Original Paper

Effects of Ventral Pallidum–Nucleus Accumbens Shell Neural Pathway Modulation on Sucrose Consumption and Motivation in Female Rats: Chemogenetic Manipulation

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Abstract

Background: The neural control of food intake involves interactions between homeostatic and nonhomeostatic systems. The nucleus accumbens shell (AcbSh) and ventral pallidum (VP) play key roles in regulating ingestive behavior and project to each other. Previous studies have shown that these projections influence food consumption, with sex differences reported in the modulation of sucrose intake by VP projections.

Objective: This study aimed to investigate the effects of chemogenetic activation or inhibition of projections from the VP to the AcbSh on sucrose consumption and the motivation to work for sucrose in female rats.

Methods: Chemogenetic tools (DREADD [designer receptors exclusively activated by designer drugs]) were used to selectively activate or inhibit VP projections to the AcbSh in female Sprague-Dawley rats (Gi [inhibitory G protein] DREADD: n=11; Gq [excitatory G protein] DREADD: n=10; and no DREADD: n=12). Rats were trained on a progressive ratio operant task to assess motivation to work for sucrose. Additionally, free-access sucrose consumption tests were conducted using a 20% sucrose solution. The effects of chemogenetic modulation were analyzed using two-way ANOVA.

Results: Chemogenetic manipulation of VP projections to the AcbSh did not significantly affect the motivation to work for sucrose in the progressive ratio task ($F_{2,31}$=1.780; P=.18). However, a significant interaction between DREADD type and drug administration was observed in the sucrose consumption test. Activation of the VP-AcbSh projection (using Gq DREADD) decreased sucrose intake, while inhibition (using Gi DREADD) increased sucrose intake ($F_{2,31}$=18.891; P=.001). No significant changes in sucrose consumption were observed in the control group without DREADD expression (P=.50).

Conclusions: This study shows that projections from the VP to the AcbSh modulate sucrose intake but do not affect the motivation to work for sucrose. Chemogenetic activation reduced sucrose consumption, while inhibition increased it, suggesting that distinct neural circuits within the VP-AcbSh pathway may differentially regulate feeding behaviors. These findings highlight the role of this pathway in the consumption of palatable foods and indicate that future research should consider factors such as sex, food macronutrient composition, and specific neural subpopulations to better understand their role in feeding behavior.

(JMIRx Bio 2025;3:e68519) doi: 10.2196/68519

KEYWORDS

ventral pallidum; nucleus accumbens shell; chemogenetics; sucrose; feeding behavior; food motivation; palatable food; DREADD; designer receptors exclusively activated by designer drugs

Introduction

The neural control of food intake and energy balance involves interactions between homeostatic and nonhomeostatic systems. Traditionally, homeostatic regulation was attributed to hypothalamic and brainstem circuits responding to metabolic signals [1].

Critically, ventral striatopallidal structures, including the nucleus accumbens shell (AcbSh) and ventral pallidum (VP), exert a major influence on ingestive behavior by acting on some of these structures, mainly the lateral hypothalamus (LH). Inhibition of AcbSh neurons through gamma-aminobutyric acid (GABA) agonists or glutamate antagonists elicits intense feeding responses and activates LH neurons, as evidenced by increased *Fos* expression [2]. The AcbSh projects to both the LH and VP, with unilateral lesions of either structure attenuating AcbSh-induced feeding [3]. The LH also modulates AcbSh activity directly through neurotransmitters like orexin and melanin-concentrating hormone, and indirectly via subcortical relay regions such as the VP [4,5]. Relatedly, blockage of GABA receptors in the VP elicits food intake in satiated rats [2], and this feeding presents a clear fat preference [6].

Recent studies have suggested a role of sex in the mediation of sucrose consumption. In female rats, optogenetic stimulation of AcbSh projections to the VP decreased sucrose intake and altered its hedonic value [7]. Additionally, increased sucrose intake has been reported in male rats, but not female rats, because of chemogenetic activation of GABAergic projection neurons in the VP [8].

Both the AcbSh and VP regulate food intake. Notably, the relationship between the VP and AcbSh is that of a loop, and the role that projections between the 2 play in feeding remains understudied. The directionality of the circuit is relevant, as projections from the AcbSh to the VP have different effects compared to projections from the VP to the AcbSh [9]. Additionally, as mentioned above, sex differences have been reported when modulating the projections of the VP [8]. Here, we aim to study the role that chemogenetic activation or inhibition of projections from the VP to the AcbSh have on the motivation to work for sucrose and on the consumption of sucrose in female rats. We hypothesize that chemogenetic modulation of the VP-AcbSh pathway, either inhibition or excitation, will alter the motivation to work for sucrose and sucrose consumption.

Methods

Subjects

A total of 36 female Sprague-Dawley rats (Envigo) were used for these studies; they were 75 days old and weighed 250-300 g (at the time of arrival). After all the procedures described in this section were completed, the final number of rats per group were as follows: Gi (inhibitory G protein) DREADD (designer receptors exclusively activated by designer drugs), n=11; Gq (excitatory G protein) DREADD, n=10; and no DREADD, n=12. All rats were pair-housed in temperature- and humidity-controlled rooms with a 12:12 light-dark cycle. In their home cages, rat pairs had access to chewing bones and a polyvinyl chloride pipe hut. After arrival at the facility, the rats were allowed to acclimate to the colony room for at least 1 week before starting behavioral testing; during this time, the rats were handled once a day by researchers. The rats were also handled regularly for the duration of the behavioral experiments. All rats had ad libitum access to food and water for the duration of the experiments. Behavioral testing took place during the light cycle between 10:00 AM and 5:00 PM.

Ethical Considerations

The experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Wisconsin-Parkside and were in accordance with the guidelines on animal care and use of the National Institutes of Health.

Surgeries

Surgeries were performed using standard, aseptic, flat-skull stereotaxic techniques under isoflurane anesthesia (5% induction and 2% maintenance) delivered by a precision vaporizer. Once a stable plane of anesthesia was achieved, a sterile eye ointment was applied to both eyes (to prevent corneal desiccation), the analgesic was administered, the scalp was prepped for an incision (hair trimming with alcohol and iodine scrub), an incision was used to expose the skull, and burr holes were created above the target structures for the injection of adeno-associated viruses (AAVs).

An AAV, double-floxed inverse open reading frame (DIO) construct containing an inverted form of either Gi (AAV5 AAV-hSyn-DIO-hM4D(Gi)-mCherry; Addgene) or Gq (AAV5 AAV-hSyn-DIO-hM3D(Gq)-mCherry; Addgene) DREADD was injected into the VP (from bregma: anterior posterior: –0.2 mm; medial lateral: ±1.8 mm; and dorsal ventral: –8.7 mm). A retrograde AAV-Cre viral vector (AAVrg pENN.AAV.hSyn.HI.eGFP-Cre.WPRE.SV40; Addgene) was injected into the AcbSh (from bregma: anterior posterior: 1.6 mm; medial lateral: ±0.8 mm; and dorsal ventral: –8.1 mm). Injections were performed using a Harvard micropump, Hamilton microsyringes connected to fluid-filled flexible tubing, and Plastics One injectors for a final volume of 1 uL at an injection rate of 300 nL per minute.

For pain management, meloxicam (2 mg/kg, subcutaneous) was administered during the surgery and 24 hours later. Triple antibiotic was applied around the incision after closure using wound clips. Clips were removed 7 to 10 days after the surgery. The rats were allowed to recover for 2 weeks before behavioral testing.

Clozapine-N-Oxide Preparation

Clozapine-N-oxide (CNO) was obtained from the National Institute on Drug Abuse Drug Supply Program. CNO was administered intraperitoneally 20 minutes before behavioral testing at a dose of 3.0 mg/kg. CNO was freshly prepared daily by dissolving it in 100% dimethyl sulfoxide (DMSO) and then diluting it with sterile water to a final concentration of 6% DMSO. A 6% DMSO solution in sterile water was used as the vehicle control.

Sucrose Access Under a Progressive Ratio Operant Task

The rats were trained in a progressive ratio (PR) operant task using identical, standard, twin-lever operant chambers (Med-Associates) housed within sound-attenuating chambers. First, the animals got 2 daily, 30-minute, magazine training sessions in the operant boxes, during which reinforcers (45-mg, sucrose, banana-flavored Dustless Precision Pellets; BioServe) were presented at 1-minute intervals, with a "click" generated at the same time as food delivery. Next, the rats were shaped to press the lever and then placed on a fixed ratio (FR) 1 reinforcement schedule for 2 days. The rats got one session of training on an FR2 schedule, followed the next day by one on an FR4 schedule. The rats were then switched to a PR6 schedule, which continued for the remainder of the experiment. Each day, the rats were placed into operant chambers with the house light on and both levers extended; only one lever was associated with the sucrose reward, although presses on both levers were recorded. The first response on the correct lever was followed by a sucrose pellet reward, paired with the operation of the clicker. The number of responses required to earn each subsequent sucrose pellet was increased by 6 after each reinforcer, so that 7 responses were required to earn the second pellet, 13 to earn the third, and so on. The time of each lever press was recorded. Each session continued until a 3-minute pause in responding occurred—a cutoff value that has been used in other studies [10,11]—or 60 minutes had elapsed, at which time the house lights were turned off, the levers were retracted, and the rats were removed from the chambers. The animals ran for 5 days on the PR6 schedule prior to drug treatment. After that, and 20 minutes before behavioral testing, the rats were injected with either CNO (3.0 mg/kg) or the vehicle. All rats were administered 2 injections of CNO on 2 different days and 2 injections of the vehicle, also on 2 different days.

Free-Access Sucrose Consumption Test

The rats were placed in individual home cages with wired bottoms and given access to a 20% sucrose solution for 60 minutes. This procedure was repeated over 2 consecutive days to acclimate the rats to the sucrose solution and minimize neophobia. After these 2 days, the rats were administered with either CNO (3.0 mg/kg) or the vehicle 20 minutes before being placed in the individual home cages. The sucrose bottles were weighed before and after the experiment to measure consumption. As described before, all rats got 2 CNO and 2 vehicle injections, with each injection on a different day.

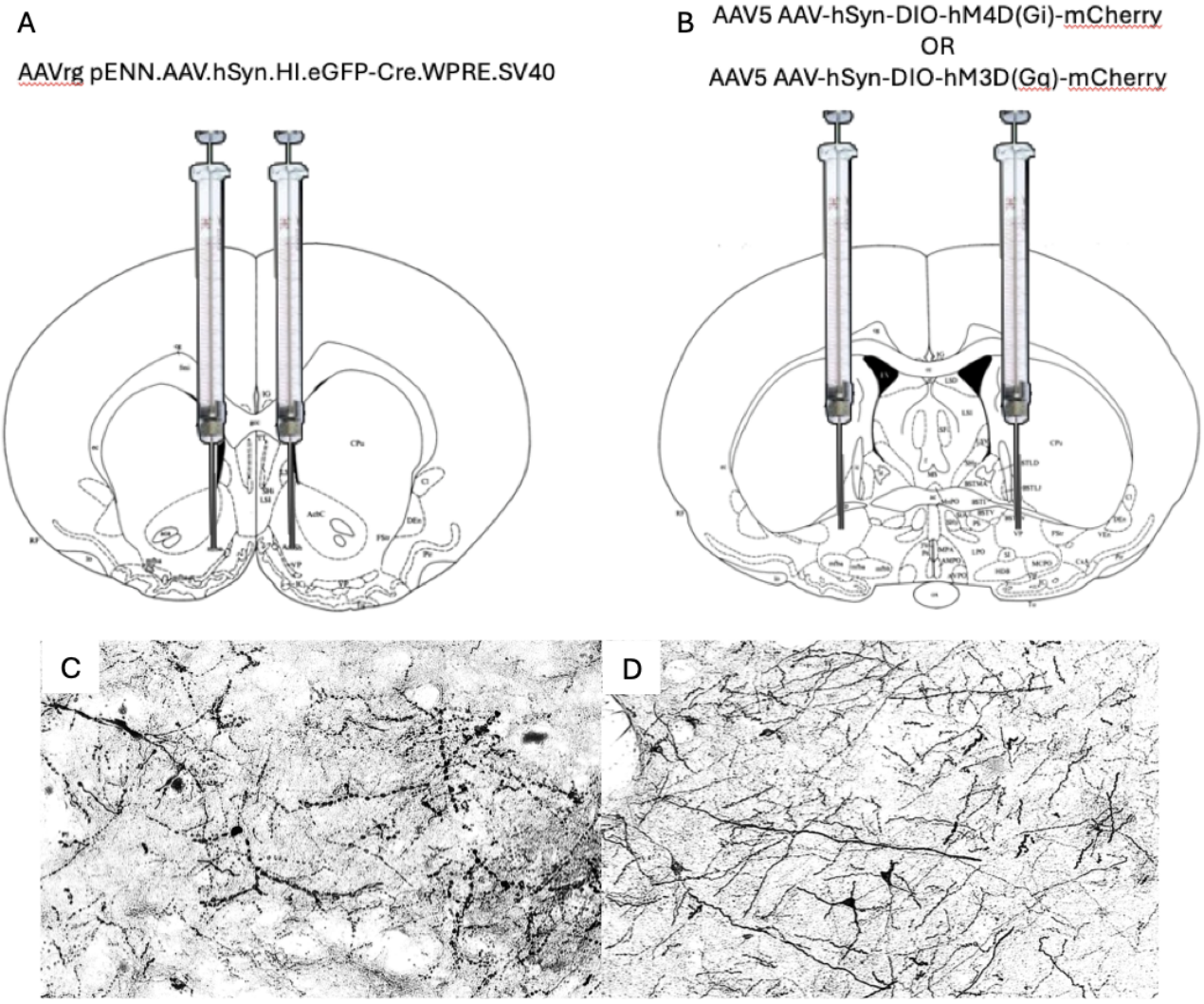
Perfusion and Tissue Processing

After completing the behavioral experiments, the rats were anesthetized with 5% isoflurane and transcardially perfused with 0.9% saline followed by 4% formaldehyde (pH=7.4) for fixation. The brains were extracted, postfixed in 4% formaldehyde for 24 hours at 4°C, and immersed in increasing concentrations of sucrose solutions every 24 hours (10%, 20%, and then 30% sucrose in 0.1 M phosphate-buffered saline [PBS], pH=7.4) at 4°C over the course of 3 days. The brains were then encased in Tissue-Plus O.C.T. (Fisher HealthCare), frozen using dry ice, and subsequently sectioned in the coronal plane (45 µm) using a cryostat.

Immunohistochemistry

The accuracy of DREADD expression in the VP and AcbSh was assessed using immunohistochemistry aimed at visualizing mCherry protein in DREADD-expressing neurons using procedures described previously [12]. Free-floating coronal sections from the VP and AcbSh were first rinsed 3 times in 0.1 M PBS (pH=7.4). Endogenous peroxidase activity was blocked by incubating sections in 1% H_2O_2 for 10 minutes, followed by 3 additional rinses. To prevent nonspecific binding of the secondary antibody, sections were incubated in 0.1 M PBS containing 0.4% Triton X-100 (TX) and 2.5% normal donkey serum (NDS; Jackson ImmunoResearch Laboratories, Inc). Sections were then incubated overnight at room temperature with the primary antibody (rabbit anti-mCherry; Abcam; diluted 1:30,000) in 0.1 M PBS + 0.4% TX + 1% NDS. Then, sections were rinsed again before being incubated for 1 hour in a biotinylated, donkey, anti-rabbit secondary antibody (Jackson ImmunoResearch Laboratories, Inc; diluted 1:500) in 0.1 M PBS + 0.4% TX + 1% NDS. Peroxidase staining was obtained by using a standard avidin-biotin procedure using the Vectastain Elite ABC Kit (Vector Laboratories, Inc; diluted 1:1000 for A and B). Chromogenic reaction occurred by incubating sections in a 0.1 M PBS solution containing 0.02% 3,3'-diaminobenzidine tetrahydrochloride and 0.012% H_2O_2. Sections were rinsed and stored at 4°C until mounted, air dried, and covered with slips using a toluene-based mounting medium (Permount; Thermo-Fisher Scientific). Bright-field images containing the VP or AcbSh were captured using a Zeiss Axioscan light microscope and were analyzed by an experimenter blinded to the experimental groups. The location of mCherry expression was confirmed using a rat brain atlas [13]. A schematic representation of the approach and representative mCherry pictures can be found in Figure 1 [14].

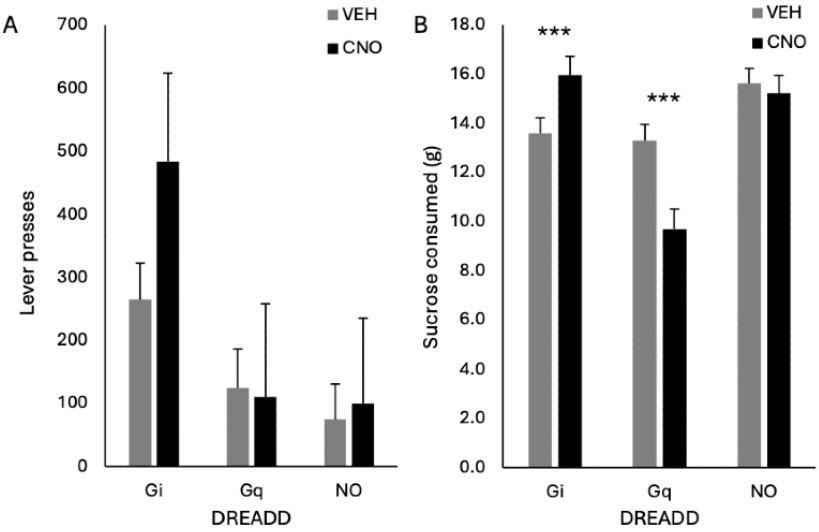
Figure 1. (A) A retrograde AAV-Cre viral vector was injected into the AcbSh. (B) An AAV DIO construct containing an inverted form of either Gi or Gq DREADD was injected into the VP (adapted from Paxinos and Watson [14]). Representative AcbSh (C) or VP (D) 10× microphotograph of mCherry immunohistochemistry. AAV: adeno-associated virus; AcbSh: nucleus accumbens shell; DIO: double-floxed inverse open reading frame; DREADD: designer receptors exclusively activated by designer drugs; Gi: inhibitory G protein; Gq: excitatory G protein; VP: ventral pallidum.



Results

A 2-way ANOVA was performed to evaluate the effects of DREADD type (Gq, Gi, or no DREADD) and drug administered (vehicle or CNO) on lever presses in a sucrose PR task. The results indicated no significant main effect for DREADD type ($F_{2,31}$=2.421; P=.10); no significant main effect for drug administered ($F_{1,31}$=2.004; P=.17); and no significant interaction between DREADD type and drug administered ($F_{2,31}$=1.780; P=.18; Figure 2A).

Figure 2. (A) CNO administration did not affect motivation to work for sucrose, as measured using a progressive ratio task in non–food-deprived, DREADD-expressing rats (Gi and Gq) and control rats (no DREADD). (B) Non–food-deprived rats expressing inhibitory (Gi), excitatory (Gq), or no DREADD were given 1 hour to consume a 20% sucrose solution after being injected with either the vehicle or CNO. CNO-induced chemogenetic inhibition of the VP-AcbSh pathway increased sucrose consumption in rats (P=.001), excitation decreased it (P=.001) and had no effect on rats not expressing DREADD (P=.50). CNO: clozapine-N-oxide; DREADD: designer receptors exclusively activated by designer drugs; Gi: inhibitory G protein; Gq: excitatory G protein; VEH: vehicle.



A 2-way ANOVA was performed to evaluate the effects of DREADD type (Gq, Gi, or no DREADD) and drug administered (vehicle or CNO) on 20% sucrose consumption in non–food-deprived rats. The results indicated a significant main effect for DREADD type ($F_{2,31}$=11.170; P=.001); no significant main effect for drug administered ($F_{1,31}$=3.148; P=.09); and a significant interaction between DREADD type and drug administered ($F_{2,31}$=18.891; P=.001; Figure 2B).

Post hoc testing using Bonferroni correction for multiple comparisons indicated that sucrose consumption was significantly higher for rats expressing Gi DREADD when CNO was administered than when the vehicle was administered (P=.003). Additionally, sucrose consumption was significantly lower for rats expressing Gq DREADD when CNO was administered than when the vehicle was administered (P=.001). There was no significant difference between the sucrose consumption of rats expressing no DREADD administered with either CNO or the vehicle (P=.50; Figure 2B).

Discussion

In female rats, chemogenetic excitation or inhibition of projections from the VP to the AcbSh influenced consumption of a 20% sucrose solution but had no effect on the motivation to work for a sucrose pellet, as measured using a PR task. Specifically, chemogenetic activation of projections from the VP to the AcbSh in non–food-deprived female rats decreased consumption of the 20% sucrose solution. Conversely, chemogenetic inhibition of the same projection increased consumption of the 20% sucrose solution.

In contrast, Scott et al [8] reported that chemogenetic activation of VP projection neurons resulted in no significant changes in rat chow or sucrose consumption. This apparent discrepancy between the 2 studies can be explained by multiple reasons. Possibly the most crucial difference between the 2 studies is that, here, we used a dual vector approach to express DREADD in VP neurons that project to the AcbSh, while Scott et al [8] used a single vector approach, leading to all GABAergic VP projection neurons expressing DREADD. Thus, here, chemogenetic manipulations affected a small subset of VP projection neurons, namely those that project to the AcbSh, while in the study conducted by Scott et al [8], all VP projections were affected by chemogenetic modulation. It is nonetheless informative that we observed different behavioral effects, as this suggests that different VP efferents might have a variety of behavioral effects. This matter could be addressed by future studies dissecting the role of each VP efferent. Additional studies should also consider the sex differences noted by Scott et al [8].

Other differences to consider between the 2 studies include the concentration of sucrose used in the free-access test, as we used a 20% concentration while Scott et al [8] used 10%; the fact that our rats remained pair housed as opposed to single housed; and the differences in rat strain, as they used Long-Evans rats and we used Sprague-Dawley rats. Additionally, there were also differences in the DREADD agonist used: JHU37160 versus CNO in our experiment. While all these differences possibly contributed to some extent to the different behavioral results between the 2 studies, we consider that the most likely difference stems from the targeting of all GABAergic VP projecting neurons in Scott et al [8] versus only VP neurons projecting to the AcbSh in this study.

The directionality of the VP-AcbSh pathway has also been studied by Smedley et al [9]. Interestingly, this group saw no effect on free feeding on male rats when the projections from the VP to the AcbSh were chemogenetically inhibited. Besides the sex differences in the subjects, it is also notable that Smedley et al [9] measured the intake of standard rat chow. In contrast, here, we measured the consumption of a 20% sucrose solution. It is then possible that either or both factors, sex and food stuff,

might contribute to the different behavioral results observed. Thus, it appears that projections from the VP to the AcbSh mediate sucrose consumption but not motivation to work for sucrose. Future studies looking at other VP effects might be able to dissect which projections are involved in the motivation to work for sucrose and other palatable foods.

Additionally, it has been reported that pharmacological activation of the VP leads to increased preference for fat consumption [6]. In contrast, the food used in this study contained mainly carbohydrates, 94% in the case of the sucrose pellets used in the PR task and 20% in the case of the free-access task. It is then plausible that identical manipulations of the VP-AcbSh pathway could result in different behavioral effects if fats instead of carbohydrates were used as food rewards. Future studies should consider the possibility that different behavioral effects might be observed by using fats or offering a choice of different macronutrients.

Further, it has been described that arkypallidal neurons located in the VP inhibit AcbSh neurons and increase consumption of a 5% sucrose reward in mice [15]. In contrast, in this study, activation of the VP-AcbSh pathway led to a decrease in the consumption of the 20% sucrose reward in rats. This discrepancy could be caused, at least in part, by the difference in the nature of the projection neurons recruited and their putative roles, as we targeted all VP neurons projecting to the AcbSh, while Vachez et al [15] specifically targeted ventral arkypallidal neurons. It is then possible that the behavioral effects of modulating the whole VP-AcbSh pathway, as done here, differ from that of specific neural subpopulations. Also intriguing is the possibility that the VP-AcbSh pathway underlies different behavioral outcomes depending on the timing of the stimulation applied. Vachez et al [15] used phasic optogenetic stimulation, while we used more tonic chemogenetic manipulations. Future studies should contemplate the examination of phasic versus tonic stimulation in this pathway.

In conclusion, our findings indicate that the VP-AcbSh pathway mediates the consumption of a palatable sucrose solution. Chemogenetic manipulation of VP projections to the AcbSh selectively influenced sucrose intake without affecting motivation to work for sucrose pellets, suggesting that distinct VP efferents play differential roles in feeding behavior versus food-seeking motivation. Additionally, the findings indicate a nuanced role for the VP-AcbSh pathway in modulating the intake of specific macronutrients. Future studies that dissect the role of the VP-AcbSh pathway should consider variables such as macronutrient profile, sex, and neural subpopulations as well as their possible interactions.

Acknowledgments

The authors would like to thank the College of Natural and Health Sciences for the support; the National Institute on Drug Abuse Drug Supply Program for providing the clozapine-N-oxide; and the following students for their help with this work: Megane Beaupre, Ari Hjelmeseth, Miranda Johnson, Hedi Morris, Zach Wilson, Aryan Patel, Mark Huckeby, and Dylan Jensen.

Conflicts of Interest

None declared.

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Abbreviations

AAV: adeno-associated virus
AcbSh: nucleus accumbens shell
CNO: clozapine-N-oxide
DIO: double-floxed inverse open reading frame
DMSO: dimethyl sulfoxide
DREADD: designer receptors exclusively activated by designer drugs
FR: fixed ratio
GABA: gamma-aminobutyric acid
Gi: inhibitory G protein
Gq: excitatory G protein
LH: lateral hypothalamus
NDS: normal donkey serum
PBS: phosphate-buffered saline
PR: progressive ratio
TX: Triton X-100
VP: ventral pallidum

Edited by O Singh; submitted 07.11.24; peer-reviewed by D Wirtshafter, J Grimm; comments to author 01.01.25; revised version received 08.01.25; accepted 18.01.25; published 08.03.25

Please cite as:
Peroutka M, Rivero Covelo I
Effects of Ventral Pallidum–Nucleus Accumbens Shell Neural Pathway Modulation on Sucrose Consumption and Motivation in Female Rats: Chemogenetic Manipulation
JMIRx Bio 2025;3:e68519
URL: https://bio.jmirx.org/2025/1/e68519
doi: 10.2196/68519
PMID: