

Spring 5-19-2021

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Memon, Ariba, "Development of a Binge-Like Eating Animal Model Using Foods of Varying Palatability: Effects of the Catecholamine Uptake Blocker Lisdexamfetamine" (2021). *Honors Scholar Theses*. 814. https://opencommons.uconn.edu/srhonors_theses/814

**Development of a Binge-Like Eating Animal Model
Using Foods of Varying Palatability: Effects of the
Catecholamine Uptake Blocker Lisdexamfetamine**

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Acknowledgments

First, I would like to thank Dr. Salamone for welcoming me into his undergraduate lab team as a Sophomore, and for introducing me to the field of behavioral neuroscience. His mentorship and support helped me complete my research and thesis, as well as with my personal journey to become a physician. The words of encouragement and stories he shared made the lab a place I was excited to learn at, and made Dr. Salamone's passion for teaching evident. I also want to thank Rose Presby for answering my questions, listening to my poster presentation practice runs, and for her unwavering support on this project. Her enthusiasm for her work and overall patience allowed me to learn the behavioral procedures and pharmacology behind this project. I looked forward to coming to the lab and working with her this past year because of kindness and willingness to teach. I would also like to thank Renee Rotolo and Emma Zorda for their guidance and for sharing their valuable knowledge on the many projects in the lab. Lastly, I would like to acknowledge all my fellow undergraduates in the Salamone lab, and thank all the rats and mice that I have worked with over the years—they will be missed.

Abstract

Binge Eating Disorder (BED) is a psychiatric disorder that is characterized by the consumption of an excessive amount of food in a short period of time despite not being hungry. Numerous animal models have been developed that can induce binge-like eating behavior through limited access to a highly palatable food. One such model utilizes Cadbury's milk chocolate that is very successful in inducing binge-like eating behavior in both male and female rats. Lisdexamfetamine (LDX), a d-amphetamine prodrug and the only FDA approved pharmaceutical treatment for BED, has been shown to significantly reduce chocolate consumption in the chocolate binge-like animal model. The current project aimed to determine if similar binge-like eating behavior can be obtained through the use of either high carbohydrate pellets, the standard highly palatable food used in effort-related operant tasks, and/or grain-based pellets, similar to the standard lab chow that animals have ad libitum. It is hypothesized that if the two types of pellets generate a similar binge-like eating behavior, then LDX may have a similar effect as in the chocolate model. Results show a significant increase in pellet consumption with increased exposure but not to the same degree as chocolate. LDX suppressed intake of all three types of food, though with different dose-related patterns. These findings show a combination of similarities and differences when studying the consumption of palatable foods, like chocolate and pellets, and less palatable food, like grain-based pellets, and the effects of LDX administration.

Introduction

Binge-eating disorder (BED) affects about 3% of adults in the United States over their lifetime (Brownley et al. 2016). According to the DSM-5, BED is characterized by the consumption of an excess amount of food more than once per week for 3 months, each occurrence lasting less than two hours. Bouts of binge eating are psychologically distressing, such that patients feel a loss of self-control, and feelings of depression or guilt, from a binge-eating episode (Brownley et al. 2016). These individuals, however, do not engage in compensatory behavior like purging or excessive exercise, which is why in 2013, the American Psychiatric Association recognized BED as its own eating disorder, separate from bulimia nervosa and anorexia nervosa (Brownley et al. 2016). The age of onset of BED is around 21 years old, women are more likely to be diagnosed than men and those struggling with obesity are more commonly diagnosed (Eating Disorders 2017). BED is also associated with poor psychological health, chronic pain, and obesity, and predisposes individuals to type 2 diabetes (Brownley et al. 2016). It has one of the highest comorbidity rates with anxiety disorder, after Bulimia Nervosa (Eating Disorders 2017).

Numerous studies have been conducted that evaluate methods for inducing binge-like eating behavior in animal models using a variety of palatable foods. Oswald et al. (2011) used Double Stuff Oreo cookies as the highly palatable food with a particularly high carbohydrate and fat content. M&M Candies were also used in this study to measure the rat's motivation (Oswald, 2011). Avena et al. (2004) developed a model of binge-eating behavior in rats using sucrose solutions, while Corwin et. al (2007) provided non-food restricted rats with vegetable shortening to design a model of excessive behavior in relation to a highly palatable food, which is characteristic of binge eating disorder. In the model of sucrose bingeing, rats are given sugar solutions at repeated, intermittent intervals (Avena, 2004), and in the model of a high-fat food bingeing, rats are given a sporadic, limited access to the shortening (Corwin, 2007). It is important to note the varying palatable foods

used to develop a binge-eating model, and the contrasting schedules in which the palatable food is offered. For models in which the rats are not food restricted, they are then given access to the highly palatable food at random, sporadic intervals. This is to ensure that the binge-like behavior is as a result of the palatability of the food, not the rat's hunger. The current study, similarly, offered non-food restricted rats, limited, sporadic access to high-carbohydrate (HC) or grain based (GB) pellets to determine whether binge-behavior could be developed. The model was developed based on the Presby et. al (2020) study that utilized Cadbury's milk chocolate as the highly palatable food offered to non-food restricted rats.

Psychological and behavioral treatments for BED aim to directly reduce both the frequency of episodes, and cognitions related to disordered eating (Brownley et al. 2016). For individuals with comorbid symptoms, treatments also aim to regulate mood and improve overall health (Brownley et al. 2016). One class of drugs, central nervous system stimulants, are used to enhance both mental and physical processes (Brownley et al. 2016). The d-amphetamine prodrug lisdexamfetamine (LDX), a psychostimulant typically used to treat attention deficit-hyperactivity disorder (i.e., Vyvanse), is currently the only medication approved by the United States Food and Drug Administration to treat BED (Brownley et al. 2016). Presby et al. (2020) demonstrated that LDX reduced the chocolate intake and standard laboratory chow in a dose-dependent manner, suggesting that LDX acts as an appetite suppressing agent. These findings served as the basis for the current study that aims to identify if binge-like feeding behavior can be induced by foods with a varying degree of palatability.

HC pellets are the standard highly palatable food used as reinforcers in operant behavior experiments, thus the aim of these studies was to see if binge-like eating behavior could be induced with these over chocolate. To further the distinction between varying palatable foods in inducing a binge-like eating behavior, an additional study explored whether the behavior could be induced

using grain-based pellets that are similar to the laboratory chow given ad libitum to the rats. It was hypothesized that the HC pellets would be able to induce a binge-like behavior similar to that of Cadbury's milk chocolate, and that LDX would act to reduce the pellet intake in a dose-dependent manner. Furthermore, the grain-based pellets were expected to produce lower levels of binge-like eating behavior because they are not as highly palatable as the high-carbohydrate pellets or the Cadbury's milk chocolate that was the focus of previous studies.

Materials and Methods

Animals

Twenty six adult male Sprague Dawley rats (Charles River) were single-housed in a colony maintained at 23°C, with a 12-h light/dark cycle (lights on at 7:00 h). There was ad libitum access to standard laboratory chow (5P00 ProLab RMH 3000; ScottPharma Solutions; composed of approximately 14% fat, 60% carbohydrate and 26% protein with a total of 4.18 kcal/g) and water throughout the study. Weights of both the rats and ad libitum laboratory chow were taken daily to monitor for any fluctuations in weight and daily food intake that may be associated with the binge-like behavior. Animal protocols were in accordance with University of Connecticut Institutional Animal Care and Use Committee guidelines.

Acquisition of Binge-Like Behavior

Acquisition of the binge-like behavior took place over the course of 12 exposure sessions. A 3-day, 1-hr exposure to an empty feeding cage with a ceramic dish took place before chocolate exposure. Separate groups of rats received either finely ground Cadbury's milk chocolate (composed of 0.3g fat, 0.57g carbohydrate, and 0.073g protein with a total of 5.34kcal/g; n=7), high-carbohydrate (HC) pellets (Bio-serv Inc., Prospect CT, composed of approximately 5.6% fat, 59.1%

carbohydrate and 18.7% protein with a total of 3.6 kcal/g; n=12) or grain-based (GB) pellets (Bio-serv Inc., Prospect, CT, composed of approximately 3.8% fat, 54% carbohydrate and 21.3% protein with a total of 3.35 kcal/g; n=7) on days 1, 2, 4, 6, 7, 9, 12, 14, 15, 18, 23 and 28 (schedule from Presby et al. 2020). On exposure days, rats were placed in the empty feeding cage with a ceramic dish containing assigned food for 1 hr. Weight of food was taken before and after each session. The rats were not food restricted during the course of the experiment, and the amount of food given during the exposure session was determined by the rat's intake during the previous session, so that more food was provided than the rat could consume during the sessions.

Drug Treatments

Upon completion of the acquisition of the binge-like eating rats continued to be exposed to chocolate twice a week for 1-hr in empty feeding cages with a ceramic dish containing assigned food. One session was for maintenance of the binge-like behavior, and the second was for drug treatment. These sessions took place randomly throughout the week with the maintenance session always occurring prior to the drug treatment session. Trained rats were administered IP injections of LDX at doses of 0.1875, 0.375, 0.75, 1.5mg/kg or vehicle (saline) 60 minutes prior to testing. The experiment used a within-groups design, with each rat receiving each drug treatment in a randomly varied order. Food was weighed before and after each session to determine consumption.

Statistical Analysis

A repeated measures factorial analysis of variance (ANOVA) was used to compare the effect of the varying palatable foods on inducing binge-like behavior. To evaluate the effect of LDX on the amount of food in grams consumed during a food intake session. Planned comparisons (Keppel 1973) were used to compare each treatment to the VEH group.

Results

Repeated measures factorial ANOVA for the acquisition of binge-like eating behavior of the varying foods (Fig 1) showed that a significant overall increase in consumption across sessions was seen [$F(11,264)=23.157, p<0.001$] with a significant session x group interaction [$F(22,264)=2.206, p<0.01$] and a significant difference between the food types [$F(2,24)=8.232, p<0.01$]. Furthermore, administration of LDX produced a significant overall suppressive effect on chocolate intake [$F(4,24)=11.593, p<0.001$] (Fig. 2), HC pellet intake [$F(4,44)=19.527, p<0.001$] (Fig. 3) and GB pellet intake [$F(4,24)=5.149, p<0.01$] (Fig. 4). Planned comparisons showed a significant decrease in chocolate intake at the 2 highest doses (Veh vs. LDX 0.75mg/kg [$F(1,6)=7.17, p<0.05$] & Veh vs. LDX 1.5mg/kg [$F(1,6)=28.88, p<0.01$]) (Fig 2) and HC pellet intake at the 3 highest doses of LDX (Veh vs. LDX 0.375mg/kg [$F(1,11)=5.06, p<0.05$], Veh vs. LDX 0.75mg/kg [$F(1,11)=23.16, p<0.001$] & Veh vs. LDX 1.5mg/kg [$F(1,11)=53.64, p<0.001$]) (Fig 3). Planned comparisons showed a significant decrease in GB pellet intake at the highest dose of LDX (Veh vs. LDX 1.5mg/kg [$F(1,6)=9.76, p<0.05$]) (Fig 4).

Acquisition of Binge-Like Eating Behavior

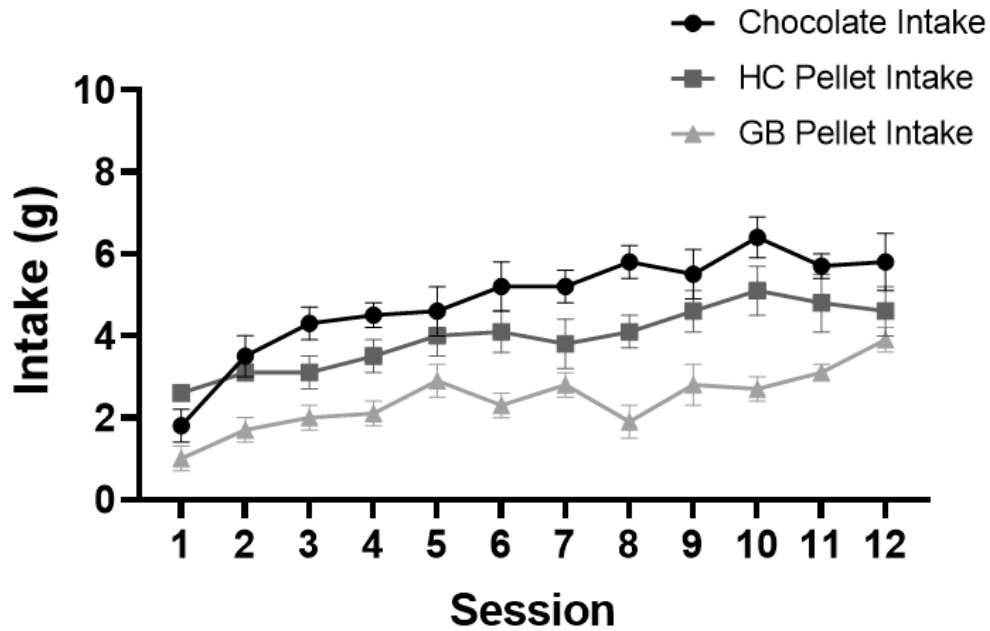


Figure 1: Comparison of mean (\pm SEM) high-carbohydrate pellet, grain-based pellets and chocolate consumption (in grams) of rats per session during acquisition.

LDX Chocolate Intake

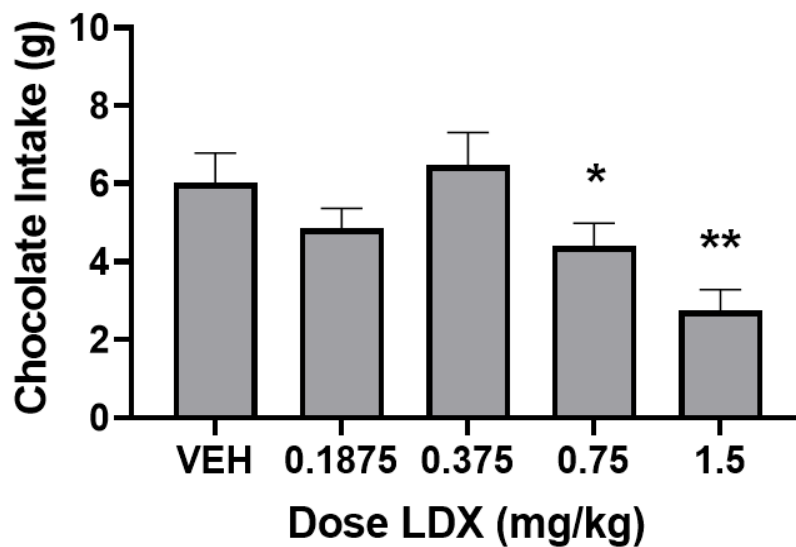


Figure 2: The effects of LDX on chocolate intake (mean \pm SEM). An overall significant effect of LDX (* $p < 0.05$, ** $p < 0.01$) on chocolate consumption at the two highest doses was seen.

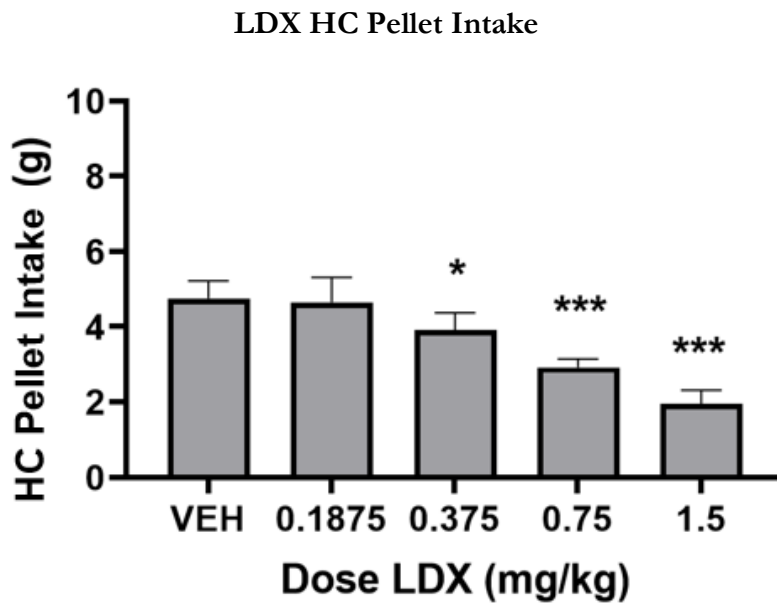


Figure 3: The effects of LDX on HC pellet intake (mean +SEM). An overall significant effect of LDX (* $p < 0.05$, *** $p < 0.001$) on pellet consumption at the three highest doses was seen.

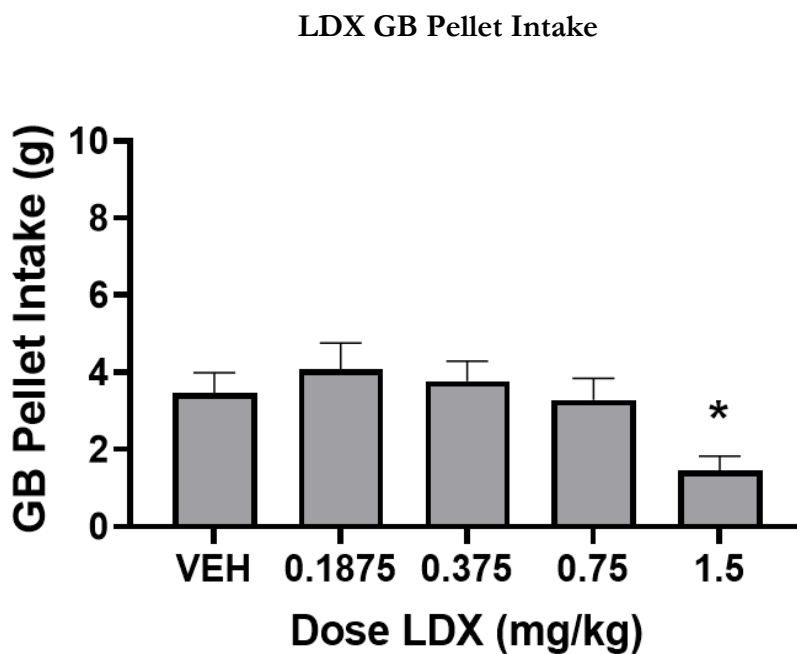


Figure 4: The effects of LDX on GB pellet intake (mean +SEM). An overall significant effect of LDX (* $p < 0.05$) on GB pellet consumption at the highest dose was seen.

Discussion

The aim of this study was to determine if binge-like eating behavior in rats, which is known to be induced by chocolate access, could be induced using HC pellets, a highly palatable food used in operant chamber experiments, or GB pellets, a food very similar to the standard lab chow animals are given ad libitum. The non-food restricted rats were given intermittent, limited exposure to chocolate, HC, or GB pellets which led to an increased level of intake over the course of the 12, 60 minute sessions. There is an acquisition of the binge-like eating behavior using the HC pellets, similar to that for chocolate but the consumption of pellets is less than that seen in the chocolate exposure paradigm (Fig. 1). There was an increase in GB pellets consumption but it was lower than both chocolate and HC pellets. This adds to the distinction made by each palatable food in that those of greater palatability (chocolate > HC pellets > GB pellets), the greater extent to which access to that food will lead to robust binge-like eating behavior.

LDX was then administered to identify if it would reduce the HC or GB pellet consumption similar to that seen in the Cadbury's milk chocolate model. The experiment demonstrated that LDX significantly decreases HC pellet consumption in 60-minute exposure sessions at the three highest doses of LDX (Fig. 2). Only the highest dose of LDX was able to significantly suppress GB pellet intake (Fig. 3). This indicates that LDX is more potent (i.e., active at low doses) for suppression of intake of the more highly palatable foods.

Since BED encompasses a number of different psychological and physiological symptoms, research has focused on identifying the regions of the brain responsible for appetite regulation, which in turn, can be the target of pharmacological treatments. The lateral hypothalamus is of particular interest here because it is associated with the inhibition of feeding behavior, which is a potential target for therapeutic agents in treating BED. Catecholamines induce anorexigenic, or appetite suppression, responses in both animals and humans. Amphetamines (AMPH) can induce

this response by increasing the extracellular catecholamine level by blocking reuptake or increasing levels of catecholamines in the hypothalamus. Furthermore, studies have shown that low doses of AMPH can induce anorexic effects when locally injected into the lateral hypothalamus, but not other forebrain structures (Leibowitz 1975a&b).

Overall, it is clear that LDX reduces food intake, and it seems evident that the effect of LDX is not limited to foods considered highly palatable consumption. Thus, a part of the effect of LDX appears to be a general suppression of food intake, as indicated by the reductions in GB pellet intake that also were seen. Previous studies have shown that LDX suppresses chow intake in rats in the context of studies using binge-like eating procedures (Vickers et al., 2015, Presby et al., 2020). The active moiety in LDX, d-amphetamine, is a well-known appetite suppressant, thus leading to its use as a weight loss drug for several decades (Coleman 2005). This is consistent with the fact that a general suppression of appetite has been reported as a side effect of using LDX to treat BED in humans (Citrome 2015; McElroy et al. 2016; Ward and Citrome 2018). Nevertheless, the present results suggest that the effect of LDX on intake of the GB pellets is less potent than the actions on the other foods, so the effect is not uniform across all foods tested.

The present study aimed to identify if binge-like eating behavior could be developed utilizing foods of varying degrees of palatability. The result indicated that intake of the three foods differed during acquisition, however, there was a tendency to increase from the first few sessions shown across all the food groups (Figure 1). Nevertheless, we cannot conclude what specific characteristics of each food makes one more desirable than another. Characteristics such as taste, texture, ease of consumption, or contrast between the standard home cage food probably work jointly to dictate the ability of a food to develop a robust binge-like pattern of eating behavior. As previously discussed, there are a number of binge-like animal models that use various food types to develop the behavior (Oswald et al., 2011; Avena et al., 2004; Corwin et al., 2007; Presby et al., 2020). These previous

studies demonstrated that offering highly palatable foods to rats can lead to the development of binge-like eating behavior. The current study illuminates a distinction in the palatability across the foods used, however, LDX was able to suppress intake of all three foods, although at different doses. As a result, future directions for studies on BED could investigate what properties of foods of varying palatability contribute to the development of a binge-like behavior. This would provide insight into why the development of a binge-like eating behavior in response to chocolate is more robust than the other types of foods.

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