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Dopamine D1 receptor signalling in the lateral shell of the nucleus accumbens controls dietary fat intake in male rats

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A B S T R A C T

Central dopamine signaling regulates reward-related aspects of feeding behavior, and during diet-induced obesity dopamine receptor signaling is altered. Yet, the influence of dopamine signaling on the consumption of specific dietary components remains to be elucidated. We have previously shown that 6-hydroxydopamine-mediated lesions of dopamine neuron terminals in the lateral shell of the nucleus accumbens promotes fat intake in rats fed a multi-component free-choice high-fat high-sugar (fcHFHS) diet. It is however not yet determined which dopamine receptors are responsible for this shift towards fat preference. In this study, we assess the effects of D1- or D2 receptor acute inhibition in the lateral shell of the nucleus accumbens on fcHFHS diet consumption. We report that infusion of the D1 receptor antagonist SCH2 3390, but not the D2 receptor antagonist raclopride, promotes dietary fat consumption in male Sprague Dawley rats on a fcHFHS diet during 2 h after infusion. Furthermore, anatomical analysis of infusion sites revealed that the rostral region, but not the caudal region, of the lateral shell of the nucleus accumbens is sensitive to the D1 receptor inhibition effects on fat consumption. Our data highlight a role for D1 receptors in the rostral region of the lateral shell of the nucleus accumbens to control dietary fat consumption.

1. Introduction

The modern food environment exposes us to an abundance of palatable food choices that can be readily consumed throughout a 24 h cycle. This has promoted the consumption of saturated fat and sugars beyond our metabolic needs and drives the current global obesity epidemic (Popkin, Adair, & Ng, 2012; Yau & Potenza, 2013). Both sugar and fat are highly palatable and perceived as rewarding (DiFeliceanto, 2018; Johnson, 2013). The mesolimbic dopamine system plays a key role in reward-related feeding behaviour, and the nucleus accumbens (NAc) is a key dopaminergic target in which enhanced dopamine signalling is associated with reward (Berke, 2018; Cox & Witten, 2019; Volkow, Wise, & Baler, 2017; Wise, 2004; Wise & Robble, 2020). Various dopamine receptors, of which the dopamine receptor 1 (D1R) and dopamine receptor 2 (D2R) have received most attention, have been implicated in the control of palatable food consumption and thus in the development of obesity (de Weijer et al., 2011; Hryhorczuk et al., 2016; van de Giessen et al., 2013; Wang et al., 2001). Conflicting data exist on the role of D2R on palatable feeding; for example, lentivirus-mediated knockdown of D2R in the dorsal lateral
entially promotes fat intake in rats consuming a fcHFHS diet (Joshi et al., 2016). Moreover, weight loss induced by psychostimulants and appetite suppressants is reversed by systemic administration of a D1R antagonist (Gilbert & Cooper, 1985) or a combination of D1R and D2R antagonists (Kalynyanudar et al., 2015), whereas various D1R agonists produce a dose-dependent suppression of palatable food consumption (Cooper, Francis, Al-Naser, & Barber, 1992; Martin-Ivenson & Dourish, 1988; Setter, Sarau, Zirkle, & Saunders, 1978; Stoo & Rekabian, 1984). In addition to receptor inhibition, optogenetic inhibition of D1R-expressing medium spiny neurons (D1R-MSNs), but not medium spiny neurons expressing D2R (D2R-MSNs), promoted liquid fat consumption in ad libitum-fed mice (O’Connor et al., 2015). Similarly, optogenetic activation of terminals of the NAc D1R-MSNs that project to the lateral hypothalamus (LH) suppressed palatable feeding, even when the mice were food-deprived for 24 h (Luo et al., 2018; O’Connor et al., 2015). GABAergic neurons in the LH were found to be the functional target of NAc D1R-MSNs and direct inhibition of these GABAergic LH neurons suppressed liquid fat consumption, even in 24 h food-deprived mice (O’Connor et al., 2015).

Many of the studies that investigated the effects of dopamine infusions on palatable feeding were not specific regarding the location of the infusion sites. For example, several studies mention the NAc as target site, yet the NAc consists of several subdivisions, including the core and lateral and medial shell, that all receive input from anatomically and functionally distinct ventral tegmental area (VTA) neuron populations (Lammel et al., 2012). We recently showed that depletion of dopamine terminals in the lateral shell of the NAc, but not the medial shell of the NAc or the dorsolateral striatum (DLS), promotes the intake of saturated fat in rats that were consuming a multi-component free-choice high-fat diet (fchFFHS) (Joshi, Faivre, la Fleur, & Barrot, 2021). However, it is currently unclear which specific dopamine receptor controls consumption of fat.

Because dopamine depletion in the lateral shell of the NAc preferentially promotes fat intake in rats consuming a fchFFHS diet (Joshi et al., 2021), we investigated if targeted infusion of the D1R antagonist SCH2 3390, the D2R antagonist raclopride, or a combination of SCH2 3390 and raclopride, enhanced fat intake in rats consuming a fchFFHS diet. As these experiments revealed an injection site-specific sensitivity, we next investigated the effects of the D1R inhibition on fat intake along the rostro-caudal axis of the lateral shell of the NAc.

2. Methods and materials

2.1. Animals

Male Sprague Dawley rats (Janvier labs, France) weighing 250–300 g were group-housed (4 per cage) in a temperature- (21 °C–23 °C) and light-controlled room (standard 12:12 light conditions, lights on at 07:00–19:00) with ad libitum access to standard control diet (CD; Teklad global diet 2918, 18.6% protein, 44.2% carbohydrate, and 6.25% fat, 3.1 kcal/g, Envigo), a container with saturated fat (beef tallow Osewitt/Blanc de Boeuf, Vamendoometiele, Belgium; 9 kcal/g), a bottle with 30% sucrose water (commercial-grade table sugar dissolved in tap water; 1.2 kcal/g), and a bottle with tap water. Consumption of diet components, as well as body weight, was measured daily. Consumption of the diet components was assessed by measuring pre-weighted food hoppers (CD diet), pre-weighted metal cups (fat), and pre-weighted bottles (water and 30% sucrose water). All rats gained weight constantly during the experiment. To familiarize the rats and to ensure that the cannula did not stick or block, dummies caps were unscrewed twice per week.

2.2. Surgery

After seven days of acclimatization, rats were handled several times and rats underwent intracranial surgery during which two 26-gauge stainless steel guide cannula (C315G-SPC, cut 9 mm below pedestal, Plastics One, Bilaney Consultants GmbH, Düsseldorf, Germany), aimed bilaterally at the lateral shell of the NAc, were implanted at anteroposterior (AP): +1.8 mm, mediolateral (ML): ±2.9 mm, dorsoventral (DV): 6.0 mm (coordinates from bregma and using an angle of 2° in the frontal plane, verticality was taken from dura). To investigate injection site-specific sensitivity, an additional cohort of rats was implanted with cannulas more caudally in the lateral shell of the NAc, at AP: +1.5 mm, ML: ±2.9 mm, DV: 6.0 mm (with similar angle as described above). All rats were kept under adequate anesthesia during the surgery, with an intraperitoneal injection of a mixture of ketamine, xylazine, and atropine before the onset of surgery, and ketamine during the surgery. This mixture was prepared by combining 0.8 mL ketamine (100 mg/mL), 0.4 mL xylazine (20 mg/mL) and 0.2 mL atropine (0.05 mg/mL) and was injected at 1.4 mL/kg body weight. The animals were fixed in a stereotactic frame and guide cannulas were secured to the skull using dental cement and four screws. A 26-gauge stainless steel dummy cannula (C315DC without protection, Plastics One) was kept in the guide cannula. Immediately after surgery, rats received carprofen (0.5 mg/100 g body weight, subcutaneous) as an analgesic, and animals were housed individually. On post-surgery day 1, rats received a second carprofen injection.

2.3. Drugs

Drugs were purchased from Sigma-Aldrich®: the selective D1R antagonist R (+) SCH-23390 hydrochloride (D054-25 mg; source #125M4614V, Batch #000016657 for experiment 1 and D054-5 mg; source #125M4614V, Batch #000030852 for experiment 2) and the selective D2R antagonist S(−)-raclopride(+)tartrate (R121-25 mg; lot# BCBW8974, Pcode 102087834). The drugs were dissolved in sterile 0.9% saline to obtain a concentration of 0.6 μg/0.5 μL for SCH-23390, and 1 μg/0.5 μL for raclopride. The SCH-23390 and raclopride concentrations were determined based upon a thorough literature survey of studies investigating the involvement of D1 and D2 receptor signalling in motivated or feeding behaviour (e.g. Steidl et al., 2017; Stuber et al., 2011; Yates & Bardo, 2017).

2.4. Experimental design and infusion

One week after surgery, rats were provided with the fchFFHS diet, enabling them to choose between the following components: a container with nutrients of a nutritionally complete standard diet (Teklad global diet 2918, 18.6% protein, 44.2% carbohydrate, and 6.25 fat, 3.1 kcal/g, Envigo), a container with saturated fat (beef tallow Osewiit/Blanc de Boeuf, Vamendoometiele, Belgium; 9 kcal/g), a bottle with 30% sucrose water (commercial-grade table sugar dissolved in tap water; 1.2 kcal/g), and a bottle with tap water. Consumption of diet components, as well as body weight, was measured daily. Consumption of the diet components was assessed by measuring pre-weighted food hoppers (CD diet), pre-weighted metal cups (fat), and pre-weighted bottles (water and 30% sucrose water). All rats gained weight constantly during the experiment. To familiarize the rats and to ensure that the cannula did not stick or block, dummies caps were unscrewed twice per week.

2.4.1. Cohort 1

Following two weeks of fchFFHS diet consumption, 0.6 μg/0.5 μL SCH2 3390, 1 μg/0.5 μL raclopride, a combination of SCH2 3390 (0.6 μg/0.5 μL) and raclopride (1 μg/0.5 μL), or 0.9% saline was administered in a balanced crossover design. After each injection, 3 days of washout was allowed. Before infusions, all food components were removed from the cage at 09:00. Injector cannula (C315SPC, Plastics One, Bilaney Consultants GmbH, Düsseldorf, Germany), projecting 1 mm below the guide cannula, were inserted into the guide cannula at around 15:00, and animals received bilateral infusions of 0.5 μL fluid per site at a rate of 0.3 μL/min via a syringe infusion pump in a volume mode.
Injections were confirmed by observing fluid movement in the tubing (0.46 mm diameter) with the help of a small air bubble. After completion of the injection, the injector was left in place for 1 min to allow for diffusion. Upon completion of the infusion, all food components were returned to the cage and individual food components were measured 2, 5, and 24 h following infusion.

2.4.2. Cohort 2
To investigate injection site-specific sensitivity, 0.6 μg/0.5 μL SCH23390 (0.6 μg/0.5 μL) or 0.9% saline was administered in a balanced crossover design in the caudal (AP: +1.5 mm, ML: ±2.9 mm, DV: 6.0 mm) or rostral (AP: +1.8 mm, ML: ±2.9 mm, DV: 6.0 mm) lateral shell of the NAc. See Cohort 1 for procedural details.

2.5. Perfusion
Rats were anesthetized with an overdose of pentobarbital and transcardially perfused with ice-cold 0.9% saline followed by 4% paraformaldehyde in 0.9% saline, and collected brains were postfixed overnight. Brains were washed in phosphate buffered saline, cryoprotected in 30% sucrose at 4 °C overnight, and subsequently frozen on dry ice and stored at −80 °C. Cryostat sections were cut at 35 μm and mounted on Superfrost Plus slides (Fisher, Gerhard Menzel GmbH, Germany) and stained for Nissl staining with thionine. Stained sections were examined under the microscope to determine the placement of the cannula.

Fig. 1. **D1R and D2R inhibition in the lateral shell of the NAc and fCHFS diet consumption.** Experimental timeline for the infusion study (A). An example of cannula placement, with injection site indicated by an asterisk symbol (B). Reconstruction of correct cannula placement (indicated by blue dots), based on the atlas of Paxinos and Watson (2014); the distance in mm from bregma is given on the right side of each neuroanatomical reconstruction image (C). Consumption of fCHFS diet components following infusion with saline, SCH23390 (D1-anta), raclopride (D2-anta), or both (infusions were done in randomized crossover design) over 2 h following infusion (D), with enlarged figure for fat consumption following SCH23390 infusion (E), and consumption over 5 h (F) and over 24 h (G) following infusion. *, p < 0.05; **, p < 0.01. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
2.6. Data analysis and statistics

Data are presented as mean ± SEM and were analysed using GraphPad Prism 8.04 (GraphPad Software, La Jolla California USA). Two group comparisons were performed by two-tailed Student’s t-test (total kcal intake). Repeated measure analysis of variance (RM-ANOVA) was performed to compare drug treatment, individual timepoint, food component and interactions between these factors. Post hoc analysis was performed using Bonferroni’s multiple comparison paired t-tests using saline treatment as control. For all cases, a p value < 0.05 was considered significant. See Results section for statistical details of individual experiments, including statistical tests used, t, p, F-values, and number of subjects or samples tested.

3. Results

3.1. Inhibition of D1R in the lateral shell of the NAc promotes fat intake during consumption of a fcHFHS diet

To determine which receptor mediates the effect of dopamine on fat intake when animals are consuming a fcHFHS diet, we infused the D1R antagonist SCH2 3390 and the D2R antagonist raclopride in the lateral shell of the NAc (Fig. 1A and B). From the 24 animals that underwent cannula placement surgery, 12 animals showed a correct placement (depicted in Fig. 1C as blue dots). Cumulative diet component intake was measured over the first 2 h, over 5 h, and over 24 h following infusion (Fig. 1D-G). Two-way RM ANOVA on the 2 h data revealed a significant food type * drug effect (F(6, 66) = 2.660, p = 0.0226), and post hoc RM analysis on mean kcal intake for different diet components revealed a significant drug effect for fat consumption at 2 h (F(2.5, 27.0) = 5.4, p = 0.0075), but not for consumption of chow, sucrose, or total caloric consumption over 2 h following infusion (Fig. 1D). Bonferroni’s multiple comparisons paired t-tests revealed that infusion of SCH2 3390 (p = 0.0023) and the co-infusion of SCH2 3390 and raclopride (p = 0.0478) promoted fat intake 2 h following infusion (Fig. 1D). Fig. 1E depicts the individual changes per animal between the saline and SCH2 3390 infusion. No significant difference for any diet component or total caloric consumption was observed for consumption over the 5 h or 24 h following infusion (Fig. 1F and G).

3.2. Inhibition of D1R in the rostral, but not caudal, region promotes fat intake during consumption of a fcHFHS diet

As mentioned above, we observed that inhibition of D1R in the lateral shell of the NAc promotes fat intake during consumption of a fcHFHS diet. Furthermore, detailed inspection of infusion sites along the rostro-caudal axis of the lateral shell of the NAc revealed that two out of three rats with cannulas that were placed more caudally (bregma < 1.8 mm) had normal fat consumption in response to D1R inhibition. Thus, to investigate this infusion site-specificity along the rostro-caudal axis of

Fig. 2. D1R inhibition in the rostral part of the lateral shell of the NAc and fcHFHS diet consumption. An example of cannula placement, with injection site indicated by an asterisk symbol (A). Reconstruction of correct cannula placement (indicated by blue dots), based on the atlas of Paxinos and Watson (2014); the distance in mm from bregma is given on the right side of each neuroanatomical reconstruction image (B). Consumption of fcHFHS diet components following infusion with saline or D1-antagonist SCH2 3390 (infusions were done in randomized crossover design) over 2 h following infusion (C), with enlarged figure for fat consumption following D1-antagonist SCH2 3390 infusion (D), and consumption over 5 h (E) and over 24 h (F) following infusion. *, p < 0.05. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
the lateral shell of the NAc, we performed a follow-up experiment with additional infusion sites along this axis. From the 23 rats that underwent cannula placement surgery, eight rats had correct placements in the rostral lateral shell of the NAc and seven rats showed correct placements in the caudal lateral shell of the NAc (see Fig. 2A and B and 3A,B, respectively). Within the rostral extent of the lateral shell of the NAc, infusion of SCH2 3390 promoted fat consumption at 2 h following infusion (Fig. 2C; \( t_7 = 3.3, p = 0.013 \)). Fig. 2D depicts the individual changes per animal between the saline and D1-antagonist infusion (Fig. 2D). No effects were observed at other time points or for other diet components (Fig. 2C,E,F). Within the rostral extent of the lateral shell of the NAc, only a small but significant effect of SCH2 3390 on sugar intake was observed at 24 h (Fig. 3F; \( t_6 = 2.5, p = 0.045 \)). No additional drug effect on mean kcal intake for other diet components was observed over 2 h (Fig. 3C) or over 5 h (Fig. 3E) following infusion. Fig. 3D depicts the individual changes for fat intake per animal between the saline and SCH2 3390 infusion at 2 h. In addition, we also combined the data of Figs. 2 and 3 in a separate analysis to test for interaction effect between drug and cannula placement. The RM repeated ANOVA detected an effect of drug (\( F (1.13) = 10.325, p = 0.0007 \)), but no interaction effect. Taken together, we show that inhibition of D1R in the lateral shell of the NAc promotes fat intake during consumption of a fcHFHS diet and that this effect is stronger in the rostral part of the lateral shell of the NAc than in the caudal part.

4. Discussion

We have recently demonstrated that lesioning of dopaminergic inputs to the lateral part, but not to the median part, of the NAc shell promotes consumption of the dietary fat component in rats that are consuming a fcHFHS diet (Joshi et al., 2021). In this study, we demonstrate that inhibition of D1R, but not inhibition of D2R, in the lateral shell of the NAc promotes fat consumption in rats consuming fcHFHS diet. This highlights the role of D1R in the lateral shell of the NAc to mediate the effects of dopamine on fat preference in the fcHFHS paradigm. Moreover, this study also reveals that the effects of D1R inhibition are most pronounced in the rostral part of the lateral shell of the NAc.

We demonstrate that inhibition of D1R, but not inhibition of D2R, in the lateral shell of the NAc promotes fat consumption in rats consuming the fcHFHS diet. Although dopamine effects within the NAc on fat intake have been studied extensively (Baldo, Sadeghian, Basso, & Kelley, 2002; Durst, Konczol, Balazsa, Eyre, & Toth, 2019; Lardeux, Kim, & Nicola, 2015; Ragnauth, Znamensky, Moroz, & Bodnar, 2000; Will, Pratt, & Kelley, 2006), these studies often focused on the medial part of the NAc shell. For example, a D1 agonist injected in the median shell of rats suppressed consumption of fat food (Durst et al., 2019). However, several studies also failed to observe an effect of dopamine signaling manipulation in the NAc on feeding behavior in general, or on fat consumption in particular (Baldo et al., 2002; Lardeux et al., 2015; Will et al., 2006). These observations are in line with our own previous observation that local lesions of dopamine neuron terminals in the medial part of the shell of the NAc did not alter fat consumption in rats consuming the fcHFHS diet (Joshi et al., 2021). One study has targeted the lateral part of the ventral striatum (Inoue et al., 1995), which included the lateral shell of the NAc; this study demonstrates that D2R antagonism and agonism in the ventral lateral striatum reduces and promotes consumption of a standard control diet, respectively, whereas D1R receptor activation or inhibition did not alter feeding behavior in female rats (Inoue et al., 1995). Consumption of fat intake was...
unfortunately not investigated in this study (Inoue et al., 1995).

Given the proposed role for dopamine in enhancing reward value (Berke, 2018; Cox & Witten, 2019; Volkow et al., 2017; Wise, 2004; Wise & Robble, 2020), it might seem surprising that we observed an increase in fat intake following D1R inhibition in the lateral shell of the NAc. A potential explanation could be that the downstream areas of the lateral NAc are distinct from the medial part and involve inhibiting projections to neuronal populations that are involved in the promotion of fat consumption. Thus, when removing this inhibitory dopamine tone, this may promote fat consumption. Exploring the downstream anatomical targets is a logical next step in understanding the role of the lateral shell of the NAc in feeding behavior.

Against our expectation, we did not observe effect of D2R inhibition on the consumption of any chHFHS diet component. Systemic administration of a relatively low and high dose of raclopride, increases and decreases, respectively, the consumption of a high fat diet (Baker, Osman, & Bodnar, 2001). Raclopride increases dopamine release, whereas quinpirole decreases dopamine release, in the striatum of freely moving rats (See, Sorg, Chapman, & Kalivas, 1991). A potential explanation is that D2-MSNs in the lateral shell of the NAc are not involved in feeding-related behavior under the conditions tested in our study.

Observations in our first experimental cohort revealed a larger effect of D1R inhibition on fat consumption when the cannula was placed more rostrally in the lateral shell of the NAc. We therefore inhibited D1R in either the more rostral part or the caudal part of the lateral shell of the NAc in a second experimental cohort. Interestingly, D1R inhibition in the rostral part of the lateral shell of the NAc promoted fat consumption in all animals tested, but D1R inhibition in the caudal part of the lateral shell of the NAc failed to reach significance. However, we do have to be cautious with our conclusion that there is a clear difference between the results observed following rostral or caudal placement, as we did not observe an interaction effect. Furthermore, some animals with caudal placements did increase their fat intake following infusion. Earlier studies have revealed contrasting control over appetitive and aversive states along the rostro-caudal axis of the NAc shell. Microinjections of opioids in the rostral shell exert positive hedonic orofacial reactions to sucrose taste, whereas in the caudal shell opioids exert an aversive response, and such a difference along the rostro-caudal axis has been shown for the ventral pallidum as well (e.g. Castro & Berridge, 2014; Castro, Terry, & Berridge, 2016; Ho & Berridge, 2014; Mahler, Smith, & Berridge, 2007; Mitchell, Berridge, & Mahler, 2018; Smith & Berridge, 2007). In addition, blocking glutamate signaling in the rostral NAC shell promotes eating, whereas in the caudal shell it elicited defensive behavior to a predator; and these effects were dependent on NAc dopamine (Reynolds & Berridge, 2002; Richard & Berridge, 2011).

Therefore, it is possible that the lateral shell of the NAc might have a similar hedonic hotspot organization along its rostro-caudal axis in response to dopamine receptor modulation. However, it seems that this would be opposite to the organization as described for opioid and glutamate modulation as our data point to a suppressing effect of dopamine on palatable fat consumption. In addition, a heterogenous function over the rostro-caudal axis may be due to different innervation and neurotransmitter and modulator systems along this axis (Delfs, Zhu, Druhan, & Aston-Jones, 1998; Park, Aragona, Kile, Carelli, & Wightman, 2010; Vaccarino & Rankin, 1989) or different downstream targets, clearly warranting further future investigation in relation to consumptive behavior (palatable) food. Our experiments were performed at the end of the light period (ZT8), when dopamine tonic influence in consummatory memories increases in order to prepare for the active (dark) period. As often relative little information is given regarding specific timing of experiments (Nelson, Bumgarner, Walker, & DeVries, 2021), it is difficult to compare our data with previous studies. Dopamine levels in the striatum increase during the time window in which we assessed caloric intake (Castaneda, de Prado, Prieto, & Mora, 2004), thus it would be of interest to study whether the effect of D1R inhibition on fat intake is specific to this time window of increasing dopamine levels or whether the effect would be similar during the active (dark) period.

In this study we focused on effects of dopamine signaling in the NAc on fat intake in male rats, as our previous work on dopamine depletion and fat intake was also performed in males (Joshi et al., 2021). However, it is currently unclear how female rats respond to the chHFHS diet. Therefore, future experiments should also address this critical point to include studies in female rats, in order to characterize their response to the diet, and to determine how dopamine is involved in feeding behavior in females.

In summary, our observations highlight a role for D1R in the lateral shell of the NAc in control of dietary fat intake. Moreover, our data emphasizes the need for further research on the specific neural mechanisms and anatomical circuits that mediate the effects of dopamine signaling on (palatable) food consumption.

Declaration of competing interest

None.

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