Midbrain and Lateral Nucleus Accumbens Dopamine Depletion Affects Free-choice High-fat high-sugar Diet Preference in Male Rats

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Abstract—Dopamine influences food intake behavior. Reciprocally, food intake, especially of palatable dietary items, can modulate dopamine-related brain circuitries. Among these reciprocal impacts, it has been observed that an increased intake of dietary fat results in blunted dopamine signaling and, to compensate this lowered dopamine function, caloric intake may subsequently increase. To determine how dopamine regulates food preference we performed 6-hydroxydopamine (6-OHDA) lesions, depleting dopamine in specific brain regions in male Sprague Dawley rats. Food preference was assessed by providing the rats with free choice access to control diet, fat, 20% sucrose and tap water. Rats with midbrain lesions targeting the substantia nigra (which is also a model of Parkinson's disease) consumed fewer calories, as reflected by a decrease in control diet intake, but they surprisingly displayed an increase in fat intake, without change in the sucrose solution intake compared to sham animals. To determine which of the midbrain dopamine projections may contribute to this effect, we next compared the impact of 6-OHDA lesions of terminal fields, targeting the dorsal striatum, the lateral nucleus accumbens and the medial nucleus accumbens. We found that 6-OHDA lesion of the lateral nucleus accumbens, but not of the dorsal striatum or the medial nucleus accumbens, led to increased fat intake. These findings indicate a role for lateral nucleus accumbens dopamine in regulating food preference, in particular the intake of fat. © 2021 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: substantia nigra, 6-OHDA, lateral nucleus accumbens, fCHFS, diet preference, fat.

INTRODUCTION

Food intake is a highly reinforced behavior that not only provides nutrients needed for survival, but that also induces feelings of joy and pleasure (Hoebel, 1985). Modern human diet and natural rewards include a substantial amount of sugars and fats, which can modulate dopamine signaling in the brain reward system (DiFeliceantonio et al., 2018; Fritz et al., 2018; Fernandes et al., 2020) and could disturb the internal homeostatic mechanism which regulates hunger and satiety, ultimately contributing to food over-consumption and obesity (de Araujo

et al., 2008; Han et al., 2018; Zimmerman and Knight, 2020).

Homeostatic signals that influence the excitability of midbrain dopamine neurons can influence the sensitivity to drugs (Volkow et al., 2017) and it is an ongoing debate whether over-consumption of palatable food and drug addiction do share a similar mechanism (Fletcher and Kenny, 2018). Dopamine is one of the important neurotransmitters involved in reward processing, including in the rewarding aspects of food intake (Hernandez and Hoebel, 1988; Berke, 2018; Cox and Witten, 2019). The midbrain dopamine neurons of the substantia nigra *pars compacta* (SNc) and of the ventral tegmental area (VTA) are the main sources of dopamine projections to the forebrain striatal complex (Gerfen and Bolam, 2016), which in rodents includes the dorsal striatum that is analogous to the caudate and putamen nuclei in primates and humans (Haber, 2016), and the ventral striatum that includes the nucleus accumbens and the olfactory tubercle. The nucleus accumbens, which has been proposed

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Abbreviations: 6-OHDA, 6-hydroxydopamine; ANOVA, analysis of variance; AP, anteroposterior; DA, dopamine; DLS, dorsolateral striatum; fCHFS, free-choice high-fat high-sugar; L, lateral; INAc, lateral nucleus accumbens; mNAC, medial nucleus accumbens; PB, phosphate buffer; PBS, phosphate buffer saline; PBS-T, PBS with Triton X-100; SNc, substantia nigra pars compacta; TH, tyrosine hydroxylase; V, vertical; VTA, ventral tegmental area.

as an interface from motivation to action (Mogenson et al., 1980), is itself heterogeneous (Castro and Bruchas, 2019; Park et al., 2019), with two main subregions, the core and the shell (Záborszky et al., 1985; Zahm, 1999), as well as mediolateral and/or anteroposterior anatomical and functional heterogeneity. Classically, the VTA dopamine neurons that project to the ventral striatum have been linked to reward processes (Lammel et al., 2012; Hamid et al., 2016; Hu, 2016; Morales and Margolis, 2017), whereas SNc dopamine neurons that project to the dorsal striatum are more often associated with motor control (Howe and Dombek, 2016; da Silva et al., 2018). However, this dichotomy has been challenged and several studies have shown that SNc neurons projecting to the dorsal striatum can also be linked to food-motivation (Ilango et al., 2014; London et al., 2018; Lee et al., 2020) and associated movements (Lee et al., 2020). Little is known however about SNc striatal projections in relation to obesogenic diets. Dopamine deficient mice lack goal-directed feeding behavior and die of starvation by the age of 4 weeks (Palmiter, 2008); however, if the dopamine signaling is restored in the striatum (Szczycka et al., 2001) or in the dopamine neurons that project to the dorsal striatum (Sotak et al., 2005; Hnasko et al., 2006), then these mice consume enough for survival. Similarly, feeding inhibition is seen when dopamine signaling is altered in the dorsal striatum (Sotak et al., 2005).

As observed for drugs of abuse, palatable food can elicit altered dopaminergic signaling in the striatum. It has, for example, been shown that intragastrical fat infusions increase extracellular dopamine levels in the dorsal striatum (Ferreira et al., 2012). Dopamine signaling is also altered in the nucleus accumbens during the consumption of diets that are rich in fat and/or sugar (Hajnal et al., 2004; Liang et al., 2006; Rada et al., 2012) or during food restriction (Carr, 2020). An excessive consumption of fats has been shown to reduce brain dopaminergic function, and it has been hypothesized that this dopamine deficiency may aggravate obesity by favoring overfeeding as a compensatory mechanism to restore reward sensitivity (Tellez et al., 2013). A palatable high-fat diet has thus been proposed to promote addictive-like behavior in rats by downregulating D₂ receptors while promoting obesity (Johnson and Kenny, 2010), which is in agreement with human positron emission tomography (PET) scanning in obese subjects showing lower availability of D₂ receptor in the striatum (Wang et al., 2001; de Weijer et al., 2011). It is however to be noted that the hypothesis of dopamine deficiency in obesity is controversial as other publications did not support it (Eisenstein et al., 2013; Gaiser et al., 2016), or even suggested that changes in D₂ receptor availability may relate to age rather than to body mass index (Dang et al., 2016). In rodents, it has been shown that rats under a free-choice high-fat high-sugar (fCHFS) paradigm have decreased striatal D₂ receptor availability (van de Giessen et al., 2013), and that male rats fed with a diet rich in saturated dietary lipids (palm oil) have reduced D₁-mediated signaling in the nucleus accumbens (Hryhorczuk et al., 2016). Systemic manipulation of dopamine transmission using uptake inhibitors (van de Giessen et al., 2012; Randall et al., 2014)

or receptor agonist/antagonists (Rolls et al., 1974; Gilbert and Cooper, 1985; Clifton et al., 1991; Terry and Katz, 1992; Baker et al., 2001) can decrease food intake. More localized optogenetic stimulation of the nucleus accumbens medium spiny neurons expressing the D₁ receptors (or of their terminals in the lateral hypothalamus) decreased feeding in mice, while the inhibition of these neurons favored it (O'Connor et al., 2015); and chemogenetic activation of these neurons also decreased food intake (Luo et al., 2018). However, the influence that dopamine projections may exert on the preference between different types of food remains to be detailed.

Parkinson's disease is a neurodegenerative disorder associated with a loss of dopamine neurons in the midbrain. This loss preferentially concerns dopamine neurons of the SNc (Bezard and Przedborski, 2011; Zimmerman and Knight, 2020), which are more sensitive to cell death than VTA ones. Interestingly, some studies suggested that food preference may be altered in Parkinson's disease patients. Indeed, increased preference for palatable food, such as chocolate (Hellenbrand et al., 1996; Wolz et al., 2009), ice-cream (Meyers et al., 2010), cakes, buns, milk (Lorefält et al., 2006) and carbohydrate (Ådén et al., 2011), have been reported, with a decrease in consumption of fresh fruits, vegetables (Hellenbrand et al., 1996; Lorefält et al., 2006) and protein (Ådén et al., 2011). In rodents, models of Parkinson's disease have not been studied yet for potential changes in food choice.

In the present study, we used 6-hydroxydopamine (6-OHDA) lesions of midbrain SNc dopamine neurons, a model of Parkinson's disease (Faivre et al., 2019), to study the influence of this dopamine cell loss in the fCHFS paradigm, an obesogenic diet known to facilitate obesity and insulin resistance (la Fleur et al., 2010, 2011). Besides the known decrease in global food and calorie intake, the results revealed a surprising increase in fat intake following 6-OHDA SNc lesion. To understand which dopamine projection may underlie this impact on fat intake, we then lesioned terminals of specific dopamine projections within the striatal complex. This study, conducted in the rat, highlights a role for dopamine in the lateral nucleus accumbens in fat choice and intake.

EXPERIMENTAL PROCEDURES

Animals

Adult male Sprague-Dawley rats (Janvier Labs, France) were housed under standard conditions (2 per cage, 22 ± 1 °C, 12-h light–dark cycle) and habituated to the animal facility for at least a week before starting procedures. A total of 128 rats were purchased for the various experiments and, out of these, 118 rats were finally used for food intake behavior. Animal care and use were performed in accordance with the Centre National de la Recherche Scientifique (CNRS) and the European Union directives, with procedures approved by the regional ethical committee (CREMEAS).

Surgical procedures

Rats (7–8 weeks old; 250–325 g) were anesthetized using either ketamine (Imalgene® 1000)/xylazine (Rompun® 2%)/acepromazine (Calmivet®) (80 mg/kg, 4 mg/kg and 1 mg/mL respectively; intraperitoneal (i.p.)) or using zolazepam (Zoletil® 50)/xylazine (Rompun®) (65 mg/kg and 14 mg/kg respectively; i.p.), and placed in a stereotaxic frame (Kopf Instruments). Ocri-gel® was used to protect the eyes; and subcutaneous bupivacaine (40 µL/100 g) and Metacam® (50 µL/100 g) were used as local anesthetic for surgery and as anti-inflammatory drug for postsurgical pain relief respectively. Stereotaxic coordinates relative to the bregma were adjusted to the animal weight based on trial animals with blue dye injections. Coordinates (in mm) were as follows (Paxinos and Watson, 2013): SNc, anteroposterior (AP) = −5.1, lateral (L) = ±2.2, vertical (V) = −7.4; dorsolateral striatum, AP = +1.7, L = ±3.1, V = −4.2; medial nucleus accumbens (mNAc), AP = +1.8, L = +1.5, V = −6.9; and lateral nucleus accumbens (lNAc), AP = 1.5, L = ±2.6, V = −7.0. Verticality was taken from the dura. Hamilton syringes with 33 gauge needles were used to deliver 2 µL of 6-OHDA (Sigma-Aldrich, France; 2.5 µg/µL in 0.9% NaCl with 0.01% ascorbic acid) (Faivre et al., 2020) bilaterally, over 4 min. Needles were removed 7 min after the end of the injection. The sham surgeries were performed in a similar way, without injection. Rats were allowed to recover for 3 weeks before starting the behavioral experiments.

fcHFHS experiments

The fcHFHS paradigm (la Fleur et al., 2014) was implemented to assess food/fluid choice and intake following 6-OHDA lesions. This fcHFHS feeding setup provides rodents an easy access to choose from several food components which are varying in palatability, fluidity, texture, form, and nutritive content (Slomp et al., 2019). The test was performed over 7 days. Rats were single housed in Type 4 cages, and given free access to normal chow (diet A04, SAFE, France), fat (Les Pâturages des Flandres pure graisse de bœuf, Sarl Buchez, estaires, France), 20% sucrose solution (Sigma-Aldrich), and water. The two bottles were placed on each side of the stainless steel lid recess, and the two types of food were placed in between with separators. On each day, the position of the water and sucrose bottles was interchanged, with a change in fat and chow positions every other day. The SNc lesion experiment initially included 25 sham and 27 lesioned rats (done over three independent batches of animals to confirm the findings), the dorsolateral striatum lesion experiment eight sham and eight lesioned rats, the mNAc lesion experiment 10 sham and 14 lesioned rats, the lNAc lesion experiment 12 sham and 14 lesioned rats.

Immunohistochemistry

After completion of behavioral testing, rats were killed with a sodium pentobarbital overdose (235 mg/kg, i.p.) and decapitated. Their brains were collected and fixed in a paraformaldehyde solution (4% in 0.1 M phosphate

buffer (PB), pH 7.4) with 20% glycerol for 24 h, and transferred to a 20% sucrose solution in PB for further cryoprotection. Coronal sections (40 µm) were cut using a cryotome (Leica SM 2000R). Immunohistochemistry against tyrosine hydroxylase (TH) was performed as previously described (Faivre et al., 2020). At room temperature, free-floating sections were washed 3 times with 0.9% NaCl/0.01 M PB pH 7.4 (PBS), incubated in 50% ethanol with 0.03% hydrogen peroxide for 30 min for endoperoxidase blocking, washed 3 times with PBS, incubated in 0.3% Triton X-100 in PBS (PBS-T) with 5% normal donkey serum for permeabilization and blocking for 45 min, and incubated overnight with the anti-TH primary antibodies (Millipore-Chemicon MAB318, 1/5000 for SNc sections and 1/2000 for striatal/NAc sections) in PBS-T with 1% normal donkey serum. On the following day, sections were washed 3 times with PBS, incubated with an anti-IgG biotinylated secondary antibody (#BA2001, Vector Laboratories 1/200) in PBS for 90 min, washed 3 times with PBS, and incubated with the avidin–biotin–peroxidase complex (ABC Elite; Vector Laboratories). The amplified complex was finally revealed with a peroxidase/3,3'-diaminobenzidine tetrahydrochloride reaction. The sections were mounted, dried with a gradient of alcohol followed by Roti®-Histol solution, and a glass coverslip was placed using Eukitt®.

Microscopy and analysis

The mounted slides were scanned in a NanoZoomer S60 Digital slide scanner C13210 (Hamamatsu) at 20x in bright field. Images were saved in NanoZoomer Digital Pathology Image (ndpi) format and the uncompressed images were viewed in NDP.view 2.6.13 and extracted in .tif format for analyses using Image J. The images were converted into greyscale and the grey densities were calculated on 5–6 sections per animal and per region. Striatum and NAc data were expressed as optical density, and SNc/VTA data were expressed as % of the mean integrated grey density in controls. Sections ranging from AP +2.2 to +1.2 from bregma were selected for analyses of the striatum and NAc, while sections ranging from AP −4.6 to −5.8 were used for SNc and VTA analyses.

Statistics

Results are expressed as mean ± SEM in figures. Statistical analyses were performed using STATISTICA 13 software (Statsoft, Tulsa, OK, USA) and GraphPad Prism 8.04 (GraphPad Software, La Jolla California USA). We used parametric statistical tests after controlling for normal distributions of data using the Kolmogorov-Smirnov test and for equal variances in sampled distributions using the Levene's test. Student's t-test was used for two group comparison for lesion extent and for total kcal intake. ANOVA was used for comparing different food/fluid intakes over days (within factors) between the sham and lesion groups (between factor), followed by Duncan *post hoc*, with the level of significance at $p < 0.05$.

RESULTS

Effects of substantia nigra lesion on high-fat high-sugar free choice feeding

The SNc was lesioned using 6-OHDA and the extent of the lesions at cell body and terminal levels was controlled by TH immunohistochemistry at the end of the experiments (Fig. 1A–D). Lesioned animals were considered for the analysis of behavioral data if they bilaterally displayed at least a 50% loss in SNc TH staining (Fig. 1C, E), which concerned 22 out of the 27 rats that received 6-OHDA. In those animals, the lesions concerned the SNc, but could also extend to the lateral parts of the VTA (Fig. 1E). The impact on TH density in the striatal and nucleus accumbens terminal field was also controlled for (Fig. 1D, F).

The fCHFS paradigm was conducted over 7 days. Overall, the SNc lesion led to a decrease in total kcal intake *per* 100 g body weight ($F_{1,45} = 4.41$, $p = 0.04$) (Fig. 2A, C). With time, the rats also displayed slightly lower body weight than control ($F_{4,200} = 7.29$, $p < 0.0001$) (Supplementary Fig. 1SA). Interestingly, the decrease in kcal intake was associated with a change in the nutrient choice ($F_{2,90} = 8.23$, $p = 0.0004$): the rats decreased their chow intake (*post-hoc*, $p = 0.00002$), increased their fat intake ($p = 0.01$), and maintained their sugar intake ($p = 0.44$). As total intake differed between lesioned animals and their controls, we also standardized the data (% of intake for each animal) (Fig. 2B), which confirmed the increased intake of high-fat food to the detriment of regular chow ($F_{2,90} = 4.88$, $p = 0.009$; *post hoc*: decreased chow $p = 0.006$, increased high-fat $p = 0.006$, unchanged sucrose $p = 0.99$). This difference appeared as robust as it was stable over days ($F_{12,540} = 1.42$, $p = 0.15$).

When looking more closely at the individual pattern of nutrient choice (Fig. 2D; Supplementary Fig. S2A), a highly stable pattern was observed among the 25 animals of the Sham group. This pattern of choice was however strongly disrupted in some of the 6-OHDA lesioned animals. In particular, the mean increase in high-fat food intake was in fact due to 6 animals only (27% of the cohort), and those animals were among the ones with the largest extent of striatal loss in TH staining (blue animal numbers in Fig. 1; blue lines in Fig. 2D and in Supplementary Fig. S2A). This observation led us to study more closely the role of dopamine terminals from different striatal subregions in the fCHFS paradigm and high-fat food intake.

Effects of dopamine depletion in the dorsolateral striatum on high-fat high-sugar free choice feeding

We first tested the influence of dopamine terminals in the dorsolateral striatum, by performing local 6-OHDA injections (Fig. 3A–C). TH staining was used to control the extent of these lesions, which were limited to the lateral and dorsolateral parts of the dorsal striatum (Fig. 3C). With the fCHFS paradigm, we observed no impact of the lesions on the total kcal intake *per* 100 g

body weight ($F_{1,14} = 0.05$, $p = 0.81$) (Fig. 3D, F), or on the choice between regular chow, high-fat diet and sucrose solution ($F_{2,28} = 1.38$, $p = 0.26$) (Fig. 3E). The individual patterns of nutrient choice (Fig. 3G; Supplementary Fig. S2B) further supported this lack of impact of the dorsolateral striatum lesions, except for one animal with higher fat intake (blue line in Fig. 3G and in Supplementary Fig. S2B) that displayed a ventrolateral extent of the lesion (picture insert in Fig. 3G). We then lesioned the dopamine terminals in the INAc to test their influence on the fCHFS paradigm and high-fat food intake.

Effects of dopamine depletion in the nucleus accumbens on high-fat high-sugar free choice feeding

The 6-OHDA lesion of the INAc (Fig. 4A–C) led to an overall increase in total kcal intake *per* 100 g body weight ($F_{1,24} = 11.53$, $p = 0.002$) (Fig. 4D, F). This increase was more specifically due to a change in the nutrient choice ($F_{2,48} = 6.92$, $p = 0.002$), with an increased intake of high-fat food (*post hoc*, $p = 0.00006$) and no quantitative change in chow ($p = 0.72$) and sucrose ($p = 0.64$) intake. When data were standardized (% of intake for each animal) (Fig. 4E), it confirmed the increased choice of high-fat food, mostly to the detriment of regular chow ($F_{2,48} = 7.80$, $p = 0.001$; *post hoc*: decreased chow $p = 0.01$, increased high-fat $p = 0.0003$, unchanged sucrose $p = 0.18$). The individual patterns of nutrient choice (Fig. 4G; Supplementary Fig. S2C) further supported the overall increase in high-fat food intake.

We then tested whether this role could be extended to the rest of the NAc or was specific to the INAc subregion. In the fCHFS paradigm, the 6-OHDA lesion of the mNAC (Fig. 5A–C) had no significant impact on the total kcal intake *per* 100 g body weight ($F_{1,22} = 0.002$, $p = 0.96$) (Fig. 5D, F), or on the choice between regular chow, high-fat diet and sucrose solution (intake: $F_{2,44} = 0.50$, $p = 0.60$; %: $F_{2,44} = 0.44$, $p = 0.64$) (Fig. 5D–G; and in Supplementary Fig. S2D), which supported a specific influence of the INAc on high-fat choice.

DISCUSSION

In the present study, we used a fCHFS diet preference paradigm in rats in order to identify the impact of dopamine loss on food intake and preference. Our results highlighted a role of dopamine terminals in the lateral nucleus accumbens in the regulation of fat intake.

6-OHDA is a neurotoxin widely used to model Parkinson's disease (Faivre et al., 2019) and to study reduced dopamine states. This toxin enters the dopamine and noradrenaline neurons and terminals through the dopamine transporter and the noradrenaline transporter, and it produces reactive oxygen species thus causing the death of the catecholaminergic neurons and/or their terminals (Ungerstedt, 1968). The nigrostriatal dopamine system is important for feeding behavior as complete bilateral degeneration of SNc with 6-OHDA causes adipisia and aphagia (Ungerstedt, 1971). Similarly, dopamine

Fig. 2. High-fat High-sugar free choice in SNc lesioned animals. Daily nutrient intake pattern in sham ($n = 25$) and 6-OHDA animals ($n = 22$) for the three nutrient types over 7 days, in kcal per 100 gram of body weight (A), and in percentage of kcal consumed from different nutrient types (B). (C) Individual average kcal intake per 100 g of body weight in sham and 6-OHDA animals. (D) Individual patterns of nutrient choice (% of kcal intake) in sham and 6-OHDA animals. The blue lines identify the animals with the largest extent of striatal loss in TH staining. Data are presented as mean $\pm$ SEM. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$. 6-OHDA, 6-hydroxydopamine; Avg, average; SNc, substantia nigra pars compacta.

deficient mice are hypoactive and aphagic, leading to starvation and death if they are not given L-Dopa (Palmiter, 2008). However, an appropriate postoperative care allows animals with partial bilateral SNc lesion to consume sufficient food and prevents animal loss (Favre et al., 2020). In the present study, tests were performed after such postoperative care and 3 weeks of post-surgical recovery, with regular monitoring of body-weight. It allowed ensuring that SNc lesioned animals were in capacity to eat, drink and gain weight, even

though a slowdown of weight intake was present (Supplementary Fig. S1A).

As previously observed (Favre et al., 2020), the animals with bilateral SNc lesion displayed lower body weight gain. This decreased weight gain may likely be due to the lower kcal intake from standard chow in comparison with sham animals. This reduced weight gain was however only observed with midbrain SNc lesions, but was not present with more selective terminal lesions. Decreased weight gain or even weight loss is not limited

Fig. 1. Midbrain 6-OHDA lesions. Examples of tyrosine hydroxylase (TH) immunostaining in the SNc/VTA area and in the Str/NAc area for sham ($n = 25$) (A) and for 6-OHDA ($n = 27$) (B) injected rats (scale bars, 1 mm). Individual extent of the lesion: the colored area corresponds to the lesioned area at the site of injection (C) and at Str/NAc projection level (D) after 6-OHDA injection. The experimental identity number of each rat is displayed nearby drawings; the red color identifies animals with less than 50% of bilateral TH immunostaining loss in the SNc that were removed from behavioral analyses and the blue color identifies animals with the largest extent of striatal loss in TH staining. (E) Graph representing the integrated grey density (I.G.D.) of TH immunostaining in the SNc and VTA. (F) Optical density (O.D.) of TH immunostaining in different subregions of the Str/NAc. 6-OHDA, 6-hydroxydopamine; NAc, nucleus accumbens; SNc, substantia nigra pars compacta; Str, striatum; VTA, ventral tegmental area.

Fig. 3. High-fat High-sugar free choice in DLS lesioned animals. Schematic of injection site (A), example of tyrosine hydroxylase immunostaining (B) and schematic reconstruction of individual lesion extents (C). Daily nutrient intake pattern in sham ($n = 8$) and 6-OHDA animals ($n = 8$) for the three nutrient types over 7 days, in kcal per 100 gram of body weight (D), and in percentage of kcal consumed from different nutrient types (E). (F) Individual average kcal intake per 100 g of body weight in sham and 6-OHDA animals. (G) Individual patterns of nutrient choice (% of kcal intake) in sham and 6-OHDA animals. The picture insert displays TH immunostaining in the animal with high fat intake (blue line). Data are presented as mean $\pm$ SEM. Scale bars, 1 mm. 6-OHDA, 6-hydroxydopamine; Avg, average; DLS, dorsolateral striatum.

to the 6-OHDA model of Parkinson's disease. Indeed, weight loss is also present with aging in the MitoPark transgenic mouse model (Li et al., 2013). Besides, mice expressing the A53T human alpha-synuclein mutation (Giasson et al., 2002), the Thy1-aSYN Mice (Cuvelier et al., 2018), and the PINK1 deficient mice (Gispert et al., 2009), also display reduced body weight gain over time. Similarly, in the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) model of Parkinson's disease in the

primate, a daily care of the animals is essential otherwise animals may die due to adipisia, aphagia and loss of body weight (Porras et al., 2012). However, it is to be noted that MPTP-treated mice (Sundstrom et al., 1990; Munoz-Manchado et al., 2016; Zhang et al., 2017) and the LRRK2 G2019S transgenic mice (Bieri et al., 2019) may not display noticeable change in body weight. Clinically, Parkinson's disease patients are known to have weight fluctuations. Weight loss has been reported in early as

Fig. 4. High-fat High-sugar free choice in lateral NAc lesioned animals. Schematic of injection site (A), example of tyrosine hydroxylase immunostaining (B) and schematic reconstruction of individual lesion extents (C). Daily nutrient intake pattern in sham ($n = 12$) and 6-OHDA animals ($n = 14$) for the three nutrient types over 7 days, in kcal per 100 gram of body weight (D), and in percentage of kcal consumed from different nutrient types (E). (F) Individual average kcal intake per 100 g of body weight in sham and 6-OHDA animals, the insert details the individual fat intake. (G) Individual patterns of nutrient choice (% of kcal intake) in sham and 6-OHDA animals. Data are presented as mean $\pm$ SEM. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Scale bar, 1 mm. 6-OHDA, 6-hydroxydopamine; Avg, average; INAc, lateral nucleus accumbens.

well as advanced forms of the Parkinson's disease (Kistner et al., 2014; Ma et al., 2018), whereas some patients may show again increased weight gain with dopamine replacement therapy, pallidotomy or subthalamic nucleus deep brain stimulation (Kistner et al., 2014;

Ma et al., 2018). Beside weight fluctuations, it has been proposed that Parkinson's disease patients may also display alterations in food preference (Aiello et al., 2015), with an increased preference for palatable food rich in fat and sugar (Hellenbrand et al., 1996; Wolz et al.,

Fig. 5. High-fat High-sugar free choice in medial NAc lesioned animals. Schematic of injection site (**A**), example of tyrosine hydroxylase immunostaining (**B**) and schematic reconstruction of individual lesion extents (**C**). Daily nutrient intake pattern in sham ($n = 10$) and 6-OHDA animals ($n = 14$) for the three nutrient types over 7 days, in kcal per 100 gram of body weight (**D**), and in percentage of kcal consumed from different nutrient types (**E**). (**F**) Individual average kcal intake per 100 g of body weight in sham and 6-OHDA animals. (**G**) Individual patterns of nutrient choice (% of kcal intake) in sham and 6-OHDA animals. Data are presented as mean $\pm$ SEM. Scale bar, 1 mm. 6-OHDA, 6-hydroxydopamine; Avg, average; mNac, medial nucleus accumbens.

2009; Meyers et al., 2010), to the detriment of fresh fruits, vegetables and protein (Hellenbrand et al., 1996; Lorefält et al., 2006; Ådén et al., 2011). In the animals, food choice paradigms were however not yet applied to the 6-OHDA SNc lesion model of Parkinson's disease. The use of the fCHFHS paradigm allowed us to observe that, beside the expected decreased in kcal intake, SNc lesioned

animals did not display notable change in sucrose consumption but had a perturbed food intake pattern, with about a third of the animals surprisingly displaying an increased kcal consumption from the fat source. This heterogeneity in individual data suggested that the subpopulation of lesioned dopamine neurons may be of importance and could explain interindividual variability in

the consequences of the lesion. We thus targeted different dopamine terminal fields to test their influence on the fCHFS paradigm.

The pharmacological or viral-mediated rescue of dopamine system in the dorsal striatum has been shown to restore feeding behavior in dopamine (tyrosine hydroxylase) deficient mice (Zhou and Palmiter, 1995; Szczypka et al., 2001; Sotak et al., 2005; Hnasko et al., 2006; Palmiter, 2008). These mice could indeed consume sufficient food for survival when a recombinant adeno-associated virus was delivered in the central or lateral region of the caudate putamen to ectopically co-express tyrosine hydroxylase and the GTP-cyclohydrolase (required by striatal cells to make tetrahydrobiopterin, an essential co-factor for tyrosine hydroxylase) (Szczypka et al., 2001), or when a retrograde canine adenovirus expressing the tyrosine hydroxylase was injected in the dorsal striatum (Sotak et al., 2005). Furthermore, a retrograde CAV2-Cre viral strategy could rescue feeding in tyrosine hydroxylase deficient mice by simply restoring the tyrosine hydroxylase gene selectively in neurons that project to the caudate putamen (Hnasko et al., 2006). These data converge to show that dopamine in the dorsal striatum may be critical to the aphagia associated with dopamine loss, and could partly explain the food-intake deficit that can be observed after bilateral SNc lesion. However, a 6-OHDA lesion that targets dopamine terminals only in the dorsolateral striatum is not sufficient *per se* to significantly alter weight gain, food and kcal intake, and preference for a specific food type. While this lack of impact was observed overall, some effect on food preference (increased fat intake) was however present in an animal whose lesion was extended to the ventrolateral part of the striatal complex.

Previous studies have shown that activation of VTA dopamine neurons projecting to the NAc is reinforcing (Tsai et al., 2009; Witten et al., 2011) and favors the frequency of feeding with smaller meal size, without affecting total food intake (Boekhoudt et al., 2017). When a D1 dopamine receptor agonist is given peripherally, it dose dependently affects palatable food consumption (Martin-Iverson and Dourish, 1988; Cooper et al., 1992). In this regard, the D1-expressing medium spiny neurons of the mNAc appears to be particularly sensitive to palatable food (Durst et al., 2019). Using recording and selective optogenetic manipulation of these neurons in the NAc shell, it has been shown that these neurons projecting to the lateral hypothalamus provide a rapid control over feeding and particularly feeding duration (O'Connor et al., 2015). Despite this well established and important control of fine aspects of feeding, we show that the more global overnight food intake and food choice were not altered by mNAc dopamine loss.

After high fat consumption, several studies have shown alterations in dopamine receptors, in dopamine transporter and in their mRNA levels in the nucleus accumbens (Huang et al., 2005, 2006; South and Huang, 2008; Sharma and Fulton, 2013; Adams et al., 2015; Hryhorczuk et al., 2016) and in the striatum (Alsio et al., 2010; Johnson and Kenny, 2010; Tellez et al., 2013). While fat intake can alter the dopamine system,

less is reciprocally known on the role of the dopamine system in fat intake or preference. The binge consumption of sweetened high fat liquid in long Evans rats has for example been shown to be independent from NAc dopamine signaling (Lardeux et al., 2015), but this study was entirely carried out either in the core or medial NAc and did not address the potential influence of the INAc.

Previously, it has been shown that bilateral 6-OHDA lesions of dopamine terminals in the NAc can enhance food intake during 30-min sessions (Koob et al., 1978). In the present study, we found that more specific bilateral lesions of the INAc (but not of the mNAc) increased the daily total kcal intake, which was mainly driven by an increased intake of fat. This anatomical specificity within the NAc may be related to differences in connectivity within subregions of this nucleus. Indeed, the INAc and the mNAc receive different dopamine innervation from the VTA, the INAc receiving dopamine inputs from the lateral region of the VTA and projecting back in turn to GABAergic neurons of the lateral VTA causing disinhibition, while mNAc receives dopamine inputs from the medial region of the VTA and sends back GABAergic projection to both the medial and lateral VTA dopamine neurons thus causing inhibition (Yang et al., 2018). This organization may for example contribute to the information flow related to the ascending spiral moving from the ventral to the dorsal striatum (Haber et al., 2000). Furthermore, the VTA dopamine neurons projecting to the INAc may receive afferents primarily from anterior cortical regions, including the prefrontal cortex, while the VTA dopamine neurons projecting to the mNAc may receive notable inputs from the dorsal raphe nucleus (Beier et al., 2015).

While we compared the respective impact of 6-OHDA lesions of the dorsolateral striatum, mNAc and INAc, it is to be noted that a subregion may be missing in this comparison: the dorsomedial part of the striatum. Indeed, this part of the striatum was also affected in animals with extended midbrain lesions. The dorsal striatum in rodents can be divided into its dorsomedial and dorsolateral regions, which would be somewhat analogous to the caudate and putamen nuclei in higher species with a prominent internal capsule (Haber, 2016). Clinically, a decreased activation of the caudate nucleus in response to the consumption of energy-dense food has been reported in obese relative to lean adolescent girls (Stice et al., 2008). In rats, an increase in enkephalin release was observed in the dorsomedial striatum after consumption of a palatable (chocolate) food (DiFeliceantonio et al., 2012); and the excitotoxic lesion of the dorsomedial striatum was shown to lower high-fat diet consumption, which was followed by increased chow consumption (Cole et al., 2017). Together, these data are supportive of a role of the dorsomedial striatum in food reward and food choice processing, but the impact of the excitotoxic lesion of this subregion on fat intake was opposite from what we observed after midbrain or INAc dopaminergic lesions.

It was somewhat surprising to observe that dopamine loss did not affect the sucrose consumption in the fCHFS paradigm. Indeed, anhedonic response towards sucrose

solution has been clearly reported with manipulation of dopamine systems or loss of dopamine neurons (Der-Avakian and Markou, 2012; Santiago et al., 2014; Zhang et al., 2016; Kaminska et al., 2017; Faivre et al., 2020). However, dopamine deficient mice have higher rate of licking, bout size and duration with fewer total licks, without change in preference for sucrose (Cannon and Palmiter, 2003). Importantly, most of the anhedonia-related studies are carried with low to mild concentrations of sucrose solution (0.5–5%), while with higher concentrations of sucrose there can be a ceiling effect in the amount of sucrose taken daily (Wallace et al., 2008). It suggests that anhedonia-related studies are mostly highlighting dose-related shifts in sucrose preference rather than total loss of interest. In our study, we used the fCHFS paradigm that relies on a high concentration of sucrose, which may mask dopamine-related modulation of the preference for sucrose (usually detected at thresholds doses) and explains why we did not observe any differences for overall sucrose consumption between 6-OHDA-lesioned and control animals.

With most NAc functional studies focusing on the mNAc, the importance of the INAc has been mostly neglected. The present study provides behavioral evidence that dopamine in the INAc is influential for food-type preference in food intake. Our results more specifically indicate that reducing the dopamine tone in this region was sufficient to favor fat intake in male rats. These findings provide a new insight into how dopamine influences food intake and food preference, opening the path for further research on INAc regulation of fat intake in normal and pathological states.

Funding

The present study was supported by the Centre National de la Recherche Scientifique (CNRS UPR3212), the University of Strasbourg, the University of Amsterdam, the Agence Nationale de la Recherche [ANR-15-CE37-0005-02; Euridol ANR-17-EURE-0022], the NeuroTime Erasmus Mundus Joint Doctorate, and by a NARSAD distinguish investigator grant from the Brain and Behavior Research Foundation [24220].

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ACKNOWLEDGEMENTS

We thank the core facility Chronobiotron UMS3415 (Strasbourg, France) for animal care, and the UPS3156 *in vitro* imaging core facility (Strasbourg, France) for NanoZoomer scanning.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuroscience.2021.05.022>.

(Received 5 January 2021, Accepted 19 May 2021)
(Available online 25 May 2021)