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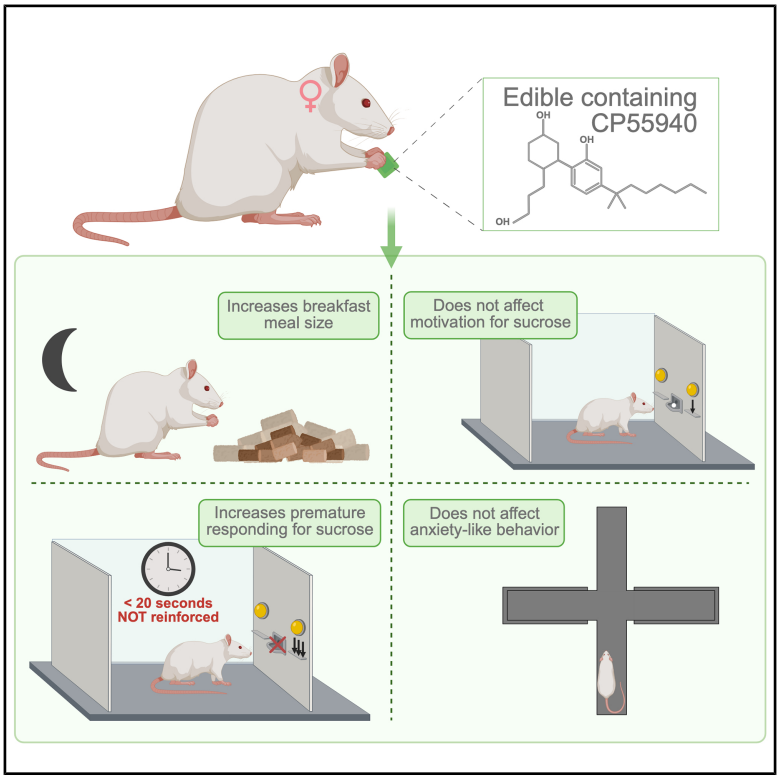
Edible cannabinoids impact meal structure and food impulsivity in female rats

Graphical abstract



Highlights

- Edible cannabinoid CP55940 acutely increases chow intake via increased meal size
- At the hyperphagic dose, edible CP55940 elevated impulsivity for sucrose reward
- The hyperphagic dose did not affect motivation for sucrose or anxiety-like behavior
- Voluntary edible cannabinoid models enhance translatability of preclinical findings

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In brief

Behavioral neuroscience; Biological sciences; Natural sciences; Neuroscience

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Edible cannabinoids impact meal structure and food impulsivity in female rats

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SUMMARY

Cannabinoid receptor agonists increase eating in a dose-dependent manner. However, the behavioral mechanisms by which cannabinoids modulate food intake control aren't clear, particularly in females. We utilized a rodent model of cannabinoid administration modeling a common route of cannabinoid consumption in humans: edibles. Herein, we administered the dual cannabinoid receptor agonist CP55940 in edible form to female rats and observed acute increases in standard chow intake due to an increase in meal size with no change in meal number. We further observed that the hyperphagic dose of edible CP55940 increases impulsive responding for sucrose, but this did not coincide with changes in motivation for sucrose. Finally, cannabinoids can affect anxiety-like behavior, but the acutely hyperphagic dose used in our studies had no effect on anxiety-like behavior. We conclude that edible cannabinoid administration delays satiation and increases impulsive eating behavior without impacting food motivation, potentially by reducing inhibitory control.

INTRODUCTION

Cannabis (marijuana) use in America has increased in the past decade, with nearly 30% of young adults (aged 19–30) and over 19% of mid-life adults (aged 35–50) self-reporting having used cannabis in the past thirty days.[1] Changing legality has largely shifted the cultural opinion of cannabis use, with some being misled to believe use has little consequence.[2,3] However, compounds in cannabis act on cannabinoid receptors to modulate a host of physiological functions including modulation of pain processes, sleep, anxiety, energy homeostasis, and appetite regulation.[4–7] This wide array of functions modulated by cannabinoids is due to the vast central and peripheral distribution of cannabinoid receptors,[8] conferring equally vast behavioral effects.

One of the known behavioral effects of cannabinoids is an upregulation in food intake, colloquially coined as "the munchies". Marijuana's effect on food intake in healthy individuals was reported as early as 1986, when a Johns Hopkins group observed increased snacking behavior in adult males following marijuana cigarettes.[9] Laboratory rodents also get the munchies, as has been demonstrated using various cannabinoids of differing dosages.[10–13] The munchies, as an observed behavior, can be the result of multiple potential neurobiological changes, such as motivated appetitive drive, reduced satiation, or impaired inhibitory control. Therefore, we set out to determine the impact of voluntary edible cannabinoid consumption on eating behavior in female Wistar rats, with a focus on meal patterns, food impulsivity, and food motivated behavior.

Cannabinoids have been shown to be anxiogenic in some individuals.[14] Another potential contributor to the enhanced ingestive behavior associated with cannabinoid usage is eating for anxiety reduction and mood regulation. In women, anxiety is associated with increased calorie consumption at a buffet and reduced activation of brain regions associated with satiety when visualizing high-fat palatable food cues.[15] Therefore, we further investigated whether a dose of cannabinoids sufficient to increase food intake also affects anxiety-like behavior in female rodents.

Basic mechanisms underlying how cannabinoids modulate behavior and metabolic processes in preclinical models have generally been studied using injection of cannabinoid receptor ligands as the route of administration. One benefit of injectable cannabinoid administration is that the dose in the blood can be controlled. However, cannabinoid drugs are not typically injected during recreational or clinical cannabinoid use; rather, cannabinoids are generally smoked or taken orally. Oral ingestion of cannabinoids is of particular importance to investigate due to its greater clinical utility over smoking. For example, the only FDA-approved cannabinoid therapeutics currently available are in oral or oromucosal preparations.[16] Within the last decade, it has become of interest to develop models of cannabinoid consumption that more closely model humans' administration methods, i.e., inhalation and ingestion of edibles in rodents. Self-administration of THC (tetrahydrocannabinol)-containing gelatin or cookies provided the first models of voluntary oral ingestion of THC edibles in rodents.[17–20] Subsequently, others built upon the self-administration model by incorporating palatable agents, such as Ensure (Abbott), to further encourage voluntary consumption of THC.[21] These revolutionary models of voluntary oral consumption of cannabinoids are credited with initiating this vital area of study. However, the self-administration model produces a variety of THC concentrations and volumes of gelatin consumed, and

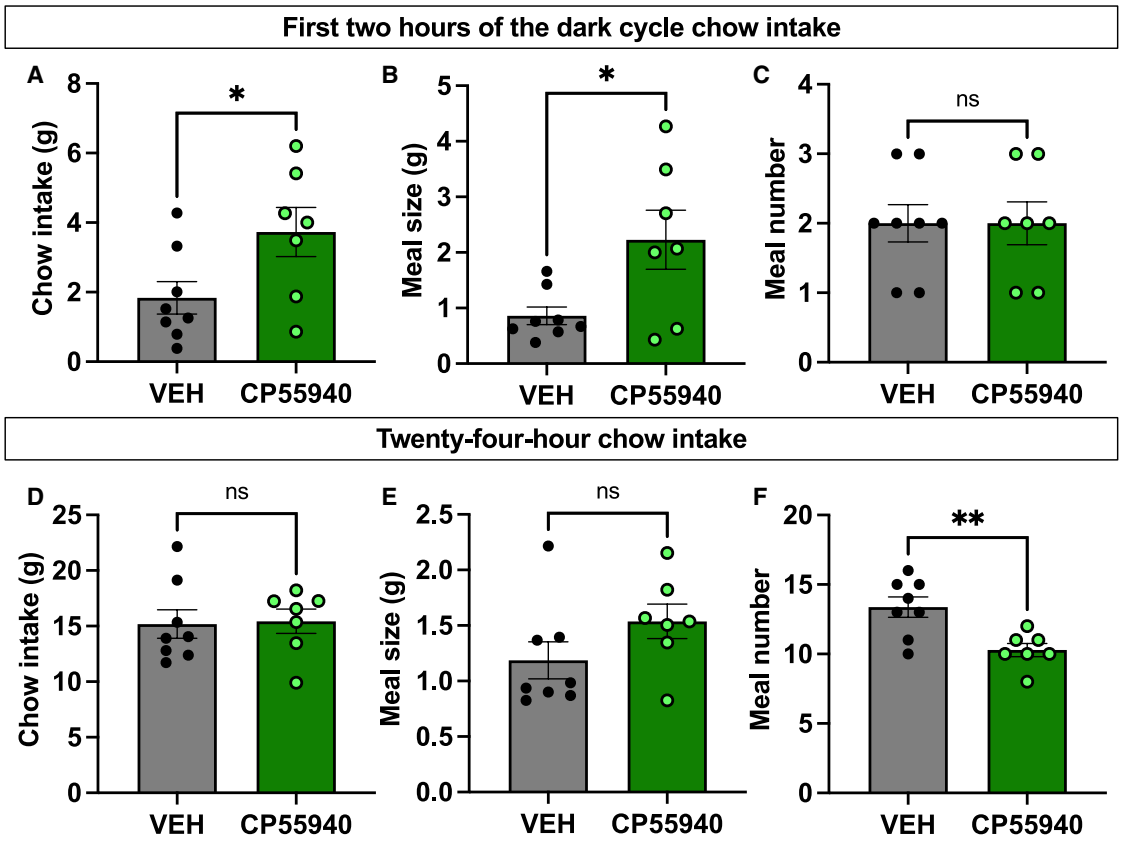

Figure 1. Edible cannabinoid receptor agonist acutely promotes eating behavior via an increase in meal size

(A–F) Female rats ($n = 15$) increased standard chow intake over the first 2 h of the dark cycle (A) via an increase in meal size (B) with no changes in meal number (C). However, over the course of 24 h, there was no difference in overall chow intake (D), nor meal size (E), and a decrease in meal number (F). Data are means +/− SEM; *$p < 0.05$, **$p < 0.01$.

cannabimimetic responses can only be categorized based on dose averages. To circumvent this dose and ingested volume range that self-administration confers, Amissah and colleagues utilized the hyperpalatable vehicle Nutella (Ferrero) to dissolve the precise dose each rodent needs based on their weight.[22] The study of eating behavior following consumption of an edible requires the volume ingested to remain consistent. Therefore, utilizing a combination of these techniques, we have developed a model of edible cannabinoid consumption wherein the synthetic CP55940, a THC-like cannabinoid, is dissolved in coconut oil and incorporated into a gelatin-based edible with enhanced palatability from Jello (Kraft-Heinz). The precise dose for each subject is then portioned according to the weight of the animal. All data were collected using edible cannabinoid administration, wherein we examined female rats' behavioral responses to a cannabinoid-containing edible or its vehicle preparation.

RESULTS

Edible cannabinoid receptor agonist acutely promotes eating behavior via an increase in meal size

Female rats given the CP55940-containing edible increased their intake of chow compared to rats given vehicle edible over the first two hours of the dark cycle (t = 2.230, df = 10.67, p = 0.048; Figure 1A). Meal number and meal size were analyzed within this two hour window, and results revealed that in response to edible CP55940, female rats elevated their meal size (t = 2.467, df = 7.047, p = 0.043; Figure 1B) without changing the number of meals eaten (t = 0, df = 12.40, $p > 0.99$; Figure 1C) compared to rats given a vehicle edible. These results were acute, as over the twenty-four-hour period, chow intake (t = 0.1446, df = 12.90, p = 0.89; Figure 1D) and meal size (t = 1.541, df = 13, p = 0.15; Figure 1E) were not different between groups, and there was a notable decrease in meal number in the edible CP55940 group compared to the vehicle edible group (t = 3.548, df = 11.71, p = 0.0042; Figure 1F). Taken together, these data indicate CP55940 acutely elevates chow intake in female rats via an increase in meal size, with compensatory reductions in meal number over the course of twenty-four hours.

Edible cannabinoid receptor agonist increases impulsive action for sucrose

Female rats were trained in the differential reinforcement of low rates of responding (DRL) task prior to testing the effects of the cannabinoid-containing edible on impulsive action for sucrose (visual representation shown in Figure 2A). Rats given edible

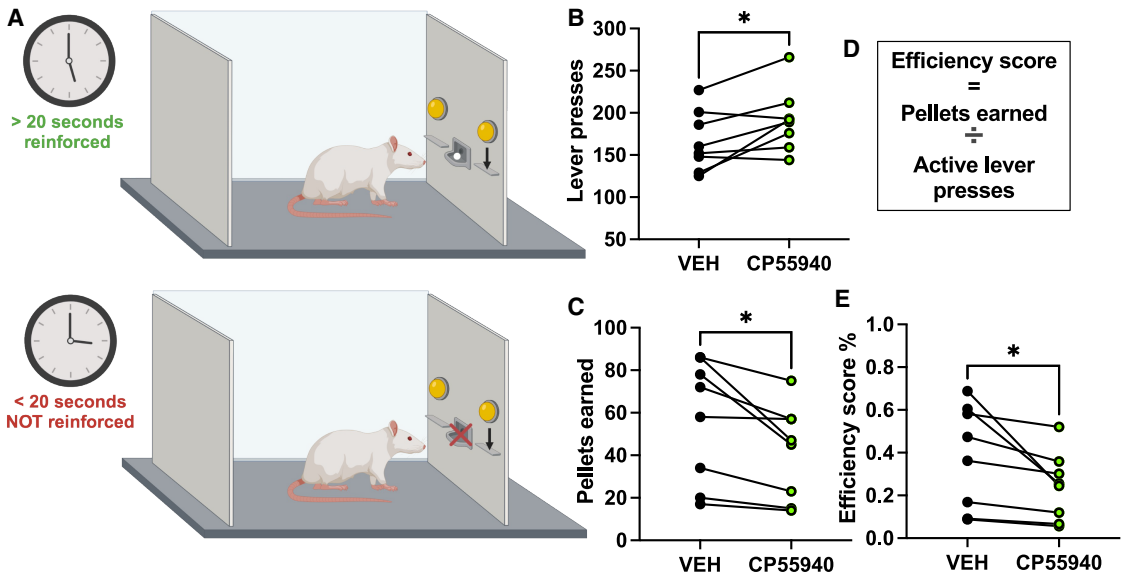

Figure 2. Edible cannabinoid receptor agonist increases impulsive action for sucrose in female rats (n = 8)

(A–E) The differential reinforcement of low rates of responding task was utilized to measure impulsive behavior; a schematic of the task shows the binary outcome of either pressing the lever after the 20-s interval or prematurely pressing the lever (A). Compared to vehicle, cannabinoid-treated females pressed the active lever more (B), and earned fewer pellets (C). An efficiency score is calculated by the equation in (D). Cannabinoid-treated females were less efficacious in obtaining sucrose in the task (E) indicating that edible CP55940 elevates impulsive action for sucrose in female rats. All behavior was examined during the dark cycle. Data are means +/− SEM; *$p < 0.05$.

CP55940 prior to testing in DRL 20 pressed the active lever more (t = 2.766, df = 7, p = 0.028; Figure 2B) yet earned fewer pellets when compared to responses following a vehicle edible (t = 2.908, df = 7, p = 0.021; Figure 2C). This increase in lever pressing from the CP55940 group was not due to increased nonspecific activity as there was no difference in lever pressing on the nonreinforced, inactive lever (t = 1.34, df = 7, p = 0.22; Figure S2A). An efficiency score was calculated by dividing the number of pellets earned by the number of active lever presses (Figure 2D), which revealed that the edible CP55940 group was less efficient in obtaining sucrose than the vehicle group (t = 2.491, df = 7, p = 0.042; Figure 2E). Taken together, these data indicate that animals given edible CP55940 exhibit greater impulsive action for sucrose when compared within-subjects to responses given the vehicle edible.

Edible cannabinoid receptor agonist does not affect motivation for sucrose

Rats were tested in the progressive ratio (PR) task to determine if the acute, hyperphagic dose of edible CP55940 that increases impulsive responding for sucrose also increases motivation to obtain sucrose. In an exponential PR schedule, (Figure 3A), there were no differences between vehicle and CP55940 groups in number of active lever presses (t = 0.2364, df = 14, p = 0.82; Figure 3B) nor pellets earned (t = 0.314, df = 14, p = 0.76; Figure 3C). We reasoned that the exponential progression may have advanced too quickly to detect differences between groups, and thus we tested a separate cohort of rats using a more gradual PR schedule wherein the number of lever presses that it took to obtain one sucrose pellet increased linearly by three (Figure 3D). Again, no differences were detected between vehicle and CP55940 groups in number of active lever presses (t = 1.308, df = 13, p = 0.21; Figure 3E) nor pellets earned (t = 1.452, df = 13, p = 0.17; Figure 3F) on the linear PR schedule. Neither PR schedule produced differences in pressing on the inactive nonreinforced lever (PR schedule 1: t = 0.3537, df = 14, p = 0.73; PR schedule 2: t = 0.5953, df = 13, p = 0.56; Figures S2B and S2C). Taken together, we conclude that an acute, hyperphagic dose of edible CP55940 does not affect motivated responding for sucrose.

Edible cannabinoid receptor agonist does not affect anxiety-like behavior in the elevated plus maze

Rats were tested in the elevated plus maze (EPM) to determine if the acute, hyperphagic dose of edible CP55940 increases anxiety-like behavior. Given five minutes in the EPM, no differences were observed between groups in total distance traveled (t = 0.9031, df = 14, p = 0.38; Figure 4A), mean speed in the maze (t = 0.8978, df = 14, p = 0.38; Figure 4B), nor time spent immobile (t = 0.08136, df = 14, p = 0.94; Figure 4C). Furthermore, no differences were observed in time spent in the closed arms (t = 0.2918, df = 14, p = 0.77; Figure 4D), the center of the maze (t = 0.9630, df = 14, p = 0.36; Figure 4E), nor the open arms (t = 0.02406, df = 14, p = 0.98; Figure 4F). Taken together, these data indicate that an acute, hyperphagic dose of edible CP55940 does not affect anxiety-like behavior in female Wistar rats.

DISCUSSION

The route of administration of cannabinoids is critically important for the interpretation of behavioral outcomes. Orally ingested

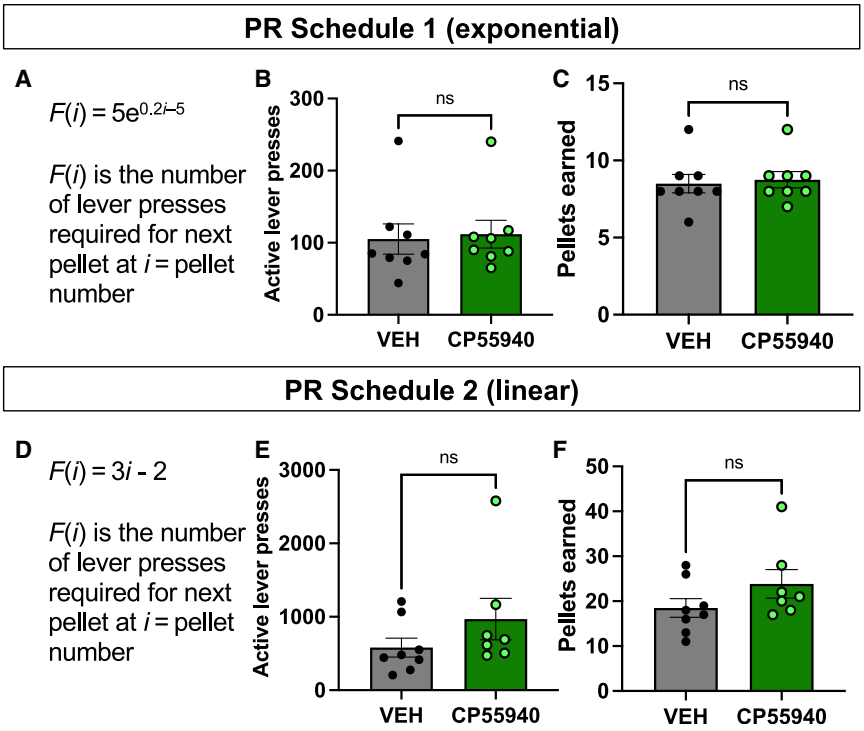

Figure 3. Edible cannabinoid receptor agonist does not affect motivation for sucrose

(A–F) Two progressive ratio (PR) tasks were used to examine motivated responding for sucrose with two separate cohorts (n = 16 in each cohort). In PR, rats must work progressively harder (more lever presses) to obtain a single sucrose pellet. In schedule 1, the number of lever presses needed for a single pellet increased exponentially by the equation shown in (A). In schedule 2, the number of lever presses needed for a single pellet increased linearly by the equation shown in (D). No differences were detected in lever presses (B and E) nor pellets earned (C and F) using either schedule. All behavior was examined during the dark cycle. Data are means +/− SEM.

cannabinoids have access to a vast distribution of cannabinoid receptors in the body, especially in the enteric nervous system.[23–25] Gelatin-based edibles more closely model human cannabinoid use when compared with injection and injection as the route of administration may bypass putative sites of cannabinoid action via gut to brain communication, which likely contributes to the hyperphagic effect of cannabis-containing edibles.[26–28] Furthermore, the pharmacokinetics of cannabinoids differ between injection and oral administration. Using THC as the model cannabinoid, it has been shown that orally administered cannabinoids are slowly and erratically absorbed,[29] and surprisingly result in the highest cannabinoid concentrations in the brain as compared to other routes of administration.[30] Oral gavage is an existing method of non-voluntary oral cannabinoid administration,[11] albeit rarely used, but has been shown to induce stress in rodents,[31] which is not ideal when measuring many physiological and behavioral parameters, such as eating behaviors. Our results show that precisely dosed gelatin-based edibles are well accepted by rats and induce hyperphagia when they contain a cannabinoid receptor agonist. To the best of our knowledge, this is the first evidence showing that oral administration of a cannabinoid-containing gelatin increases meal size in female rodents.

While it is well established that CB1 receptor agonists increase food intake, there is a relative paucity of data into the effects of cannabinoids on food intake control in females.[32] Furthermore, it is not clear at which point(s) in the sequence of a meal these ligands have their impact when cannabinoids are administered orally. Blundell and McArthur identified three stages to the "feeding cycle": appetitive, consummatory, and satiety phases.[33] Pharmacological agents, e.g., cannabinoids, modulate one or more of these feeding cycle phases to induce their largely hyperphagic effects, and understanding how pharmacotherapies impact the feeding cycle is crucial to determining their clinical utility.[34] We show here that the hyperphagic effects of oral cannabinoid administration in female Wistar rats are due to increases in meal size and not meal number. Our data are consistent with prior research conducted by Ogden and colleagues in intact female rats where the CB1 receptor agonist AM11101 injected intraperitoneally produced hyperphagia via an increase in meal size with no changes in meal frequency, a meal as defined by intake bouts greater than 0.3 g spaced not more than 15 min apart.[35] Importantly, these data further elucidate how cannabinoid receptor agonists are modulating food intake control in females, suggesting that acute CB1 receptor agonism may delay satiation within the consummatory phase of the feeding cycle.

Our findings demonstrate that cannabinoids not only increase food intake by elevating meal size, but also increase impulsive responding for a palatable reinforcer. Impulsivity is a complex behavioral trait of particular interest in the context of psychoactive drug use, defined as acting without consideration of the consequences.[36] Previous reports support a role for the endocannabinoid system in modulating impulsivity; for example, systemically administered CB1 receptor antagonist rimonabant diminishes stimulant-induced impulsivity in male rats.[37,38] The direct effect of CB1 receptor agonism on impulsive behavior may be dependent on dosing or duration of use. One group found that three weeks of chronic intraperitoneal injection of THC reduced impulsive responding in adult male rats,[39] while another group found that chronic exposure during adolescence also reduced impulsive responding for sucrose in young males, but only in the lower-dose group.[40] Further evidence suggests CB1 receptor agonism impairs response inhibition and CB1 receptor antagonism improves inhibitory control in male rats,[41–43] with one study showing no effect of THC on response inhibition in female rats.[43] In the acute study herein, we utilized the DRL task to investigate whether a hyperphagic dose of

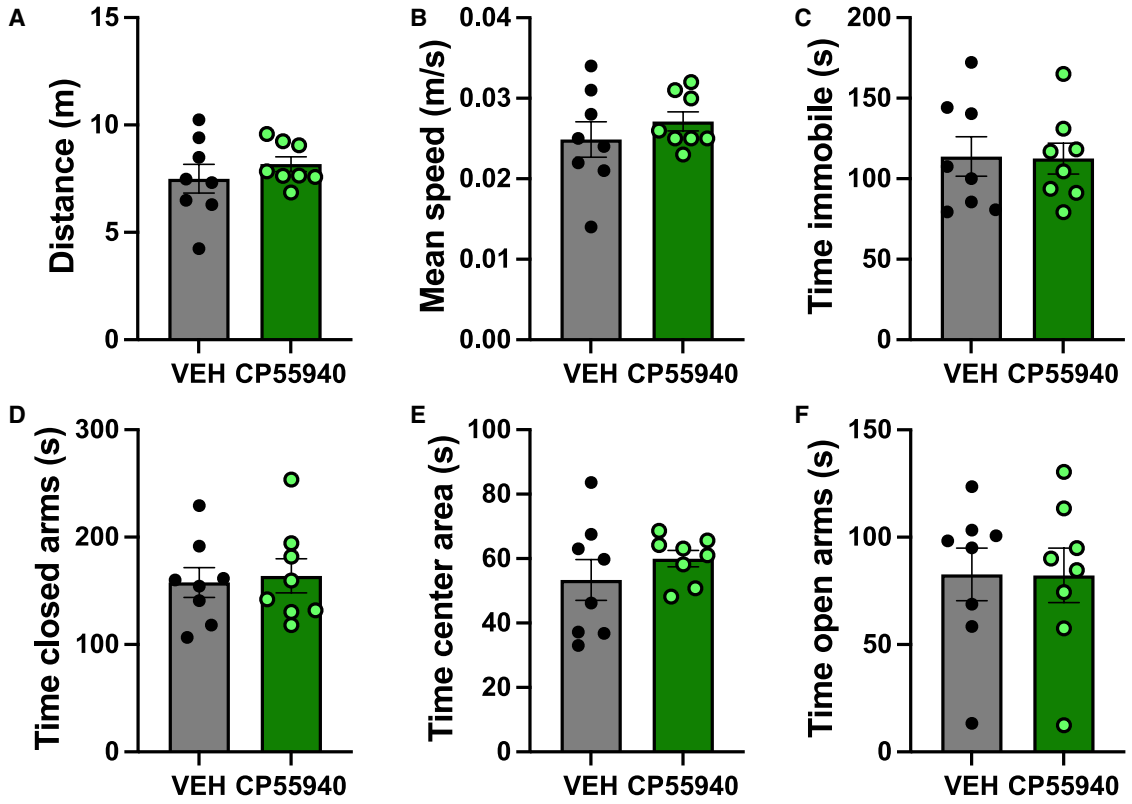

Figure 4. Edible cannabinoid receptor agonist does not affect anxiety-like behavior in the elevated plus maze

(A–F) In female rats (n = 16), no differences were detected between groups in total distance traveled in the maze (A), speed in the maze (B), time spent immobile in the maze (C), time spent in the closed arms (D), time spent in the center area (E), nor time spent in the open arms (F). Data are means +/− SEM.

CP55940 modulates impulsive action in female rats. Cannabinoid-treated females showed greater impulsive lever pressing for obtaining the palatable sucrose reinforcer compared to themselves when given vehicle. This is not due to a general increase in nonspecific lever pressing, as there was no increase in lever activity on the inactive lever. These data indicate that an edible cannabinoid receptor agonist that acutely increases meal size also elevates impulsive responding for sucrose in female rats.

Given this finding, we further investigated what could be driving elevated impulsivity in females in response to an oral cannabinoid receptor agonist. Increases in impulsive behavior in the DRL task may be due to increased motivation to seek sucrose.[44] A substantial body of literature shows that antagonizing the endocannabinoid system leads to decreased motivation to work for a food reward in male rats.[45–51] It's also been shown in male rats that CB1 receptor agonists THC and anandamide further enhance sucrose palatability.[52,53] However, few studies have directly interrogated the effect of CB1 receptor agonism on motivated responding.[54,55] While one study in male mice shows that an acute dose of intraperitoneal CP55940 increases responding for palatable reinforcers,[56] others show a biphasic response to THC vapor wherein lower dose THC vapor increases and higher dose THC vapor decreases PR breakpoint.[57] Similarly, Wheeler and colleagues show a transient increase in operant responding for a sucrose reinforcer in male rats following whole-plant cannabis vapor exposure.[58] In our study, we utilized two schedules of reinforcement to investigate motivation to obtain a palatable sucrose reinforcer in females. Using an exponential formula that has previously been used to evaluate willingness to work for drugs of abuse,[59] we found no differences in willingness to work for sucrose. We questioned whether an exponential progression with this PR schedule may have advanced too quickly to detect differences between groups using sucrose as the reinforcer. Therefore, a more conservative, linear progression that is used to evaluate food motivation was adapted from[60] and utilized as the second schedule of reinforcement. We found no differences in motivation to work for the sucrose reinforcer in CP55940 vs. vehicle treated animals in either version of the PR task, indicating that this dose of oral CP55940 that elevates impulsive responding for sucrose does not affect motivation for sucrose in female rats. While the limited existing literature suggests increased motivation for palatable rewards in response to CB1 receptor agonism, we highlight that this low dose of CP55940 was used to investigate the behavioral underpinnings of elevated impulsivity observed with this dose in female rats.

Finally, given that cannabinoids can induce anxiolytic or anxiogenic effects depending on dose,[61] we further investigated whether this model of edible cannabinoid administration affected anxiety-like behavior. Our findings suggest that this acutely hyperphagic dose of edible CP55940 has no effect on

anxiety-like behavior in female rats, demonstrating that cannabinoid-induced hyperphagia is not secondary to changes in anxiety-like behavior.

Limitations of the study

Voluntary consumption of a cannabinoid receptor agonist-containing edible by female rats produced acute hyperphagia of standard chow via an increase in meal size. While our study demonstrates that an acutely hyperphagic dose of a cannabinoid receptor agonist increases impulsive responding for food without impacting food motivated behavior or anxiety-like behavior, further study should investigate how varying the dosage of cannabinoid and how chronic dosing may influence eating behavior over the long term. Furthermore, the model cannabinoid CP55940 has been used extensively in the literature to investigate preclinical outcomes, but to further enhance the translatability of future findings; investigators may consider the use of whole-plant cannabis extract.

Impulsive eating may have several underlying causes. Increases in food motivation are one potential factor driving impulsive eating, but in our studies, we did not observe increases in motivated responding for sucrose. Emotional eating to alleviate anxiety may be another underlying cause of impulsive eating, but we did not observe changes in anxiety-like behavior. Future study may investigate an augmented sense of internal timing as a contributing factor; when an animal's internal sense of time is expanded, they may be more likely to prematurely respond on the lever.

One final limitation is that these studies were only conducted in female rodents. The exclusion of male conspecifics from our study may affect the generalizability of these results; however, there have been several studies investigating the effects of cannabinoids on motivation and impulsivity in male rodents, and there is considerably less work conducted in females. Our contribution to the field aims to alleviate this discrepancy.

Overall, adopting this preclinical gelatin-based edible model of cannabinoid consumption simulates the human experience of edible consumption with a high degree of integrity and enhances translational relevance in the mechanistic study of cannabinoids.

RESOURCE AVAILABILITY

Lead contact

Requests for further information and resources should be directed to and will be fulfilled by the lead contact, Emily E. Noble (emily.noble@uga.edu).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- Any and all data reported in this paper will be shared by the lead contact upon request.
- This code utilized to operate the Med Associates operant chambers is included in the supplemental information.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

Conceptualization, M.N.L., J.R.H., and E.E.N.; methodology, M.N.L., J.R.H., and E.E.N.; formal analysis, M.N.L. and E.E.N.; investigation, M.N.L., M.O.S., J.R.H., and R.K.B.; resources, E.E.N.; writing—original draft, M.N.L.; writing—review and editing, M.N.L. and E.E.N.; visualization, M.N.L. and E.E.N.; supervision, E.E.N.; project administration, M.N.L. and E.E.N.; funding acquisition, E.E.N.

DECLARATION OF INTERESTS

The authors declare no competing interests.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, peptides, and recombinant proteins		
CP55940	Cayman Chemical	Cat#13241
Experimental models: Organisms/strains		
Rat: Wistar	Inotiv	Strain: Hsd:WI
Software and algorithms		
Prism (Version 10.3.0)	GraphPad	RRID:SCR_002798

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Fifty-six female Wistar rats (Envigo, Indianapolis, IN, USA) were singly housed in standard shoebox cages on a 12:12 reverse light/dark cycle in a temperature-controlled vivarium (22°C) with *ad libitum* access to standard chow (LabDiet 5053, LabDiet, St. Louis, MO, USA) and water except when noted below. All animals arrived between eight to ten weeks of age as determined by the supplier with the exception of the $n = 8$ females utilized in the differential reinforcement of low rates of responding task, which arrived at three and a half weeks of age. A timeline of experiments is provided in Figure S1 relative to the age of the rat at the time of testing. Rats were handled and weighed daily except during three U.S. national holidays. All procedures were approved by the Institute of Animal Care and Use Committee at the University of Georgia (Athens, GA, USA) (protocol number A2022 06-035-A12).

METHOD DETAILS

Cannabinoid administration via gelatin-based edibles

Edibles were made in the laboratory by combining coconut oil and lecithin; Jello and potassium sorbate; and set gelatin in a 1:1:1 ratio. The lipophilic nature of cannabinoids requires the use of a lipophilic solvent, coconut oil. The nonselective dual cannabinoid receptor agonist CP55940 (Item No. 13608; Cayman Chemical, Ann Arbor, MI, USA) was first dissolved in 14 g of coconut oil (Simple Truth Organic) and ¾ tsp lecithin (Earthfare, Athens, GA, USA) at the concentration of 0.18 mg/mL. In a separate container, 11.3 g Jello and ¼ tsp potassium sorbate were added to 18 mL boiling deionized water after removal from the heat. The use of Jello allowed for multiple flavors to be employed and enhanced palatability, while potassium sorbate was used as a mold inhibitor. In a third vessel, 5 g of gelatin was combined with 10 mL of water and allowed to set. Next, equal parts Jello and coconut oil mixtures were combined on a stir plate with constant stirring while a third equal part of set gelatin was added. The mixture was constantly stirred on a hot plate at 35°C–45°C. After 5 min of constant stirring, the homogeneous mixture was portioned into 2-mL molds using a syringe and allowed to set overnight at 4°C. Vehicle edibles were made in the exact same manner, absent of drug. This recipe makes a total of 12 2-mL edibles.

CP55940 was selected for these studies because, like THC, CP55940 is an agonist at both cannabinoid receptors, with stronger activation of downstream effectors at the CB1 receptor compared to the CB2 receptor,[62] making it an ideal THC-like model cannabinoid. A pilot study was performed to determine a hyperphagic dose of orally administered CP55940. Edibles were delivered to subjects at 0.12 mg/kg by portioning the edible according to the weight of the animal. The 2-mL molded edible contains 0.06 mg/mL (0.12 mg/2mL). Vehicle edibles were portioned and administered based on 2 mL/kg to match the size of the drug edible. Once administered, edibles were voluntarily consumed by the rodents in 2 min or less. Bedding was meticulously scoured for any unconsumed edible, and rodents with leftover edible were excluded from analyses ($n = 1$ rat utilized in the progressive ratio schedule 2 experiments was excluded).

Chow intake and meal patterns

To analyze meal patterns with minimal disturbance to the animal, food intake measurements were automatically recorded with Sable Systems Food Intake Monitoring Cages (4826 Rat cage; Sable Systems International, North Las Vegas, NV, USA). Data were recorded over 24-h, with a food bout being recorded each time the animal removed food from the food hopper. With eight cages and sixteen females, rats were habituated and tested in two groups. Each group was first acclimated to the food intake monitoring cages for seven days, with testing occurring on the eighth day in the specialty cages. On three of the seven acclimation days, rats were habituated to the vehicle edible by giving them one-fourth of a whole 2-mL edible (containing no drug) to consume to reduce neophobia on the day of testing. The eighth day in the specialty cages was test day. Subjects were aged ten to eleven weeks old on

the day of testing. Each test day ran as follows: chow was removed 1.5 h before the start of the dark cycle. Thirty minutes prior to the start of the dark cycle, rats received either CP55940-containg edible at 0.12 mg/kg or vehicle edible. At the immediate beginning of the dark cycle, standard chow was replaced in the food hopper, and data were collected from the monitoring software (Promethion Live Software Platform; Macro Interpreter) 24 h after the animals were given food back. Total food intake was calculated by the hour, and meals were defined as single food bouts in an amount greater than 0.2 g spaced no more than 15 min apart. One rat was excluded from analysis due to not eating.

Differential reinforcement of low rates of responding (DRL)

DRL is an operant chamber task designed to test impulsive action in rodents (protocol modified from[63]). The Med Associates code used to operate DRL is included as supplemental information. Rats were placed in an operant chamber with two retractable levers and one food receptacle and trained to associate one of the levers with earning a sucrose reinforcer (45 mg sucrose pellets, F0023, Bio-Serv, Flemington, NJ). During the first week of training, animals were given a fixed ratio 1 schedule (FR1), where a lever press results in a pellet delivery to the food receptable. A pellet was automatically dispensed if a rat did not press the lever for 600 s (autoshaping). The subsequent week a 5 s delay was enforced, wherein rats must wait for 5 s after each lever press before pressing again or the reinforced lever would not deliver a sucrose pellet. For the subsequent two weeks a 10 s period elapsed between presses for a reinforcer to be earned. Finally, a delay of 20 s was enforced for the last two weeks of training. Training sessions lasted for 45 min (one training session per day). In each session, the light above the active lever flashed on for presses that resulted in a reward. For the final week of training, a tone accompanied active presses that resulted in a reward. Rats were considered trained in the task when they achieved a steady efficiency score over several days. The efficiency score was calculated by dividing the number of pellets earned by the number of lever presses on the reinforced (active) lever. All training and testing occurred during the dark cycle.

A group of drug naive female rats ($n = 8$) were trained in DRL for five days per week over seven weeks at the start of the dark cycle. Animals were initially trained in this task during early adulthood (postnatal day 73–119) and then retrained in the task periodically prior to testing (for 5 days at PND 138 and at PND 178 they were retrained a final time on the 20 s delay with the tone for six days). Rats were aged 27 weeks at the time of testing. Animals were tested using a within-subjects design with test days separated by a three-day washout period. On each test day, animals received a CP55940-containing edible or a vehicle edible 30 min in a counterbalanced manner prior to being placed in the operant chambers. The number of active and inactive presses, as well as the number of pellets earned were measured, and efficiency scores were calculated.

Progressive ratio (PR)

The PR task was conducted in a cohort of females (PR schedule 1, $n = 16$), and subsequently repeated in a separate cohort of females utilizing a different progressive ratio schedule (PR schedule 2, $n = 16$). Training and testing occurred in eight Med Associates operant conditioning chambers (Med Associates; Fairfax, VT, USA). The Med Associates code used to operate PR is included as supplemental information. With eight operant chambers and sixteen females in each cohort, each cohort was split into two groups. In every session regardless of schedule, there was an active lever which when pressed dispensed sucrose pellets (45 mg sucrose pellets, F0023, Bio-Serv, Flemington, NJ) to the food cup and an inactive lever that provided no reinforcement. All training sessions lasted 1 h, and PR test sessions lasted for 2 h maximum. All testing occurred early in the dark cycle.

For all training and testing sessions, home cage chow is pulled 2 h before the start of the task and returned after the task. Animals were habituated to vehicle edibles (containing no drug) before the training sessions to reduce neophobia on the day of testing. During PR schedule 1, rats were trained in the operant chambers in fixed ratio-1 (FR1; one press delivers one pellet) sessions for four to six days until they reached a passing threshold of >50 presses on the active lever. Rats were then switched to the fixed ratio-3 (FR3; three presses deliver one pellet) schedule for two days. After two days off from training, rats were tested using an exponential PR schedule where an exponential increase in the number of presses was required for the rat to receive a reinforcer, according to the equation: $F(i) = 5e^{0.2i-5}$, where $F(i)$ is the number of lever presses required for next pellet at i = pellet number. On test day, subjects received either edible CP55940 or vehicle edible 30 min prior to the start of PR schedule 1. Animals were aged fifteen and a half weeks at the time of testing with all subjects being tested the same day, one group of eight immediately following the other.

For PR schedule 2, female rats were the same cohort utilized in the meal patterning experiment. Rats were trained and tested in the PR task following the conclusion of the meal patterning experiment in order to keep animals that received the vehicle edible in that experiment drug-naïve for PR testing. During PR schedule 2 training, home cage chow was removed 2 h before the start of the dark cycle. Rats were trained on an FR1 schedule for six days with autoshaping (pellet automatically dispensed if a rat did not press the lever for 600 s). For the first four days of FR1, the task began immediately after the start of the dark cycle. On the fifth day of FR1, the task began 1 h after the start of the dark cycle. On the final day of FR1, the task began 4 h into the dark cycle. This was done to gradually increase fasting time prior to the start of the task. Rats were then trained on an FR3 schedule for six days starting 4 h into the dark cycle. Rats were given one day of rest prior to testing in a linear PR schedule, which required an additional three presses for each additional pellet after the first initial press modeled by $F(i) = 3i\text{-}2$, where $F(i)$ is the number of lever presses required for next pellet at i = pellet number. Rats were tested 4 h into the dark cycle (same time as training) and food was pulled 2 h prior to the start of the task (2 h into the dark cycle, to alleviate the influence of hunger on motivation). Subjects received either edible CP55940 or vehicle edible 30 min prior to the start of PR schedule 2. As mentioned above, these cohorts of sixteen were split into two groups for training

and testing in the eight operant chambers. For schedule 2 testing, the first group was tested at thirteen weeks of age, and the second group was tested at sixteen weeks of age. One female was excluded from analysis due to nonconsumption of the edible.

Elevated Plus Maze (EPM)

The EPM task is used to measure anxiety-like behavior in rodents by comparing the time they spend in the "closed" arms of the apparatus to the amount of time they spend in the "open" arms of the apparatus.[64] The EPM is made of treated wood and consists of two opposing open arms (8.75 × 45 cm) and two opposing closed arms (10.3 × 45 cm) with walls that are 40 cm high. The arms of the EPM were elevated 56 cm off the floor. Lux was equal over the two open (60 lux) and the two closed (10 lux) arms. White noise was played while the animal was in the maze. The open arms were kept brighter than the closed arms and white noise was played to simulate an anxiogenic environment. A closed arm entry was counted when the rat's center was registered as being in a closed arm. An open arm entry was recorded when the rat's center was registered as being in an open arm. The apparatus was cleaned with 10% ethanol between animals to eliminate olfactory cues.

Female rats (n = 16) aged ten and a half weeks were tested using a between-subjects experimental design. One week prior to testing, rats were habituated to the vehicle edible by giving them one-fourth of a whole 2-mL edible (containing no drug) to consume to reduce neophobia on the day of testing. Animals were tested one at a time with timing balanced by alternating the order in which vehicle- and cannabinoid-treated animals were tested. Animals always had access to food and water except when in the apparatus. The task began 2 h into the dark cycle to ensure animals were satiated upon the start of the task, with the last animal being tested approximately 5 h into the dark cycle. Animals were placed in the maze 30 min post-edible administration facing away from the researcher and toward the open arm of the maze. A video camera overhead was used to record the behavior of the rat over a 5-min period. Testing was recorded and analyzed using ANYmaze software (Stoelting, CO, USA). Comparisons were made between animals' time spent in the closed vs. the open arms of the maze, as well as the speed with which they explored the maze and total distance traveled.

QUANTIFICATION AND STATISTICAL ANALYSIS

Data were analyzed with GraphPad Prism (Version 10.3.0). DRL data were analyzed using a two-tailed paired t-test. Food intake and meal pattern data were analyzed with two-tailed unpaired t-test with Welch's correction. PR and EPM data were analyzed with a two-tailed unpaired t-test.