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by

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Abstract

Eating a high fat diet causes several negative health consequences, including dysfunction to dopamine systems. For example, eating a high fat diet enhances sensitivity of rats to methamphetamine-induced locomotor sensitization. However, it is not known if sensitivity to other (i.e., the rewarding) effects of methamphetamine are similarly enhanced in rats eating a high fat diet. Females are more sensitive than males to the behavioral effects of stimulants in general, and therefore might also be particularly vulnerable to the effects of diet on the rewarding effects of stimulant drugs. To test the hypothesis that eating high fat chow enhances sensitivity of rats to the rewarding effects of methamphetamine, female and male Sprague-Dawley rats were fed standard (17% kcal from fat) or high fat chow (60% kcal from fat) for 4 weeks prior to conditioned place preference (CPP) training, using a biased design. Before training, rats were given free access to both sides of the chamber in order to determine a side preference. Rats were trained on alternating days with saline or methamphetamine (0.1, 0.32 and 1.0 mg/kg, i.p.) with drug conditioned in the initially non-preferred side. Methamphetamine induced a significant CPP among female rats at the two largest doses (0.32 and 1.0 mg/kg; at least compared to the smaller dose [0.1 mg/kg], in the absence of a saline conditioned control group). While the two largest doses of methamphetamine also induced a significant CPP among male rats when compared to the saline conditioned group, the smallest dose of methamphetamine (0.1 mg/kg) resulted in preference scores that did not differ significantly from male rats conditioned with saline. Future studies will examine a wider range of doses of methamphetamine, as well as other addiction-relevant behaviors (i.e., self-administration).

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Introduction

Individuals that consume a high fat or high calorie diet are at an increased risk of developing obesity (Obesity, 2014). Obesity is a major risk factor for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer (Adult Obesity Facts, 2018). As of 2018, 39% of adults over the age of 20 years old in the United States were diagnosed as obese, and this trend continues to rise, according to the Centers for Disease Control (CDC; Adult Obesity Facts, 2018). The consumption of high fat foods causes neuroadaptations in dopamine systems, which are similar to the neuroadaptations observed among individuals with substance use disorder (Volkow et al., 2017). For example, PET images of individuals with cocaine use disorder or obesity demonstrate significantly lower levels of dopamine D2 receptors in the dorsal and ventral striatum, as compared to control subjects (Volkow, 2017). Further, radioligand binding and western blotting procedures using postmortem brain tissue from methamphetamine users showed decreases levels of striatal dopamine transporters (DAT; Kish et. al., 2016). Similarly, high fat diet induced obesity in rats, results in decreases in membrane-bound DAT, dopamine D2 receptor expression and a reduced rate of dopamine reuptake (Cone et. al., 2013; Speed et al., 2011). Additionally, dopamine receptors in the striatum are also downregulated among humans eating high fat or high sugar diets or rats that are exposed to psychomotor stimulants (e.g., cocaine or methamphetamine; Volkow et al., 2008).

Both highly palatable foods (Rada et. al., 2005) and drugs of abuse (Imperato et. al., 1992) impact dopamine reward pathways acutely, which might underlie the long term neuroadaptations seen with chronic exposure to highly palatable foods (e.g., in the case of obesity) or drugs of abuse (e.g., in the case of substance use disorder; Kalivas, 2007; Roberts et al.,1977). For example, the mesolimbic reward pathway is activated when highly palatable foods

are consumed (Figlewicz & Sipolis, 2010). Binging on foods that are high in sugar and fat induces an increase of dopamine in the nucleus accumbens, mimicking the pharmacological effects of many drugs of abuse, including methamphetamine (Morris et. al., 2015). Under acute conditions methamphetamine structurally mimics dopamine and acts as a substrate at both DAT and vesicular monoamine transporters (VMAT; Cruickshank & Dyer, 2009). At higher concentrations, methamphetamine diffuses into the cytoplasm through the plasma membrane, due to it being highly lipophilic (Mack & Bönisch, 1979) and results in an exchange/diffusion transport mechanism (Fleckenstein et al., 2007). This in turn releases dopamine (DA) from its intraneuronal binding sites, causing a displacement of dopamine from vesicles into the cytosol, resulting in an accumulation of dopamine (Courtney & Ray, 2014). This overabundance of dopamine causes DAT to reverse, releasing dopamine into the synaptic cleft (Panenka et al., 2013; Shin et al., 2017), resulting in increased dopamine receptor binding. This methamphetamine-induced dopamine release, combined with purported increased exocytotic release (Daberkow et al., 2013), causes reward within the mesolimbic pathway in the brain and is largely responsible for the abuse potential of methamphetamine (Baumann et al., 2002). Given that both food and drugs impact the reward pathway under acute conditions, it is perhaps not surprising that chronic exposure to food or drugs results in the downregulation of dopamine receptors (Volkow et. al., 2008).

While it is known that highly palatable foods and drugs of abuse impact the same brain reward pathways, it is less understood how food and drugs might interact within individuals that are exposed to both. However, several previous reports have revealed that a history of eating high fat or high sugar diets can increase sensitivity of rats to drugs that act on dopamine systems (Baladi et al., 2015; Baladi et al., 2012; Baladi et al., 2011; Serafine et al., 2015; McGuire et al.,

2011). For example, eating high fat chow enhances the development of methamphetamine-induced locomotor sensitization in rats (McGuire et. al., 2011). While locomotor sensitization is often used to predict abuse vulnerability, it is not a direct measure of the rewarding effects of drugs (Lynch et. al., 2010). Therefore, while previous literature suggests that eating high fat chow might also enhance sensitivity of rats to the rewarding effects (and therefore to the abuse-related effects) of methamphetamine, to date, no empirical assessment has investigated this hypothesis using an assay that is sensitive to measuring the rewarding effects of drugs (e.g., conditioned place preference [CPP] Riley & Roma, 2005).

The CPP paradigm is a standard behavioral model used to study the rewarding and aversive effects of drugs, in that the basic characteristics of this test involves the association of a particular environment with a drug and the absence of the drug. Animals exhibit a conditioned preference after spending more time in the drug- paired compartment when compared with the non-drug paired compartment with a drug that works as positive reinforcers, and avoid environments that are associated with an aversive drug (i.e., conditioned place aversion; Swerdlow et al., 1989). One important aspect of designing a CPP study is choosing to utilize a biased or unbiased design as it can affect the outcome of the study. In a biased design, the preference each animal has for a particular environment is assessed before the start of conditioning, by examining the amount of time spent in each compartment. The least preferred compartment is then assigned as the compartment that is paired with the drug. In an unbiased design, the assignment of a particular compartment to be paired with a specific drug is determined by the researcher. This pairing is done regardless of the preference of each subject for either compartment prior to conditioning (Prus et al., 2009). One advantage of a biased design is that an initial pre-test allows one to reveal an absolute CPP to the initially non-preferred

compartment during testing when compared to an unbiased design. The advantage of this strategy is that it allows for the experimenter to take into account the initial preference, and to condition against it – thereby avoiding any potential confound of combining an initially preferred compartment with a rewarding stimulus. A disadvantage of this approach is that once an initial preference is revealed, the drug stimulus must be sufficiently powerful enough to overcome any potential aversiveness of the initially non-preferred compartment. Further, the bias design then can lead to interpretational difficulties, since in this design when animals spend more time in the drug-paired compartment post-conditioning, it could be due to either the motivational effects of a drug or a decrease in the aversive properties of the initially non-preferred compartment (Kõks S., 2015). Despite this potential interpretational limitation, in the present report the biased design was determined to be the optimal approach, given that the chambers used were new, as was the testing facility, necessitating an initial characterization of the chambers themselves as part of our experiment**.**

While methamphetamine itself induces several neural changes, the experience of classical conditioning can also result in neural changes. Specifically, conditioning the drug to one compartment creates a form of physiological response to certain cues and contexts that would be predictive of drug availability, also known as cue or context- elicited drug-seeking behavior, similar to the drug-seeking behavior of cocaine users that are triggered by environmental cues (Shinohara et al., 2017). There are also several known neuronal circuits and neurotransmitters that underlie cue elicited drug-seeking including the basolateral amygdala complex, prelimbic cortex, and nucleus accumbens (Ito et al., 2004). Within the nucleus accumbens previous studies using animal models have shown that there are different contributions of its two subregions, the core which is involved in the rewarding effects of drugs of abuse (Ito et al., 2004), while the

shell is required for maintaining cue-elicited drug-seeking behavior (Fuchs et al., 2004, Ito et al., 2004). While mechanistically, extracellular signal-regulated kinase ½ (ERK) has also been shown to have implications in the central nervous systems effects to drugs of abuse and the ERK signaling pathway in the nucleus accumbens core, helps establishes a drug paired context cue memory (Miller & Marshall, 2005). Western blot analysis using rats has revealed that CPP expression induces phosphorylation of ERK, CREB and Elk-1 and this activation is specific to the core of the nucleus accumbens, which again is responsible for the rewarding effects of drugs (Miller & Marshall, 2005). This provides the basis for which CPP uses contextual cue-elicited craving, in which rats learn to associate the rewarding effects of a drug with an environmental context in which it is administered and in which rats later show a preference for that environment (compartment), even during testing in a drug-free state.

After conditioning, animals are allowed access to both compartments and are tested in a drug-free state, this is done in order to make the test more sensitive towards the rewarding effects of the drug. Testing in a drug-free state comes from the idea that in humans, relapse, or drug seeking, depends on the association formed between drug-paired cues and the rewarding effects of the drug, in this case methamphetamine (Childress et al., 1988). Previous studies have shown that rats conditioned with cocaine vs. those who are conditioned without cocaine, showed an increase of time spent in the cocaine paired compartment from baseline testing, when tested in a drug-free state (Miller & Marshall, 2005), displaying that this drug-seeking behavior is prevalent and visibly seen during testing. Dopamine signaling has also shown to be crucial in the mediation of producing a place preference. Specifically, previous studies have shown that male Sprague Dawley rats who were trained using a cocaine-induced CPP and given systemic injections of dopamine D1 and dopamine D2 antagonists 20 minutes before testing (after

conditioning), showed a significant reduction in cocaine-induced CPP (Adams et al., 2001), demonstrating the strong role of dopamine in even the drug-free aspects of CPP testing.

To test the hypothesis that eating a high fat chow enhances the sensitivity of rats to the rewarding effects of methamphetamine the present report examined methamphetamine-induced CPP in male and female rats eating standard or high fat chow.

Methods

All experimental procedures were conducted in accordance with the Institutional Animal Care and Use Committee, The University of Texas at El Paso, and the 2011 Guide for Care and Use of Laboratory Animals (Institute of Laboratory, Animal Resources on Life Sciences, the National Research Council, and the National Academy of Sciences).

SUBJECTS

Male and female Sprague Dawley Rats (67 = females, 34 = males; Envigo, Livermore, CA), males weighing 49-65 g and females weighing 43-53 g upon arrival (Post-natal day (PND) 20-21), were single housed in Tecniplast™ 1284L (365 x 207 x 140 mm) individually ventilated cages, in an environmentally controlled room (23±3°C, 50±20% relative humidity) in a 12:12h light dark cycle (lights on at 8:00am). All rats had ad libitum access to food and water except where indicated.

FEEDING CONDITIONS

Upon arrival (PND 20-21), rats were habituated to the laboratory for 3-5 days and then were randomly assigned to two different dietary conditions. The Sprague-Dawley rats were fed standard laboratory chow (17% kcal from fat) or high fat chow (60% kcal from fat) for 4 weeks prior to CPP training. The separated groups of rats thereafter had free access to either standard laboratory chow or free access to a high fat chow for the duration of the experiment. All subjects were fed and weighed daily at the same time throughout the experiment (0800-1000 hrs.). The nutritional content of the standard chow (Envigo Teklad 7912) is 5.7% fat, 44.3% carbohydrate, and 19.9% protein (by weight) with a calculated gross energy content of 4.1 kcal/g. The high fat

chow (Envigo Teklad 06414) contains 34.3% fat, 27.3% carbohydrate, and 23.5% protein (by weight), with a calculated energy content of 5.1 kcal/g. Throughout the entire length of the study, body weight and food consumption were be measured daily.

DRUGS

Methamphetamine hydrochloride (Sigma Aldrich, St. Louis, MO, USA) was dissolved in 0.9% saline and administered intraperitoneally in a volume of 1 ml/kg body weight. Doses of methamphetamine hydrochloride used were 0.1, 0.32, and 1.0 mg/kg.

BIASED CONDITIONED PLACE PREFERENCE DESIGN

A total of 8 CPP chambers were used (Med Asssociates, MED-CPP2-013C) each containing two plastic conditioning compartments (17.5" L x 8" x 12" H each) separated by a plastic panel. Each compartment was different regarding the flooring (wire rod or wire mesh), but no other distinguishing features were present. The chamber floor was equipped with a photobeam array for recording activity (e.g., time spent in each side of the chamber). A biased CPP design was utilized as has been described by previous reports (Riley & Roma, 2005). Briefly, side preference for each individual subject prior to conditioning was assessed whereby the amount of time each individual subject spend in each side of the chamber was recorded during a drug-free initial pre-test. Following assessment of pre-test activity, animals were conditioned with drug in the initially non-preferred side of the chamber (determined on an individual-rat basis). Rats were conditioned on alternating days; with saline or methamphetamine (0.1, 0.32, or 1.0 mg/kg, i.p.) and were restricted to one of two sides (wire mesh vs rod flooring) of the CPP chamber (based on the results of their initial preference test). This alternation of drug and saline treatment was continued for 8 conditioning days (such that each rat received four days

of drug conditioning and four days of saline conditioning). Following conditioning, rats were tested for post-conditioning preference, during which the rats had access to both sides of the chamber for 30 minutes in a drug-free state. Additionally, some rats were conditioned with saline on both sides of the chamber (e.g., a saline control group); however, these data are only included below for male rats, and remain pending for females.

STATISTICS

Data were calculated as a preference score by subtracting the time (s) spent in the drug-paired side during test day (Day 10) from the time spent on the same compartment during the pre-test day (Day 1). For example, the total amount of time spent in the drug-paired side during the post-conditioning test was subtracted from the total amount of time spent in the drug-paired side during the initial pre-test. The results are expressed for figures as preference score in seconds. Separate analyses were conducted across males and females and the significance level for all analyses was considered significant when the p-value was less than 0.05. Differences in preference score were analyzed using a two-way Analysis of Variance (ANOVA) with diet and dose of methamphetamine as factors. Unpaired t-tests were used for analyses of two-group comparisons such as saline conditioned and doses of methamphetamine. Similar ANOVAs were used to compare differences among body weight and food consumption.

Results

FOOD AND BODY WEIGHT DATA

Throughout experimental testing, rats eating high fat chow weighed more than rats eating standard chow (Figure 1A and 1D). Males (Figure 1A) weighed more than females (Figure 1D) during conditioning, regardless of diet. While rats eating high fat chow ate less grams of food on average daily than rats eating standard chow (Figure 1B and 1E); there were only significant differences among females in regards to average daily caloric (kcal) ($t(18)=3.955$, $p<.05$) intake between groups, since no differences were found in the males (Figure 1C and 1F). That is, females eating high fat chow consumed more kcal on average daily than females eating standard chow (Figure 1C).

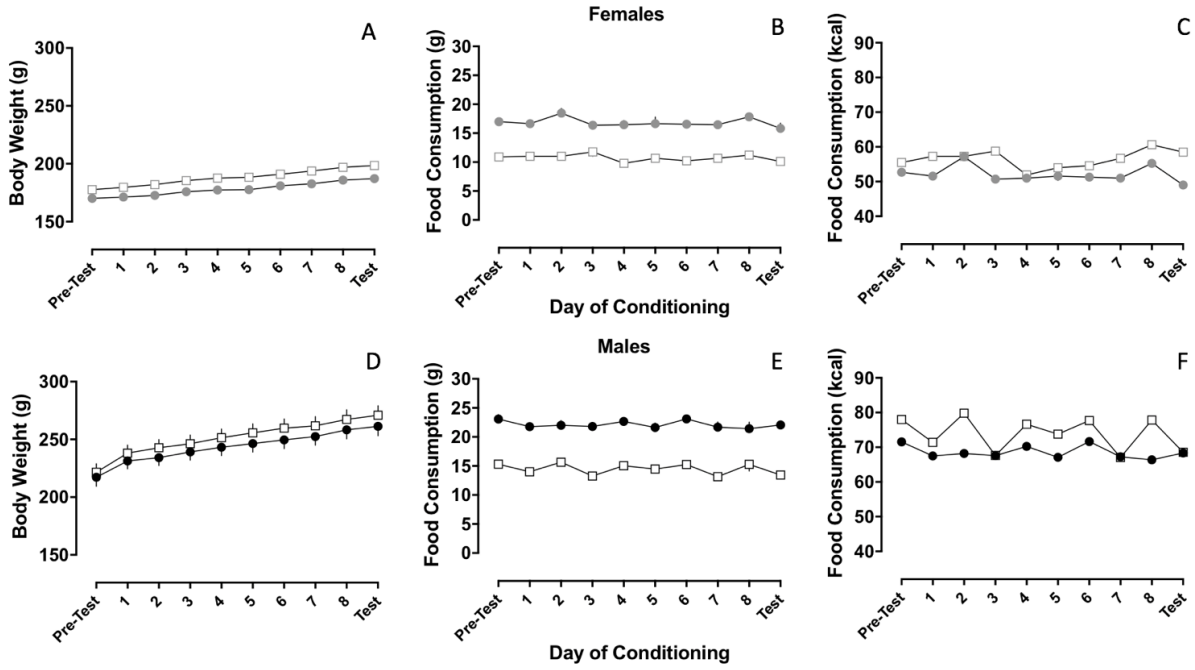

Figure 1.
Mean ± SEM body weights (A & D), food consumption in grams (B & E), and food consumption in kcal (C & F) during the pre-test, conditioning, and post-conditioning test for female rats (A) and male rats (D) eating standard chow (females, gray circles, n=34; males, black circles, n=36)

or high fat chow (females, gray squares, n=31; males, black squares, n=32) and conditioned with methamphetamine.

CONDITIONED PLACE PREFERENCE

The pre-test revealed an initial preference for one side as opposed to the other for most rats (Figure 2). During the pre-test, all but 6 female rats (Figure 2A) spent more time in the wire mesh compartment and similarly, all but 8 male rats (Figure 2B) spent more time in the wire mesh compartment. CPP preference score was calculated by subtracting the time (s) spent in the cocaine-paired side during test day (Day 10) from the time spent on the same compartment during the pre-test day (Day 1), for the full 30 minute session. Therefore, a positive number indicates a higher preference for the methamphetamine-paired side and a negative number indicates an avoidance or lack of preference of the methamphetamine-paired side (Figure 3). CPP data were analyzed using a 2-way ANOVA, with diet (standard or high fat) and methamphetamine dose (saline, 0.1, 0.32, 1.0 mg/kg) as factors. As such, preference scores were analyzed using a 2 × 3 (females) and 2 x 4 (males) between-subjects ANOVA. Once the additional missing cohort for females (e.g., saline conditioned) are completed, a 2 x 4 between-subjects ANOVA will be completed, along with a 3 way ANOVA (sex x diet x dose) to examine sex differences. Tukey's HSD multiple comparisons were examined where appropriate.

Mean CPP preference scores for females eating either a standard or high fat chow and tested for methamphetamine-induced CPP are graphed in Figure 3A. The 2 × 3 between-subjects ANOVA revealed a significant main effect of methamphetamine dose, $n = 65$, $F(2, 59) = 4.927$ $p = .011$, but no main effect of diet, $F(1, 59) = .4337$ $p = .434$, and no significant diet x dose interaction, $F(2, 59) = 1.364$ $p = .264$. Tukey HSD post-hoc analyses examining the main effect of dose revealed that regardless of diet, female rats conditioned with 0.32 or 1.0 mg/kg (both p values <0.05) methamphetamine displayed significantly larger preference scores than female rats conditioned with 0.1 mg/kg methamphetamine. That is, these two largest doses of

methamphetamine induced a significant CPP among female rats, (at least compared to the smaller dose, in the absence of a saline conditioned control group). There were no significant differences in preference score for females conditioned with 0.32 mg/kg and 1.0 mg/kg of methamphetamine (e.g., these two larger doses were equally effective at inducing CPP). Saline conditioned females will be added after the laboratory can reopen following COVID-19, and it will be especially critical to assess whether or not the smallest dose (0.1 mg/kg methamphetamine) differs from saline in order to determine if this small dose was effective at inducing a CPP at all among females.

Mean CPP preference scores for males eating either a standard or high fat chow and tested for methamphetamine-induced CPP are graphed in Figure 3B. The 2 × 4 between-subjects ANOVA revealed a significant main effect of methamphetamine dose, $n = 66$, $F(3, 58) = 6.185$ $p = .001$, but no main effect of diet, $F(1, 58) = .91$ $p = .344$, and a non-significant interaction between diet and methamphetamine $F(3, 58) = 2.052$ $p = .117$, similar to females. Tukey HSD post-hoc analyses revealed that regardless of diet, male rats conditioned with 0.32 mg/kg ($p = .0008$) and 1.0 mg/kg ($p = .0215$) methamphetamine displayed significantly larger preference scores than male rats conditioned with saline. That is, these two largest doses of methamphetamine induced a significant CPP among male rats, though there were no differences between doses (e.g., 0.32 and 1.0 mg/kg methamphetamine were equally effective at inducing CPP). Male rats conditioned with the smallest dose of methamphetamine (0.1 mg/kg) had preference scores that did not differ significantly from male rats conditioned with saline (e.g., 0.1 mg/kg was an ineffective dose in this assay, not statistically different from saline). However, Tukey's HSD multiple comparisons also revealed that regardless of diet, preference scores for male rats conditioned with 0.1 mg/kg methamphetamine were not significantly different than preference scores for the other two doses of methamphetamine.

Regarding sex differences, at this time, one remaining group (saline conditioned female controls) is needed to conduct a 3-way ANOVA with sex, diet and dose as factors to examine potential sex differences. Based on previous literature, we expect that females were more sensitive in general to methamphetamine-induced CPP (Schindler et al. 2002).

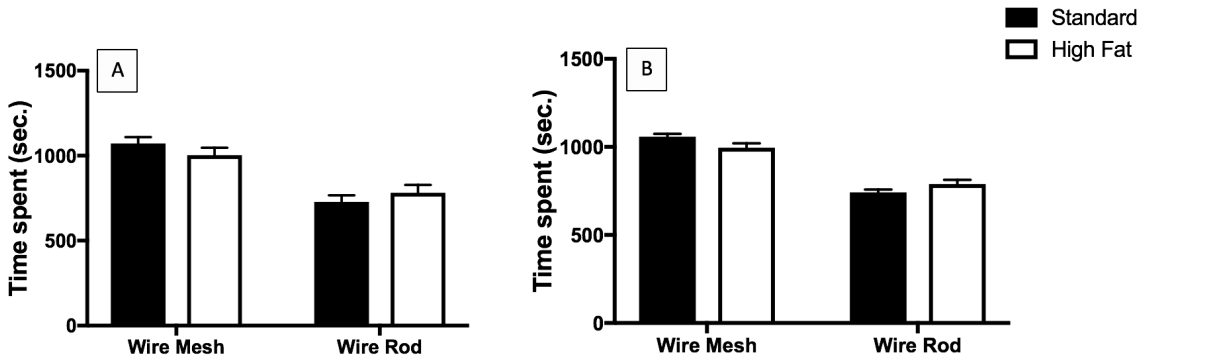

Figure 2.
Mean ± SEM pre-test raw data of time spent in seconds on either side of the CPP chamber for female (A) and male (B) Sprague Dawley rats for a 30 minute session. Both males and females (regardless of diet) tended to spend more time in the wire mesh side than the wire rod side of the CPP chambers during the initial pre-test.

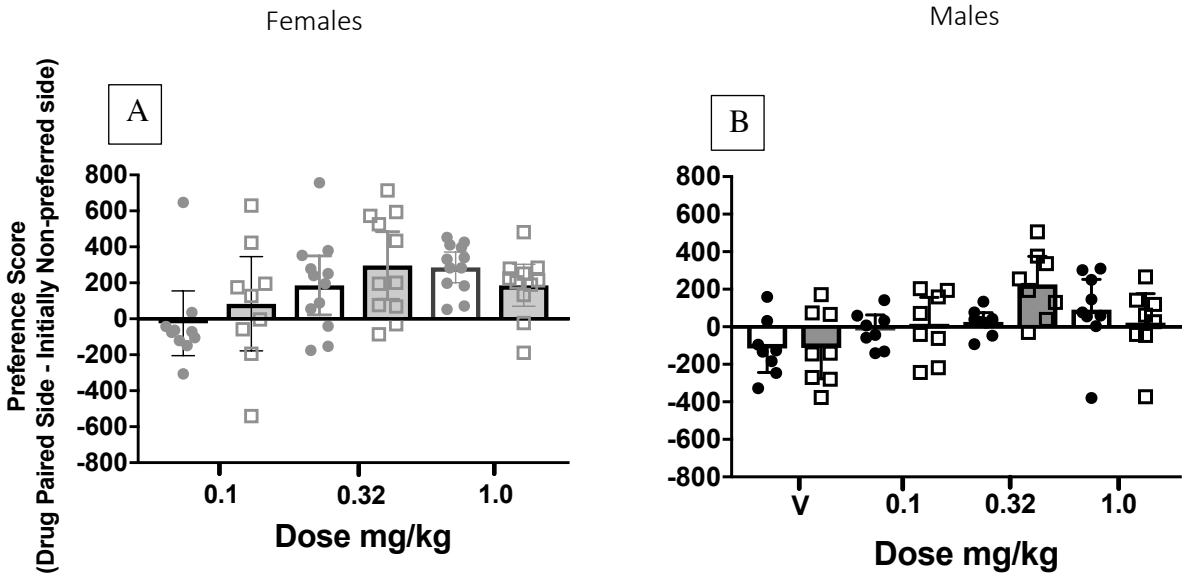

Figure 3.
Mean ± SEM percent of preference score (time spent on test day drug paired side minus the pre-test day initially non-preferred side) for Females (A) and Male (B) Sprague Dawley rats eating standard chow (females, gray circles, n=35; males, black circles, n=22) or high fat chow (females,

gray open squares, n=32; males, black open squares, n=22). Regardless of diet, female rats conditioned with 0.32 or 1.0 mg/kg methamphetamine displayed significantly larger preference scores than female rats conditioned with 0.1 mg/kg methamphetamine (A). Male rats conditioned with 0.32 or 1.0 mg/kg methamphetamine displayed significantly larger preference scores than male rats conditioned with saline, regardless of diet, though there were no differences between doses (e.g., 0.32 and 1.0 mg/kg methamphetamine were equally effective at inducing CPP). Male rats conditioned with the smallest dose of methamphetamine (0.1 mg/kg) had preference scores that did not differ significantly from male rats conditioned with saline (B). Results, collapsed across diet are also illustrated in Figure 4 below.

Figure 4.
Mean ± SEM percent of preference score (time spent on test day drug paired side minus the pre-test day initially non-preferred side) for Females (A) and Male (B) Sprague Dawley rats, collapsed across diet, (females n=67, males=44), for each dose of methamphetamine. (^) Represents a significantly larger preference score than the lowest dose, 0.1 mg/kg methamphetamine. (*)Represents a significantly larger preference score than saline conditioned animals (Tukey HSD, $p<0.05$)

Discussion

Eating a high fat diet can lead to several negative health consequences, including cardiovascular disease, metabolic disease and obesity (USDA, 2010). Preclinical studies consistently demonstrate that eating high fat chow also increases sensitivity of rats to the unconditioned behavioral effects of drugs acting on dopamine systems (Serafine et. al., 2014). These dopamine systems are also impacted by drugs of abuse and contribute to addiction and obesity through their role in reward and motivation (Baladi et al., 2012; Volkow et al., 2017). The aim of the present study was to determine the effects of a high fat diet on the rewarding effects of methamphetamine, as measured using CPP.

Previous literature has demonstrated that eating high fat chow enhances sensitivity of rats to methamphetamine-induced locomotion and sensitization (McGuire et al., 2011). These behaviors are often used to predict abuse-related vulnerability in animal models (Wallace et. al., 1999). Therefore, it was hypothesized that rats eating high fat chow would be more sensitive to the rewarding effects of methamphetamine than rats eating standard chow, and that this effect would be greater among females as compared to males. However, in the present report, there were no significant differences between male or female rats eating high fat chow and rats eating standard chow in terms of magnitude of methamphetamine-induced CPP (Figure 3). Further, previous literature describes sex differences regarding sensitivity to methamphetamine-induced locomotion and sensitization (Ramos et al., 2020; Slamberova et al., 2014). At the present time, we have not analyzed these data to examine sex differences, as we are still collecting the final group of female control data (e.g., saline conditioned rats) before conducting a 3-way ANOVA.

Finally, there were significant differences in magnitude of methamphetamine-induced CPP between rats conditioned with different doses of methamphetamine (Figure 3). Control groups were originally omitted from this study as the smallest dose (0.1 mg/kg) of methamphetamine, based on previous studies, was thought to have been an ineffective dose in producing a CPP and therefore could have served as a control group (Matthews & McCormick, 2007). Subsequently, a

control group was assessed among male rats eating standard and high fat diets, and our analysis revealed that male rats conditioned with either 0.32 mg/kg or 1.0 mg/kg methamphetamine spent significantly more time in the initially non-preferred compartment (e.g., the drug-paired compartment) than rats conditioned with saline, when collapsed across diet (see Figure 4). Consistent with previous literature, the smallest dose of methamphetamine used in the present report did not produce behavior that was significantly different than saline (see Figure 4). Taken together these data suggest that while diet had no impact on CPP, methamphetamine did result in a significant place preference among male rats, in a dose-dependent manner. Although sex specific comparisons cannot be made until the control group is also added for females, it is worth noting that among males, there was no statistical difference between preference score for rats conditioned with the smallest dose of methamphetamine (0.1 mg/kg) and the two larger doses (see Figure 4). In contrast, female rats conditioned with 0.1 mg/kg had significantly smaller preference scores than female rats conditioned with the two larger doses of methamphetamine, suggesting a potential differential sensitivity to at least smaller doses of methamphetamine between sexes. This will be explored further once a control group is added for systematic comparison between sexes.

As mentioned, there was no impact of diet in the present study, despite previous literature demonstrating that rats eating high fat diet are more sensitive to other (e.g., locomotor stimulating) effects of methamphetamine (McGuire et al., 2011). One possibility for the absence of this effect might be related to the duration of access to high fat chow. For example, in previous studies that examine changes to sensitivity to the locomotor-stimulating effects of stimulant drugs (i.e., cocaine), 4-5 consecutive weeks of eating a high fat diet was necessary before the enhanced drug sensitivity was revealed among rats eating a high fat diet (Baladi et al., 2011). In the present report, rats also ate high fat chow for 4 consecutive weeks; however, while that duration might be sufficient to induce changes related to the locomotor-stimulating effects of methamphetamine, it might be insufficient to induce changes related to the rewarding effects of methamphetamine. Although the locomotor stimulating effects as well as the rewarding effects of methamphetamine are both mediated, in part, by activation of dopamine D1 and D2 receptors (Brennan et al., 2009),

the specific downstream mechanisms underlying reward versus locomotion are likely overlapping, but non-identical, and might require different durations of chronic exposure to the high fat diet in order to observe behaviorally relevant changes.

Another consideration is that enhanced locomotion, while indicative of changes to drug sensitivity, might not actually predict enhanced vulnerability to addiction (e.g., enhanced reward). For example, while locomotor sensitization has been posited to be a behavioral model underlying a central neural mechanisms underlying addiction (Robinson & Berridge, 1993; 2003) it is possible that some conditions (in this case: eating a high fat diet) which enhance locomotor sensitization do not always consistently enhance other effects of drugs in animals. For example, there are conditions under which certain variables can selectively impact locomotion but not CPP (Hemby et al, 1992), or where variables that can block self-administration do not block sensitization or locomotion (Olmstead & Franklin, 1994). Beyond these examples, there are other reports that demonstrate enhancement of sensitization, yet a reduction in CPP (Chefer & Shippenberg 2008; Runegaard et al., 2018), further suggesting that these two animal models do not always correlate perfectly with one another. Therefore, while it is possible that diet had no effect because of the reasons outlined above, another possibility is that the evidence (from locomotor assays) which our hypothesis was based on, is simply not predictive of results using a different assay (CPP). That the sensitization model of the neural mechanisms underlying addiction remains debated in the field further supports this possibility (Hyman et al., 2006).

As mentioned above, at least with our preliminary assessments, no differences between sexes were revealed regarding sensitivity of rats to methamphetamine-induced CPP (Figure 3). This is consistent with some literature using CPP (Matthews & McCormick, 2007); however, the larger body of literature suggests that there typically is a robust sex difference often observed regarding sensitivity of rodents and humans to stimulant drugs. For example, females exhibit greater vulnerability toward substance use disorder at many stages of the addiction process, including initiation of drug use to relapse (Anker & Carroll, 2010). Further, women are more likely to initiate drug use at an earlier age than men (Chen & Kandel, 2002), have a hard time quitting

(Becker & Hu, 2008), and exhibit greater drug craving (Robbins et al., 1999), as compared to men. Animal research also demonstrates robust sex differences with regard to animal models of addiction. Specifically, female rats are more sensitive than male rats to the locomotor stimulating effects of methamphetamine (Schindler et al. 2002), acquire cocaine self-administration at a faster rate than males (Lynch & Carroll, 1999), and exhibit greater binge-like drug intake patterns (Carroll & Anker, 2009). Regarding previous research examining CPP, it is well known that estrous cycle can impact sensitivity to CPP induce by a range of drugs of abuse. For example, female rats show greater methamphetamine CPP during the dioestrous than during the oestrous phase of the estrous cycle (Mathews & McCormick, 2007). We did not measure estrous cycle for females in the present report; however, given that testing occurred weekly and that the estrous cycle in rats is only 3-4 days long, it is probable that rats were experiencing different phases on different test days. Further, rats in the present report were housed in the same facility as males, and olfactory and social cues have been shown to impact cycle phasing (McClintock, 1981), and could therefore have also indirectly impacted CPP (Carroll et al., 2004; Lacy et al., 2016). Is it also important to mention that this current study is ongoing and will include the saline conditioned female cohort (functioning as a control). Once completed, an additional 3-way ANOVA will be conducted to be able to compare all doses of methamphetamine to a control and determine whether there was a greater magnitude of place preference in those drug conditioned groups.

Another factor that might be important to consider for the present results is the contextual stimuli of the CPP chambers themselves. As the basis of the CPP paradigm involves conditioning to a distinct context, it is critical that the two chambers are in fact distinct and distinguishable from each other by the animal. It could be the case that our CPP compartments were not distinct enough from each other to facilitate strong conditioning to the drug. In other words, if the context itself was not salient enough, conditioning strength might have been decreased. Indeed, this cannot be ruled out as a possibility since this was the first complete CPP experiment done in these new CPP chambers. One way to amplify conditioning strength for future studies is to make the two compartments more different than each other through different visual and contextual clues. For

example, many investigators include the addition of distinct visual inserts (white vs. black walls; spots vs. vertical stripes), distinct bedding (pine vs. corn), distinct flooring (horizontal grid vs. cross-grid flooring) or even distinct scents (Lynch et al., 2010). These different contextual cues that comprise of a range of sensory modalities, including sight (vision), hearing (audition), smell (olfaction), taste (gustation), and touch (taction) could help to enhance the distinction between the two compartments, in order to provide a more salient environmental cue for conditioning (Kummer et al., 2011). If these had been implemented for the present report, it is possible that the differences between time spent in one compartment versus the other would be greater.

Another factor that should be considered for the present report is the potential impact of age on the magnitude of CPP. Animals used in this study were tested at PND 51-54, which in rats starts the stage of sexual maturity and still considered to be late adolescence (Sengupta, 2013). CPP is often stronger among adolescents as compared to adults (Schramm-Sapyta et al. 2009) and might be due to differential activation of the mesolimbic pathway during development (Wahlstrom et. al., 2010). It is possible that the specific age of rats in the present study might have contributed to the lack of consistency between our results and previous reports regarding sex differences. Specifically, most studies examine CPP during younger adolescent windows or older adulthood windows (Schramm-Sapyta et al., 2009). Our age rage is somewhere in the middle of both major developmental stages, and as such could be providing a unique snapshot of an age during which these normally robust sex differences, seem to dissipate temporarily just prior to sexual maturity. In order to explore this possibility, future studies should examine and compare differential age ranges using different drugs of abuse and multiple doses.

The present study demonstrated that methamphetamine induced a significant CPP; and although, there were no significant differences between groups regardless of sex or diet, these data did reveal a significant dose-dependent difference in male and female rats, using these preliminary data for the female rats. While, concrete sex specific comparisons cannot be made at this time, due to the lack of a control group in females, there could be a potential sensitivity at these two smaller doses of methamphetamine between the two sexes. As these preliminary findings

suggests that female rats may be more sensitive to the rewarding effects of methamphetamine due to the significant difference in magnitude of CPP between the lowest dose of methamphetamine and the two larger doses, which was not found in males. These findings also suggest that eating a high fat diet enhances sensitivity of rats to some (e.g., locomotor-stimulating) but not all (e.g., rewarding) effects of methamphetamine. As described above, there are several factors that might contribute to the lack of effects for sex and diet demonstrated here; however, it is also possible that eating a high fat diet, sex hormones, and amount of methamphetamine are not necessarily driving factors contributing to the strength of CPP. Further, it is possible that age might be a stronger factor determining magnitude of CPP than all other factors manipulated in the present report, since rats even in late adolescence might be more sensitive generally to drugs of abuse. Future directions will examine the effects of eating a high fat diet in other paradigms which are used to assess abuse liability of drugs, including self-administration, and will also investigate a wider range of doses of methamphetamine, as well as other drugs, and different durations of access to high fat chow to capture effects that were absent in the present study.

References

1. Adams, J.U.; Careri, J.M.; Efferen, T.R.; Rotrosen, J. Differential effects of dopamine antagonists on locomotor activity, conditioned activity and conditioned place preference induced by cocaine in rats, Behavioural Pharmacology: December 2001 - Volume 12 - Issue 8 - p 603-611

2.Adult Obesity Facts. (2018, August 13). Retrieved from https://www.cdc.gov/obesity/data/adult.html

3.. Anker, J. J., & Carroll, M. E. (2010). Females Are More Vulnerable to Drug Abuse than Males: Evidence from Preclinical Studies and the Role of Ovarian Hormones. Biological Basis of Sex Differences in Psychopharmacology Current Topics in Behavioral Neurosciences, 73–96. doi: 10.1007/7854_2010_93

4. Baladi, M. G., & France, C. P. (2010). Eating high-fat chow increases the sensitivity of rats to quinpirole-induced discriminative stimulus effects and yawning. Behavioural Pharmacology, 21(7), 615–620. doi: 10.1097/fbp.0b013e32833e7e5a

5. Baladi, M. G., Newman, A. H., & France, C. P. (2011). Influence of body weight and type of chow on the sensitivity of rats to the behavioral effects of the direct-acting dopamine-receptor agonist quinpirole. Psychopharmacology,217(4), 573-585. doi:10.1007/s00213-011-2320-6

6. Baladi, M. G., Koek, W., Aumann, M., Velasco, F., & France, C. P. (2012). Eating high fat chow enhances the locomotor-stimulating effects of cocaine in adolescent and adult female rats. Psychopharmacology,222(3), 447-457. doi:10.1007/s00213-012-2663-7

7. Baladi, M. G., Daws, L. C., & France, C. P. (2012). You are what you eat: Influence of type and amount of food consumed on central dopamine systems and the behavioral effects of direct-

and indirect-acting dopamine receptor agonists. Neuropharmacology, 63(1), 76–86. doi: 10.1016/j.neuropharm.2012.02.005

8. Baladi, M. G., Horton, R. E., Owens, W. A., Daws, L. C., & France, C. P. (2015). Eating High Fat Chow Decreases Dopamine Clearance in Adolescent and Adult Male Rats but Selectively Enhances the Locomotor Stimulating Effects of Cocaine in Adolescents. International Journal of Neuropsychopharmacology,18(7). doi:10.1093/ijnp/pyv024

9. Baumann, M. H., Ayestas, M. A., Sharpe, L. G., Lewis, D. B., Rice, K. C., & Rothman, R. B. (2002). Persistent Antagonism of Methamphetamine-Induced Dopamine Release in Rats Pretreated with GBR12909 Decanoate. Journal of Pharmacology and Experimental Therapeutics, 301(3), 1190–1197. doi: 10.1124/jpet.301.3.1190

10. Becker, J. B., & Hu, M. (2008). Sex differences in drug abuse. Frontiers in Neuroendocrinology, 29(1), 36–47. doi: 10.1016/j.yfrne.2007.07.003

11. Blanco-Gandía, M. C., Cantacorps, L., Aracil-Fernández, A., Montagud-Romero, S., Aguilar, M. A., Manzanares, J., … Rodríguez-Arias, M. (2017). Effects of bingeing on fat during adolescence on the reinforcing effects of cocaine in adult male mice. Neuropharmacology, 113, 31–44. doi: 10.1016/j.neuropharm.2016.09.020

12. Brennan, K. A., Carati, C., Lea, R. A., Fitzmaurice, P. S., & Schenk, S. (2009). Effect of D1-like and D2-like receptor antagonists on methamphetamine and 3,4-methylenedioxymethamphetamine self-administration in rats. Behavioural Pharmacology, 20(8), 688–694. doi: 10.1097/fbp.0b013e328333a28d

13. Carroll, M. E., Lynch, W. J., Roth, M. E., Morgan, A. D., & Cosgrove, K. P. (2004). Sex and estrogen influence drug abuse. Trends in Pharmacological Sciences, 25(5), 273–279. doi: 10.1016/j.tips.2004.03.011

14. Carroll, M. E., Anker, J. J., & Perry, J. L. (2009). Modeling risk factors for nicotine and other drug abuse in the preclinical laboratory. Drug and Alcohol Dependence, 104. doi: 10.1016/j.drugalcdep.2008.11.011

15. Chefer, V. I., & Shippenberg, T. S. (2008). Augmentation of Morphine-Induced Sensitization but Reduction in Morphine Tolerance and Reward in Delta-Opioid Receptor Knockout Mice. Neuropsychopharmacology, 34(4), 887–898. doi: 10.1038/npp.2008.128

16. Chen, K., & Kandel, D. (2002). Relationship between extent of cocaine use and dependence among adolescents and adults in the United States. Drug and Alcohol Dependence, 68(1), 65–85. doi: 10.1016/s0376-8716(02)00086-8

17. Childress, A., Ehrman, R., McLellan, A.T., O'Brien, C. Conditioned craving and arousal in cocaine addiction: a preliminary report, NIDA Res. Monogr., 81 (1988), pp. 74-80

18. Cruickshank, C. C., & Dyer, K. R. (2009). A review of the clinical pharmacology of methamphetamine. Addiction, 104(7), 1085–1099. doi: 10.1111/j.1360-0443.2009.02564.x

19. Cone, J. J., Chartoff, E. H., Potter, D. N., Ebner, S. R., & Roitman, M. F. (2013). Prolonged High Fat Diet Reduces Dopamine Reuptake without Altering DAT Gene Expression. PLoS ONE, 8(3). doi: 10.1371/journal.pone.0058251

20. Courtney, K. E., & Ray, L. A. (2014, October 1). Methamphetamine: an update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4164186/.

21. Cummins, S., & Macintyre, S. (2005). Food environments and obesity—neighbourhood or nation? International Journal of Epidemiology, 35(1), 100–104. doi: 10.1093/ije/dyi276

22. Daberkow, D. P., Brown, H. D., Bunner, K. D., Kraniotis, S. A., Doellman, M. A., Ragozzino, M. E., … Roitman, M. F. (2013). Amphetamine Paradoxically Augments Exocytotic

Dopamine Release and Phasic Dopamine Signals. Journal of Neuroscience, 33(2), 452–463. doi: 10.1523/jneurosci.2136-12.2013

23. Davis, J. F., Tracy, A. L., Schurdak, J. D., Tschöp, M. H., Lipton, J. W., Clegg, D. J., & Benoit, S. C. (2008). Exposure to elevated levels of dietary fat attenuates psychostimulant reward and mesolimbic dopamine turnover in the rat. Behavioral Neuroscience, 122(6), 1257–1263. doi: 10.1037/a0013111

24. Drewnowski, A. (2004). Obesity and the food environment. American Journal of Preventive Medicine, 27(3), 154–162. doi: 10.1016/j.amepre.2004.06.011

25. Mack F, Bönisch H. (1979) Dissociation constants and lipophilicity of catecholamines and related compounds. Naunyn Schmiedebergs Arch Pharmacol, 310(1):1-9. doi: 10.1007/BF00499868.

26. Figlewicz, D. P., & Sipols, A. J. (2010). Energy regulatory signals and food reward. Pharmacology, biochemistry, and behavior, 97(1), 15–24. doi:10.1016/j.pbb.2010.03.002

27. Fleckenstein AE, Volz TJ, Riddle EL, Gibb JW, Hanson GR. (2007) New insights into the mechanism of action of amphetamines. Annu Rev Pharmacol Toxicol, 47:681-98. doi: 10.1146/annurev.pharmtox.47.120505.105140.

28. Fuchs, R. A., Evans, K. A., Parker, M. C., & See, R. E. (2004). Differential involvement of the core and shell subregions of the nucleus accumbens in conditioned cue-induced reinstatement of cocaine seeking in rats. Psychopharmacology, 176(3-4), 459–465. doi: 10.1007/s00213-004-1895-6

29. Fordahl, S. C., Locke, J. L., & Jones, S. R. (2016). High fat diet augments amphetamine sensitization in mice: Role of feeding pattern, obesity, and dopamine terminal changes. Neuropharmacology, 109, 170–182. https://doi.org/10.1016/j.neuropharm.2016.06.006

30. Hemby, S. E., Jones, G. H., Justice, J. B., & Neill, D. B. (1992). Conditioned locomotor activity but not conditioned place preference following intra-accumbens infusions of cocaine. Psychopharmacology, 106(3), 330–336. doi: 10.1007/bf02245413

31. Hyman, S. E. (2006). Annual review of neuroscience. Palo Alto, CA: Annual Reviews.

32. Imperato, A., Mele, A., Scrocco, M. G., & Puglisi-Allegra, S. (1992). Chronic cocaine alters limbic extracellular dopamine. Neurochemical basis for addiction. European Journal of Pharmacology, 212(2-3), 299–300. doi: 10.1016/0014-2999(92)90349-9

33. Ito, R., Robbins, T. W., & Everitt, B. J. (2004). Differential control over cocaine-seeking behavior by nucleus accumbens core and shell. Nature Neuroscience, 7(4), 389–397. doi: 10.1038/nn1217

34. Kalivas P. W. (2007). Cocaine and amphetamine-like psychostimulants: neurocircuitry and glutamate neuroplasticity. Dialogues in clinical neuroscience, 9(4), 389–397.

35. Karriker-Jaffe, K. J. (2013). Neighborhood socioeconomic status and substance use by U.S. adults. Drug and Alcohol Dependence, 133(1), 212–221. doi: 10.1016/j.drugalcdep.2013.04.033

36. Kish, S. J. (2008). Pharmacologic mechanisms of crystal meth. Canadian Medical Association Journal, 178(13), 1679–1682. doi: 10.1503/cmaj.071675

37. Kish, S. J., Boileau, I., Callaghan, R. C., & Tong, J. (2016). Brain dopamine neurone 'damage': methamphetamine users vs. Parkinsons disease - a critical assessment of the evidence. European Journal of Neuroscience, 45(1), 58–66. doi: 10.1111/ejn.13363

38. Kõks, S. (2015). Experimental Models on Effects of Psychostimulants. International Review of Neurobiology The Neuropsychiatric Complications of Stimulant Abuse, 107–129. doi: 10.1016/bs.irn.2015.03.002

39. Kummer, K., Klement, S., Eggart, V., Mayr, M. J., Saria, A., & Zernig, G. (2011). Conditioned place preference for social interaction in rats: contribution of sensory components. Frontiers in behavioral neuroscience, 5, 80. https://doi.org/10.3389/fnbeh.2011.00080

40. Lacy, R. T., Strickland, J. C., Feinstein, M. A., Robinson, A. M., & Smith, M. A. (2016). The effects of sex, estrous cycle, and social contact on cocaine and heroin self-administration in rats. Psychopharmacology, 233(17), 3201–3210. doi:10.1007/s00213-016-4368-9

41. Lynch, W. J., & Carroll, M. E. (1999). Sex differences in the acquisition of intravenously self-administered cocaine and heroin in rats. Psychopharmacology, 144(1), 77–82. doi: 10.1007/s002130050979

42. Lynch, W. J., Nicholson, K. L., Dance, M. E., Morgan, R. W., & Foley, P. L. (2010). Animal models of substance abuse and addiction: implications for science, animal welfare, and society. Comparative medicine, 60(3), 177–188

43. Mathews, I. Z., & Mccormick, C. M. (2007). Female and male rats in late adolescence differ from adults in amphetamine-induced locomotor activity, but not in conditioned place preference for amphetamine. Behavioural Pharmacology, 18(7), 641–650. doi: 10.1097/fbp.0b013e3282effbf5

44. Mcguire, B. A., Baladi, M. G., & France, C. P. (2011). Eating high-fat chow enhances sensitization to the effects of methamphetamine on locomotion in rats. European Journal of Pharmacology, 658(2-3), 156–159. doi: 10.1016/j.ejphar.2011.02.027

45. Mcclintock, M. K. (1981). Social Control of the Ovarian Cycle. BioScience, 31(2), 138–139. doi: 10.2307/1308257

46. Miller, C. A., & Marshall, J. F. (2005). Molecular Substrates for Retrieval and Reconsolidation of Cocaine-Associated Contextual Memory. Neuron, 47(6), 873–884. doi: 10.1016/j.neuron.2005.08.006

47. Morris, M. J., Beilharz, J. E., Maniam, J., Reichelt, A. C., & Westbrook, R. F. (2015). Why is obesity such a problem in the 21st century? The intersection of palatable food, cues and reward pathways, stress, and cognition. Neuroscience & Biobehavioral Reviews, 58, 36–45. doi: 10.1016/j.neubiorev.2014.12.002

48. Obesity. (2014, September 5). Retrieved from https://www.who.int/topics/obesity/en/

49. Olmstead, M. C., & Franklin, K. B. (1994). Lesions of the pedunculopontine tegmental nucleus block drug-induced reinforcement but not amphetamine-induced locomotion. Brain Research, 638(1-2), 29–35. doi: 10.1016/0006-8993(94)90629-7

50. Pampel, F. C., Krueger, P. M., & Denney, J. T. (2010). Socioeconomic Disparities in Health Behaviors. Annual Review of Sociology, 36(1), 349–370. doi: 10.1146/annurev.soc.012809.102529

51. Panenka, W. J., Procyshyn, R. M., Lecomte, T., Macewan, G. W., Flynn, S. W., Honer, W. G., & Barr, A. M. (2013). Methamphetamine use: A comprehensive review of molecular, preclinical and clinical findings. Drug and Alcohol Dependence, 129(3), 167–179. doi: 10.1016/j.drugalcdep.2012.11.016

52. Prus AJ, James JR, Rosecrans JA. Conditioned Place Preference. In: Buccafusco JJ, editor. Methods of Behavior Analysis in Neuroscience. 2nd edition. Boca Raton (FL): CRC Press/Taylor & Francis; 2009. Chapter 4. Available from: https://www.ncbi.nlm.nih.gov/books/NBK5229/

53. Rada, P., Avena, N., & Hoebel, B. (2005). Daily bingeing on sugar repeatedly releases dopamine in the accumbens shell. Neuroscience, 134(3), 737–744. doi: 10.1016/j.neuroscience.2005.04.043

54. Ramos, J., Flores-Robles, G., Gonzalez, A. T., Cruz, B., Martinez, A. K., Beltran, N. M., & Serafine, K. M. Females are more sensitive than males to enhanced sensitivity to dopaminergic drugs caused by eating a high fat diet. Under Review The Journal of Pharmacology and Experimental Therapeutics.

55. Robbins, S. J., Ehrman, R. N., Childress, A. R., & Obrien, C. P. (1999). Comparing levels of cocaine cue reactivity in male and female outpatients. Drug and Alcohol Dependence, 53(3), 223–230. doi: 10.1016/s0376-8716(98)00135-5

56. Roberts, D. C., Corcoran, M. E., & Fibiger, H. C. (1977). On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. Pharmacology Biochemistry and Behavior, 6(6), 615–620. doi: 10.1016/0091-3057(77)90084-3

57. Roma, P. G., & Riley, A. L. (2005). Apparatus bias and the use of light and texture in place conditioning. Pharmacology Biochemistry and Behavior,82(1), 163-169. doi:10.1016/j.pbb.2005.08.004

58. Rommel, N., Rohleder, N. H., Wagenpfeil, S., Haertel-Petri, R., & Kesting, M. R. (2015). Evaluation of methamphetamine-associated socioeconomic status and addictive behaviors, and their impact on oral health. Addictive Behaviors, 50, 182–187. doi: 10.1016/j.addbeh.2015.06.040

59. Runegaard, A. H., Sørensen, A. T., Fitzpatrick, C. M., Jørgensen, S. H., Petersen, A. V., Hansen, N. W., … Gether, U. (2018). Locomotor- and Reward-Enhancing Effects of Cocaine

Are Differentially Regulated by Chemogenetic Stimulation of Gi-Signaling in Dopaminergic Neurons. Eneuro, 5(3). doi: 10.1523/eneuro.0345-17.2018

60. Schindler, C. W., Bross, J. G., & Thorndike, E. B. (2002). Gender differences in the behavioral effects of methamphetamine. European Journal of Pharmacology,442(3), 231-235. doi:10.1016/s0014-2999(02)01550-9

61. Schramm-Sapyta, N. L., Walker, Q. D., Caster, J. M., Levin, E. D., & Kuhn, C. M. (2009). Are adolescents more vulnerable to drug addiction than adults? Evidence from animal models. Psychopharmacology, 206(1), 1–21. doi:10.1007/s00213-009-1585-5

62. Sengupta P. (2013). The Laboratory Rat: Relating Its Age With Human's. International journal of preventive medicine, 4(6), 624–630.

63. Serafine, K. M., Bentley, T. A., Grenier, A. E., & France, C. P. (2014). Eating high fat chow and the behavioral effects of direct-acting and indirect-acting dopamine receptor agonists in female rats. Behavioural Pharmacology,25(4), 287-295. doi:10.1097/fbp.0000000000000052

64. Serafine, K. M., Bentley, T. A., Kilborn, D. J., Koek, W., & France, C. P. (2015). Drinking sucrose or saccharin enhances sensitivity of rats to quinpirole-induced yawning. European journal of pharmacology, 764, 529–536. doi:10.1016/j.ejphar.2015.07.036

65. Shin, E.-J., Dang, D.-K., Tran, T.-V., Tran, H.-Q., Jeong, J. H., Nah, S.-Y., … Kim, H.-C. (2017). Current understanding of methamphetamine-associated dopaminergic neurodegeneration and psychotoxic behaviors. Archives of Pharmacal Research, 40(4), 403–428. doi: 10.1007/s12272-017-0897-y

66. Shinohara, F., Kamii, H., Minami, M., & Kaneda, K. (2017). The Role of Dopaminergic Signaling in the Medial Prefrontal Cortex for the Expression of Cocaine-Induced Conditioned

Place Preference in Rats. Biological & Pharmaceutical Bulletin Biological and Pharmaceutical Bulletin, 40(11), 1983–1989. doi: 10.1248/bpb.b17-00614

67. Šlamberová, R., Macúchová, E., Nohejlová, K., Štofková, A., & Jurčovičová, J. (2014). Effect of Amphetamine on Adult Male and Female Rats Prenatally Exposed to Methamphetamine. Prague Medical Report, 115(1-2), 43–59. doi: 10.14712/23362936.2014.5

68. Speed, N., Saunders, C., Davis, A. R., Owens, W. A., Matthies, H. J., Saadat, S., … Galli, A. (2011). Impaired striatal Akt signaling disrupts dopamine homeostasis and increases feeding. PloS one, 6(9), e25169. doi:10.1371/journal.pone.0025169

69. Swerdlow NR, Gilbert D, Koob GF. Conditioned drug effects on spatial preference: critical evaluation. In: Boulton AA, Baker GB, Greenshaw AJ, editors. Psychopharmacology. Neuromethods, vol. 13. Clifton, NJ: Humana Press; 1989. p. 399–446 [241].

70. U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2010. 7th Edition, Washington, DC: U.S. Government Printing Office, December 2010

71. Volkow, N. D., Wang, G.-J., Fowler, J. S., & Telang, F. (2008). Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. Philosophical Transactions of the Royal Society B: Biological Sciences, 363(1507), 3191–3200. doi: 10.1098/rstb.2008.0107

72. Volkow, N. D., Wang, G. J., Tomasi, D., & Baler, R. D. (2012). Obesity and addiction: neurobiological overlaps. Obesity reviews: an official journal of the International Association for the Study of Obesity, 14(1), 2-18.

73. Volkow, N. D., Wise, R. A., & Baler, R. (2017). The dopamine motive system: Implications for drug and food addiction. Nature Reviews Neuroscience,18(12), 741-752. doi:10.1038/nrn.2017.130

74. Wahlstrom, D., White, T., & Luciana, M. (2010). Neurobehavioral evidence for changes in dopamine system activity during adolescence. Neuroscience and biobehavioral reviews, 34(5), 631–648. doi:10.1016/j.neubiorev.2009.12.007

75. Wallace, T. L., Gudelsky, G. A., & Vorhees, C. V. (1999). Methamphetamine-induced neurotoxicity alters locomotor activity, stereotypic behavior, and stimulated dopamine release in the rat. The Journal of neuroscience: the official journal of the Society for Neuroscience, 19(20), 9141–9148. doi:10.1523/JNEUROSCI.19-20-09141.1999

Vita

Kayla Galindo was born and raised in El Paso, TX where she graduated from Canutillo High School in El Paso, in 2008. She thereafter attended the University of Texas at El Paso (UTEP) and graduated with a Bachelor's of Science in Fall 2012. Following her interest and previous undergraduate research in Evolutionary Genetics, she completed a Professional Master's of Science in Bioinformatics in 2014. After graduation she found employment as a research assistant in a behavioral pharmacology laboratory at the University Health Science Center in San Antonio, TX. Under the guidance of Dr. Gregory Collins, she was able to conduct, manage, and perform the surgeries necessary to conduct research being done on synthetic cathinones (e.g. MDPV) and their effects on self-administration and locomotion in rats. In order to continue work in the field of behavioral pharmacology and work towards a Ph.D. she entered the Behavioral Neuroscience graduate program at UTEP. She joined the laboratory of Dr. Katherine Serafine who studies the behavioral factors that contribute to individual differences in vulnerability to drug abuse, including diet, age, and sex. Since her start at UTEP she has conducted several experiments including self-administration, conditioned place preference, locomotion/open field activity, and directly observable behavior. Throughout her time at UTEP, Kayla has had 7 poster abstracts accepted at several national conferences and has presented her first year project to the psychology department at UTEP. She has also been awarded numerous travel awards and was awarded the Caetano Alcohol Research Award in 2019. She plans to continue her research and work towards her dissertation proposal and defense and UTEP under the mentorship of Dr. Katherine Serafine. Her long term goals are to pursue a research-oriented career at an academic or government funded institution.

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