 antagonist eticlopride decreased cocaine-induced locomotor activity in male Japanese quail, but did not block cocaine-induced CPP. Similarly, rodent studies have found no effect of D2 antagonists on cocaine-induced CPP (Cervo & Samanin, 1995; Morency & Beninger, 1986; Spyraki, Fibiger, & Phillips, 1982), but have attenuated cocaine and amphetamine-induced CPP with D1 antagonists (Hiroi & White, 1991; Hoffman & Beninger, 1989; Leone & Di Chiara, 1987). Additionally, Akins and colleagues (Akins, Levens, Prather, Cooper, & Fritz, 2004) attenuated cocaine-induced CPP in male Japanese quail with SCH23390, a D1 antagonist. It should be noted that in Akins et al., (2004), cocaine-induced CPP was blocked with significantly lower doses of SCH23390 in quail (0.0025 mg/kg) than the lowest dose of

SCH23390 found to attenuate cocaine-induced CPP in rats (0.2 mg/kg) (Cervo & Samanin, 1995). While speculative, this result may be due to the difference in D2:D1 receptor availability in birds compared to rodents. Altogether, these studies suggest that D1-like and D2-like receptor function and pharmacology may be conserved between aves and mammals, but that the density and distribution of DA receptors is reportedly different.

In addition to species differences, sex differences in DA receptor density and function have been observed in rodents and quail. Male rats have 10% more D1 receptors in the striatum, and have a higher density of D1 receptors in the NAc compared to female rats (Andersen, Rutstein, Benzo, Hostetter, & Teicher, 1997; Hruska, Ludmer, Pitman, De Ryck, & Silbergeld, 1982). Studies have indicated that a sex difference in DA receptor density may exist in Japanese quail. For example, Ottinger et al. (1986) indicated that DA content in the right telencephalon and NE in the optic lobes differs in male quail compared to female quail, which suggests a possible sex difference in monoamine content in the Japanese quail brain. Unfortunately, experiments comparing male and female Japanese quail specifically targeting DA content are sparse and have focused almost exclusively on the neuroendocrine basis of copulatory behavior (Bailhache & Balthazart, 1993), rather than receptor density in the brain. Therefore, further investigation of sex differences in monoamine content in the quail brain is warranted.

Serotonin. Approximately 90% of the total serotonin content in the human body is located peripherally in the gastrointestinal tract to aid in digestive processes (Iversen et. al, 2009). The remaining 10% is synthesized in the CNS, where serotonin (5-HT) plays important roles in mood regulation, sleep, and appetite, as well as aid in learning and

memory processes (Iversen et al., 2009). While the role of DA in cocaine abuse has been established as the primary mediator of the drug's effects, cocaine also has a high affinity for the serotonin transporter (SERT) (Koe, 1976). Much like the interaction with DAT in dopaminergic neurons, cocaine binds to the SERT of serotonergic neurons to inhibit reuptake, which leaves 5-HT in the synapse to continue acting on neighboring neurons (Taylor & Ho, 1978; Reith, Meisler, Sershen, & Lajita, 1986). Some studies with DAT knockout mice have shown that cocaine self-administration (Rocha et al., 1998) and cocaine-induced place preference (Sora et al., 1998) are conserved in the absence of DAT. Furthermore, Hall and colleagues (Hall et al., 2002) were only able to completely eliminate cocaine reward in the CPP paradigm when both DAT and SERT were knocked out. Broderick and colleagues (Broderick, Hope, Okonji, Rahni, & Zhou, 2004) demonstrated that cocaine administration increases 5-HT in the NAc, and it has been reported that several mesolimbic regions associated with drug addiction (such as the VTA) are rich in 5-HT receptors (Filip & Bader, 2009; Koob, 2009; Muller & Huston, 2006). Taken together, these studies indicate that 5-HT may play a modulatory role in the mechanisms of action of cocaine.

The serotonergic system is complex in mammals, with 14 different receptor types currently identified (Iversen et al., 2009). To date, the 5-HT_{1a}, 5-HT_{1b}, 5-HT_{2a}, 5-HT_{2c}, and 5-HT_{3} receptors in particular have been shown to play important roles in cocaine-induced behavioral effects (see Filip, Alenina, Bader, Przegalinski, 2010 for review). Carey, DePalma, & Damianopoulos (2001) found that the 5-HT_{1a} agonist, 8-OHDPAT, enhanced locomotor stimulant effects while the 5-HT_{1a} antagonist, WAY 100635, reduced locomotor stimulant effects of 10 mg/kg cocaine in rats. 5-HT_{1b} receptor

antagonists have been shown to block cue-induced reinstatement of cocaine-seeking behavior (Przegalinski, Golda, & Filip, 2008) and have additional anxiolytic effects (Tatarczynska, Klodzinska, Stachowicz, & Chojnacka-Wojcik, 2004) that could be therapeutically relevant in reducing withdrawal symptoms in cocaine addicts. Risperidone, a nonselective 5-HT_{2A} antagonist, has been found to decrease cocaine-induced craving and be effective in decreasing the chance of relapse in humans. However, risperidone is also an antagonist at the D2 receptor (de la Garza, Newton, & Kalechstein, 2005). Interestingly, activation of the 5-HT_{2c} receptor has been shown to inhibit DA transmission in the reward pathway (Di Matteo, Giovanni, Mascio, Esposito, 2000; Navailles, Moison, Cunningham, & Spampinato, 2007). In a recent study, Craig and Unterwald (2013) investigated the ability of Ro 60-0175, a 5-HT_{2c} receptor agonist, to alter cocaine-induced CPP and sensitization in male mice. The researchers found that Ro 60-0175 attenuated cocaine-induced hyperactivity and sensitization in both acute and repeated administration as well as decreased cocaine-induced CPP (Craig & Unterwald, 2013). Finally, 5-HT_3 receptor antagonists have been shown to inhibit the development of cocaine-induced behavioral sensitization in rats (King, Xiong, & Ellinwood, 1997; Szumlinski, Frys, & Kalivas, 2003) as well as attenuate cocaine-induced CPP (Kankaanpaa, Meririnne, & Seppala, 2002; Suzuki, Shiozaki, Masukawa, & Misawa, 1992). Collectively, these studies indicate that cocaine's actions on the serotonin system are critical in understanding the addictive properties of psychostimulant drugs.

The serotonergic system has been mapped in the Japanese quail brain (Cozzi, Viglietti-Panzica, Aste, & Panzica, 1991; Duchala, Ottinger, & Russek, 1984; Holladay & Edens, 1983; Ottinger et al., 1986). However, species comparisons of the serotonin

system between birds and mammals are speculative (see Cozzi et al., 1991 for review). A study by Cedraz-Mercez and colleagues (Cedraz-Mercez et al., 2003) examined the role of the 5-HT_{2c} receptor in feeding behavior in Japanese quail and found that fenfluramine (FEN) induced a significant decrease in food intake by food-deprived quail. Substances that are similar to FEN are used as anorexics for obesity control in humans and have been shown to also decrease feeding behavior in other mammals (Blundell, 1984, 1992; Halford & Blundell, 2000). Two additional 5-HT_{2C} agonists have been shown to decrease feeding behavior in food-deprived quail further implicating the 5-HT_{2C} receptor in appetite control (Cedraz-Mercez et al., 2003). Polo and colleagues (Polo et al., 2007) demonstrated that quipazine, a 5-$HT_{2A/2C/3}$ agonist, induced long periods of yawning and sleep-like states in Japanese quail similar to results observed in cats with quipazine (Trulson, Brandstetter, Crisp, & Jacobs, 1982). This behavior was blocked by the 5-HT_{2A} antagonist, ketanserin, which has been observed in both birds and mammals (Polo et al., 2007; Trulson et. al., 1982). The results of these studies indicate that the serotonin system may be conserved between mammals and aves.

There have been several reports of sex differences in the serotonergic system of the CNS, such that female rats reportedly have higher basal levels of 5-HT compared to male rats (Carlsson & Carlsson, 1988; Festa et al., 2004). McQueen and colleagues (McQueen, Wilson, & Fink, 1997) demonstrated that estradiol (E2) increases SERT mRNA and binding sites in the female rat brain. In another study, these researchers demonstrated that SERT binding sites were decreased in castrated male rats and increased with exogenous administration of E2 and T, but not with 5-DHT (a non-aromatizable androgen) (McQueen, Wilson, Sumner, & Fink, 1999). Additionally, PET

imaging studies with humans have consistently revealed greater SERT availability in the brains of women compared to men (Staley et al., 2001). Ovarian hormones have been shown to decrease 5-HT_{2C} receptor mRNA in the hypothalamus of macaque monkeys (Gunlah, Pecins-Thompson, Schutzer, & Bethea, 1999). In contrast, Zhao, Cunningham, and Thomas (2002) demonstrated that E2 increased 5-HT_{2C} mRNA in the hypothalamus and midbrain regions of OVX rats. Inconsistent with rodent literature, studies have revealed no sex difference in serotonin levels or distribution between male and female Japanese quail (Balthazart, Foidart, Sante, & Hendrick, 1992; Ottinger et al., 1986). Behavioral research with serotonergic agonists and antagonists in Japanese quail may help elucidate any sex-specific effects serotonin may have on cocaine-induced behaviors. Taken together, research indicates that sex differences in serotonin may be partly responsible for sex differences observed in cocaine-induced behavioral effects in mammals.

Norepinephrine. Norepinephrine (NE) is a metabolic product of DA, being converted from DA into NE by the enzyme dopamine-β-hydroxylase in vertebrate animals (Iversen et al., 2009). Dopamine-β-hydroxylase is only found in NE (adrenergic) neurons or in the chromaffin tissue of the adrenal glands (Iversen et al., 2009). In the CNS, almost all adrenergic neurons originate in the locus coeruleus with projections to several brain areas associated with addiction (Iversen et al., 2009). In addition to blocking DAT and SERT, cocaine also blocks the NE transporters (NET), thus preventing reuptake of NE. As stated previously, the interaction of cocaine with peripheral NE receptors may be the primary target responsible for the autonomic effects of cocaine (Iversen et al., 2009; Ritz, Lamb, Goldberg, & Kuhar, 1987).

In general, there are three classes of adrenergic receptors based on their differential coupling to G-proteins; α1 stimulates phospholipase C activity through Gq coupling, α2 decreases cAMP activity through Gi coupling, and β stimulates cAMP activity through Gs coupling (Iversen et al., 2009). Each of these major classes have three receptor subtypes, α1a, α1b, α1d, α2a, α2b, α2c, β1, β2, and β3, respectively (see Schmidt & Weinshenker, 2014 for review). In rodents, studies have revealed that α1 and α2 receptors have opposing effects on cocaine-induced locomotor activity and sensitization with antagonism of α1 decreasing and antagonism of α2 increasing activity acutely and chronically (see Schmidt & Weinshenker, 2014 for review). Antagonism of the β subtype in the CNS has been shown to block the development of cocaine-induced sensitization, but antagonism of the β subtype peripherally has not (Bernardi & Lattal, 2012; Colussi-Mas et al., 2005). Thus far, rodent studies have indicated that adrenergic receptors do not play a role in CPP, with neither agonists or antagonists of α1, α2, or β receptors showing a preference or aversion (Robledo, Balerio, Berrendero, & Maldonado, 2004; Sahraei et al., 2004; Morales, Perez-Garcia, & Alguacil, 2001; Tahsili-Fahadan et al., 2006; Zarrindast, Bahreini, & Adl, 2002). Taken together, these studies indicate that NE may play a minor role in cocaine-induced behavioral sensitization, but may not be a relevant target for studying cocaine-induced CPP.

The adrenergic system has been characterized in radioligand studies in both birds and mammals. Cornil and Ball (2008) specifically compared the α2 receptor subtype in Japanese quail and rats. The researchers concluded that the general distribution is similar in quail with some minor variations as compared to rats (Happe et al., 2004; Smeets & Gonzales, 2000; Unnerstall, Kopajtic, & Kuhar, 1984). Interestingly, Cornil and Ball

(2008) concluded that DA binds to α2 receptors with a similar affinity as NE in Japanese quail, a finding previously discovered in rodents (Airriess, Rudling, Midgley, & Evans, 1997; Nyronen et al., 2001; Peltonen et al., 2003; Zhang, Ouyang, & Thomas, 2004). In conclusion, the adrenergic system appears to be similar in birds compared to mammals.

Sex differences in NE have been reported, particularly relating to the involvement of NE in stress (Curtis, Bethea, & Valentino, 2006). Reportedly, men have an increased probability of experiencing a cardiovascular event than women which has been attributed to this sex difference in NE (Fukumoto, Yamashita, Tawa, Ohkita, & Matsumura, 2012). In rats, Uji, Yoshida, Shintani-Ishida, & Morimoto (2006) investigated the NE surge in response to physiological stress. The study found that NE release was increased following a mild physiological stressor (cage-switching) in male rats, but not in female rats (Uji et al., 2006). Additionally, this study found that stress-induced plasma NE was significantly higher in male rats compared to female rats, but there was no sex difference in plasma levels of epinephrine in response to stressful situations (Uji et al., 2006). Balthazart and colleagues (Balthazart, Foidart, Sante, & Hendrick, 1992) found a higher baseline concentration of NE in the female Japanese quail brain compared to male Japanese quail brain. Ottinger et al., (1986) also found that female quail have greater NE concentrations in the hypothalamus, lobus paraolfactorius, and optic lobes compared to male quail. The results of these experiments suggest that sex differences in NE concentrations may be opposite in birds compared to mammals, but more research is needed to make definitive conclusions.

Glutamate. Glutamic acid (Glu) is an amino acid that serves as a neurotransmitter in the mammalian CNS. Along with gamma-aminobutyric acid (GABA), Glu can be

found in very simple organisms, leaving investigators to believe that these neurotransmitters were some of the first to evolve (Carlson, 2010). Glutamate is the most abundant excitatory neurotransmitter in the CNS. In fact, it is estimated that up to 90% of neurons use glutamate as a neurotransmitter (Siegel et al., 2006). Glutamate is synthesized from glucose in presynaptic nerve terminals and packaged into synaptic vesicles for later release (Iversen et al., 2009). Additionally, glial cells synthesize and release glutamine that can be taken up by neighboring neurons and synthesized into glutamate via the enzyme glutaminase within the nerve terminal (Iversen et al., 2009). Since glutamate receptors and projections are numerous in the brain, mesocorticolimbic structures (regions heavy in dopaminergic transmission) have substantial glutaminergic input (Gass & Olive, 2008; Groenewegen, Wright, Beijer, & Voorn, 1999; Heimer et al., 1997). In fact, cocaine has been shown to indirectly increase extracellular glutamate levels in the VTA, NAc, striatum and PFC; however these increases appear to be dependent upon DA mechanisms (Kalivas & Duffy 1995; Reid & Berger 1996; Reid, Hsu, & Berger, 1997; Smith, Mo, Guo, Kunko, & Robinson, 1995). Although cocaine does not act directly on glutamate receptors, there is a growing consensus that drugs of abuse, including cocaine, produce lasting neuroadaptations within the glutaminergic system after repeated use (see Gass & Olive, 2008 for review).

Thus far, four major types of glutamate receptors have been discovered in vertebrates. The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), N-methyl-D-aspartate receptor (NMDA), and the kainate receptor are all ionotropic; allowing for fast excitatory synaptic transmission (Iversen et al., 2009). The AMPA receptor is the most commonly found glutamate receptor, and therefore, the most

abundant receptor in the CNS. This receptor controls a sodium channel, allowing for rapid excitatory action potentials when activated by glutamate (Carlson, 2010). The kainate receptor is similar to AMPA, so much so that it is often difficult to distinguish pharmacologically from AMPA (Iversen et al., 2009). Kainate receptors are found pre and post-synaptically and have a limited distribution in the brain (Iversen et al., 2009). The NMDA receptor is permeable to both sodium and calcium ions, and is dependent upon the depolarization of AMPA for sufficient action potentials to take place (Carlson, 2010). Additionally, activation of the NMDA receptor requires binding of the co-agonist glycine for depolarization (Iversen et al., 2009). Both the AMPA and the NMDA receptor have been heavily implicated in learning and memory (Iversen et al., 2009). The fourth receptor type is a family of eight currently known metabotropic glutamate receptors known as mGluRs (named mGluR1-8 respectively). These receptors are G-protein linked which generate slow synaptic responses that maintain more of a modulatory role within the CNS (Iversen et al., 2009). mGluRs have been implicated in numerous neurological disorders including drug addiction (Iversen et al., 2009). Additionally, mGluRs are important for learning, neuroprotection, and brain development, as well as to regulate glial function, neurotransmitter release, and synaptic plasticity in the CNS (Iversen et al., 2009).

With regard to cocaine addiction, a recent and growing body of literature has revealed that glutaminergic transmission is profoundly altered with repeated cocaine use in the reward pathway, especially within the NAc (see Schmidt & Peirce, 2010 for review). Activation of the AMPA receptors in the NAc has been shown to increase drug seeking, whereas inhibition of AMPA obstructs cocaine reinstatement and self-

administration in rats (Backstrom & Hyytia, 2007; Cornish & Kalivas, 2000; Ping, Xi, Prasad, Wang, & Kruzich, 2008; Suto, Ecke, & Wise, 2009). NMDA antagonists MK-801 and CGS-19755 have been shown to increase tyrosine hydroxylase activity (Masserano, Baker, Natsukari, & Wyatt, 1996), and prevent DA autoreceptor sensitivity in the VTA (Li et al., 1990). In the NAc, both MK-801 and CGS-19755 prevent D1 sensitivity, a neuroadaptation associated with cocaine sensitization (Li et al., 1990). Additionally, MK-801 (Karler, Calder, Chaudhry, & Turkanis, 1989; Kim, Park, Jang, & Oh, 1996; Haracz, Belanger, MacDonall, & Sircar, 1995; Pudiak & Bozarth 1993; Wolf & Jeziorski, 1993) and (+)-HA966 (a glycine partial agonist) co-administered with cocaine have been shown to block the induction of behavioral sensitization (Khan and Shoaib 1996; Morrow, Taylor, & Roth, 1995; Shoaib, Shippenberg, Goldberg, & Schindler, 1995). NMDA stimulation has not been shown to alter cocaine-induced behavioral sensitization (Kalivas & Stewart, 1991; see Vanderschuren & Kalivas, 2000 for review). Of the metabotropic glutamate receptors, mGluR5 appears to be critical in long-term neuroadaptations that occur with repeated cocaine abuse (see Bird & Lawrence, 2009 for review). The mGluR5 receptor has been implicated in the salience of drug-paired cues (Backstrom & Hyytia, 2006; Iso et al., 2006; Keck et al., 2014; Kumaresan et al., 2009; Martin-Fardon et al., 2009) and the motivational and reinforcing properties of cocaine (Bird et al., 2014; Cleva et al., 2011; Gass & Olive, 2009). In conclusion, there is ample evidence to suggest an important role of glutamate receptors in cocaine addiction.

The distribution of several types of glutamate receptors has been characterized in rats (Diano, Naftolin, & Horvath, 1997; 1998; Petralia & Wenthold, 1992; Petralia,

Wang, & Wenthold, 1994a,b; Petralia, Yokotani, & Wenthold, 1994) and Japanese quail (Cornil, Foidart, Minet, & Balthazart, 2000; Martinez de la Torre, Mitsacos, Kouvelas, Zavitsanou, & Balthazart, 1996, 1998; Zavitsanou et al., 1994). In general, these studies have found that the overall distribution of glutamate receptors appears to be similar between birds and mammals. Cornil and colleagues (2000) compared the distribution of ionotropic glutamate receptor subtypes (AMPA, NMDA, & Kainate) of the Japanese quail brain to distributions currently known in rats. In this study, immunocytochemical results found that the hippocampus, thalamus, and the broad regions of the telencephalon were densely stained similarly to rats (Cornil et al., 2000). However, areas corresponding to the mammalian amygdala and caudate putamen in the quail brain were less intensely stained than what has been found in rats (Cornil et al., 2000). Cornil and colleagues (2000) found the largest species difference in the cerebellum revealing virtually no staining in the granular layers of the quail brain that have been shown to be rich in several glutamate receptor subunits in the rat cerebellum (Petralia & Wenthold, 1992; Petralia et al., 1994 a,b). Finally, this study reports fewer NMDA receptors in the lateral hypothalamus and thalamus and higher densities of NMDA receptors in tuberal regions in quail compared to rats (Cornil et al., 2000). In sum, the four major types of Glu receptors exist in the brains of Japanese quail and the general distribution is somewhat similar to the glutaminergic system in mammalian brains.

While not as widely studied as other neurotransmitter systems, sex differences in the glutaminergic system have been documented. In mammals, literature suggests that glutamate activation is closely related to reproduction control and the secretion of gonadotropic hormones (Brann, 1995). Specifically, studies have shown that estrogen

mediates NMDA expression and activity in the CNS (Cyr et al., 2001; McEwen, 2002; Woolley, 1998). Mousavi and colleagues (Mousavi, Shafaghi, Kobarfard, & Jorjani, 2007) examined glutamate levels in the NAc in male and female rats. This study focused on glutamate levels in response to acute and chronic morphine exposure and found, after a single morphine injection, that intact and gonadectomized female rats had a greater level of Glu in the NAc than intact and gonadectomized male rats (Mousavi et al., 2007). For morphine tolerant animals, intact female rats had significantly greater Glu levels in NAc than gonadectomized female rats (Mousavi et al., 2007). Gonadectomy did not alter Glu levels in NAc in morphine tolerant male rats. Since the presence of estrogen has been shown to upregulate glutamate in the CNS, this study concluded that high levels of estrogens may be responsible for the increase of Glu in the NAc (Mousavi et al., 2007).

In a different study, Honack and Loscher (1993) examined behavioral sex differences to MK-801 in rats. In a rotarod test, all male rats successfully passed at a 0.1 mg/kg dose of MK-801 where none of the female rats passed after 75 minutes (Honack & Loscher, 1993). Forty percent of female rats were still unable to pass the rotarod test 5 hours after drug injection (Honack & Loscher, 1993). When the dose of MK-801 was increased to 0.3 mg/kg in the study, male rats showed some ataxia (head weaving & hyperlocomotion), but this effect was significantly more severe in female rats (Honack & Loscher, 1993). This study suggests that female rats are more sensitive to NMDA antagonists than male rats. In Japanese quail, Martinez de la Torre and colleagues (1998) found numerous sex differences in non-NMDA binding in an autoradiography study using 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) as a radioligand. Overall, while receptor affinity appeared similar between sexes, this study found a higher number of

non-NMDA receptors in the brains of female quail compared to male quail (Martinez de la Torre et al., 1998). However, the region that corresponds to the mammalian suprachaismatic nucleus (SCN) in the quail brain revealed a greater number of non-NMDA receptors for males compared to females in this study (Martinez de la Torre et al., 1998). This nucleus is known for its control of circadian rhythms and has been shown to be involved in the activation of sexual behavior in quail (Balthazart et al., 1989; Balthazart et al., 1992; Watson & Adkins-Regan, 1989) and mammals (Hofman & Swaab, 1995; Swaab & Hofman, 1990; Zhou, Hofman, Gooren, & Swaab, 1995). In sum, these sex differences of the glutaminergic system in the CNS may play a major role in neuroendocrine control and function in birds and mammals alike.

Estrogen. Estrogens are a group of sex hormones that are produced in all vertebrate animals (Ryan, 1982), as well as some insects (Mechoulam, Brueggemeier, & Denlinger, 1984). In females, estrogens are primarily produced by the ovaries in response to gonadotropins, namely follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (Carlson, 2010). In addition to the ovaries, small amounts of estrogens are produced by the liver, adrenal cortex, and breasts in women, and by the testes in men (Carlson, 2010). Considered steroid hormones, estrogens are derived from cholesterol and can easily cross the blood-brain barrier (Nelson & Bulun, 2001).

The three major types of estrogens present in mammals are estrone (E1), estradiol (E2), and estriol (E3). Estrone is the primary circulating estrogen during menopause and in postmenopausal women (Carlson, 2010). During pregnancy, estriol becomes the primary circulating estrogen (Carlson, 2010). Overall in terms of serum levels and estrogen activity, estradiol is the primary circulating estrogen during the reproductive

years for both sexes (Nelson & Bulun, 2001). Additionally, estradiol has the strongest potency of all the estrogens, and is therefore considered to be the most important of the estrogens (Nussey & Whitehead, 2001). In scientific literature, estradiol is often referred to as 17β-estradiol and oestradiol. Estradiol is the primary estrogen involved in sexual dimorphism of the body causing breast development, growth of uterine lining, inhibition of bone growth, changes in body fat distributions, and maturation of genitalia in mammalian females (Carlson, 2010). Additionally, estradiol is heavily involved in the mammalian reproductive cycle in adult females, and interacts with the nervous system to affect both physiological and behavioral processes for both sexes (Carlson, 2010).

Estrogen activity in the brain is mediated by two different receptors, ERα and ERβ (Morissette et al., 2008). Laflamme and colleagues (1998) explored the distribution and density of both types of estrogen receptors in the male and female rat brain. This study found widespread and abundant expression of ERα in both male and female rats with very few differences between the sexes (Laflamme, Nappi, Drolet, Labrie, & Rivest, 1998). Furthermore, the expression of ERβ was also identical in both male and female rats, but distribution was much less abundant and more localized to the limbic system than ERα (Laflamme et al., 1998).

The distribution of estrogen receptors (ERs) has also been investigated in the brains of male and female Japanese quail (Balthazart, Gahr, Surlemont, 1989; Watson & Adkins-Regan, 1989). These studies found high percentages of ERs in the telencephalon, diencephalon, and mesencephalon regions, including the NAc similar to mammals (Balthazart et al., 1989; Watson & Adkins-Regan, 1989). Of note, Balthazart et al. (1989) found significant levels of aromatase in all nuclei containing ERs, suggesting that

testosterone is converted to estradiol in the quail brain. Male quail were shown to have a greater number of ERs in the preoptic medial nucleus (POM), nucleus paraventricularis (VPN), and ventromedial nucleus of the hypothalamus (VMN) compared to female quail (Balthazart et al., 1989). These studies found that sex differences in the distribution and abundance of ERs in the quail brain are similar to sex difference in ERs found in the mammalian brain (Balthazart et al., 1989; LaFlamme et al., 1998).

Estrogens have been shown to influence dopaminergic activity in the mesolimbic and nigrostriatal systems (Cyr et al., 2000; Cyr, Calon, Morissette, & Di Paolo, 2002; Di Paolo, 1994), and both ERα and ERβ have been found in the striatum, NAc, VTA, and substantia nigra in the rat brain (Creutz & Kritzer, 2002). In rats, ovariectomy has been shown to decrease striatal DA release and turnover in females, but castration has no effect on striatal DA in males (see Becker, 1990 for review). After ovariectomy (OVX), chronic, high-dose E2 administration has been shown to increase D2 receptor and DAT density in the NAc and striatum of female rats (Le Saux & Di Paolo, 2006; Le Saux, Morissette, & Di Paolo, 2006). Interestingly, Bazzett & Becker (1994) demonstrated a similar increase in striatal D2 after chronic, high-dose E2 administration in CAST male rats. Additional studies have shown that this alteration in D2 and DAT does not change with chronic estradiol treatment in ERβ knockout mice, suggesting that ERβ activation is necessary for this neuroadaptation (see Morissette et al., 2008 for review). It should be noted that Bazzett & Becker (1994) found that acute E2 treatment resulted in reduced D2 receptor availability in the caudal striatum, and suggested that, in response to E2, D2 receptor availability is dependent upon sex, E2 dose and dosing regimen, and the striatal region of interest (see Bazzett & Becker, 1994). ERα has been implicated in the potential

neuroprotective qualities of estradiol. *In vivo* and *in vitro* studies have demonstrated that E2 protects against glutamate excitotoxicity, lipid oxidative stress, and striatal dopamine depletion (see Behl, 2002 for review). Administration of 17β-estradiol and the ERα agonist propyl pyrazole triol (PPT) has been shown to prevent an observed increase in AMPA receptor levels in the striatum and cortex that occurs after ovariectomy in female rodents (see Morissette et al., 2008 for review). Taken together, these studies suggest that ERβ may be more heavily implicated in the neuromodulation of dopamine compared to ERα, and ERα may be more critical in the neuroprotective mechanisms of estradiol compared to ERβ.

Due to the interaction E2 has with DA in the mesolimbic and nigrostriatal systems, it is not surprising that cocaine has sex-specific interactions in mammals. In fact, estradiol has been shown to increase the behavioral response to drugs of abuse, including cocaine, in females compared to males (see Becker & Hu, 2008 for review). Specifically, rodent models have demonstrated that intact female rats acquire cocaine self-administration at faster rates and have higher breaking points than OVX female rats and male rats (Jackson et al., 2006, Lynch & Carroll, 1999). Russo et al. (2003) showed that female rats develop associations to environmental cues and to the rewarding properties of cocaine at lower doses and at faster rates than male rats. Hu & Becker (2003) reported that intact and estradiol-treated OVX female rats show significantly greater locomotor activity following chronic cocaine administration compared to OVX female and male rats. The results from a study by Febo and colleagues (2003) suggest that the presence or absence of estrogen in various brain structures alters the effect of cocaine administration (Febo, Gonzalez-Rodriguez, Capo-Ramos, Gonzalez-Segarra, & Segarra, 2003). This

study demonstrated that after a single cocaine injection D2-like receptor binding was decreased in OVX rats, but increased in OVX rats given 17β-estradiol treatments in the VTA (Febo, et al., 2003). Conversely, in the striatum and cingulate gyrus, D2-like receptor binding was increased in OVX rats, but decreased in OVX rats given 17β-estradiol treatments following repeated cocaine administration (Febo et al., 2003). The results of this study indicate that estrogen may modulate DA neuroadaptations that occur in cocaine abuse. To further implicate E2 in cocaine-induced behaviors, a recent study by Segarra et al., (2014) used the ER blocker, ICI-182,780, in intact female rats to determine the impact of estradiol on cocaine sensitization and reward. The study showed that estradiol enhanced cocaine-induced sensitization and CPP in female rats, but this effect was absent in females treated with ICI-182,780 (Segarra et al., 2014). These results suggest that the activation of estrogen receptors in the brain is required for the maintenance and development of both cocaine-induced sensitization and CPP. In sum, a biological mechanism through which E2 modulates cocaine-induced behaviors may, in part, explain the sex differences observed in cocaine addiction and abuse vulnerability.

Testosterone. Testosterone belongs to a group of steroid hormones known as androgens. Similar to other steroid hormones, testosterone is derived from cholesterol, and is mostly produced by the testes in male mammals (Carlson, 2010). Small amounts of testosterone are produced by the ovaries and placenta in females, as well as the adrenal cortex in both sexes (Carlson, 2010). Approximately 7% of testosterone is converted into 5α-dihydrotestosterone (DHT) by the cytochrome p450 enzyme, 5α-reductase (Randall, 1994). Additionally, testosterone can be converted into estradiol in the brain by the enzyme, aromatase (Meinhardt & Mullis, 2002). In men, testosterone is primarily

responsible for sperm production, growth of facial and body hair, muscular development, inhibition of bone growth, larynx enlargement, and sex drive (Carlson, 2010; Money & Ehrhardt, 1972).

In the mammalian brain, testosterone (T) binds directly to androgen receptors (ARs), or, after conversion to E2, binds to ERα or ERβ (see Purvis-Tyson et al., 2014). Additionally, some T is converted into DHT in the brain that acts on ARs or ERβ (Celotti, Melcangi, & Martini, 1992; Handa, Pak, Kudwa, Lund, & Hinds, 2008). Simerly, Chang, Muramatsu, and Swanson (1990) examined the distribution of ARs in the male and female rat brain. This study found that ARs were widely distributed throughout the brain and similarly to studies with ERs, no sex differences were found in AR distribution (Simerly et al., 1990).

Androgen receptor distribution has also been established in male and female Japanese quail brains. Voigt, Ball, and Balthazart (2009) found AR distribution in the hypothalamic and limbic brain regions of both male and female Japanese quail. The medial preoptic nucleus (POM), a major site of male sexual behavior, was rich in ARs in both sexes, but to a much larger degree in male Japanese quail (Voigt et al., 2009). Female quail were found to have a greater expression of ARs in the lateral septum compared to male quail (Voigt et al., 2009). These results of that study suggest a species difference in AR distribution may exist between birds and rodents. In rodents, administration of T or E2 will increase male-typical behavior in both sexes (Aren-Engelbrektsson et. al., 1970; Pfaff, 1970), but only stimulates male-typical sexual behavior in male quail, and not in female quail (see Balthazart, Taziaux, Holloway, Ball,

& Cornil, 2009 for review). This further indicates that androgens may behave differently in female aves compared to female mammals.

Androgen receptors have been shown to be distributed in dopamine-sensitive, mesocorticolimbic brain structures such as the VTA, substantia nigra, and the prefrontal cortex in male and female rats, with no obvious sex differences observed (Kritzer & Creutz, 2008; Purvis-Tyson et al, 2014). In a recent study, Purvis-Tyson and colleagues (2014) found that gonadectomy increased DA turnover in the striatum, but overall DA levels did not change with gonadectomy or with gonadectomy with T-replacement (Purviz-Tyson et al., 2014). Furthermore, results indicated that androgens increased DAT expression in the substantia nigra, but not in striatum (Purvis-Tyson et al., 2014). Purvis-Tyson and colleagues also found that testosterone increased D1 and D2 receptor gene expression in the substantial nigra, and increased D2 expression in the striatum. The results of this study suggest that, in male adolescent rats, androgens may modulate DA activity in the nigrastriatal system via androgen receptor activation. It is unclear whether similar changes occur with female rats. However, Siddiqui & Gilmore (1988) suggested that, once gonadotropin secretion has been established in adulthood, an effective relationship between T and catecholamine brain levels is nonexistent.

The role of testosterone on the behavioral effects of cocaine remains unclear, with most studies reporting no difference between castrated and intact male rodents (Becker, Molenda, Hummer, 2001; Hu & Becker, 2003; Hu, Crombag, Robinson, & Becker, 2004; Forgie & Stewart, 1994; Jackson, Robinson, & Becker, 2006; van Haaren & Meyer, 1991). Some studies have shown that testosterone exacerbates the locomotor response to cocaine in rodents (Martinez-Sanchis, Aragon, & Salvador, 2002; Menendez-Delmestre

& Segarra, 2011). Menendez-Delmestre & Segarra (2011) observed cocaine-induced sensitization at 15 and 30 mg/kg in intact and CAST male rats with testosterone replacement, but not in CAST male rats. Additionally, Martinez-Sanchis and colleagues (2002) found that exogenous T enhanced cocaine-induced locomotor activity at 4 and 10 mg/kg cocaine, but not at higher doses in intact male mice. In contrast, Hernandez and colleagues (Hernandez et al., 1994) found that amphetamine increased striatal dopamine (DA) to a greater degree in castrated male rats than in intact male rats, and that this effect was attenuated by exogenous testosterone. Furthermore, castration has been shown to increase cocaine-induced locomotor activity in some studies (Camp & Robinson, 1988a, b; Robinson, 1984). Collectively, these studies suggest male gonadal hormones potentially mediate the behavioral effects of cocaine, but the findings are inconsistent and inconclusive.

Behavioral Sensitization

Behavioral sensitization is defined as an enhanced behavioral response resulting from repeated exposure to drugs of abuse. Sensitization has been observed in laboratory rodents with repeated exposure to several substances of abuse including cocaine, amphetamine, morphine, ethanol, nicotine, and Δ9-tetrahydrocannabinol (THC) (Benwell & Balfour, 1992; Cadoni, Pisanu, Solinas, Acquas, & Di Chiara, 2001; Cunningham & Noble, 1992; Joyce & Iversen, 1979; Post, Weiss, Fontana, & Pert, 1992; Robinson & Becker, 1986) suggesting a common underlying neural mechanism for sensitization. The theory suggests that repeated drug use may lead to incremental neuroadaptations that produce a hypersensitivity to these substances (Robinson & Berridge, 1993). These neural adaptations have been shown to persist for years and may even be a permanent

change (Robinson & Berridge, 1993). Chronic cocaine administration has been shown to progressively increase DA excitability in the VTA, and increase DA release in the NAc (Henry, Greene, & White, 1989; Robinson, Jurson, Bennett, & Bentgen, 1988). The mechanisms underlying behavioral sensitization involve mesocorticolimbic DA projections from the VTA to the NAc, and glutamate projections from the mPFC to the NAc (Pierce & Kalivas, 1997; see Steketee & Kalivas, 2011 for review).

Mesotelencephalic dopamine neurons and pathways have been of particular interest in studying cocaine-induced behavioral sensitization (Anderson & Pierce, 2005; Pierce & Kalivas, 1997; Robinson & Berridge, 1993). In general, the mesolimbic pathway is associated with modulating the reinforcing effects of a drug whereas the nigrostriatal pathway is associated with regulating motor output. Additionally, the NAc has been implicated in mediating both the rewarding and locomotor stimulating effects of psychostimulants (Everitt & Robbins, 2005; Li, Acerbo, & Robinson, 2004; Sellings & Clarke, 2006). Since sensitization involves an augmented motor response, the nigrostriatal system and the NAc are particularly important. Beeler and colleagues (Beeler, Cao, Kheirbek, & Zhuang, 2009) demonstrated that the locomotor activating effects of cocaine, including sensitization, are dependent on the nigrostriatal dopamine system. This experiment utilized Pitx-3 mutant mice that lacked a nigrostriatal pathway, but retained an intact mesolimbic system. Results indicated that cocaine-induced locomotor activity was absent in these mice, while cocaine-induced conditioned place preference remained intact, further implicating the nigrostriatal pathway in behavioral sensitization (Beeler et al., 2009). Additionally, the dorsal striatum (a component of the nigrostriatal system) becomes progressively more active with repeated cocaine

administrations (Letchworth, Nader, Smith, Friedman, & Porrino, 2001; Porrino, Lyons, Smith, Daunais, & Nader, 2004) suggesting that the striatum is a critical component in cocaine-induced behavioral sensitization.

In addition to DA release in specific structures and pathways, DA receptors also play an important role in behavioral sensitization. In response to repeated cocaine administration, D1 receptors are upregulated while D2 receptors are downregulated in the striatum (Nader et al., 2006; Thompson, Martini, & Whistler, 2010; Volkow, Fowler, & Wolf, 1991). Similarly in the VTA, D2 autoreceptor sensitivity is decreased in response to repeated cocaine exposure thereby enhancing DA stimulation at D1 receptors in this region (Kalivas & Duffy, 1995; Henry et al., 1989; White & Wang, 1984; Wolf & Xue, 1998). Reports are mixed regarding the role of D1 receptors in behavioral sensitization in the NAc. Some studies report an increase in D1 sensitivity in the NAc after repeated cocaine administration (Burger & Martin-Iversen, 1993; DeVries, Cools, & Shippenburg, 1998; Henry & White, 1991, 1995; Nestler & Aghajanian, 1997), while others report no change (Mayfield, Larson, & Zahniser, 1990; Peris et al., 1990). In contrast with other DA structures, the majority of studies report an increase in D2 sensitivity and density in the NAc following repeated cocaine administration (Goeders & Kuhar, 1987, Klevin, Perry, Woolverton, & Seiden, 1990; Peris et al., 1990; Yi & Johnson, 1990). It has been hypothesized that a decrease of inhibitory presynaptic D2 autoreceptors combined with an increase in postsynaptic D1 receptors may, in part, explain cocaine-induced sensitization (Antelman & Chido, 1981; Dwoskin, Peris, Yasuda, Philpott, & Zahniser, 1988; Kalivas & Duffy, 1988; Henry et al., 1989; Peris et al., 1990; Steketee & Kalivas, 2011).

Behavioral sensitization consists of two recognized phases: initiation and expression. Initiation refers to the immediate neural event and is linked to the VTA, while expression refers to the long-term neural consequences and is linked to the NAc (Steketee & Kalivas, 2011). Additionally, some studies have implicated the medial prefrontal cortex (mPFC) in the development of sensitization (Cador, Bijou, Caihol, & Stinus, 1999; Li et al., 1999; Wolf, Dahlin, Hu, Xue, & White, 1995). The expression of behavioral sensitization is thought to be strengthened by associations with environmental cues such as drug paraphernalia and visual surroundings, and therefore, may be attributed to both the pharmacological action and a learned association with the drug (Pierce & Kalivas, 1997). After repeated pairings with interoceptive cues, the presentation of environmental stimuli may escalate DA levels and, in turn, increase drug craving. Therefore the presentation of an environmental cue to an abstaining individual may lead to drug-seeking and ultimately result in relapse (Hand, Stinus, Le Moal, 1989; Neisewander, Pierce, & Bardo, 1990).

Methodology. Behavioral sensitization is recognized as an augmented motor-like response. Therefore, it is typically measured experimentally by monitoring motor activity during acute and/or repeated drug exposure. In the laboratory, the two most common methods for assessing motor activity are recording the number of photobeam breaks an animal makes or measuring the distance an animal travels in an open field chamber within a specified time period. The magnitude of sensitization may be established by observing a statistically significant increase of either photobeam break or distance traveled activity after repeated drug exposure. In a more stringent measure, animals may be considered to be sensitized by a statistically significant increase in locomotor activity

from the first trial compared to the last trial (e.g. Hu & Becker, 2003). An additional measure of behavioral sensitization uses a context-specific apparatus. Animals that are repeatedly exposed to a drug in one context show more robust sensitization when re-exposed to that drug in the same environment than when they are re-exposed to the drug in a different context (Anagnostaras & Robinson, 1996; Vezina & Leyton, 2009). This sensitization occurs through classical conditioning mechanisms in which environmental stimuli become associated with the interoceptive drug effects (Mattson et al., 2008). Sensitization in this paradigm is represented by enhanced time spent in a context that has been repeatedly paired with drug (Steketee & Kalivas, 2011). This experimental design may interfere with studies examining neural mechanisms of sensitization because it may be difficult to conclude whether various ligands are blocking conditioning or the development of sensitization itself (see Kalivas & Stewart, 1991 for review).

Evidence in humans. A subpopulation of long-term cocaine abusers develops motor-like symptoms similar to behavioral sensitization along with paranoid psychosis after repeated heavy use (Angrist, 1994). In a clinical study, Kollins & Rush (2002) examined the cardiovascular and subjective effects of repeated oral cocaine in humans with histories of substance abuse and dependence. In this study, subjects were given oral cocaine doses every other day for a total of four cocaine doses (Kollins & Rush, 2002). After each dose, a subject-rated questionnaire and cardiovascular measures, such as systolic and diastolic blood pressure, heart rates, and mean arterial pressure, were taken (Kollins & Rush, 2002). Under these conditions, a progressive increase in cardiovascular measures was evident, but there were no differences in subjective measures across trials in this study (Kollins & Rush, 2002). The results of this study suggest that cocaine-

induced sensitization may occur in humans with a past history of drug abuse and dependence.

Strakowski and Sax (1998) demonstrated behavioral sensitization in a normal human population. The subjects in this study reported no prior stimulant use or evidence of DSM III disorders (Strakowski & Sax, 1998). The subjects received repeated doses of *d*-amphetamine (AMPH) followed by a battery of tests that included eye-blink rate, motor activity, and energy ratings (Strakowski & Sax, 1998). Results showed robust behavioral enhancement for the third dose of AMPH compared to the first dose of AMPH (Strakowski & Sax, 1998). This study demonstrated that behavioral sensitization may occur in a human population that does not have a history of substance abuse. In addition to behavioral studies, alterations in dopamine release after cocaine use has been reported in human subjects. Cox and colleagues (Cox et al., 2009) reported that DA release in the ventral striatum increased after administration with intranasal cocaine in nondependent users. Furthermore, the degree of DA release was positively correlated with the degree of past cocaine use, suggesting that greater cocaine use lead to greater DA release (Cox et al., 2009).

Evidence in rodents. Downs and Eddy (1932) was the first to report that repeated cocaine administration enhanced locomotor responding in laboratory rats (Downs & Eddy, 1932). Since that experiment, behavioral sensitization has been well established with a plethora of studies showing that psychostimulants reliably and progressively enhance locomotor activity in rodents (see Kalivas & Stewart, 1991; Robinson & Becker, 1986; Robinson & Berridge, 1993 for reviews).

Rodent studies examining cocaine-induced sensitization seek to understand the neurochemical and cellular mechanisms that underlie this behavioral modification. Both D1 and D2 agonists have been shown to elicit behavioral sensitization in rats (Molloy & Waddington, 1984; Pugh, O'Boyle, Molloy, & Waddington, 1985; Ujike, Akiyama, & Otsuki, 1990; Walters, Bergstrom, Carlson, Chase, & Braun, 1987). Studies examining the effects of DA antagonists on cocaine-induced behavioral sensitization have been less clear. Some studies have successfully blocked the development of cocaine-induced behavioral sensitization using the D1 antagonist SCH 23390 (Cabib et al., 1991; Le et al., 1997; Fontana, Post, Weiss, & Pert, 1993), while others have not (Mattingly, Hart, Lim, & Perkins, 1994). Mattingly and colleagues (1994) tested SCH 23390 and the D2 antagonist sulpiride and found that both decreased cocaine-induced locomotor activity, but neither antagonist prevented the development of behavioral sensitization (Mattingly et al., 1994). Haloperidol, a non-specific D2-antagonist, has been shown to block the acute locomotor effects of cocaine and the development of behavioral sensitization at high doses (Mattingly, Rowlett, Ellison, & Rase, 1996), but not at lower doses (Martin-Iverson & Reimer, 1994; Reimer & Martin-Iverson, 1994; Weiss, Post, Pert, Woodward, & Murman, 1989). The results of these studies implicate both D1 and D2 receptors in cocaine-induced behavioral sensitization, but the mechanisms are still being studied and are not yet completely understood.

Evidence in Japanese quail. Thus far, behavioral sensitization studies using Japanese quail have yielded similar results as studies using rodents (Akins & Geary, 2008; Geary & Akins, 2007; Levens & Akins, 2001, 2004). Levens and Akins (2001) demonstrated cocaine-induced sensitization in male quail with repeated administration of

10 mg/kg cocaine after six trials. Furthermore, Akins and Geary (2008) established sensitization with 20 mg/kg cocaine in addition to 10 mg/kg cocaine in male Japanese quail. Additionally, cocaine-induced sensitization at 1, 3, and 10 mg/kg has been shown in male pigeons (Pinkston & Branch, 2010).

Evidence for the role of DA receptors in mediating cocaine-induced behavioral sensitization has also been examined in male Japanese quail. Pretreatment with the D2 antagonist eticlopride blocked cocaine-induced locomotor activity and sensitization in male Japanese quail (Levens & Akins, 2001). These results are in agreement with previous studies that show diminished activity in amphetamine-induced locomotor activity in male rats pretreated with eticlopride (Bardo, Valone & Bevins, 1999; Fowler & Liou, 1998). In pigeons, the D1 antagonist SCH-23390 has been shown to decrease locomotor activity and inhibit the development of behavioral sensitization when co-administered with apomorphine (Acerbo & Delius, 2004). As discussed previously, D1 antagonists have been shown to decrease locomotor activity and block stimulant-induced behavioral sensitization in some rodent studies (Cabib et al., 1991; Fontana, Post, Weiss, & Pert, 1993; Le et al., 1997). Taken together, these experiments in aves indicate that the DA system involved in cocaine-induced behavioral sensitization may be similar between birds and rodents.

Conditioned Place Preference

The CPP paradigm has been widely accepted as a reliable measure of drug reward. In this paradigm, a primary reinforcer (i.e. drug) is paired with contextual stimuli that, through the principles of classical conditioning, can become a secondary reinforcer (see Bardo, Rowlett, & Harris, 1995; Tzschentke, 1998 for reviews). It is suggested that

environmental cues associated with drug taking may be reinforcing even in the absence of the drug. These environmental cues are thought to evoke drug craving and may lead relapse in humans (Hand et al., 1989; Neisewander et al., 1990). Given that CPP involves repeated pairings of a specific context and a drug sensation, CPP can serve as a model of cue-elicited conditioning (see Bardo & Bevins, 2000 for review). In addition to drugs of abuse, natural reinforcers such as food (Bechara, Harrington, Nader, & van der Kooy, 1992; Swerdlow, van der Kooy, Koob, & Wenger, 1983), water (Agmo, Federman, Navarro, Padua, Velazquez, 1993), and sex (Agmo & Berenfeld, 1990; Miller & Baum, 1987; Straiko, Gudelsky, & Coolen, 2007) have been shown to elicit CPP in rats.

The establishment of cocaine-induced CPP appears to be, in part, dependent on DA mechanisms. Research indicates a very close correlation between a given drug inducing CPP and an increase in DA neurotransmission (see Tzschentke, 1998 for review). Administration with a DAT inhibitor produces CPP, mimicking cocaine's mechanism of action (Le Pen, Duterte-Boucher, & Costentin, 1996). Additionally, administration of a DA release inhibitor blocks cocaine-induced CPP (Bilsky, Montegut, Nichols, & Reid, 1998). Both D1-like and D2-like agonists have been shown to produce CPP (Abrahams, Rutherford, Mallet, & Beninger, 1998; Khroyan, Fuchs, Baker, & Neisewander, 1997; Mallet & Beninger, 1994; White, Packard, & Hiroi, 1991), and D1 antagonists block cocaine-induced CPP (Baker et al., 1996, 1998; Cervo & Samanin, 1995; Liao, Chang, & Wang, 1998; Morency & Beninger, 1986; Nazarian, Russo, Festa, Kraish, & Quinones-Janab, 2004; Pruitt, Bolanos, & McDougall, 1995). However, while some studies have blocked cocaine-induced CPP with D2 antagonists (Darland et al., 2012; Liao, Chang, & Wang, 1998), many studies have shown no effect of D2

antagonists on cocaine-induced CPP (Cervo & Samanin, 1995; Nazarian et al., 2004). It should be noted that some studies have blocked cocaine-induced CPP with D2 agonists (Hnasko, Sotak, & Palmiter, 2007; Robinson et al., 2004), further complicating the role of D2 in CPP. Taken together, these studies suggest that the neural mechanisms underlying cocaine reward may be heavily regulated by DA activity, but the precise role of specific DA receptors is less clear (see Anderson & Pierce, 2005 for review).

In addition to DA mechanisms, serotonin (5-HT) signaling has also been heavily implicated in cocaine-induced CPP (see Bardo, 1998; Filip, Alenina, Bader, & Przegalinski, 2010; Hayes & Greenshaw, 2011 for reviews). While cocaine's primary mechanism of action is blockade of DAT, genetically-modified mice without DAT still readily develop CPP to cocaine (Sora et al., 1998). Sora and colleagues (2001) found that cocaine-induced CPP is only blocked when both DAT and SERT are knocked out in mice (Sora et al., 2001). Furthermore, Hnasko, Sotak, and Palmiter (2007) found that SCH 23390 blocked cocaine-induced CPP in control mice, but did not in DA deficient mice. This study also found that fluoxetine (a SERT inhibitor) produced CPP in DA deficient mice, but did not in control mice (Hnasko, Sotak, & Palmiter, 2007). Craige and Unterwald (2013) blocked cocaine-induced CPP with a 5-HT2C agonist in C57BL/6 mice, further implicating 5-HT in cocaine reward. Collectively, these studies suggest that serotonergic mechanisms may be equally as critical as dopaminergic mechanisms in cocaine-induced CPP.

Methodology. The conditioned-place preference (CPP) paradigm is used pre-clinically as a behavioral model to study rewarding or aversive effects of drugs. In general, an animal is injected with a drug or vehicle and placed in a test chamber with

distinct environmental cues. On the following day, the animal is injected with a vehicle and confined to the opposite chamber that has different distinct environmental cues. This alternating schedule is carried out for several (typically 6-10) trials. In a drug-free test session, the animal is placed in a neutral chamber with access to both contexts. A conditioned-place preference (CPP) is evident if the animal spends significantly more time in the drug-paired compartment versus the vehicle-paired compartment. Conversely, if the animal spends significantly more time in the vehicle-paired compartment versus the drug-paired compartment, the animal is considered to have a conditioned-place aversion (CPA) to the drug (see Bardo & Bevins, 2000; Tzschentke, 1998 for reviews).

Evidence in humans. CPP is generally considered a nonhuman preclinical model of drug reward with a plethora of studies conducted using laboratory animals (see Bardo, Rowlett, & Harris, 1995 for review). Recently, a few studies have attempted to measure CPP in humans. Childs and de Wit (2009) found that humans liked a room associated with d-amphetamine significantly more than a room associated with placebo. Unlike animal studies, this experiment did not assess the participant's room preference prior to conditioning (Childs & de Wit, 2009). Childs and de Wit (2013) addressed this limitation in a follow-up study and found that men and women significantly prefer an environment associated with d-amphetamine compared to an environment associated with placebo. Furthermore, this study reveals that the context of drug administration can greatly influence subjective drug effects in humans upon re-administration (Childs & de Wit, 2013).

In addition to drug rewards, Molet, Billiet, and Bardo (2013) found that humans may develop CPP and CPA to music. This study used a virtual reality environment and

found that humans prefer houses playing consonant music and dislike houses playing dissonant music (Molet, Billiet, & Bardo, 2013). Furthermore, Astur, Carew, and Deaton (2014) found that humans develop a strong preference to a room associated with a food reward in a virtual environment. Taken together, these studies show that CPP may be reliably tested in humans, indicating that this paradigm may be clinically translatable.

Evidence in rodents. As described previously, cocaine has been shown to reliably produce CPP in laboratory rats (see Bardo, Rowlett, & Harris, 1995; Tzschentke, 1998, 2007 for reviews). Mucha, van der Kooy, O'Shaughnessy, and Bucenieks (1982) first studied place conditioning in the rat using cocaine. In this study, rats developed CPP to 0.05 and 10 mg/kg cocaine administered I.V. (Mucha et al., 1982). Nomikos and Spyraki (1988) found that rats developed CPP when cocaine was administered via IV or intraperitoneally (ip). However, this study found that ip administration required higher cocaine doses and twice the number of training trials to achieve CPP at the same magnitude as IV (Nomikos & Spyraki, 1988). Cocaine-induced CPP is such a reliable effect experimentally that cocaine has become a positive control for the patency of IV catheter construction and for drug comparison in other CPP studies (Tzschentke, 1998).

As described previously, the mesolimbic DA system appears to be heavily implicated in cocaine reward. However, the NAc may play a stronger role in sensitization than CPP. Spyraki, Fibiger, and Phillips (1982) did not block cocaine-induced CPP after lesioning the NAc. Additionally, intracranial cocaine injections directly into the NAc have failed to produce CPP (Hemby, Jones, Justice, & Neill, 1992). Sellings et al. (2006) suggested that the NAc shell is more critical to cocaine-induced CPP than the NAc core. This study found that 6-hydroxydopamine lesions to the NAc shell reduced cocaine-

induced CPP, but lesions of the NAc core left cocaine-induced CPP intact (Sellings et al., 2006). In addition to the NAc shell, excitotoxic lesions of the prelimbic PFC and the amygdala also disrupt cocaine-induced CPP (Brown & Fibiger, 1993; Fushs, Weber, Rice, & Neisewander, 2002; Tzschentke & Schmidt, 1998). Furthermore, Meyers, Zavala, and Neisewander (2003) found that excitotoxic lesions of the dorsal hippocampus disrupted cocaine-induced CPP, but lesions of the ventral hippocampus did not. Collectively, these studies implicate several brain regions involved in cocaine-induced CPP that may not play as large of a role in cocaine-induced behavioral sensitization.

Evidence in Japanese quail. Male quail have been shown to develop cocaine-induced CPP in a dose-dependent fashion that is similar to male rats (Akins et al., 2004). Levens & Akins (2001) established CPP in male Japanese quail at 10 mg/kg cocaine and found that this was attenuated with the D2 antagonist eticlopride. Akins and colleagues (2004) found that male quail developed CPP to cocaine doses of 1, 3, and 10 mg/kg, but not at 30 mg/kg cocaine (Akins et al., 2004). Additionally, this study found that SCH 23390 blocked cocaine-induced CPP, albeit at lower doses of SCH 23390 than what has been reported for rodents (Akins et al., 2004; Cervo & Samanin, 1995). These studies indicate that cocaine reward in quail is comparable to cocaine reward in rodents, and that the DA mechanisms involved may be similar.

In addition to cocaine, various studies have established CPP in Japanese quail using other rewarding stimuli. Mace, Kraemer, and Akins (1997) demonstrated that 12-day old chicks preferred a chamber paired with normal food over a chamber paired with tainted food. This study established CPP in 12-day old Japanese quail after only two training sessions (Mace, Kraemer, & Akins, 1997). Japanese quail have also been shown

to develop CPP to nicotine (Bolin, Cornett, Barnes, Gill, & Akins, 2012). Furthermore, both male (Akins, 1998) and female (Gutierrez & Domjan, 2011) quail demonstrate CPP to a chamber previously associated with a sexual encounter. To date, the study by Gutierrez & Domjan (2011) is the only study to examine CPP in female Japanese quail.

Investigating Drug-Hormone Interactions in Japanese quail

As research subjects, Japanese quail have played an important role in the history of endocrinology research (see Ball & Balthazart, 2010 for review). Therefore, their biology, behavior, and neuroendocrinology have been well characterized (see Ball & Balthazart, 2010; Mills, Crawford, Domjan, & Faure, 1997 for reviews). Additionally, quail are advantageous because their circulating hormone levels may be manipulated through alterations of photoperiod without surgical methods (Robinson & Follett, 1982).

The present set of experiments examines the potential role of gonadal sex hormones in cocaine-induced behaviors using an avian species. Given the non-surgical ability to control plasma levels of steroid hormones, Japanese quail may be of additional value when investigating cocaine-hormone interactions. Furthermore, studies involving female Japanese quail are limited and there are no documented experiments examining sex differences in drug abuse using an avian species. In a series of three experiments, I investigated 1) the effects of gonadal hormones (estradiol and testosterone) on cocaine-induced locomotor activity 2) the involvement of D2 dopamine receptors in acute (one trial) cocaine-induced locomotor activity in female quail and 3) the potential role of estradiol in cocaine-induced conditioned place preference in female quail.

Figure 1.1. Total binding of D1- and D2-like receptors in rats and quail at the level of the nucleus accumbens and olfactory tubercle. CPu = Caudate putamen; ACb.c = nucleus accumbens core; ACb.s = nucleus accumbens shell; Tu = olfactory tubercle; MSt = medial striatum; OTu.m = medial olfactory tubercle; OTu.l = lateral olfactory tubercle. Reprinted from "Species Differences in the Relative Densities of D1- and D2-Like Dopamine Receptor Subtypes in the Japanese Quail and Rats: An in vitro Quantitative Receptor Autoradiography Study" by H.K. Kleitz, C. A. Cornil, J.B. Balthazart, and G.F. Ball, 2009, *Brain, Behavior, and Evolution, 73*, 81-90. Copyright 2009 S. Karger AG, Basel.

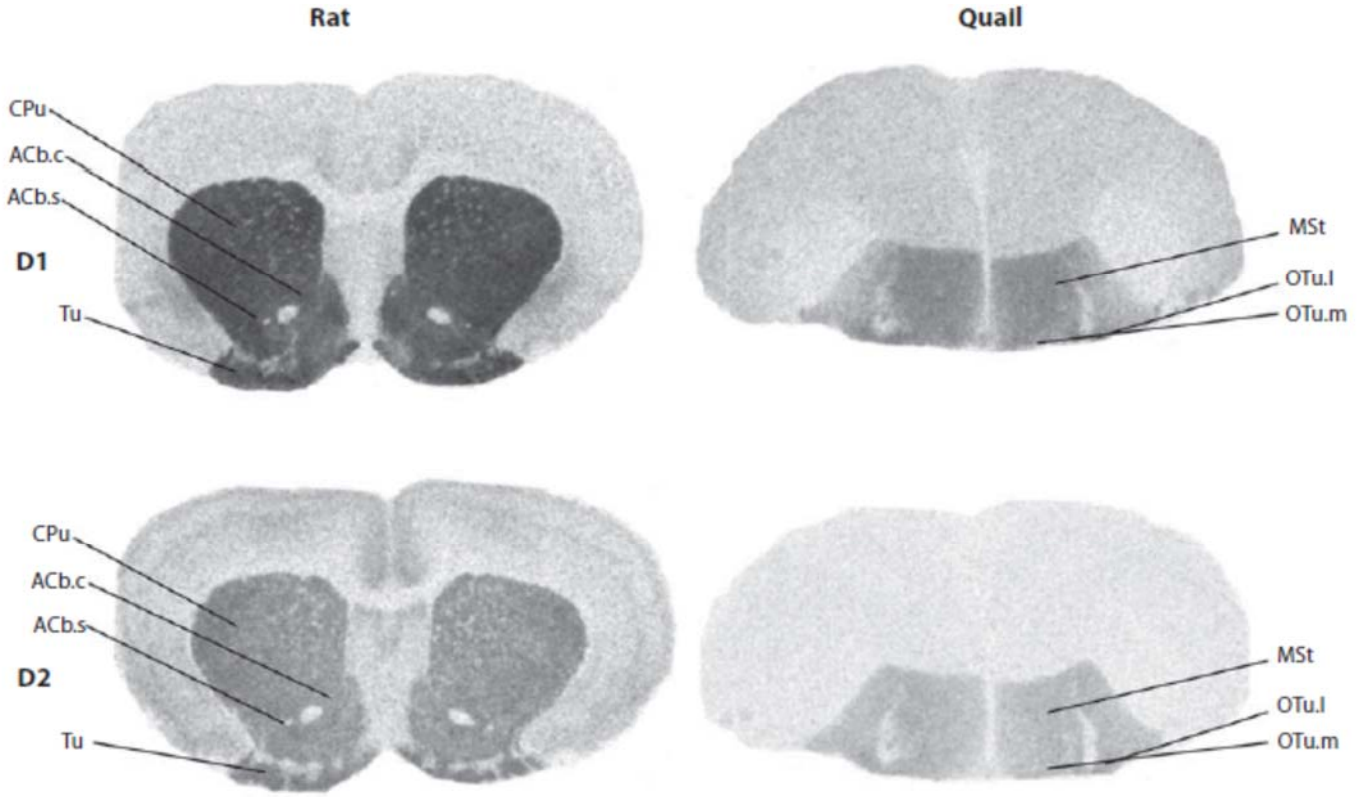
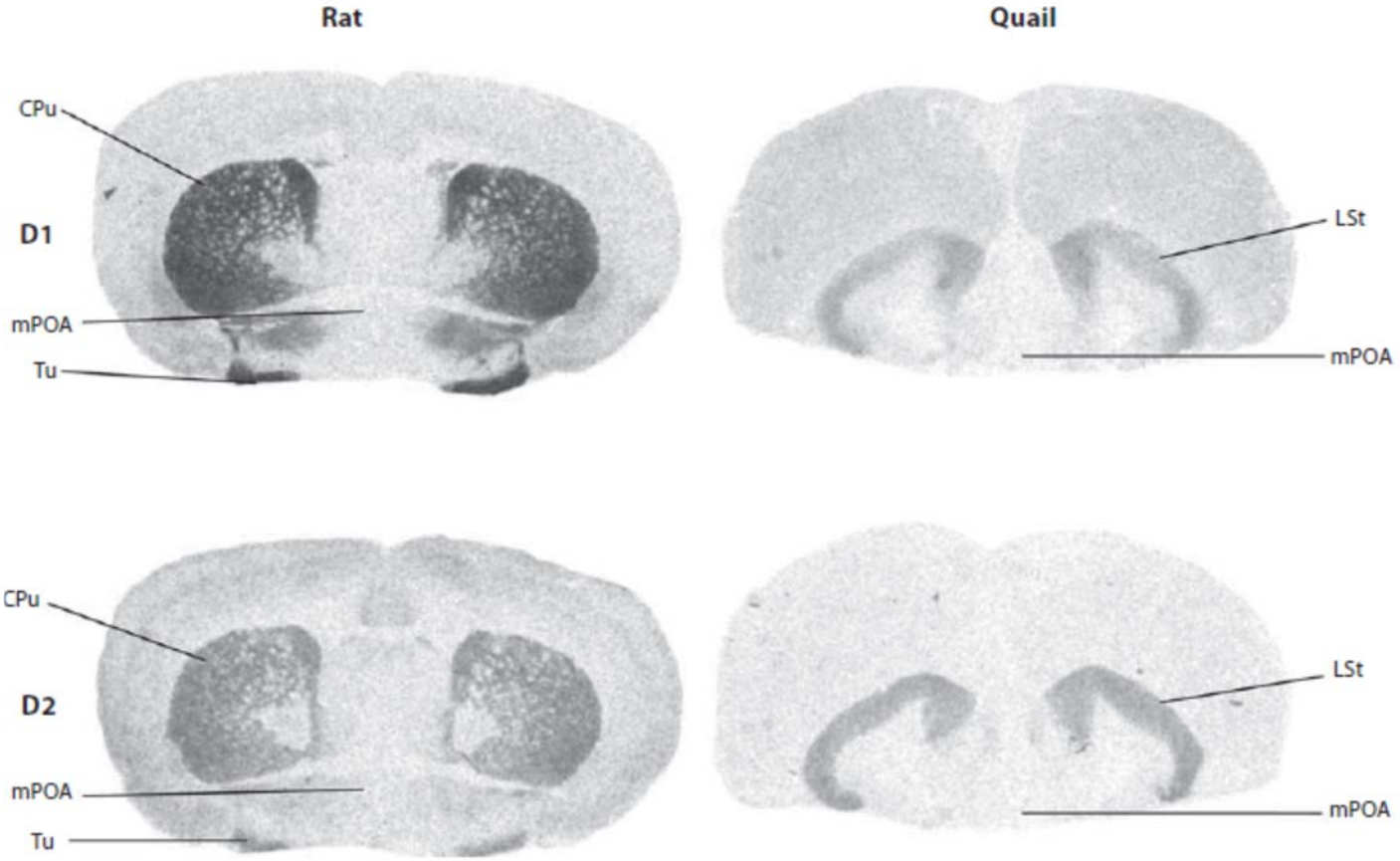


Figure 1.2. Total binding of D1- and D2-like receptors in rats and quail at the level of the anterior commissure. CPu = Caudate putamen; Tu = olfactory tubercle; mPOA = medial preoptic area; LSt = lateral striatum. Reprinted from "Species Differences in the Relative Densities of D1- and D2-Like Dopamine Receptor Subtypes in the Japanese Quail and Rats: An in vitro Quantitative Receptor Autoradiography Study" by H.K. Kleitz, C. A. Cornil, J.B. Balthazart, and G.F. Ball, 2009, *Brain, Behavior, and Evolution, 73*, 81-90. Copyright 2009 S. Karger AG, Basel.



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CHAPTER 2: EXPERIMENT 1

COCAINE-INDUCED SENSITIZATION CORRELATES WITH TESTOSTERONE IN MALE JAPANESE QUAIL BUT NOT WITH ESTRADIOL IN FEMALE JAPANESE QUAIL

(Gill, Madison, & Akins, 2015)

Introduction

While the rate of cocaine abuse and dependence has remained relatively stable over the last 15 years, abuse and dependence among women has dramatically increased, such that nearly 40% of users over the age of 26 are female (Evans & Foltin, 2010; Jackson et al., 2006). Men and women are equally likely to use cocaine if given the opportunity, but women are more likely to reach dependence criteria compared to their male counterparts (Kasperski et al., 2011; Van Etten & Anthony, 1999). Women report shorter periods of abstinence (Kosten et al., 1993), enter into treatment at younger ages (Griffin et al., 1989; Mendelson et al., 1991), and once admitted for treatment, their use is more severe compared to men (Kosten et al., 1993). Additionally, drug-related cues induce higher levels of craving in cocaine-dependent women than in cocaine-dependent men (Robbins et al., 1999). Collectively, these studies suggest that women may be more sensitive to the reinforcing properties of psychostimulants and may be more vulnerable to some aspects of drug addiction than men.

Research has indicated that gonadal hormones, particularly estrogen, may be responsible for the heightened behavioral and biological responses to cocaine in females (Evans & Foltin, 2006; Hu & Becker, 2003). Women report greater subjective responses

to cocaine when tested during the follicular phase compared to the luteal phase of the menstrual cycle (Collins et al., 2007; Evans et al., 2002; Sofuoglu et. al, 1999). In fact, sex differences only emerge in humans when men are compared with women in the luteal phase, as women in the follicular phase have similar responses to cocaine as men (Collins et al., 2007; See Quinones-Jenab & Jenab, 2012 for review). Rodent models have demonstrated that intact female rats acquire cocaine self-administration at faster rates and have higher breaking points than ovariectomized (OVX) female rats and male rats (Jackson et al., 2006, Lynch & Carroll, 1999). Russo et al. (2003) showed that female rats develop associations to environmental cues and to the rewarding properties of cocaine at lower doses and at faster rates than male rats. Additionally, intact and estradiol-treated OVX female rats show significantly greater locomotor activity following chronic cocaine administration compared to intact and castrated male rats and OVX female rats (Hu & Becker, 2003). It should be noted that estradiol has been shown to rapidly down regulate D2 in the striatum (Bazzett & Becker, 1994) and may, in part, account for the increased sensitivity to repeated cocaine observed in female rodents (Hu & Becker, 2003; Becker & Hu, 2008). Taken together, these studies suggest that ovarian hormones may play a role in the increased vulnerability to psychostimulants among females.

Research on the role of testosterone in cocaine-induced locomotor effects in male rodents is mixed and inconclusive. Some studies have reported no differences between castrated (CAST) and intact male rats in cocaine-induced locomotor activity (Becker et al., 2001; Forgie & Stewart, 1994; Hu & Becker, 2003; Hu et al., 2004; Robinson et al., 1981; van Haaren & Meyer, 1991). In these studies, cocaine increased locomotor activity in both CAST and intact male rats. Other studies have reported increased cocaine-

induced locomotor activity and striatal dopamine in CAST male rats relative to intact rats (Camp & Robinson, 1988a, b; Hernandez et al., 1994; Purvis-Tyson et al., 2014; Robinson, 1984). In contrast, Menendez-Delmestre and Segarra (2011) observed cocaine-induced sensitization at 15 and 30 mg/kg in intact and CAST male rats with testosterone replacement but not in CAST male rats. Thus, it is difficult to decipher the role of testosterone on cocaine-induced locomotor based on the current literature.

The current study proposes to examine the effects of gonadal hormones (estradiol and testosterone) on cocaine-induced locomotor activity using a visually-oriented animal model, Japanese quail. Japanese quail have color vision and high visual acuity (Fidura & Gray, 1966) unlike rodent species. While the current study will not manipulate visual cues, it will serve to inform future studies involving the interaction between hormones, drug effects, and visual cues. There are currently no studies investigating this interaction. However, several clinical studies have shown that environmental visual cues play a role in drug addiction and relapse (e.g., Childress et al., 1988; O'Brien et al., 1992). Environmental stimuli may become associated with interoceptive drug cues and later, in the absence of the drug, trigger drug-seeking and ultimately relapse. Therefore, studying drug-hormone interactions in the context of how visual cues may induce relapse may be of importance to understanding drug addiction mechanisms.

Cocaine-induced behavioral sensitization (Akins & Geary, 2008; Geary & Akins, 2007; Levens & Akins, 2001) and cocaine reward (Akins et al., 2004; Levens & Akins, 2001) have been demonstrated in our laboratory in male Japanese quail. These studies utilized male quail that were on long-light photoperiods (functionally intact males). The current study proposes to compare cocaine effects on locomotor activity in long-light

males and short-light (functionally CAST) males and then to determine whether testosterone is correlated with those effects. Similarly, no studies have examined cocaine effects on locomotor activity in female quail nor whether estradiol levels are correlated with those effects.

Japanese quail allow for utilization of a practical laboratory technique for manipulating hormone levels. In quail, circulating hormone levels can be manipulated through alterations of photoperiod without surgical methods (Robinson & Follett, 1982). Male and female quail exposed to long photoperiods exhibit increased plasma levels of testosterone and estradiol, respectively (Adkins & Adler, 1972; Balthazart et al., 1979; Balthazart et al., 1983; Brain et al., 1988; Delville et al., 1986; Delville & Balthazart, 1987; Doi et al., 1980; Domjan, 1987; Guyomarc'h & Guyomarc'h, 1994; Mills et al., 1997; Noble, 1972). Male and female quail exposed to short photoperiods exhibit decreased plasma levels of testosterone and estradiol, respectively (Adkins & Adler, 1972; Balthazart et al., 1979; Brain et al., 1988; Delville et al., 1986; Delville & Balthazart, 1987; Doi et al., 1980; Domjan, 1987; Guyomarc'h & Guyomarc'h, 1994; Mills et al., 1997; Noble, 1972). Furthermore, exposure to short-light conditions has been shown to be comparable to surgical gonadectomy in both male and female quail (Adkins & Nock, 1976).

The present study was designed to investigate the role of gonadal sex hormones in cocaine-induced behavioral sensitization in a visual species. The overarching hypothesis was that increases in plasma sex hormones would correlate with increases in cocaine-induced locomotor activity in Japanese quail and that female quail would be more sensitive to the locomotor-activating effects of cocaine than males. Specifically, it was

predicted that photostimulated (long-light) female and male quail would dose-dependently exhibit increases in locomotor activity to repeated administration of cocaine, and that photostimulated female quail would sensitize to a greater degree than male quail. Based on previous cocaine sensitization studies in male quail and the rodent literature, it was predicted that cocaine-induced locomotor effects would be correlated with testosterone in male quail and with estradiol in female quail.

Materials and Methods

Subjects

Forty-six male and 45 female Japanese quail *(Coturnix japonica),* approximately 5-8 months old were subjects in the experiment. Eggs were supplied by Northwest Gamebirds (Kennewick, WA) and quail chicks were hatched and then raised in mixed-sex groups until approximately 28 days of age. At 28 days of age, male quail were housed individually and female quail were group housed in wire mesh cages (GQF Manufacturing, Savannah, GA). Female quail were housed individually when selected for the experiment. Subjects were raised in a long-light (16L: 8D) cycle with food and water available *ad libitum*. Approximately 3 weeks (21 days) prior to the start of the experiment, twenty-two male and twenty-one female quail were transferred to a short-light (8L: 16D) cycle with lights on at 0900 (Adkins, 1973; Henare et al., 2011, Robinson & Follett, 1982). In the current experiment, the short-light cycle resulted in plasma T (0.65 ± 0.71 ng/ml) and E2 (43.72 ± 41.62 pg/ml) levels similar to previous reports (Balthazart et al., 1979, 1983; Brain et al., 1988). Thus, male and female steroid hormone levels were adequately low under short-light conditions in the current experiment.

All subjects were drug and sexually naïve prior to experimentation. All experimental procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

Plasma Testosterone and Estradiol ELISA

Blood samples were taken two days prior to the start of the experiment. Approximately 0.5 ml of blood was taken from the brachial (wing) vein of the quail and placed into heparinized tubes. To minimize corticosteroid release, the time between removal of quail from carrier box and collection did not exceed 5 min (Dallman & Bhatnager, 2001; Mizrahi et al., 2001). Blood was immediately centrifuged at 1500 RPM for 5 min and plasma was stored at -20^{0}C until assayed.

Plasma testosterone (T) and estradiol (E2) were measured in duplicate via an enzyme-linked immunoassay kit (DRG Diagnostics; testosterone EIA-1559, estradiol EIA-2693) modified from the procedure described by Wilhelms et al. (2005). The kits were validated for use with quail plasma by testing for parallelism and recovery of added mass (standard biochemical validations). To test for parallelism, high and low T and E2 pools were pipetted at five different volumes in quadruplicate to ensure that the dose response curves were parallel to the standards under dilution and to confirm that the sample bound to the antibody had the same affinity. The test for parallelism ensures the assay maintains linearity under dilution, and recovery of exogenous T or E2 verifies accurate measurement throughout the working range of the assay. To test for recovery of added mass, three standard curve points (from the middle of the standard curve) were

added to the high and low pool to ensure that the added mass could be detected, indicating that the sample was not blocking the antibodies ability to bind with the standard. The intra-assay and inter-assay coefficient of variance (CV) for the T ELISA was 8% and 10%, respectfully. The intra-assay and inter-assay CV for the E2 ELISA was 9% and 12%, respectively.

Drugs

Cocaine hydrochloride was dissolved in physiological saline (0.9%) and injected intraperitoneally (i.p.) at a volume of 1 ml/kg of body mass. Doses were 10 or 20 mg/kg and were chosen based on previous research that demonstrated cocaine-enhanced locomotor activity (e.g. Hu & Becker, 2003; Levens & Akins, 2001; Geary & Akins, 2007). Physiological saline (0.9%) was used as a vehicle and was injected i.p. at a volume of 0.1 ml.

Apparatus

Distance traveled was used as an index of locomotor activity and was measured in 8 identical open field chambers. Each chamber had white plastic walls, screen mesh ceilings, and white corrugated paper as the floor. The chambers measured approximately 45.72 cm tall and 55.88 cm in diameter. Distance traveled was collected using ANY-Maze video tracking software (San Diego Instruments, San Diego, CA).

Procedure

Male and female quail were randomly assigned to receive 20 mg/kg cocaine (n = 16 males, n = 16 females), 10 mg/kg cocaine (n = 15 males, n = 14 females), or saline (n = 15 males, n = 15 females). Subjects were assigned to the same box for each trial and were given two days of habituation for 30 min prior to the start of the experiment. Birds

were weighed each day, injected i.p. with 10 or 20 mg/kg cocaine or saline and immediately placed in the open field chambers. Distance traveled was recorded in 5 min time bins for 30 min. Trials were conducted once per day for 10 days with each subject receiving the same treatment throughout the experiment.

Studies have demonstrated that male and female quail may be sensitive to auditory stimulation (Guyomarc'h & Guyomarc'h, 1984, 1989; Li & Burke, 1987; Millam et al., 1985). To ensure that vocalizations did not affect locomotor activity, male and female quail were tested separately. After all male subjects were tested, chamber walls were cleaned and papers were changed, then all female subjects were tested. On alternate days, females were tested first, followed by males to minimize any potential time-of-day confounds.

Statistical Analysis

For locomotor activity, the total amount of distance traveled (in meters) during the 30 min test period for each trial was recorded. A repeated measures analysis of variance (ANOVA) was performed with trials as a repeated measure and sex, treatment, and photoperiod as between-subjects variables. To further probe interactions, independent ANOVAs served as post-hoc analyses where appropriate.

Quail were considered to be sensitized to cocaine if their distance traveled was significantly greater on trial 10 compared to trial 1 (e.g. Hu & Becker, 2003). A repeated-measures ANOVA with trials as a repeated measure and sex, treatment, and photoperiod as between-subjects variables was conducted. For significant interactions, independent ANOVAs were conducted where appropriate.

To analyze whether activity was correlated with hormone levels, a univariate analysis of covariance (ANCOVA) was conducted with total distance traveled activity on trial 10 and hormone plasma levels. Trial 10 was selected as the dependent measure because sensitization effects were most evident on that trial. Treatment (cocaine or saline) served as a fixed factor independent variable and hormone level as a covariate. Following a significant ANCOVA, linear regression analyses were performed for each treatment group.

All data were analyzed using SPSS software version 20 (International Business Machines Corp. (IBM), Armonk, NY). A Grubb's test was used prior to analyses which indicated that there were no outliers in the data set. One female bird escaped her chamber multiple times throughout the experiment and was removed from the final data set. Effect sizes were estimated by calculating eta squared (η^2) using the formulas, η^2 = SSbetween/SStotal for between-subjects effects and η^2 = SSinteraction/SStotal for within-subjects effects. The sample size for the current experiment was 91 birds. Post-hoc power analyses using G*Power software version 3.0.10 (Buchner, Erdfelder, Faul, & Lang, 2008) indicated that the total sample size of 91 subjects was sufficient to detect a medium effect (d = 0.22) with 99% power (1-β) for a repeated measures ANOVA within-between interaction. For all analyses, the statistical significance level was set at $p < 0.05$.

Results

Locomotor Activity

Figure 2.1 shows the mean distance traveled for male and female quail housed in long-light (see figure 2.1.A) or short-light (see figure 2.1.B) conditions across all 10 trials for saline, 10 and 20 mg/kg cocaine. Overall, male quail had significantly higher activity

levels (M = 63.21, *S.E.M.* = 6.95) than female quail (M = 26.41, *S.E.M.* = 7.05) as revealed by a main effect of sex, [F (1, 79) = 13.81, p = 0.0004, η^2 = 0.13]. Quail treated with 10 mg/kg cocaine (M = 64.0, *S.E.M.* = 8.80) had significantly greater locomotor activity relative to saline-treated quail (M = 29.59, *S.E.M.* = 8.61) and quail treated with 20 mg/kg cocaine (M = 40.23, *S.E.M.* = 8.32) as indicated by a main effect of treatment, [F (2, 79) = 4.24, p = 0.018, η^2 = 0.09]. No other main effects were evident. A repeated measures ANOVA revealed a significant Sex x Treatment x Photoperiod x Trials interaction, [F (18, 711) = 2.18, p = 0.003, η^2 = 0.05]. Further analyses were then conducted for each treatment.

For saline-treated quail, a significant Sex x Trials interaction indicated that males had significantly higher activity levels than females across trials, [F (9, 234) = 2.25, p = 0.02, η^2 = 0.07]. There was not a significant Sex x Photoperiod x Trials interaction, [F (9, 234) = 1.42, p = 0.179, η^2 = 0.05]. Therefore, no further analyses were conducted for saline-treated quail.

For quail treated with 10 mg/kg cocaine, a main effect of sex indicated that male quail (M = 94.48, *S.E.M.* = 16.23) had significantly greater cocaine-induced activity than female quail (M = 34.72, *S.E.M.* = 16.94), [F (1, 25) = 6.49, p = 0.017, η^2 = 0.20]. Additionally for quail treated with 10 mg/kg, there was a significant Sex x Photoperiod x Trials interaction, [F (9, 225) = 2.41, p = 0.013, η^2 = 0.08]. Further analyses within each sex revealed a significant Photoperiod x Trials interaction for female quail, [F (9, 108) = 2.39, p = 0.016, η^2 = 0.17], but not for male quail, [F (9, 117) = 1.71, p = 0.095, η^2 = 0.12]. Analyses within each photoperiod were not significant.

For quail treated with 20 mg/kg cocaine, a significant Sex x Photoperiod x Trials interaction was revealed, [F (9, 252) = 2.00, p = 0.04, η^2 = 0.07]. Further analyses within each sex were not significant. Analyses within each photoperiod indicated that a Sex x Trials interaction was significant for long-light quail, [F (9, 126) = 1.99, p = 0.045, η^2 = 0.13], but not for short-light quail, [F (9, 126) = 0.93, p = 0.502, η^2 = 0.06]. However, analysis with short-light quail revealed a main effect of sex which indicated that male quail had significantly greater activity (M = 75.38, *S.E.M.* = 16.99) than female quail (M = 15.25, *S.E.M.* = 16.99), [F (1, 14) = 6.26, p = 0.025, η^2 = 0.31].

To test for cocaine-induced sensitization, trial 10 was compared to trial 1 (refer to figure 2.1.A & figure 2.1.B). A repeated measures ANOVA revealed a significant Sex x Treatment x Photoperiod x Trials interaction, [F (2, 79) = 7.06, p = 0.002, η^2 = 0.15]. Further analyses were then conducted for each treatment. An analysis within the 10 mg/kg cocaine group showed a Sex x Photoperiod x Trials interaction, [F (1, 25) = 7.86, p = 0.01, η^2 =0.24]. Further analyses within each sex revealed a significant Photoperiod x Trials interaction for male quail, [F (1, 13) = 7.42, p = 0.017, η^2 = 0.36], indicating that male quail housed in long-light conditions exhibited significantly greater activity for Trial 10 (M = 123.82, *S.E.M.* = 37.12) than for Trial 1 (M = 75.94, *S.E.M.* = 24.78), [F (1, 7) = 8.23, p = 0.024, η^2 = 0.54 (see figure 2.1.A)]. Analyses within each photoperiod showed a significant Sex x Trials interaction for short-light quail treated with 10 mg/kg cocaine, [F (1, 11) = 7.05, p = 0.02, η^2 =0.39], revealing that female quail showed significantly greater activity on Trial 10 (M = 40.04, *S.E.M.* = 10.88) than for Trial 1 (M = 12.12, *S.E.M.* = 7.11), [F (1, 5) = 10.12, p = 0.025, η^2 =0.67 (see figure 2.1.B)]. No other interactions were found when comparing trial 10 to trial 1.

Hormone Correlational Analyses

Testosterone. A univariate analysis of covariance (ANCOVA) revealed a significant Treatment x Hormone interaction for male quail on Trial 10, [F (3, 39) = 7.09, p = 0.001, η^2 = 0.37]. Linear regression analyses were then conducted to determine whether testosterone levels were correlated with males' activity for saline, 10 mg/kg cocaine, and 20 mg/kg cocaine groups (see figure 2.2.A). Results indicated that levels of testosterone significantly predicted activity levels for male quail treated with 10 mg/kg cocaine, R^2 = 0.35, F (1, 12) = 5.96, p = 0.033. Activity levels did not correlate with testosterone levels for saline-treated males, R^2 = 0.00, F (1, 12) = 0.00, p = 0.99, nor for males treated with 20 mg/kg cocaine, R^2 = 0.02, F (1, 13) = 0.24, p = 0.63.

Estradiol. There was not a significant Treatment x Hormone interaction for female quail as indicated by a univariate ANCOVA, [F (3, 37) = 2.53, p = 0.074, η^2 = 0.18 (see figure 2.2.B)]. Therefore, no further analyses were conducted. In addition, the effect size was not large enough to warrant further consideration.

Discussion

Contradictory to our original hypothesis, long-light cycle females did not show greater cocaine sensitization than long-light cycle males. Following chronic exposure to 10 mg/kg cocaine, long-light cycle male quail demonstrated cocaine-induced sensitization. Conversely, short-light cycle female quail demonstrated behavioral sensitization to chronic administration of 10 mg/kg cocaine. Testosterone levels were positively correlated with cocaine-induced sensitization in male quail at the 10 mg/kg dose but estradiol levels were not correlated with cocaine-induced sensitization in female quail.

In the present study, the findings with male quail are in agreement with some rodent studies that demonstrated cocaine-induced sensitization and involvement of testosterone, but are not in agreement with others. Martinez-Sanchis et al. (2002) found that exogenous testosterone significantly enhanced activity at 4 mg/kg cocaine and 10 mg/kg cocaine in intact male mice. Similar to the current experiment, Martinez-Sanchis et al. (2002) did not find an effect of testosterone at doses greater than 10 mg/kg cocaine. Furthermore, Menendez-Delmestre and Segarra (2011) found that 15 and 30 mg/kg of cocaine progressively increased locomotor activity in intact and CAST male rats with testosterone replacement but not in CAST male rats. In contrast, several studies examining the role of testosterone in the behavioral effects of cocaine have failed to find differences between castrated (CAST) and intact male rodents (Becker et al., 2001; Forgie & Stewart, 1994; Hu & Becker, 2003; Hu et al., 2004; Robinson et al., 1981; van Haaren & Meyer, 1991). Therefore, while the current findings implicate the role of testosterone in cocaine sensitization in male quail, other findings are inconsistent with this.

In the current study, sensitization to 10 mg/kg cocaine in female Japanese quail did not appear to correlate with circulating levels of estradiol. The majority of studies in rodents have indicated that estradiol contributes to a greater locomotor response to cocaine following chronic or acute administration in intact or estradiol-treated OVX females compared to OVX females (Camp & Robinson, 1988a, b; Hu & Becker, 2003; Peris et al., 1991; Robinson et al., 1982; Robinson, 1984; Sircar & Kim, 1999; van Haaren & Meyer, 1991). One possible explanation for the lack of correlation between estradiol and cocaine-induced activity in the present study may be ethological in that

circulating estradiol may have a suppressant effect on activity in female Japanese quail. In nature, Japanese quail breed during the summer months and this is mimicked in the laboratory by long-light conditions (see Mills et al., 1997 for review). Quail maintained on long-light photoperiods have increased plasma sex steroids (Delville et al., 1986). Female quail with increased levels of plasma estradiol display low activity levels enabling them to nest, lay eggs, and to be sexually receptive to a male conspecific (see Mills et al., 1997 for review). While this explanation is speculative, it is possible that the locomotor-suppressant effects of estradiol were sufficiently strong to override any cocaine-locomotor enhancing effects.

An equally surprising finding in the current report was that short-light cycle female quail showed cocaine sensitization to chronic cocaine exposure (10 mg/kg). Plasma estradiol was substantially lower in short-light females compared to long-light females, therefore it was not expected that females housed on a short-light cycle would have shown sensitization. However, since estradiol may suppress locomotor activity in female Japanese quail, as discussed above, it may be that the reduction of estradiol in the short-light females was sufficient to allow cocaine (10 mg/kg) to increase locomotor activity. Another possibility is that corticosterone (CORT) may have played a role. CORT release is seasonally modulated in birds with maximal levels occurring during short-light periods (Romero et al., 1998). Additionally, female Japanese quail have greater plasma concentrations of CORT compared to male Japanese quail when housed in short-light conditions (Peczely and Pethes, 1981). Therefore, even with low levels of estradiol, CORT levels may have been sufficiently high in short-light females to elicit a greater response to cocaine compared to long-light females. This is speculative, however,

but might suggest that CORT levels need to be measured in future studies that utilize female birds on short-light cycles.

In general, the differences between the current findings and those of rodents may be due to inherent species differences in the dopaminergic system. It has been shown that the general organization of the dopamine (DA) system may be conserved between birds and mammals (Smeets & Reiner, 1994). However, the distribution and density of D1 and D2 receptors have been found to be different (Kleitz et al., 2009; Richfield et al., 1987). In an autoradiography labeling study, Kleitz and et al. (2009) found a species difference in the D2:D1 ratio in target sites for DA between Japanese quail and rats. Specifically, quail had a higher D2:D1 receptor ratio in the striatal regions of the brain compared to rats (Kleitz et al., 2009). While speculative, the current findings may suggest that increased stimulation of D2 receptors in female quail resulted in an opposite effect on behavior compared to female rodents. D2 receptor activation has been shown to decrease cocaine-induced locomotor activity in rats (Schindler & Carmona, 2002), and decrease cocaine-seeking behaviors in non-human primates (Czoty et al., 2004). Thus, an increase in D2 receptors in female quail may, in part, explain the lack of cocaine-induced locomotor activity in long-light females observed in the present study.

Estrogens have been shown to influence dopaminergic activity in the mesolimbic and nigrostriatal systems (Cyr et al., 2000, 2002; Di Paolo, 1994). In female rats, estradiol has been shown to rapidly downregulate D2 in the striatum, shifting the D2:D1 ratio towards D1 (Bazzett & Becker, 1994). Thus, a decrease in D2 receptors may, in part, explain the increased sensitivity to repeated cocaine observed in female rodents (Hu & Becker, 2003; Becker & Hu, 2008). Studies with Japanese quail have suggested that a

sex difference in the availability of D1 or D2 receptors may not exist (Ball et al., 1995). Therefore, it may be possible that in female quail, estradiol may not interact with dopamine receptors in the same way as rodents. However, this is speculative. Further neurobiological studies are needed in Japanese quail but the current study adds to our knowledge of cocaine-hormone interactions in behavioral sensitization in a visually-oriented species.

In should be noted that the present results may be due to a buildup of cocaine in body tissue. Cocaine is lipophilic and may become longer acting with repeated dosing (Schwartz-Bloom & Halpin, 2003). Due to cocaine's lipophilic nature, it is possible that the results of the present experiment were due to this accumulation of cocaine in tissue rather than an alteration in neurochemical signaling in the brain.

Summary/Conclusions

In sum, male quail housed under long-light conditions demonstrated cocaine-induced sensitization to 10 mg/kg cocaine. This was correlated with increased levels of plasma testosterone. Female quail housed under short-light conditions demonstrated sensitization to 10 mg/kg cocaine, but this did not appear to be correlated with levels of plasma estradiol. Our results suggest that male sex hormones might be contributing to the greater magnitude of cocaine sensitization in Japanese quail. Further investigation of the quail dopamine system may lead to a better understanding of the underlying neurobiological mechanisms mediating this sex difference.

Figure 2.1.A: Total distance traveled activity across trials for saline (panel A), 10 (panel B) and 20 mg//kg cocaine (panel C) comparing males and females for the long-light photoperiod. Each data point represents the mean meters traveled ± SEM. * indicates ignificance from female quail ($p < 0.05$). ** indicates significance from Trial 1 ($p < 0.05$).

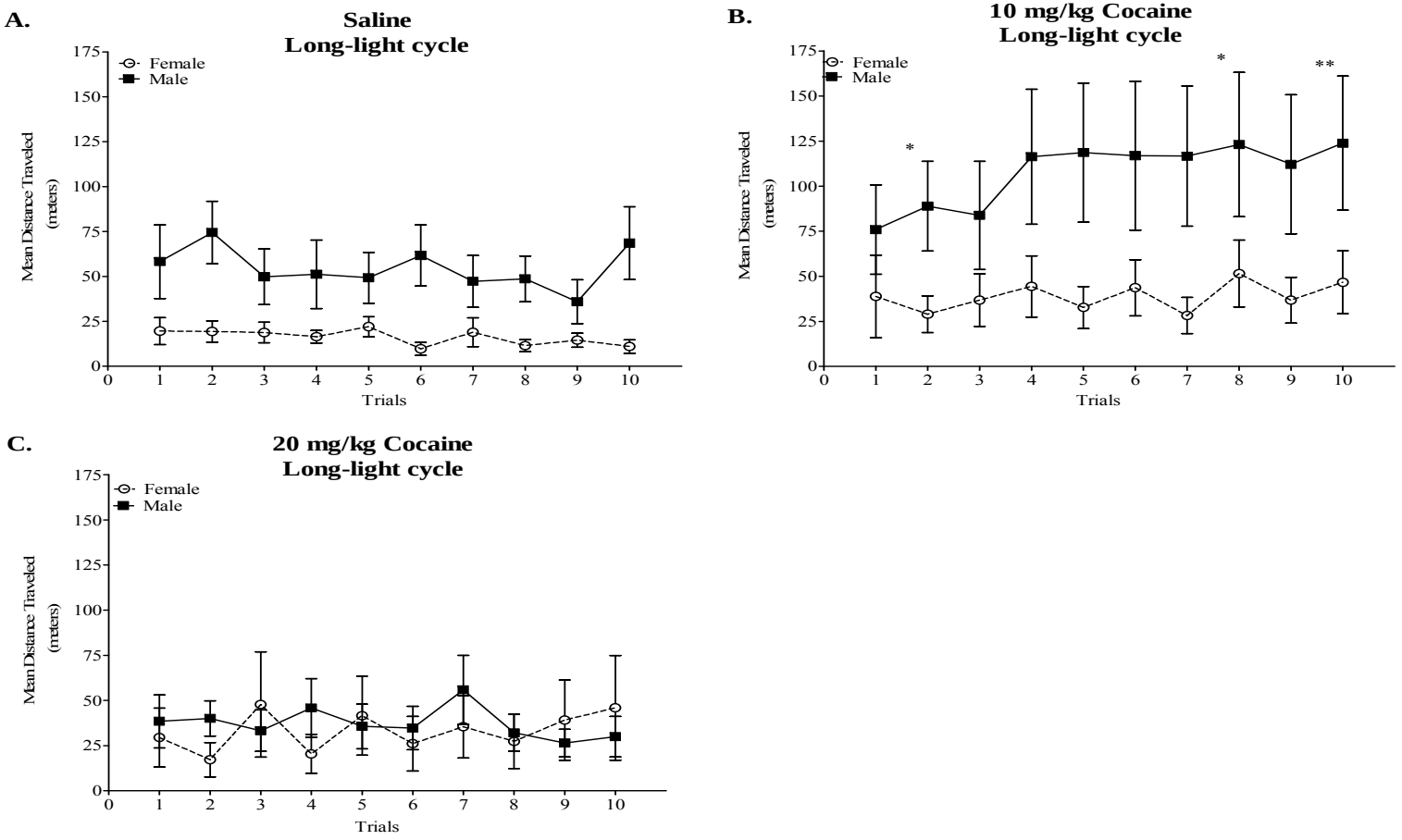


Figure 2.1.B Total distance traveled activity across trials for saline (panel A), 10 (panel B) and 20 mg//kg cocaine (panel C) comparing males and females for the short-light photoperiod. Each data point represents the mean meters traveled ± SEM. * indicates significance from female quail ($p < 0.05$). ** indicates significance from Trial 1 ($p < 0.05$).

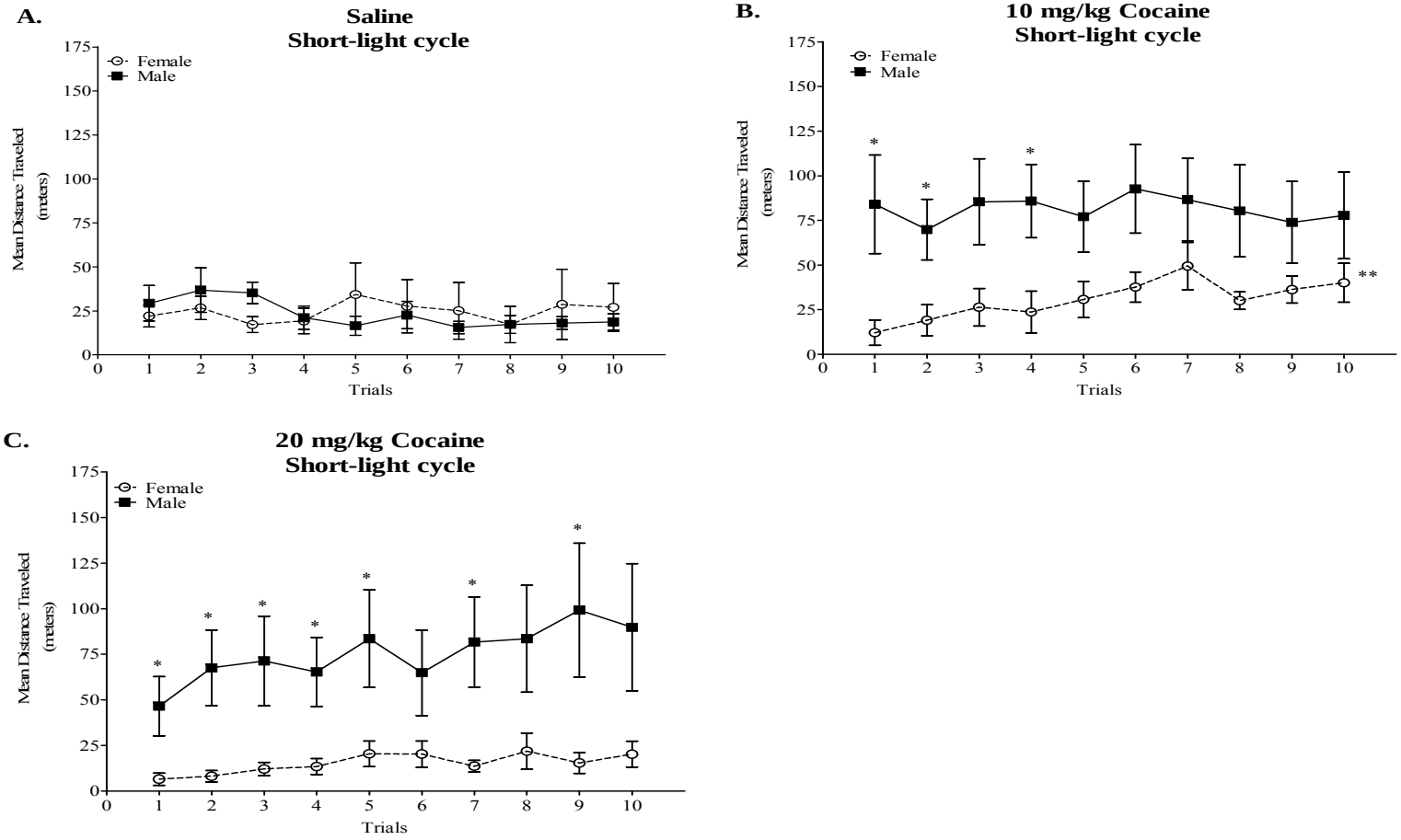


Figure 2.2.A: Relationship between the mean distance traveled activity on Trial 10 for saline (panel A), 10 (panel B) and 20 mg/kg cocaine (panel C) and plasma testosterone in male quail. Each solid diamond represents the mean hormone level and meters traveled of an individual bird. Linear regression analysis represented by the solid line on each graph. * indicates a significant correlation between activity and hormone level ($p < 0.05$).

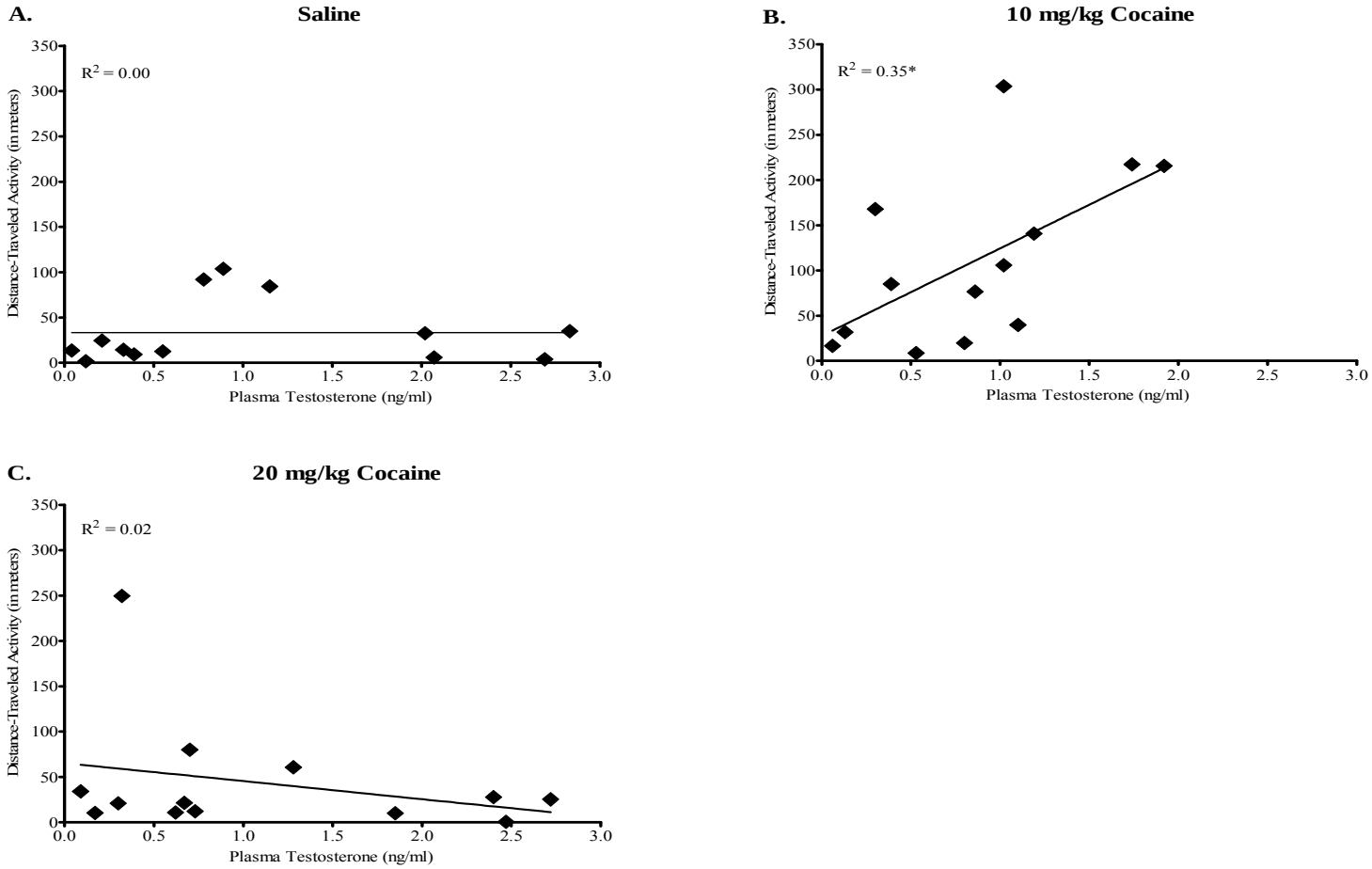
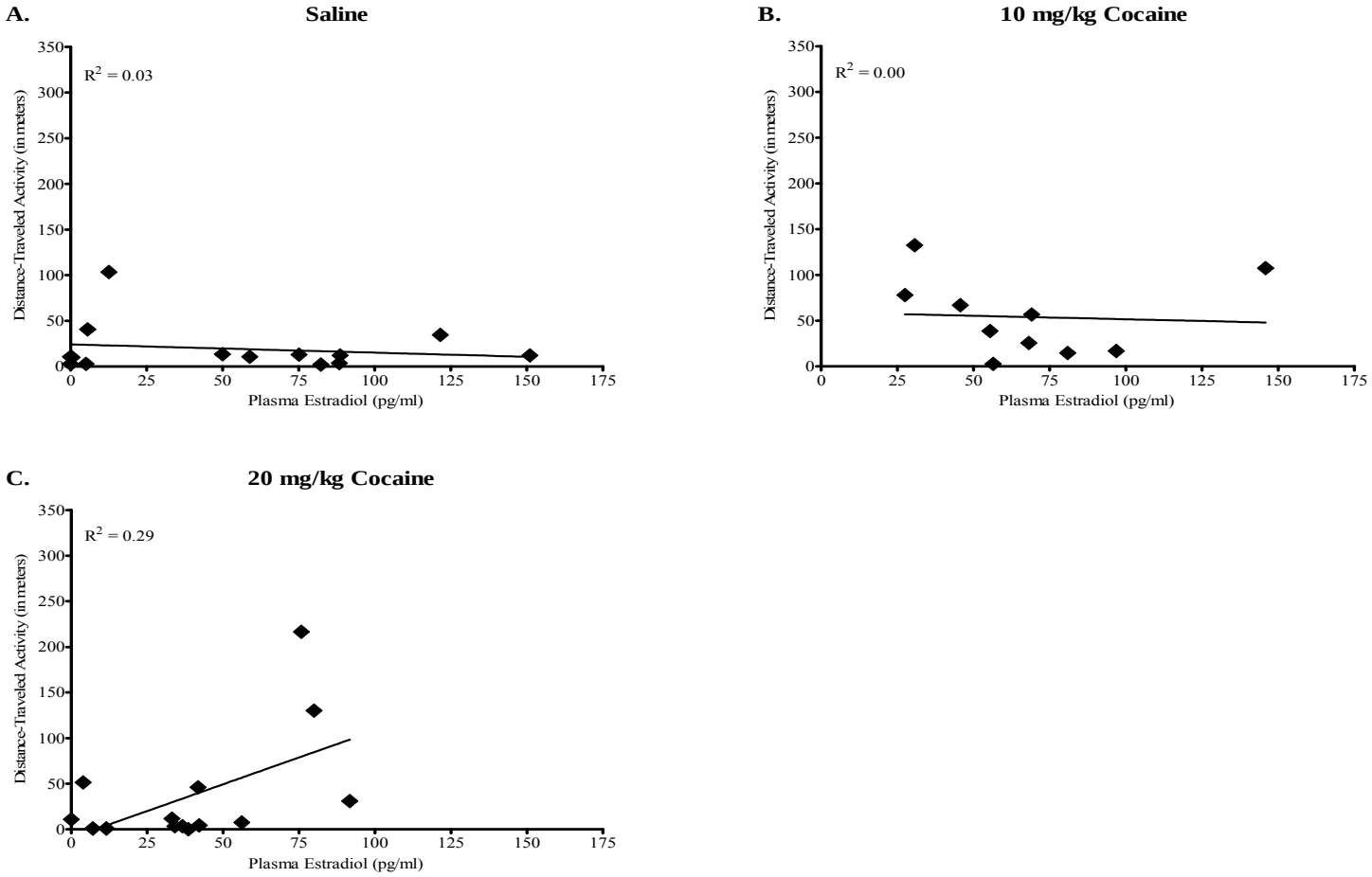


Figure 2.2.B: Relationship between the mean distance traveled activity on Trial 10 for saline (panel A), 10 (panel B) and 20 mg/kg cocaine (panel C) and plasma estradiol in female quail. Each solid diamond represents the mean hormone level and meters traveled of an individual bird. Linear regression analysis represented by the solid line on each graph. * indicates a significant correlation between activity and hormone level ($p < 0.05$).



CHAPTER 3: EXPERIMENT 2

DOPAMINE D2 RECEPTOR ANTAGONISM ENHANCES LOCOMOTOR ACTIVITY IN ACUTE COCAINE-TREATED FEMALE JAPANESE QUAIL

Introduction

Sex differences in cocaine-induced behaviors have been well documented in mammals (see Becker & Hu, 2008 for review). In rodents, intact female rats demonstrate a more robust response to cocaine than intact male rats (Hu & Becker, 2003; van Haaren & Meyer, 1991). Specifically, female rats have significantly greater locomotor activity levels following acute cocaine administration compared to male rats (Harrod et al., 2005; Sell et al., 2002; van Haaren & Meyer, 1991; Zhou et al., 2002). Ovariectomy (OVX) has been shown to attenuate this response which suggests that ovarian hormones contribute to the increased sensitivity to acute cocaine observed in female rodents (Harrod et al., 2005; Hu & Becker, 2003; Sell et al., 2002).

D2 receptors are prominently found pre-synaptically as an autoreceptor and are particularly relevant due to their major role in regulating dopamine transmission, release, and signaling (Ford, 2014; Sibley & Monsma, 1992). An extensive amount of research has shown that estradiol (E2) regulates cocaine-induced locomotor activity by modulating dopaminergic activity in the female rat brain (see Becker, 1990; Becker & Hu, 2008; Segarra et al., 2010; Watson et al., 2006; Zhou et al., 2002 for reviews). Estradiol has been shown to rapidly downregulate D2 in the striatum of female rats, shifting the D2:D1 ratio towards D1 (Bazzett & Becker, 1994). Additionally, dopamine has a lower affinity for D2 autoreceptors in female rats compared to male rats which may be due to estradiol

(Festa et al., 2006; Schindler & Carmona, 2002). Studies with nonhuman primates have shown that greater D2 receptor availability decreases cocaine-seeking behaviors suggesting that low D2 availability may be a risk factor for stimulant abuse (Czoty et al., 2004; Nader et al., 2006). Taken together, a decreased D2 receptor availability and sensitivity due to estradiol compared to male rodents may, in part, explain the increased sensitivity to acute cocaine observed in female rodents (Hu & Becker, 2003; Becker & Hu, 2008).

In the avian brain, the general organization and pharmacological profile of the dopamine (DA) system has been shown to be homologous to that of rodents (Kleitz et al., 2009; Kubikova, Vyboh, Kostal, 2009; Richfield, Young, & Penney, 1987; Smeets & Reiner, 1994). However, the density and distribution of D1 and D2 receptors in the Japanese quail brain are different from rodents, particularly in the striatal regions (Kleitz et al., 2009; Richfield, Young, & Penney, 1987). Specifically, Japanese quail have been reported to have a higher D2:D1 ratio compared to rodents (Kleitz et al., 2009). Kleitz and colleagues (Kleitz et al., 2009) posit that inhibitory D2 autoreceptors are more readily activated in this species compared to mammals, which may explain why dopamine itself is inhibitory in quail (Absil et al., 1994; Castagna et al., 1997; Cornil et al., 2005). Gill and colleagues (Gill et al., 2015) found that long-light cycle female Japanese quail do not exhibit cocaine-induced increases in activity, and that increased estradiol levels did not enhance cocaine-induced sensitization. The differential expression of D2 receptors in Japanese quail may have contributed to the absence of cocaine-induced locomotor activity observed in female quail in the latter.

Cocaine is known to cause a progressive increase in locomotor activity, resulting from a cascade of time-dependent neuroadaptations; initiated by increased activity of the ventral tegmental area (VTA) DA neurons (see Stekeetee & Kalivas, 2011 for review). Giovanni and colleagues (Giovanni et al, 1998) found that acute (one trial) administration of a D2/D3 antagonist increased the basal firing rate of dopaminergic neurons in the substantia nigra and the VTA in rodents. Additionally, biochemical studies have shown that acute administration of low dose D2 antagonists in rodents preferentially blocks presynaptic D2 receptors, thus enhancing dopamine release (Schoemaker et al., 1997). However, at higher doses these antagonists also block postsynaptic D2 receptors (Schoemaker et al., 1997) and antagonize D2-mediated behavior in rodents (Fowler & Lou, 1998; Perrault et al., 1997). Despite this DA increase, several experiments investigating low-dose D2 antagonists on acute cocaine-induced locomotor activity report that D2 antagonists prevent the acute locomotor stimulant effects of cocaine in rodents (Mattingly et al., 1994; Neisewander et al., 1995; Schindler & Carmona, 2002; White et al., 1998). Since Japanese quail have a greater availability of D2 receptors compared to rodents, administration of a D2 antagonist would be even more likely to block D2 receptors, preferentially affecting autoreceptors and thus, increasing dopamine release and transmission. Considering these species differences, it would be expected that acute (one trial) co-administration of a D2 antagonist and cocaine would enhance locomotor activity in Japanese quail. These comparative studies may add to our understanding of the neural mechanisms underlying the induction of cocaine-induced locomotor activity.

The present study was designed to evaluate the involvement of D2 dopamine receptors in acute (one trial) cocaine-induced locomotor activity in female Japanese quail.

The overarching hypothesis was that the D2 antagonist eticlopride would dose-dependently enhance locomotor activity to a single administration of cocaine relative to saline. Based on previous experiments in our laboratory (Gill et al., 2015), it was predicted that cocaine alone would not enhance locomotor activity relative to saline in female Japanese quail.

Materials and Methods

Subjects

Forty-nine female Japanese quail approximately 6 months (n = 42) and 17 months (n= 7) old were subjects in the experiment. Eggs were supplied by Northwest Gamebirds (Kennewick, WA) and quail chicks were hatched and then raised in mixed-sex groups until approximately 28 days of age. At 28 days of age, female quail were group housed in wire mesh cages (GQF Manufacturing, Savannah, GA). Female quail were housed individually when selected for the experiment. Subjects were raised on a long-light (16L: 8D) cycle with food and water available *ad libitum*.

All subjects were drug naïve prior to experimentation. All experimental procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

Drugs

Cocaine hydrochloride was dissolved in physiological saline (0.9%) and injected intraperitoneally (ip) at a volume of 1 ml/kg of body mass. A dose of 10 mg/kg was chosen based on previous research that demonstrated cocaine-induced locomotor activity in Japanese quail (Akins & Geary, 2008; Geary & Akins, 2007; Gill et al., 2015; Levens

& Akins, 2001). Physiological saline (0.9%) was used as a vehicle and was injected ip at a volume of 0.1 ml.

S(-) eticlopride hydrochloride was obtained from Research Biomedical, Inc., Natick, Mass, USA. Doses of 0.01, 0.05 & 0.1 mg/kg were dissolved in physiological saline (0.9%) and injected intraperitoneally (ip) at a volume of 1 ml/kg of body mass. Doses of eticlopride were chosen based on previous research that attenuated cocaine-induced locomotor activity (Festa et al., 2006; Schinder & Carmona, 2002; White et al., 1998) and quail (Levens & Akins, 2001).

Apparatus

Distance traveled was used as an index of locomotor activity and was measured in 8 identical open field chambers. Each chamber had white plastic walls, screen mesh ceilings, and white corrugated paper as the floor. The chambers measured approximately 45.72 cm tall and 55.88 cm in diameter. Distance traveled was collected using ANY-Maze video tracking software (San Diego Instruments, San Diego, CA).

Procedure

Since the effect of D2 antagonists on cocaine-induced locomotor activity in female quail is unknown, a one trial procedure was chosen. The procedure for this experiment was similar to Gill et al., 2015. Female quail were randomly assigned to a treatment group and randomly assigned to a chamber. Two days of habituation was given prior to the start of the experiment for 30 min each day. Birds were weighed on the morning of the experiment. On the trial day, subjects received an intraperitoneal (ip) injection of saline or eticlopride (0.01, 0.05 or 0.1 mg/kg) and were placed back in their home cage for 15 min. After the 15 min wait, birds were taken into the test room and

administered a second ip injection of either saline or 10 mg/kg cocaine. Injection procedures were similar to studies that tested D2 antagonists on cocaine-induced behaviors (Bardo et al., 1999; Festa et al., 2006; Levens & Akins, 2001; White et al, 1998). Following the 2nd injection, birds were immediately placed in open field chambers. Distance traveled was recorded in 5 min time bins for 30 min. White noise was used throughout each phase of the experiment to attenuate extraneous noise.

A 4 (3 doses of eticlopride or saline) x 2 (cocaine or saline) factorial design was used in this experiment. Therefore, there were a total of 8 groups (n's of 5-7) (see Table 1).

Statistical Analysis

For locomotor activity, the mean total amount of distance traveled (in meters) during the 30 min test period was recorded. A univariate analysis of variance (ANOVA) was performed with trial as a dependent measure and pre-treatment (Sal or Eti) and treatment (Coc or Sal) as independent variables. To further probe interactions, independent ANOVAs served as post-hoc analyses where appropriate. To analyze the 5 min time data, a repeated-measures ANOVA was performed with time as a repeated measure and pre-treatment (Sal or Eti) and treatment (Sal or Coc) as between-subjects variables. Independent and one-way ANOVAs served as post-hoc analyses where appropriate.

All data were analyzed using SPSS software version 22 (International Business Machines Corp. (IBM), Armonk, NY). A Grubb's test was used on each treatment group prior to analyses to remove outliers. A total of four outliers were removed using this method, one from the saline pre-treatment group, one from the 0.01 mg/kg eticlopride

pretreatment group, and two from the 0.05 mg/kg eticlopride pretreatment group. Effect sizes were estimated by calculating eta squared (η^2) using the formulas, η^2 = SSbetween/SStotal for between-subjects effects and η^2 = SSinteraction/SStotal for within-subjects effects. The sample size for the current experiment was 49 birds. Post-hoc power analyses using G*Power software version 3.0.10 (Buchner, Erdfelder, Faul, & Lang, 2008) indicated that the total sample size of 49 subjects detected a large effect (d = 0.48) with 78% power (1-β) for the univariate ANOVA. For the repeated measures ANOVA within-between interaction, post-hoc power analyses indicated that the total sample size of 49 was sufficient for detecting a medium effect (d = 0.27) with 96% power (1-β). For all analyses, the statistical significance level was set at $p < 0.05$.

Results

Figure 3.1 represents the mean total distance-traveled activity level for each pre-treatment group. A univariate ANOVA revealed a significant Pre-treatment x Treatment interaction, [F (3, 41) = 3.26, p = 0.031, η^2 = 0.19]. Further analyses were then conducted for each pre-treatment group. These analyses revealed that cocaine-treated birds had significantly higher activity levels (M = 10.50, *S.E.M.* = 1.97) than saline-treated birds (M = 2.81, *S.E.M.* = 1.66) when pre-treated with 0.01 mg/kg eticlopride, [F (1, 10) = 8.92, p = 0.014, η^2 = 0.47]. Additionally, when birds were pre-treated with 0.1 g/kg eticlopride, cocaine-treated birds had significantly higher activity levels (M = 18.36, *S.E.M.* = 5.04) than saline-treated birds (M = 1.65, *S.E.M.* = 5.04), [F (1, 12) = 5.51, p = 0.037, η^2 = 0.31]. No other interactions or main effects were significant for mean total activity.

Figure 3.2 depicts the mean distance-traveled activity for each 5 min time bin for saline, 0.01, 0.05, and 0.1 mg/kg eticlopride on the 30 min trial. A repeated measures

ANOVA revealed a significant Treatment x Time interaction, [F (5, 205) = 3.03, p = 0.012, η^2 = 0.07]. A one-way ANOVA indicated that cocaine-treated quail had significantly greater activity than saline-treated quail for each 5 min time bin after 10 min (see figure 3.2.). No other interactions or main effects were found for mean distance-traveled activity across time.

Discussion

In the current study, pretreatment with 0.01 or 0.1 mg/kg eticlopride enhanced the acute psychomotor stimulant effects of cocaine in female Japanese quail. Additionally, results indicated that the locomotor enhancing effects of cocaine occurred after 10 minutes. The current findings oppose those of previous studies investigating the effects of D2 antagonism on acute cocaine locomotor activity in rodents (Mattingly et al., 1994; Neisewander et al., 1995; Schindler & Carmona, 2002; White et al., 1998), and this was not surprising. Japanese quail have been shown to have a greater availability of D2 receptors in striatal regions compared to rodents (Kleitz et al., 2009). In fact, dopamine itself is inhibitory in this species (Absil et al., 1994; Castagna et al., 1997; Cornil et al., 2005; Kleitz-Nelson et al., 2010). Therefore, cocaine-induced DA influx may be more likely to inhibit the firing of DA neurons through a feedback mechanism by the D2 autoreceptor. Studies have shown that when D2 receptors are antagonized, the inhibitory autoreceptor response is reversed (Tanabe et al., 2004; Zhang et al., 2008). The findings of Kleitz-Nelson et al. (2010) suggested that the use of a D2 antagonist would be more likely to block D2 receptors in quail compared to rodents, thus preferentially affecting autoreceptors and increasing dopamine release. The present findings support this view.

Research with rodents indicates that cocaine-induced locomotor activity may be initiated by increased activity of VTA DA neurons and followed by a cascade of time-dependent neuroadaptations (see Stekeetee & Kalivas, 2011 for review). Febo and colleagues (Febo et al., 2003) found that exogenous E2 increased D2 receptor binding in the VTA after a single cocaine injection in female rats. In the current study, female quail were housed under long-light conditions and presumably had high levels of circulating estradiol (Adkins, 1973; Adkins & Adler, 1972; Brain et al., 1988; Delville et al., 1986; Delville & Balthazart, 1987; Doi et al., 1980; Gill et al., 2015; Mills et al., 1997). Since quail have even more D2 receptors available compared to rodents, it may be likely that high levels of E2 further enhance D2 binding in response to cocaine leading to a blunted response in activity. In line with this, results of the present experiment show that female quail pre-treated with saline did not show an enhanced response to cocaine.

The results of the present study extend previous work examining cocaine-induced locomotor activity in female Japanese quail. Gill and colleagues (Gill et al., 2015) found that cocaine did not enhance locomotor activity relative to saline in females housed in long-daylight conditions. The authors of that study suggested that the differences between the psychomotor stimulant effects of cocaine in female quail compared to female rodents may be due to a higher D2:D1 receptor ratio in striatal regions found in the quail brain compared to the rat brain (Kleitz et al., 2009). The present study examined this possibility by blocking the D2 receptor and then administering cocaine to female quail. The results show that eticlopride dose-dependently enhances the psychomotor stimulant properties of acute cocaine. This suggests that D2 receptor activation may have contributed the null findings in photostimulated female quail in the Gill et al. (2015) study.

It should be noted that the 0.05 mg/kg eticlopride dose did not enhance acute cocaine-induced locomotor activity in the current experiment. Several birds were excluded from this group prior to statistical analysis due to high variability which may have contributed to the results. Individual differences in D2 receptor density has been shown to have several behavioral consequences including the vulnerability to drug addiction (Czoty et al., 2010). Individual differences were not considered in the current experiment and may have influenced the present findings.

Seven of the quail in the present study had been used as copulation partners in previous experiments. These females had no more than two sexual encounters with males during these previous experiments. Sexual experience has been shown to cause alterations in the mesolimbic dopamine system that in turn, alters responses to psychostimulant drugs (Frohmader et al., 2010; Pitchers et al., 2010). This potential confound was considered during statistical analyses and none of the sexually-experienced birds had activity levels outside of the mean for their group. Therefore, it is unlikely that previous sexual experience enhanced the effects of cocaine in these females in this study.

In sum, eticlopride dose-dependently enhanced the acute locomotor stimulant effects of cocaine in female Japanese quail. Comparative studies in this manner are critical for our understanding of the mechanisms involved in the induction of cocaine-induced locomotor activity. Further neurobiological studies are needed in Japanese quail to characterize the dopaminergic system in females and to further explore sex differences in the DA system in quail. In light of the D2:D1 ratio species difference, the present study adds to our knowledge of cocaine-dopamine interactions in cocaine-induced locomotor activity and extends previous work in female Japanese quail.

Table 1. Total number of subjects per pre-treatment and treatment group.

1st Injection (home cage)	2nd Injection (test room)
Saline (n = 11)	Saline (n = 6) or (Cocaine n = 5)
0.01 Et (n= 12)	Saline (n = 7) or (Cocaine n = 5)
0.05 Et (n = 12)	Saline (n = 7) or (Cocaine n = 5)
0.1 Et (n = 14)	Saline (n = 7) or (Cocaine n = 7)

Figure 3.1. Total distance traveled activity for saline, 0.01, 0.05, and 0.1 mg/kg eticlopride for saline and cocaine treatment groups. Each bar represents the mean meters traveled ± SEM. * indicates significant difference from the corresponding saline treatment group ($p < 0.05$).

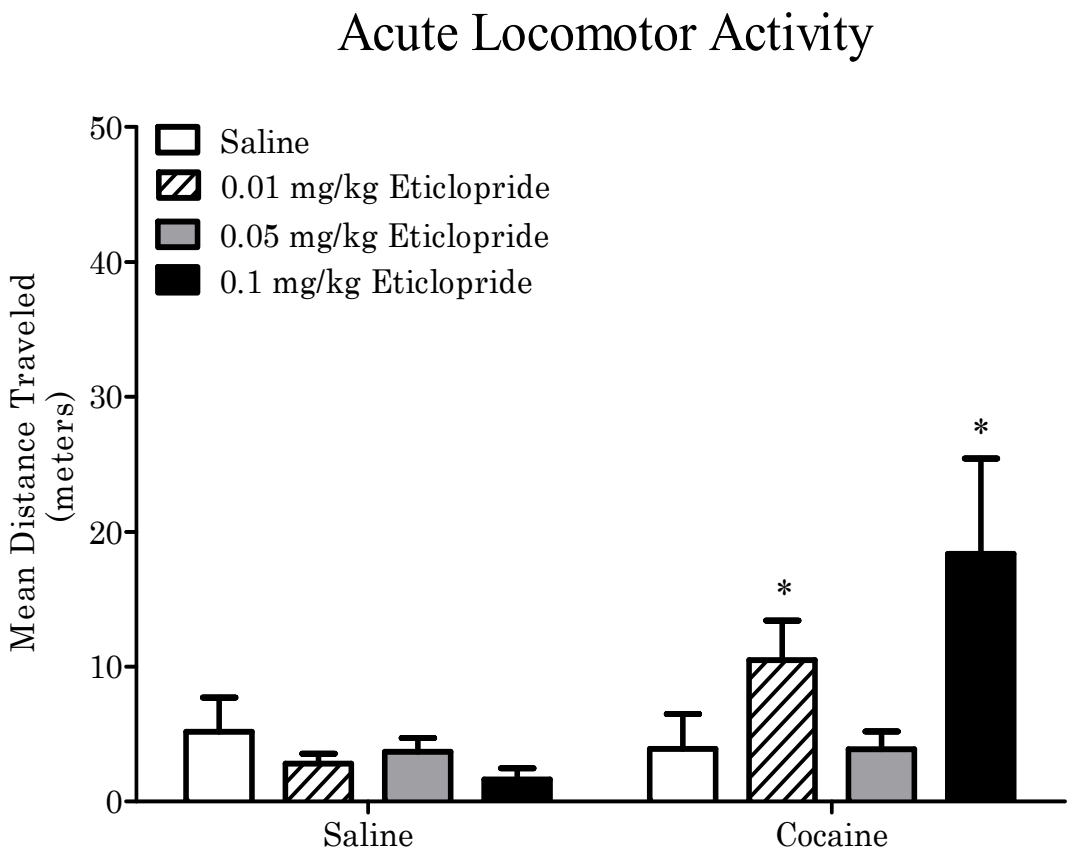
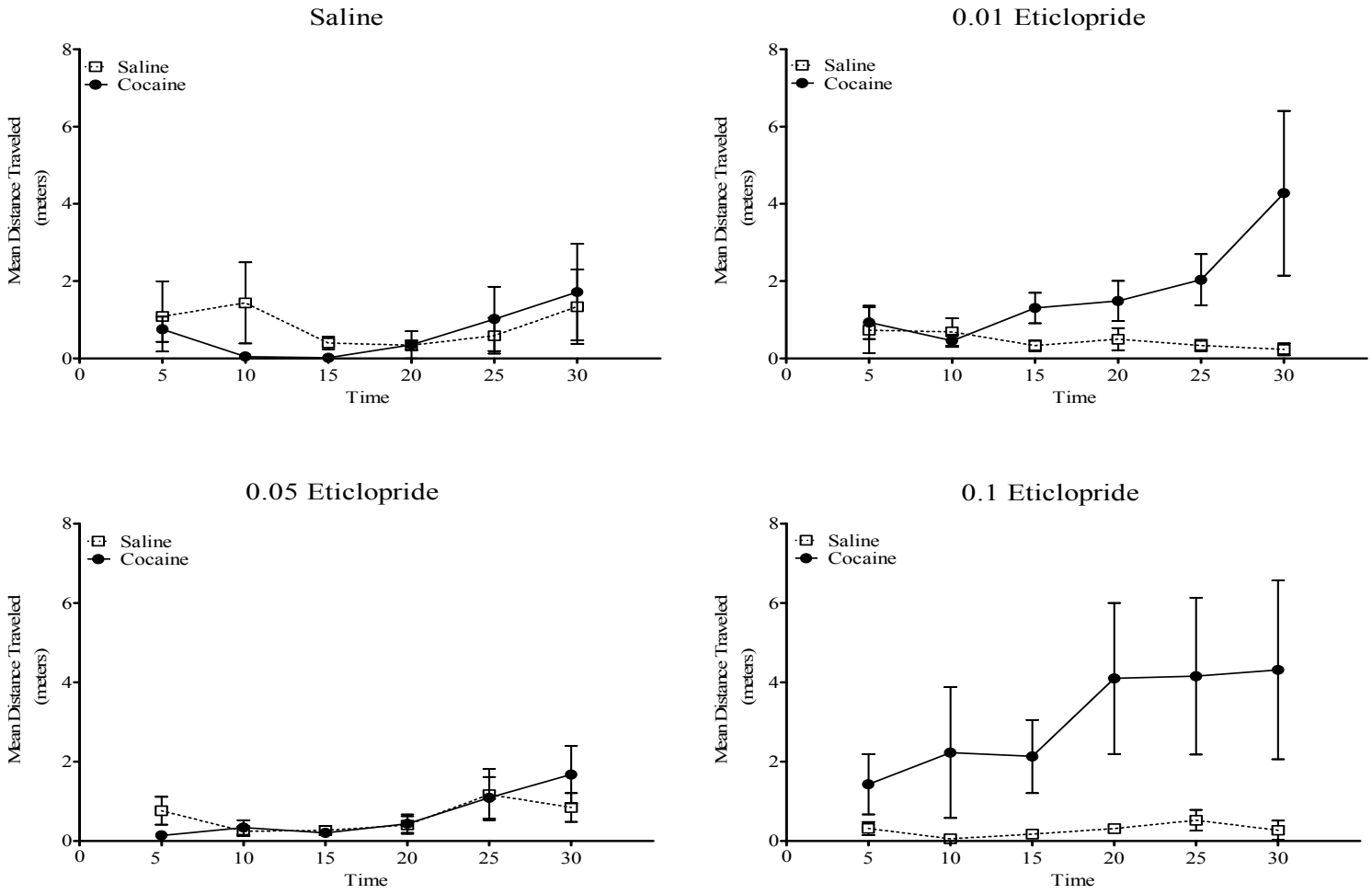


Figure 3.2. Mean distance traveled across 5 min time bins for saline, 0.01, 0.05, and 0.1 mg//kg eticlopride for saline and cocaine treatment groups. Each data point represents the mean meters traveled ± SEM.



CHAPTER 4: EXPERIMENT 3

COCAINE-INDUCED CONDITIONED PLACE PREFERENCE IN FEMALE JAPANESE QUAIL

Introduction

The conditioned place preference (CPP) paradigm is a reliable and widely accepted measure of drug reward (see Tzschentke, 1998; 2007 for reviews). Given that CPP involves repeated pairings of a specific context and a drug sensation, CPP can serve as a model of cue-elicited conditioning (see Bardo & Bevins, 2000 for review). With chronic drug use, drug-taking behavior becomes associated with environmental cues which may, in turn, elicit drug craving and relapse in humans (Hand et al., 1989; Neisewander et al., 1990). For example, Childs and de Wit (2013) found that men and women significantly prefer an environment associated with d-amphetamine compared to an environment associated with placebo. Furthermore, this study revealed that the context of drug administration can greatly influence subjective drug effects in humans upon re-administration (Childs & de Wit, 2013).

The role of gonadal hormones in the rewarding properties of cocaine has been less studied than other behavioral phenomena associated with drug abuse. However, research shows that sex differences in cocaine reward may be similar to sex differences observed in other cocaine-induced behaviors. In humans, cocaine-dependent women report higher levels of craving when presented with drug-related cues compared to cocaine-dependent men (Robbins et al, 1999). In rodents, Russo and colleagues (2003a) demonstrated that cocaine-induced CPP is established in fewer sessions and at lower doses in female rats

compared to male rats (Russo et al., 2003a). In a follow up study, Russo and colleagues (2003b) found that both gonadectomized male and female rats exhibited cocaine-induced CPP, but ovariectomy attenuated CPP in female rats (Russo et al., 2003b). Zakharova and colleagues (Zakharova et al., 2009) found that cocaine-induced CPP is established at lower doses in female rats compared to male rats regardless of age. Collectively, these studies indicate that females may be more sensitive to the rewarding properties of cocaine and ovarian hormones may contribute to these differences.

Rodents tend to be quite visually impaired (Prusky et al., 2002; Szel & Rohlich, 1992). Therefore, researchers use tactile or olfactory cues to establish CPP (see Bardo & Bevins, 2000 for review). Environmental cues that are associated with human drug-taking behavior tend to be visual in nature (Pierce & Kalivas, 1997; Robinson & Berridge, 2003). Japanese quail are equipped with high visual acuity and color vision (Kovach, 1974; Kovach & Wilson, 1975; Mills et al., 1997) which may make them ideal subjects for use in a CPP paradigm. Using a visually oriented species may add to our understanding of cue-elicited drug cravings.

Cocaine reward has been examined in male aves. Levens and Akins (2001) first demonstrated cocaine-induced CPP in Japanese quail using a 10 mg/kg cocaine dose. In a follow up study, Akins and colleagues (Akins et al., 2004) investigated cocaine-induced CPP using 1, 3, 10, or 30 mg/kg cocaine in quail. Results indicated that CPP was established at 1, 3, and 10 mg/kg cocaine but not at 30 mg/kg cocaine (Akins et al., 2004). These results are similar to findings in rodents (see Bardo, Rowlett, & Harris, 1995 for review) and suggest that aves may be a useful comparable model in drug reward.

In Japanese quail, cocaine-induced CPP has been investigated in males (Akins et al., 2004; Levens & Akins, 2001), but not in females. In a previous experiment, Gill and colleagues (Gill et al., 2015) investigated the dose-dependent effects of cocaine on locomotor activity in female quail. Drug reward and locomotor activity are believed to be mediated by different neural mechanisms, and likely represent unique aspects of the motivational properties of addiction (Brown et al., 2010; Carmack et al., 2013; Hall et al., 2004; Robinson & Berridge, 1993; Ramos et al., 2012; Shin et al., 2011). The Gill et al. (2015) study revealed that cocaine did not enhance activity in female quail relative to saline. It is possible that female quail may show a place preference to cocaine, without exhibiting sensitization. Examining the rewarding properties of cocaine in female quail may add to our understanding of sex differences in cocaine-induced behaviors.

The goal of the present research was to investigate the rewarding effects of cocaine in female Japanese quail using a CPP procedure, and to determine whether estradiol plays a role in those effects. The overarching hypothesis was that high levels of estradiol would contribute to the rewarding properties of cocaine. Specifically, it was predicted that photostimulated (long-light, high E2) female quail would dose-dependently develop a preference for cocaine, and photocastrated (short-light, low E2) female quail would not. Additionally, based on previous studies in our lab (Gill et al., 2015), it was predicted that cocaine would not enhance locomotor activity during conditioning trials relative to saline in photostimulated or photocastrated female quail.

Materials and Methods

Subjects

Fifty-five female Japanese quail *(Coturnix japonica),* approximately 5-10 months old served as subjects in the experiment. Eggs were supplied by GQF Manufacturing (Savannah, GA) and quail chicks were hatched and then raised in mixed-sex groups until approximately 25 days of age. At 25 days of age, female quail were group housed in wire mesh cages (GQF Manufacturing, Savannah, GA), and were housed individually when selected for the experiment. Subjects were raised in long-light (16L: 8D) conditions with food and water available *ad libitum*. Approximately 3 weeks (21 days) prior to the start of the experiment, 28 female quail were transferred to a short-light (8L: 16D) condition with lights on at 0900. In previous studies, this procedure resulted in substantially low levels of E2 in female quail (Adkins, 1973; Gill et al., 2015; Henare et al., 2011, Robinson & Follett, 1982). All subjects were drug-naïve prior to experimentation. All experimental procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals Animal care and experimental procedures were approved by the Institutional Animal Use and Care Committee at the University of Kentucky.

Plasma Estradiol ELISA

Blood samples were taken the day after the CPP post-test. Approximately 0.5 ml of blood was taken from the brachial (wing) vein of the quail and placed into heparinized tubes. To minimize corticosteroid release, the time between removal of quail from carrier box and collection did not exceed 5 min (Dallman & Bhatnager, 2001; Mizrahi et al., 2001). Blood was immediately centrifuged at 1500 RPM for 5 min and plasma was stored at -20^{0}C until assayed.

To determine plasma estradiol levels, samples were measured in duplicate via an enzyme-linked immunoassay kit (DRG Diagnostics; estradiol EIA-2693) according to manufacturer's instructions. Where circulating concentrations were below the detection limit of the assay, values at the lowest standard were assigned for statistical analysis (7.8 pg/ml for pre-test, 10 pg/ml for post-test). The intra-assay coefficient of variance (CV) for the E2 ELISA was 2.1%. Results were determined using a four parameter logistic standard curve analysis within Sigma Plot version 13.1 (Systat Software, Inc., San Jose, CA).

Drugs

Cocaine hydrochloride was dissolved in physiological saline (0.9%) and injected ip at a volume of 1-ml/kg of body mass. Doses of 10, 20, and 30 mg/kg were chosen based on previous research that demonstrated dose-dependent cocaine-induced conditioned place preference in male Japanese quail (e.g. Levens & Akins, 2001; Akins et al., 2004). Physiological saline (0.9%) was used as a vehicle and was injected ip at a volume of 0.1 ml.

Apparatus

Eight, three compartment CPP chambers measuring approximately 68 cm long × 21 cm wide × 21 cm deep (ENV-013; Med Associates Inc., St. Albans, VT) were used. The two outermost chambers (28.6 cm long × 21.2 cm wide × 21.2 cm deep) had green or yellow walls and transparent plastic ceilings with wire-mesh floors. Green and yellow walls were chosen because Japanese quail have been shown to prefer colors in the middle range and short end of the color spectrum (Kovach, 1974; Kovach & Wilson, 1975), and were used to enhance the visual salience of each chamber. Furthermore, CPP has been

demonstrated in male Japanese quail using these colors (Akins et al., 2004; Bolin et al., 2012; Levens & Akins, 2001). Each outer chamber of the apparatus was equipped with six photobeams approximately 6.4 cm apart and 3.2 cm from the floor. The smaller central chamber (10.8 cm long × 21.2 cm wide × 21.2 cm deep) had gray walls and three photobeams also approximately 6.4 cm apart and 3.2 cm from the floor. White noise was used throughout each phase of the experiment to attenuate extraneous noise.

Procedure

Quail were randomly assigned to either 30 mg/kg cocaine (n = 14), 20 mg/kg cocaine (n = 13), 10 mg/kg cocaine (n = 14), or saline groups (n = 14). A biased design was chosen for this experiment similar to previous research in rodents (Nomikos and Spyraki, 1988b), and male quail (Akins et al., 2004; Levens & Akins, 2001). Quail were assigned to the same boxes for each trial.

Habituation. During habituation, the CPP boxes were partitioned with the opaque dividers, and each bird was confined to one end chamber for 30 min. On the following day, subjects were placed in the other end chamber for 30 min. Subjects received two 30 min habituation sessions in each end chamber, one per day for 4 days (i.e. Levens & Akins, 2001).

Pre-test. The day after habituation, a place preference pre-test was conducted to determine the subjects' initial preference. During the pre-test, subjects were allowed free access to the entire CPP apparatus for 15 min and time spent in each chamber was measured. Initial place preference was operationally defined as spending more time in one chamber (e.g., green) of the CPP apparatus compared to the other (e.g., yellow). Preference was analyzed prior to assigning subjects to a treatment group to ensure that

bias was equal across groups. If a bird did not show a distinct preference, it was randomly assigned to a chamber.

Conditioning. During conditioning, quail were injected (ip) with saline, 10, 20, or 30 mg/kg cocaine and then restricted to one of the outer green or yellow chambers of the CPP apparatus. The least preferred chamber (as determined by the pre-test) was designated as the drug-paired chamber. On alternate days, quail were given an injection of saline and placed into the opposite chamber. Conditioning sessions were carried out for 8 days, once per day for 30 min, for a total of 4 cocaine and 4 saline conditioning sessions. Locomotor activity was also recorded during conditioning sessions. The total frequency of photobeam breaks was used as an index of locomotor activity.

Post-test. Following the conditioning phase, quail were given a place preference post-test. Subjects were allowed free-access in a drug-free state to the entire CPP apparatus for 15 min and time spent in each chamber was recorded.

Statistical Analysis

Place preference data were analyzed using a repeated measures analysis of variance (ANOVA) with treatment and photoperiod as between subjects factors and time spent in the least preferred (drug-paired) chamber between test (pre and post) as the repeated measure. Following a significant interaction, independent ANOVAs were conducted. A two-way repeated measures ANOVA was used to analyze locomotor activity with treatment and photoperiod as between-subjects factors and trials (drug days or saline days) as a repeated measure. Independent ANOVAs were conducted to probe any significant interactions. To analyze hormone data, a univariate ANOVA was

conducted on each treatment group with photoperiod as an independent variable and E2 level as the dependent variable.

All data were analyzed using SPSS software version 22 (International Business Machines Corp. (IBM), Armonk, NY). A Grubb's test was used prior to analyses which removed one outlier. One short-light cycle bird was removed from the analysis due to continuous egg production throughout the experiment (an indicator that she did not respond to the short-light conditions, see Mills et al., 1997 for review). Additionally, two birds were excluded from final analyses because they did not sample both colored chambers on either pre or post-test. Effect sizes were estimated by calculating eta squared (η^2) using the formulas, η^2 = SSbetween/SStotal for between-subjects effects and η^2 = SSinteraction/SStotal for within-subjects effects. The sample size for the current experiment was 55 subjects. Post-hoc power analyses using G*Power software version 3.0.10 (Buchner, Erdfelder, Faul, & Lang, 2008) indicated that the total sample size of 55 subjects was sufficient to detect a large effect (d = 0.53) with 99% power (1-β) for a repeated measures ANOVA within-between interaction. For all analyses, the statistical significance level was set at $p < 0.05$.

Results

Conditioned Place Preference

Figure 4.1 shows the time spent in the least preferred (drug-paired) chamber during the pre-test and post-test for short-light and long-light cycle birds comparing treatment groups. A repeated-measures ANOVA revealed a significant Treatment x Photoperiod x Test interaction, [F (3, 47) = 4.40, p = 0.008, η^2 = 0.22]. Further analyses were then conducted for each photoperiod.

For short-light cycle quail there was not a significant Treatment x Test interaction, [F (3, 23) = 1.20, p = 0.33, η^2 = 0.14]. Therefore, no further analyses were conducted for short-light cycle birds.

For long-light cycle quail, a significant Treatment x Test interaction was revealed, [F (3, 24) = 4.67, p = 0.01, η^2 = 0.37]. Independent ANOVAs were then conducted for each treatment. Results indicated that females that received 10 mg/kg cocaine, [F (1, 7) = 14.92, p = 0.006, η^2 = 0.68], and 20 mg/kg cocaine, [F (1, 5) = 10.29, p = 0.024, η^2 = 0.67], shifted their preference for the cocaine-paired chamber. Females that received 30 mg/kg cocaine group, [F (1, 6) = 0.70, p = 0.34, η^2 = 0.10], or saline, [F (1, 6) = 1.95, p = 0.21, η^2 = 0.25], did not shift their preference for the cocaine-paired chamber.

As shown in figure 4.2, long-light cycle quail that received saline, [F (1, 12) = 11.07, p = 0.006, η^2 = 0.48], 10 mg/kg cocaine, [F (1, 12) = 5.36, p = 0.039, η^2 = 0.31], or 20 mg/kg cocaine, [F (1, 11) = 13.38, p = 0.004, η^2 = 0.55] had significantly greater E2 concentrations than short-light cycle quail. Long-light cycle quail that received 30 mg/kg cocaine did not, [F (1, 12) = 1.09, p = 0.32, η^2 = 0.08].

Locomotor Activity

Figure 4.3 represents the frequency of photobeam breaks for long-light and short-light cycle female quail treated with saline, 10, 20, and 30 mg/kg cocaine on drug days (panels A & B) and saline days (panels C & D). A repeated measures ANOVA did not find any significant interactions or main effects for locomotor activity data.

Discussion

The present study investigated the rewarding effects of cocaine in female Japanese quail. The results indicated that female quail housed in long-light conditions

developed a CPP to 10 and 20 mg/kg cocaine. Female quail housed in short-light conditions did not develop CPP to cocaine at any dose tested. Additionally, long-light cycle females had substantially higher levels of estradiol compared to short-light cycle females in the saline, 10, and 20 mg/kg cocaine groups. Female quail administered 30 mg/kg cocaine did not shift their preference, nor did the E2 concentration differ between short and long-light cycles for this group. Similar to Gill and colleagues (Gill et al., 2015), there was no evidence of cocaine-induced locomotor activity relative to saline in the current study.

The results of the present study extend previous work examining cocaine reward in Japanese quail. Levens and Akins (2001) established CPP in male Japanese quail with 10 mg/kg cocaine after 6 drug pairings, and Akins and colleagues (Akins et al., 2004) observed CPP in male quail at 1, 3, and 10 mg/kg cocaine after 4 drug pairings. Akins et al., (2004) utilized male quail that were housed in long-light conditions and those birds did not demonstrate CPP at a cocaine dose of 30 mg/kg, similar to the results of the present study. To our knowledge, the current study is the first to investigate cocaine reward in female aves. The results of the current study suggest that cocaine reward is similar in female quail compared to male quail.

The present study may also extend previous work with female rodents. Russo and colleagues (2003a) found that female rats acquired CPP to 5 and 10 mg/kg cocaine, but not 20 mg/kg cocaine. Additionally, female rats developed CPP after 4 drug pairings, but male rats required 8 drug pairings to develop CPP (Russo et al., 2003a). The researchers concluded that female rats were more sensitive to the rewarding aspects of cocaine compared to male rats. However, since gonadectomy was not used in the study, it was

unclear whether estradiol contributed to that sensitivity (Russo et al., 2003a). In a follow up study, Russo and colleagues (Russo et al., 2003b) found that ovariectomy attenuated cocaine-induced CPP in female rats compared to intact female rats. However, it should be noted that ovariectomized females still shifted their preference to the cocaine-paired chamber in that study (Russo et al., 2003b). The present study used photocastration to investigate the role of estradiol in cocaine reward in female quail. Results suggest that female quail with low levels of estradiol do not shift their preference to a cocaine-paired chamber. Additionally, the results of the present study indicate that high levels of estradiol contribute to cocaine reward in female quail. Taken together, cocaine reward in female quail may, in part, be similar to female rodents, but female quail may develop CPP to higher doses of cocaine then female rodents.

In the current study, estradiol may have mediated the rewarding effect of cocaine in female Japanese quail. Previous research has shown that female quail exposed to 8 hours of light a day or less have significant decreases in plasma concentrations of estradiol compared to age-matched females exposed to 14 or more hours of light a day (Adkins & Adler, 1972; Brain et al., 1988; Delville et al., 1986; Delville & Balthazart, 1987; Doi et al., 1980; Noble, 1972). In the present study, long-light cycle female quail that received 10 or 20 mg/kg cocaine shifted their preference for the cocaine-paired chamber, but short-light cycle female quail that received 10 or 20 mg/kg cocaine did not. Estradiol levels were significantly greater in the groups that demonstrated cocaine-induced CPP compared to the groups that did not. These results suggest that estradiol may contribute to the rewarding effects of cocaine.

Neither long-light nor short-light quail that received 30 mg/kg cocaine showed a shift in preference for the cocaine paired chamber in the current experiment. Interestingly, estradiol levels did not differ between long and short-light cycles in the 30 mg/kg cocaine group. In one study, Mello and colleagues (Mello et al., 2004) found that cocaine rapidly increased estradiol in rhesus monkeys with low baseline E2 levels. This rapid increase was not as pronounced in rhesus monkeys with high baseline levels of estradiol (Mello et al., 2004). While it is difficult to compare a study in rhesus monkeys to the present study, the results from the Mello et al., 2004 study elude to the possibility that 30 mg/kg cocaine may have been sufficiently high to increase E2 levels in short-light cycle birds in the current study. Another possibility is that the HPA axis may have played a role. Cocaine has been shown to activate the HPA axis (Baumann et al., 1995; Mendelson et al., 1992; Moldow & Fischman, 1987), and it may be possible that cocaine may increase the natural level of estradiol produced by the adrenal glands (O'Malley & Strott, 1999; Mello et al., 2002). Furthermore, CORT release is seasonally modulated in aves with maximal levels occurring during short-light periods (Peczely & Pethes, 1981). Taken together, the relatively high dose of cocaine used in the present study may have increased levels of circulating estradiol in short-light cycle female quail. This account may explain why plasma E2 did not significantly differ between long-light and short-light cycle birds in the 30 mg/kg cocaine treatment group in the current experiment.

It has been previously shown that exogenous progesterone inhibits cocaine-induced CPP in OVX female rats (Russo et al., 2003b). However, Russo and colleagues (Russo et al., 2003b) found that co-administration of estrogen and progesterone in OVX female rats increased preference to a cocaine-paired chamber compared to OVX female

rats administered estrogen only. While the current study focused on the change in plasma concentrations of estradiol, female quail housed in long-light cycles also have significantly high levels of progesterone compared to female quail housed in short-light cycles (Brain et al., 1988). It is possible that high levels of progesterone in combination with high levels of estradiol in long-light cycle female quail may have contributed to the current findings.

In the CPP paradigm, drug-treatment represents an unconditioned stimulus (US) that is repeatedly paired with a neutral environment that, through classical conditioning, may acquire the motivational properties of the drug (see Tzschentke, 1998 for review). Studies have shown that gonadal hormones affect learning and memory processes that underlie Pavlovian associations between cocaine and environmental cues in the CPP task (Farr et al., 1995; Gibbs, 2000; Johansson et al., 2002; Luine, 1997). Co-administration of estrogen and progesterone has been shown to enhance the acquisition of a spatial memory task in OVX rats (Gibbs, 2000). Furthermore, estradiol has been shown to enhance performance on working memory tasks in OVX rats (Luine et al., 1998). It is likely that high levels of estradiol and/or progesterone in long-light cycle female Japanese quail may have facilitated learning about cocaine-induced reward in the current experiment. To date, the effect that estradiol may have on learning and memory has not been investigated in female Japanese quail.

In sum, we have demonstrated dose-dependent cocaine-induced CPP in photostimulated female Japanese quail. The results of the present experiment suggest that high levels of E2 contribute to the rewarding properties of cocaine, and that reward-related mechanisms may be conserved between female birds and mammals. Further

investigation in the dopamine system of the female quail may provide further evidence of a similar neural mechanism underlying drug reward between species.

Figure 4.1.Time spent in the least preferred (drug-paired) context during the pre-test and post-test that received saline or cocaine for short-light and long-light cycles. * indicates significant difference from pre-test ($p < .05$).

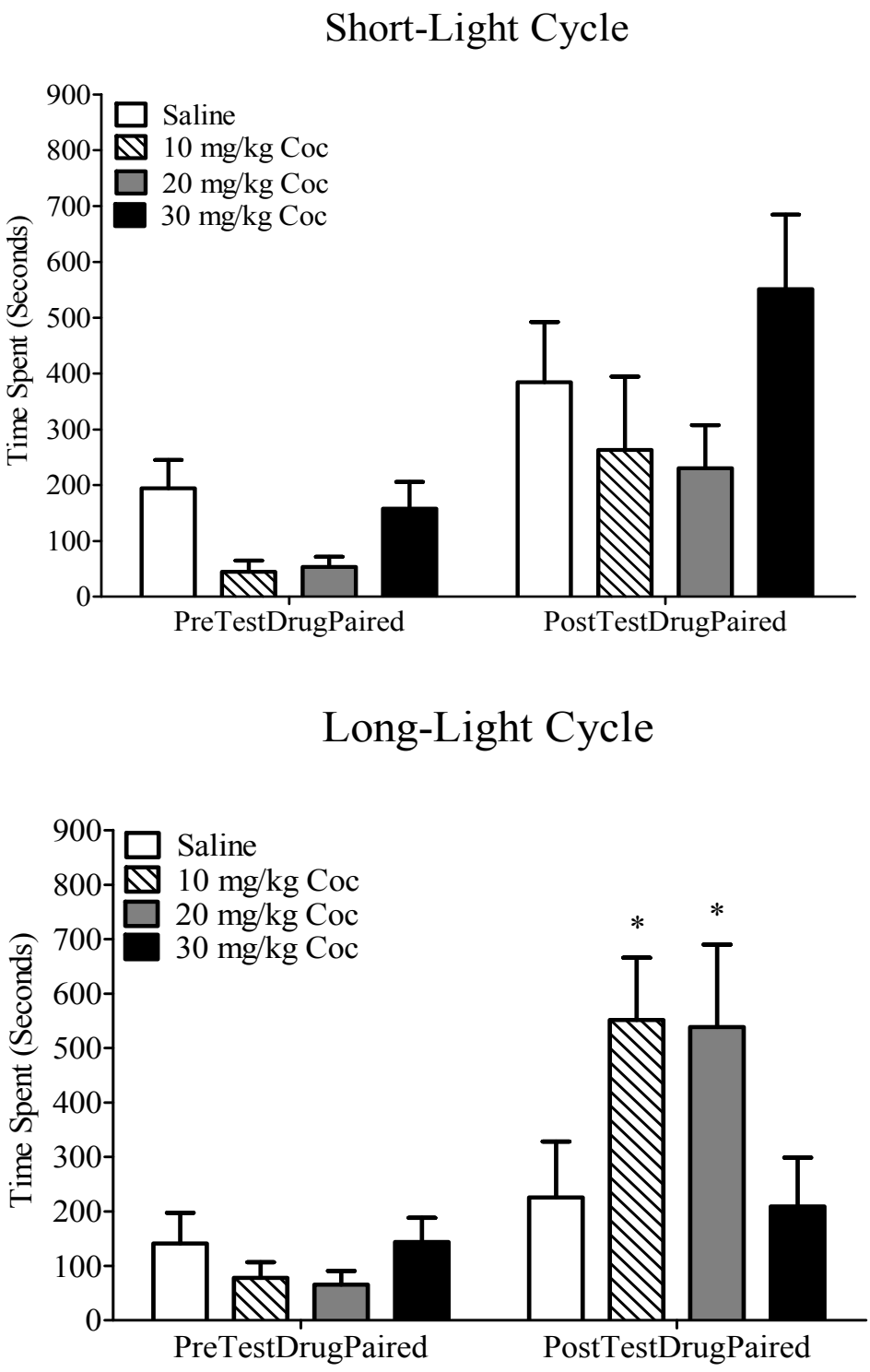


Figure 4.2. Serum levels of estradiol as mean pg/ml ± SEM. * indicates significant difference from short-light cycle ($p < 0.05$).

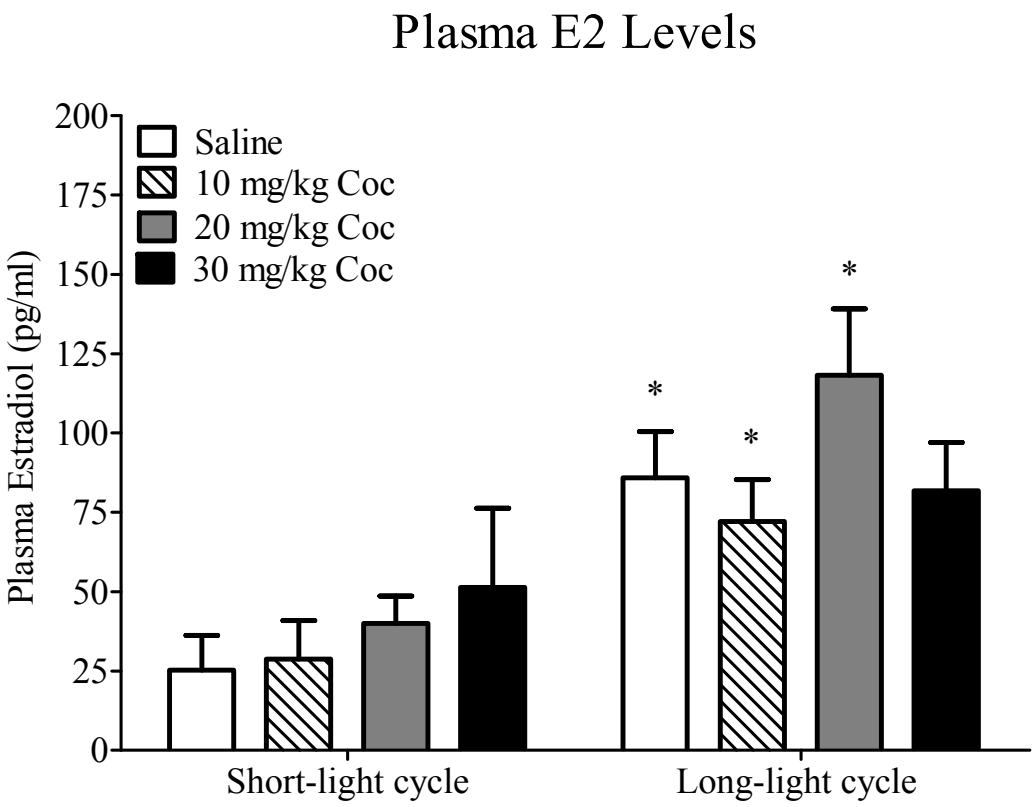
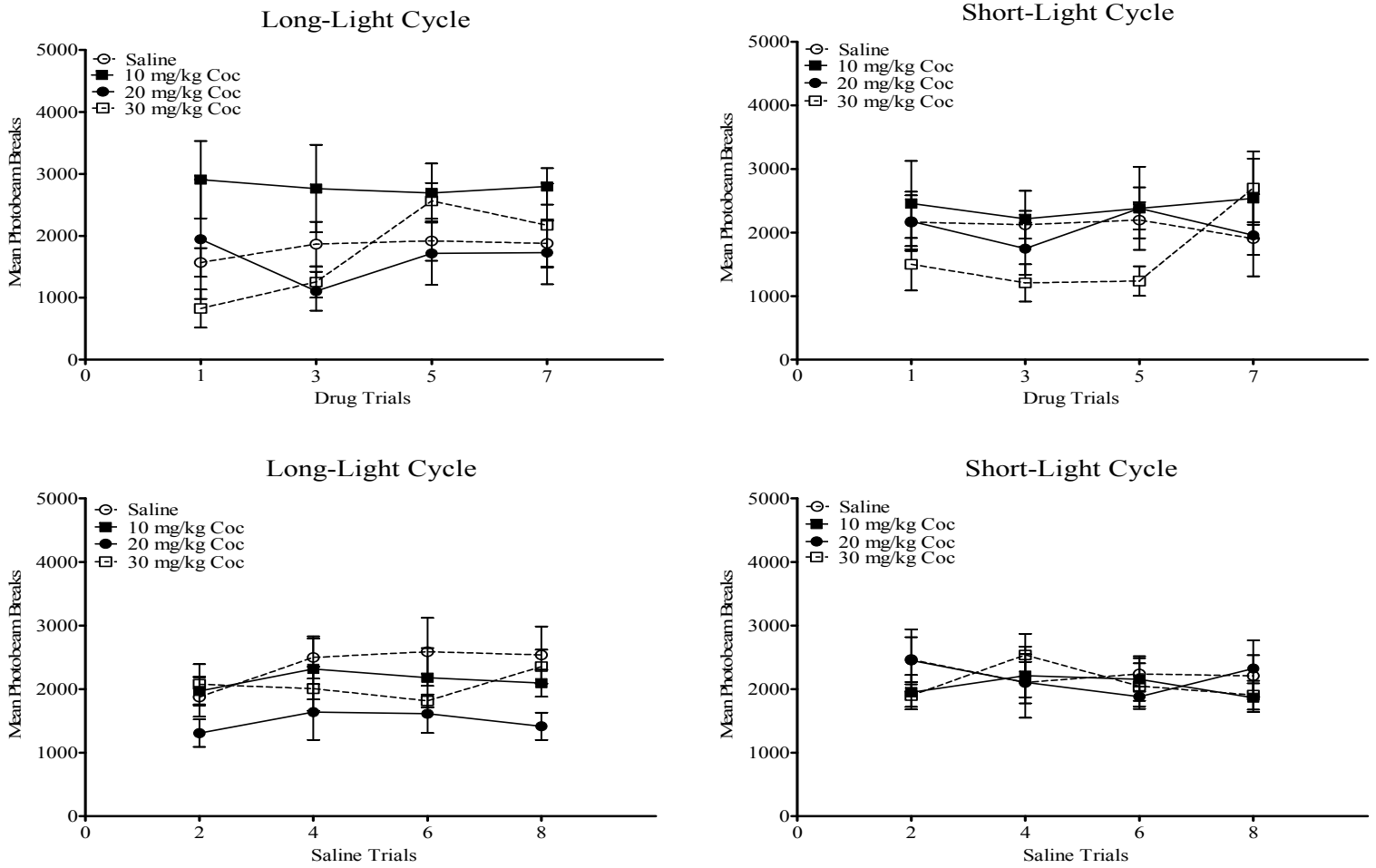


Figure 4.3. Frequency of photobeam breaks for long-light and short-light cycle female quail treated with saline, 10, 20, and 30 mg/kg cocaine on drug days (panels A & B) and saline days (panels C & D). Each data point represents the mean photobeam break activity for that trial ± SEM.



CHAPTER 5

GENERAL DISCUSSION

The overall goal of the present work was to expand our knowledge of cocaine-hormone-dopamine interactions in cocaine-induced locomotor activity and reward using a visually-oriented species, the Japanese quail. Long-light cycle male quail treated with 10 mg/kg cocaine demonstrated behavioral sensitization which was correlated with levels of circulating testosterone. Short-light cycle female quail treated with 10 mg/kg cocaine demonstrated behavioral sensitization, but cocaine-induced activity did not correlate with circulating plasma levels of estradiol. The D2 antagonist eticlopride enhanced the acute locomotor stimulant effects of cocaine in female Japanese quail, suggesting that dopaminergic mechanisms may have contributed to the lack of cocaine-induced locomotor activity in female quail. Additionally, long-light cycle female quail dose-dependently shifted their preference for a cocaine-paired chamber, and high levels of E2 may have contributed to the rewarding properties of cocaine in female quail. These findings suggest the following: 1) testosterone may contribute to cocaine-induced locomotor activity in male Japanese quail 2) dopaminergic mechanisms may be partially responsible for the absence of cocaine-induced locomotor activity in female quail and 3) cocaine may be dose-dependently rewarding in photostimulated female quail.

The current body of literature is flooded with studies using rodent models to explain the interaction between hormones, drug effects, and underlying neurobiology. In Japanese quail, circulating plasma sex hormones and reproductive behaviors are tightly controlled by photoperiod (see Mills et al, 1997 for review). For male quail, the neural

sites of action for testosterone have been well characterized (see Ball & Balthazart, 2010 for review). Furthermore, male-typical behavior is readily expressed in laboratory conditions and is highly sensitive to steroid hormones (Ball & Balthazart, 2010). In Experiment 1 testosterone levels correlated with cocaine-induced activity in male Japanese quail which are in agreement with some rodent studies (Martinez-Sanchis et al., 2002; Menendez-Delmestre & Segarra, 2011). Despite this, other rodent studies that have examined the role of testosterone in the behavioral effects of cocaine have failed to find a difference between castrated (CAST) and intact male rats (Becker et al., 2001; Forgie & Stewart, 1994; Hu & Becker, 2003; Hu et al., 2004; Robinson et al., 1981; van Haaren & Meyer, 1991). The findings of Experiment 1 suggest that testosterone may play an important role in cocaine-induced locomotor activity and sensitization in male quail which indicates that quail may be an ideal model to investigate the role of testosterone in cocaine-induced behaviors.

Female-specific behavior and circulating plasma estradiol are also tightly controlled by photoperiod (see Mills et al., 1997 for review). In contrast to rodent studies (see Becker & Hu, 2008), the current results indicated that levels of estradiol do not correlate with cocaine-induced locomotor activity, nor does cocaine enhance locomotor activity relative to saline in female quail. These results were initially surprising, but may be explained through species-specific neurobiological mechanisms. Firstly, estradiol has been shown to stimulate D2 receptor activity in female rats (Fink et al., 1996; Morissette et al., 2008). Considering the known D2:D1 ratio disparity found in quail compared to rodents, high levels of estradiol in photostimulated female quail may have further enhanced D2 binding leading to an attenuated response in activity. Secondly, baseline

activity levels do not differ by sex in rodents (Hu & Becker, 2003), but female quail have significantly lower baseline activity compared to male quail. Therefore, estradiol may ethologically suppress activity levels in female quail (Mills et al., 1997). To support these claims, short-light cycle female quail demonstrated sensitization to chronic cocaine exposure (10 mg/kg) in Experiment 1, and eticlopride dose-dependently increased acute cocaine-induced locomotor activity in long-light cycle female quail in Experiment 2. The present collection of studies is the first to examine cocaine-induced activity in female aves, and adds to our knowledge of cocaine-estradiol-dopamine interactions.

Cocaine-induced locomotor activity and reward are believed to be mediated by different neural mechanisms, and likely represent unique aspects of the motivational properties of addiction (Robinson & Berridge, 1993; Hall et al., 2004; Shin et al., 2011; Brown et al., 2010; Ramos et al., 2012; Carmack et al., 2013). In general, the mesolimbic pathway is associated with modulating the reinforcing effects of a drug whereas the nigrostriatal pathway is associated with regulating motor output (Iverson et al., 2009). Additionally, dopaminergic mechanisms are implicated in cocaine-induced locomotor activity and CPP, but CPP also appears to be heavily mediated by 5-HT (see Bardo, 1998; Filip et al., 2010; Hayes & Greenshaw, 2011 for reviews). The collective results indicated that photostimulated female quail do not show enhanced cocaine-induced locomotor activity compared to saline, but photostimulated female quail dose-dependently shifted their preference to a cocaine-paired chamber. Due to these different neural mechanisms underlying cocaine's psychomotor and rewarding effects, these results were not unexpected.

The role of serotonin in cocaine-induced CPP and the interaction between the dopaminergic and serotonergic systems might explain the results of the current experiments. Although comparisons between the rodent and avian serotonergic system remain speculative (see Cozzi et al, 1991 for review), studies in rodents may help elucidate potential mechanisms underlying these cocaine-induced effects in female Japanese quail. Female rats have higher basal and cocaine-induced serotonin levels in the NAc and striatum compared to male rats (Carlsson & Carlsson, 1988; Festa et al., 2004; McQueen et al., 1999). Furthermore, estradiol has been shown to increase SERT binding sites (McQueen et al., 1999) and 5-HT_{2C} receptor mRNA (Zhou et al., 2002) in the female rat brain. In Japanese quail, a recent study demonstrated that photoperiodic changes altered serotonergic activity in the brain (Yadav & Chaturvedi, 2014). Maintaining female quail in long or short-daylight conditions may have resulted in neurochemical alterations in the serotonergic system, thus altering the effects of cocaine which may have contributed to the current findings.

5-HT_{2C} receptors are highly expressed in the striatum (Clemett et al., 2000) where they are involved in modulating dopamine activity (Berg et al., 2008). In fact, 5-HT_{2C} agonists have been shown to inhibit DA transmission in the reward pathway (Navailles et al., 2008; Di Matteo et al., 2000), and attenuate cocaine-induced locomotor activity and CPP (Craige & Unterwald, 2013; Filip et al., 2012). A recent study by Besson and colleagues (Besson et al., 2013) reported that repeated cocaine administration decreased D2 receptors and 5-HT_{2C} receptors in the striatum. These studies indicate that these receptors may be jointly implicated in modulating the effects of cocaine. Behavior studies with serotonergic drugs suggest that the serotonin system in quail may be comparable to

rodents (Cedraz-Mercez et al., 2003; Polo et al., 2007). Future studies examining the behavioral effects of 5-HT_{2C} agonists or antagonists on cocaine-induced behaviors in Japanese quail may add to our knowledge of the role of serotonin in cocaine-induced behaviors.

In rodents, cocaine has been shown to indirectly increase extracellular glutamate levels in the VTA, NAc, and striatum via DA mechanisms (Kalivas & Duffy 1995; Smith et al., 1995; Reid & Berger 1996; Reid et al., 1997). Adrover and colleagues (Adrover et al., 2014) recently demonstrated that glutamate release is differentially modulated in response to acute and repeated cocaine administration by D2 autoreceptors in midbrain regions. While speculative, the increase in D2 receptor density in Japanese quail compared to rodents may have altered glutamatergic signaling and influenced the results of the present experiments.

Glutamate also plays a major role in long-term potentiation (LTP) involved in learning mechanisms (Carlson, 2010). Therefore, glutamatergic activity may be critical for Pavlovian associations between cocaine and environmental cues (Harris & Aston-Jones, 2003). In fact, a single administration of cocaine has been shown to induce LTP on DA neurons within the VTA (Ungless et al., 2001). Additionally, glutamate has been shown to be critical for the actions of estradiol in enhancing cocaine-induced behaviors in female rats (Martinez et al., 2014). Taken together, cocaine may have enhanced the salience of the drug-paired chamber through glutamate mechanisms and, in combination with estradiol, contributed to cocaine's rewarding effects in female Japanese quail.

The current studies further implicate D2 receptor mediation in cocaine-induced behaviors. Studies have shown that individual differences in D2 receptor availability in

humans play a role in the potential genetic predisposition to drug abuse (Volkow et al., 1999). Specifically, high levels of D2 receptors have been shown to be protective against drug abuse and addiction in humans (Volkow et al., 2006). Japanese quail may be a useful model to investigate whether high levels of D2 receptor availability are protective against drug addiction. Furthermore, information on avian neurobiology in combination with the visual ability of the Japanese quail may inform furture studies regarding the interaction between genetic and environmental factors involved in drug dependence.

In addition, the present experiments add to the body of literature on avian research. These experiments demonstrate the importance of considering the D2:D1 ratio distribution in behavioral studies with Japanese quail and other avian species. Additionally, these studies give a better understanding of female quail behavior, particularly in relation to circulating levels of estradiol that may help inform future studies.

Collectively, these studies add to the body of literature through the addition of a non-rodent species, the Japanese quail. This model may be advantageous in that hormones can be controlled through non-surgical methods via alterations in photoperiod and through the ability to apply visual cues in studies investigating drug-induced behavior. The results from the present experiments extend current research investigating potential cocaine-hormone interactions and the role that dopamine may have in those interactions. Further research examining the cocaine-hormone interaction in Japanese quail may lead to a better understanding of the underlying neurobiological mechanisms mediating sex differences in drug abuse.

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KARIN ELIZABETH GILL

Place of Birth: Winston-Salem, North Carolina

EDUCATION

Ph.D., University of Kentucky (Expected May 2015)
* Experimental Psychology: Behavioral Neuroscience & Psychopharmacology
* Graduate Certificate in College Teaching & Learning (May 2014)

M.S., University of Kentucky (Dec. 2011)
* Experimental Psychology: Behavioral Neuroscience & Psychopharmacology

B.S., University of North Carolina at Charlotte (May 2005)
* Psychology
* Minors in Biology and Sociology
* Awarded best research idea for research project titled, *Gender Differences and Acceptable Behavior in Romantic Relationships among College Students*, (Research Methods, Spring 2004)

TEACHING EXPERIENCE

Aug 2010 – Dec 2010 PSY215: Experimental Psych. Teaching Assistant
* *Quality of Teaching Score = 3.8/4.0*

Aug 2012 – Dec 2012 PSY456: Behavioral Neuroscience Teaching Assistant
* *Quality of Teaching Score = 3.8/4.0*

May 2013 – Jun 2013 PSY312: Brain & Behavior **Instructor (UK)**
* *Quality of Teaching Score = 3.8/4.0*

Aug 2013 – Dec 2013 PSY100: Introductory Psych. Teaching Assistant
* *Quality of Teaching Score = 3.7/4.0*

Jan 2014 – May 2014 PSY215: Experimental Psych. Teaching Assistant
* *Quality of Teaching Score = 3.7/4.0*

Aug 2014 – Dec 2014 PSY200: Introductory Psych. **Instructor (EKU)**
* *Quality of Teaching Score = 4.6/5.0*

Aug 2014 – Dec 2014	PSY100: Introductory Psych.	Teaching Assistant

**Quality of Teaching Score = 3.7/4.0*

Jan 2014 – May 2015	PSY311: Learning & Cognition	**Instructor (UK)**

GUEST LECTURES

Feb. 18th & 20th 2014	PSY311: Physiological Psych.	Eastern Kentucky U.

** Topics Covered: Sensation & Perception: Vision, Audition, & Mechanical Senses*

Apr. 11th	PSY312: Brain & Behavior	U. of Kentucky

** Topic Covered: Lateralization & Split Brain*

RESEARCH INTERESTS

My research interests primarily concern the investigation of sex hormones and their role in drug abuse and dependence. I am especially interested in how sex hormones affect brain mechanisms when exposed to psychostimulants in female Japanese quail (*Coturnix japonica).*

RESEARCH EXPERIENCE

Aug 2009 – Present	Graduate Research Assistant	Dr. C.K. Akins
Jan 2013 – May 2013	Research Challenge Trust Fellowship (RCFT)	

PUBLICATIONS

Gill, K.E., Madison, F.N., & Akins, C.K. (2015). Cocaine-induced sensitization correlates with testosterone in male Japanese quail but not with estradiol in female Japanese quail. *Hormones & Behavior*, 67, 21-27. doi:10.1016/j.yhbeh.2014.11.006

Gill, K.E., Rice, B.A., & Akins, C.K. (2015). Cocaine induces state-dependent learning of sexual conditioning in male Japanese quail. *Physiology & Behavior,* 138, 150-153. doi:10.1016/j.physbeh.2014.10.020

Bolin, B.L., Cornett, H.L., Barnes, A.F., **Gill, K.E.**, & Akins, C.K. (2012). Nicotine Induces a Conditioned Place Preference in Male Japanese Quail (*Coturnix japonica*). *Physiology & Behavior*, 107 (3), 364-367. doi: 10.1016/j.physbeh.2012.08.005

Akins, C.K., Bolin, B.L., **Gill, K.E.**, Reinhardt, E.K. (In Preparation). *Cocaine pre-exposure enhances sexual conditioning and increases resistance to extinction in male Japanese quail (Coturnix japonica).*

Gill, K.E., Reynolds, A.R., Prendergast, M.A., & Akins, C.K. (In Preparation). *Cocaine-induced conditioned place preference in female Japanese quail (Coturnix japonica).*

Gill, K.E., Edmiston, E.A., & Akins, C.K. (In Preparation). *Dopamine D2 receptor antagonism enhances locomotor activity in acute cocaine-treated female Japanese quail.*

POSTERS & PRESENTATIONS

Gill, K.E., Bolin, B.L., & Akins, C.K. (March 2011). *Sex Differences in Behavioral Sensitization to Cocaine in Japanese quail.* Poster presented at the annual Bluegrass Society for Neuroscience Spring Neuroscience Day, Lexington, KY.

Gill, K.E., Bolin, B.L., & Akins, C.K. (November 2011). *Sex Differences in Behavioral Sensitization to Cocaine in Japanese quail.* Poster presented at the Society for Neuroscience annual meeting, Washington, D.C.

Gill, K.E., Bolin, B.L., & Akins, C.K. (August 2012). *Sex Differences in Behavioral Sensitization to Cocaine in Japanese quail.* Poster presented at the American Psychological Association annual convention, Orlando, FL.

Gill, K.E. and Akins, C.K. (April 2013). *Sex Differences in the Locomotor-Enhancing Effects of Cocaine in Japanese quail.* Poster presented at the annual Bluegrass Society for Neuroscience Spring Neuroscience Day, Lexington, KY.

Gill, K.E. and Akins, C.K. (May 2013). *Sex Differences in Behavioral Sensitization to Cocaine in Japanese quail.* Poster presented at the Midwestern Psychological Association annual convention, Chicago, IL.

Gill, K.E. and Akins, C.K. (June 2013). *Effects of Photocastration in Cocaine Sensitization between Male and Female Japanese Quail (Coturnix japonica).* Poster presented at the annual Society for Behavioral Neuroendocrinology convention, Atlanta, GA.

Edmiston, E., **Gill, K.E.**, & Akins, C.K. (April 2014). *Sex Differences in Cocaine-Induced Sensitization in Japanese Quail.* Poster presented at the National Conference on Undergraduate Research convention, Lexington, KY.

Gill, K.E., Edmiston E.A., & Akins, C.K. (March 2015). *Cocaine-induced Locomotor Activity and Conditioned Place Preference in Female Japanese Quail.* Poster presented at the annual Bluegrass Society for Neuroscience Spring Neuroscience Day, Lexington, KY.

Gill, K.E., Edmiston, E.A., Madison, F.N., & Akins, C.K. (June 2015). *Cocaine-induced Locomotor Activity and Conditioned Place Preference in Female Japanese Quail.* Poster to be presented at the Society for Behavioral Neuroendocrinology convention, Pacific Grove, CA.

PROFESSIONAL SERVICE & OUTREACH ACTIVITIES

Oct. 2003 – Apr. 2004	Forsyth County Humane Society, Volunteer	W-S, NC
Aug 2010 – May 2011	Brownbag Co-Coordinator	
Aug. 2014 – Dec. 2014	New Graduate Student Handbook Development Committee	

SCIENTIFIC SOCIETY MEMBERSHIPS

Aug 2009 – Present	Bluegrass Chapter Society for Neuroscience	Student Member
May 2013 – Present	Midwestern Psychological Association	Student Member
June 2013 – Present	Society for Behavioral Neuroendocrinology	Student Member
Sept 2014 – Present	American Psychological Association – Div 28	Student Member

SCHOLASTIC & PROFESSIONAL HONORS/AWARDS

Nov. 2011	RCTF Travel Award	Dept. of Psychology
Jan. 2013 – May 2013	RCTF Fellowship	Dept. of Psychology
May 2013	RCTF Travel Award	Dept. of Psychology