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Research article

A high fat western diet attenuates phasic dopamine release

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ABSTRACT

Natural rewards, such as food and social interaction, as well as drugs of abuse elicit increased mesolimbic dopamine release in the nucleus accumbens (NAc). Drugs of abuse, however, increase NAc dopamine release to a greater extent and are known to induce lasting changes on the functioning of the mesolimbic dopamine pathway. Less is known about the long-term effects of diet composition on this reward pathway. In the present study, two diets were compared: a higher-fat diet (Western Diet: WD) and a control diet (standard lab chow) on their effect on the mesolimbic dopamine system. Twenty male C57BL/6 J mice were placed on one of these diets at 7 weeks old. After twelve weeks on the diet, *in vivo* fixed potential amperometry was used to measure real-time stimulation-evoked dopamine release in the NAc of anesthetized mice before and after an i.p. injection of the dopamine transporter (DAT) inhibitor nomifensine. Results indicated that diet altered mesolimbic dopamine functioning. Mice that consumed the WD demonstrated a hypodopaminergic profile, specifically reduced baseline dopamine release and an attenuated dopaminergic response to DAT inhibition compared to the control diet group. Thus, diet may play a role in mediating dopamine-related behavior, disorders associated with dopamine dysfunction, and pharmacological treatments aimed at altering dopamine transmission.

1. Introduction

The mesolimbic dopamine pathway is known for its role in reward and motivation. This pathway consists of dopamine cell bodies in the ventral tegmental area (VTA) that project to areas of the limbic system, most predominately to the nucleus accumbens (NAc). Natural rewards, such as food and social interaction, elicit NAc dopamine release, increasing the likelihood of seeking and repeating these activities [1,2]. Most drugs of abuse also target this neural pathway and either directly or indirectly increase NAc dopamine release to a greater extent than natural rewards [3]. Repeated administration of dopamine agonists is known to change dopaminergic functioning in the mesolimbic pathway in a way that reduces the reinforcing properties of natural rewards [4]. Experiencing natural rewards, such as foods, may prime this system in a similar way.

Natural rewards differ in their ability to activate the mesolimbic dopamine system. Animal studies have demonstrated increases in NAc dopamine activity and related behaviors following foods, but particulary foods higher in sugar and fat [5]. Thus, increased exposure to foods high in fat and sugar may induce compensatory changes in this reward processing pathway. Behaviorally, rodents on high-fat diets for extended periods of time have shown decreased preference for and reduced self-administration of dopamine agonists relative to rodents on low-fat control diets [6,7]. However, other studies have shown that rodents on high-fat diets display increased locomotor activity and increased sensitization following administration of dopamine agonists [8,9].

Results regarding the neurochemical effects of extended access to high-fat diets are also varied. Chronic exposure to high-fat diets has been shown to decrease the number of D1 and D2 receptors and dopamine transporters (DAT) in the NAc, creating a hypodopaminergic status [10–12]. Similarly, high-fat diets have been shown to attenuate NAc dopamine turnover and reduce striatal activity [6,13]. Other studies found no diet effect on baseline NAc expression of D2 receptors or DAT, tyrosine hydroxylase (TH) content, or basal dopamine release, but differences following administration of dopamine agonists [8,14,15]. Cone et al. [14] and Fordahl et al. [15] found that rodents on a high-fat diet had reduced stimulation-evoked dopamine release following cocaine and amphetamine, respectively, relative to those on the control diet, while Naneix et al. [8] observed increased burst activity of VTA dopamine cells, increased NAc basal dopamine release, and greater NAc TH

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expression following amphetamine in rats fed high-fat diets. Such findings may seem contradictory but are likely due to variations in diet consistency/timing and research techniques used to assess aspects of dopamine functioning.

The current study aimed to determine the effects of chronic consumption of a high-fat diet on *phasic* dopamine release in the NAc. Phasic dopamine release in the NAc is elicited by environmental stimuli and is thought to assign incentive values to reward cues, thus driving goal-directed behavior [16]. Specifically, *in vivo* fixed potential amperometry was used to quantify stimulation-evoked dopamine release, the synaptic half-life of dopamine [an indication of dopamine transporter (DAT) functioning], dopamine autoreceptor functioning, available neuronal supply of dopamine, and the effect of a DAT inhibitor (nomifensine) on dopamine release and half-life. Understanding the influence of a high-fat diet on mesolimbic dopamine dynamics may improve the prevention and treatment of disorders related to dopamine dysfunction, such as addiction, ADHD, and depression.

2. Methods

2.1. Subjects and diets

Twenty male C57BL/6J mice (Jackson Laboratories) were received at 7 weeks of age and housed 3–5 per cage in a temperature (21 ± 1 °C) controlled room on a 12 h light:dark cycle. Upon arrival, mice were immediately put on either the high-fat Western Diet (WD; n = 10) or a standard lab chow diet (control diet; n = 10). In terms of caloric information, WD pellets consisted of 17 % protein (primarily casein), 43 % carbohydrates, and 40 % fat (Research Diets, Product: D12079B). The control diet pellets consisted of 24 % protein (soy), 58 % carbohydrates, and 18 % fats (Evigo, Product: 2018). For both diet groups, food and water were available *ad libitum*. Mice were weighed weekly. All experiments were approved by our university IACUC. Sample sizes were determined based on G*Power analysis and previous effect sizes [17, 18].

2.2. Surgery and amperometric recordings

Fixed potential amperometry allows high temporal recordings (10 K samples/sec) of stimulation-evoked dopamine release in subcortical brain regions [17,18]. Each amperometric recording station consisted of a stereotaxic frame with electrode carriers (David Kopf Instruments), an electrometer (e-corder 401 and Picostat, Edaq Inc.), and a programmable stimulator (Iso-Flex/Master 8, AMP) surrounded by a faraday cage and connected to a computer.

Mice were anesthetized by urethane (1.5 g/kg i.p.; U2500 Sigma-Aldrich) and placed in a stereotaxic frame. Urethane has been shown to produce anesthesia without significantly altering dopamine release or uptake kinetics [19,20]. Body temperature was kept at 37 ± 0.5 °C, and three trephine holes (1.0 mm o.d.) were drilled through the skull. All stereotaxic coordinates are presented in mm from Bregma, midline, and dura according to Paxinos and Franklin [21]. A stimulating electrode (SNE-100; Rhodes Medical Co.) was inserted into the VTA (AP + 3.3, ML + 0.3, and DV -4.0). A stainless-steel auxiliary and Ag/AgCl reference electrode combination was positioned 2.0 mm posterior from Bregma on cortical tissue contralateral to the stimulating electrode. A carbon fiber electrode (500 μm length x7 μm o.d.; Thornel Type P, Union Carbide) was inserted in the left NAc core (AP + 1.5, ML + 1.0, and DV -4.0). A fixed current of 0.8 V was applied to the recording electrode, and current was monitored continuously (10k samples/sec). Past studies using the same electrical stimulation have pharmacologically confirmed that the measured current changes correspond to dopamine efflux [17].

Stimulation parameters varied based on the aspect of dopamine release being measured. To test for dopamine autoreceptor sensitivity, a pair of test stimulations (T1 and T2, each 10 0.5 ms duration 800μAmp pulses at 50 Hz, separated by 10 s) were applied every 30 s [17]. Six sets of conditioning pulses (1, 5, 10, 20, 40, and 80 pulses; 0.5 ms pulse duration at 15 Hz) were delivered prior to T2 with 0.3 s between the end of the conditioning pulse train and initiation of T2. Autoreceptor-mediated inhibition of evoked dopamine release was expressed in terms of the change in the amplitude of T2 with respect to T1 for each set of conditioning pulses (T2/T1). Low-to-high dopamine autoreceptor sensitivity was represented as low-to-high percent inhibition of evoked dopamine release (*i.e.*, high autoreceptor sensitivity results in a lower amplitude of T2 relative to T1).

To assess baseline (pre-drug) dopamine efflux, a series of cathodal monophasic pulses (20 0.5 ms duration 800μAmp pulses at 50 Hz) were applied every 30 s. Phasic dopamine release (the magnitude of the stimulation-evoked responses) and dopamine synaptic half-life (the time required for dopamine to be cleared from the synapse) were quantified. Dopamine synaptic half-life was defined as the time for 50 % decrease from the maximum evoked increase to the prestimulus baseline level [17,18]. After a 10 min baseline recording, mice received an injection of nomifensine (10 mg/kg, i.p.; N1530 Sigma-Aldrich; dissolved in 0.9 % saline), and recordings continued for 1 h. Next, in order to quantify the neuronal supply of dopamine, a 3-minute continuous stimulation was delivered (9,000 0.5 ms duration 800μAmp pulses at 50 Hz) [18].

At the end of each experiment, a direct anodic current (400 μAmps for 10 s) was applied to the stimulating electrode for placement confirmation. Mice were then euthanized by intracardial injection of urethane (0.345 g/mL). Brains were stored in 30 %/10 % sucrose/formalin plus 0.1 % potassium ferricyanide for cryostat sectioning. Electrode placement was confirmed with a light microscope (Fig. 1). Carbon fibers were calibrated using a flow injection system which allows for a conversion of current recordings (Amps) to dopamine concentration (M) [22].

2.3. Data analysis

Independent t-tests (two-tailed) with Levene's test for equality of variances were used to compare mouse weights, dopamine release, half-life, and supply differences between diet groups. A two-way mixed ANOVA was used to compare weekly weights of mice with the 12-week food exposure period as the within-subjects variable and diet as the between-subjects variable. A two-way mixed ANOVA was also conducted to compare autoreceptor sensitivity levels with the number of prepulses as within-subjects variable and diet as a between-subjects variable. Changes in stimulation-evoked dopamine concentration following nomifensine administration was converted to mean percent change with respect to baseline (pre-drug). Two-way mixed ANOVAs were used to compare percent change in dopamine release and percent change in dopamine half-life following the drug challenge with time (60 min post-injection) as the within-subjects variable and diet (WD or control) as the between-subjects variable. For all mixed ANOVAs, Mauchly's test was used to assess sphericity, and Greenhouse-Geisser corrections were applied if needed. Alpha levels were set at 0.05, unless the Bonferroni correction was applied.

3. Results

3.1. Weights of mice

A significant interaction between diet and time was observed [$F(2.55, 45.93) = 26.9$, $p < .001$, Fig. 2A], indicating a difference in weight gain between diet groups. Using Bonferroni-adjusted significance levels to account for multiple t-tests ($\alpha < .0039$), the mice on the western diet weighed significantly more than control diet mice from week 5–12, with the exception of week 8 ($p = .013$).

3.2. Baseline dopamine efflux

The tips of the stimulating and recording electrodes were positioned

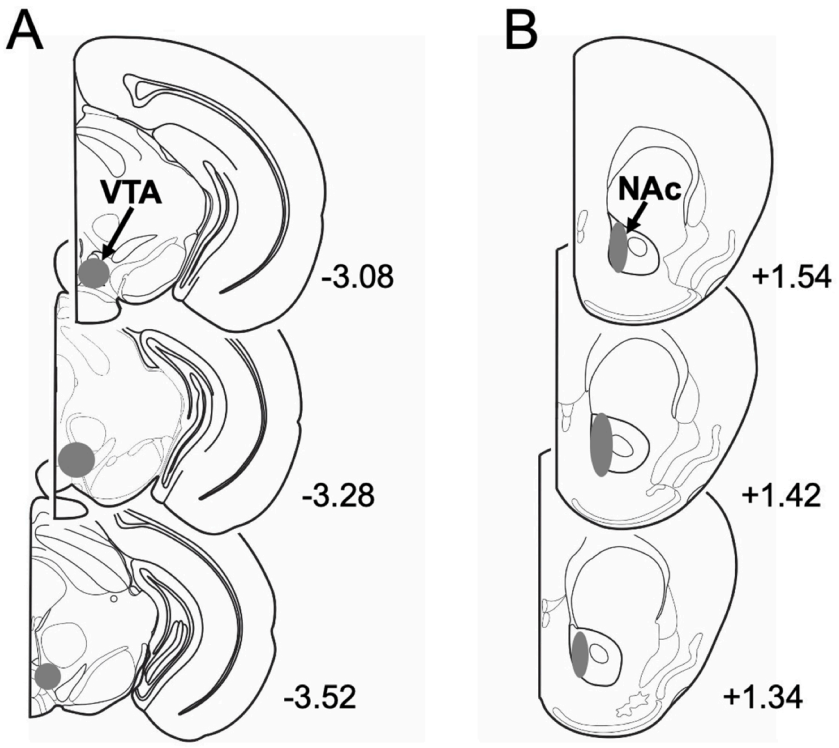

Fig. 1. Electrode placements. Representative coronal sections of the mouse brain were adapted from Paxinos and Franklin [21]. Gray shaded areas indicate the placements of (A) stimulating electrodes in the ventral tegmental area (VTA) and (B) amperometric recording electrodes in the nucleus accumbens (NAc). Numbers correspond to mm from Bregma.

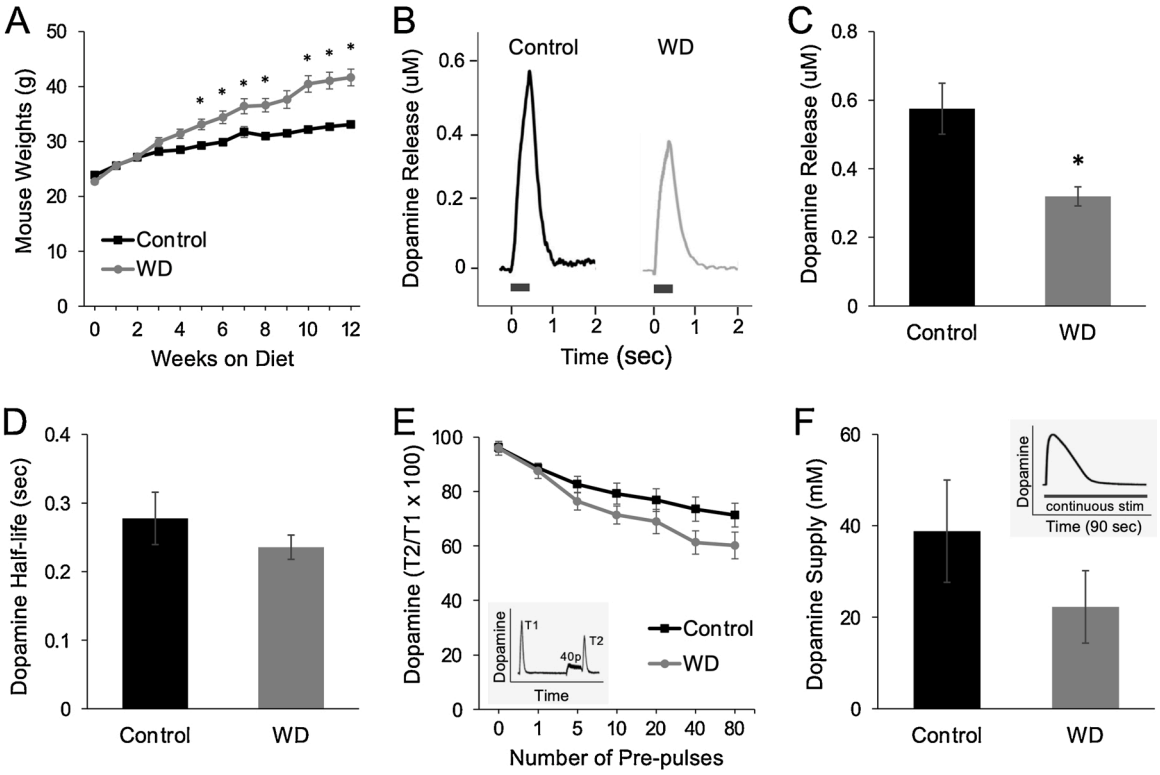

Fig. 2. Diet-induced changes in baseline phasic dopamine transmission. Mice on the Western Diet (WD) gained significantly more weight than the control diet mice (A). Example responses (B) and means ± SEM (C) show reduced stimulation-evoked dopamine in the NAc of WD mice compared to controls. No significant differences were observed in the synaptic half-life of dopamine (D), dopamine autoreceptor functioning (E), or neuronal supply of dopamine (F). Grayed insets (E and F) show example responses.

within the anatomical boundaries of the VTA and NAc core, respectively (Fig. 1). Mice maintained on a WD displayed reduced baseline dopamine release compared to the control diet group [t (11.47) = 3.22, $p <$ 0.01, d = 1.44, Fig. 2B and C], but diet had no significant effect on the synaptic half-life of dopamine [t (18) = 0.99, $p =$ 0.33, Fig. 2D].

3.3. Dopamine autoreceptor function

Autoreceptor-mediated dopamine release was calculated by percent change between T1 and T2 stimulations for each set of pre-pulse conditions with T1 being 100 % (T2/T1 × 100). Lower percent release indicates increased autoreceptor functioning. A significant main effect of the number of pre-pulses on autoreceptor-mediated dopamine release was observed [F(2.68,48.30) = 42.70, $p <$ .001, η_p^2 = .70, Fig. 2E], showing that autoreceptor-mediated dopamine release decreased as the number of pre-pulses increased. As expected, autoreceptors inhibited dopamine release to a greater extent as the number of pre-pulses increased. However, there was not a significant interaction between diets and the number of pre-pulses [F (2.68, 48.30) = 1.89, $p =$ .149], indicating that the diets did not significantly alter autoreceptor-mediated dopamine release.

3.4. Available dopamine supply

Dopamine supply (in mM) was determined by continuously stimulating at 50 Hz for 3 min to evoke the release of all available dopamine in the NAc. There were no significant differences in available dopamine supply between diet groups [t (18) = 1.21, $p =$ 0.24, Fig. 2F].

3.5. Dopamine efflux following DAT inhibition

Mice received an i.p. injection of nomifensine, a dopamine reuptake blocker, during amperometric recordings (Fig. 3A and B). There was a significant main effect of time post-injection on percent change in dopamine release [F(1.91, 34.4) = 57.96, $p <$ .001, η_p^2 = .76, Fig. 3C]. The interaction between diet and time post injection approached significance [F(1.91, 34.4) = 3.02, $p =$ .064, η_p^2 = .14], trending towards an attenuated percent change in evoked dopamine release in response to DAT inhibition in the Western diet group.

Regarding dopamine half-life following nomifensine, there was a significant main effect of time post injection [F(1.97, 35.53) = 67.56, $p <$ .001, η_p^2 = .79, Fig. 3D]. A significant interaction between diet and time post injection was also observed [F (1.97, 35.53) = 5.06, $p =$ .01, η_p^2 = .22]. Using Bonferroni-adjusted significance levels to account for multiple t-tests (α < .0167), significant differences were observed between diet groups in percent changes of dopamine half-life at 20 min [t (18) = 2.94, $p <$ .009, d = 1.31] and 40 min [t (18) = 2.97, $p =$ .009, d = 1.30], but not 60 min [t (13.4) = 2.35, $p =$ .031, d = 1.05] following nomifensine. Specifically, at 20 and 40 min post injection, the percent change in dopamine half-life was significantly less in WD mice compared to control mice.

4. Discussion

The purpose of the current study was to examine whether a chronic high-fat diet affects mesolimbic dopamine transmission. Following a 12-week dietary exposure to either the high-fat WD or standard lab chow, stimulation-evoked dopamine release in the NAc was measured using *in vivo* fixed potential amperometry in anesthetized mice. Mice on the WD displayed decreased baseline dopamine release and a reduced dopaminergic response to DAT inhibition compared to control mice. Thus, prolonged exposure to the WD resulted in a hypodopaminergic profile.

Phasic dopamine release, which is elicited by environmental stimuli such as palatable food and drugs of abuse, alters attention and drives goal-directed behaviors [16]. In the present study, prolonged exposure to the WD decreased stimulation-evoked phasic dopamine release in the NAc. Reduction in stimulated dopamine release can result in decreased reinforcing values of rewards and associated environmental stimuli, and decreased dopamine release has also been linked with reduced motivational drive and increased symptoms of depression [10,23,24]. Thus, the present results provide neurochemical support for behavioral studies showing that rodents on a high-fat diet exhibited more behaviors associated with depression and anhedonia [10,11,25]. Similarly, clinical longitudinal studies and meta-analyses have suggested an increased risk of depression in humans than consume high-fat diets [26,27].

Extracellular dopamine levels are regulated by many cellular and

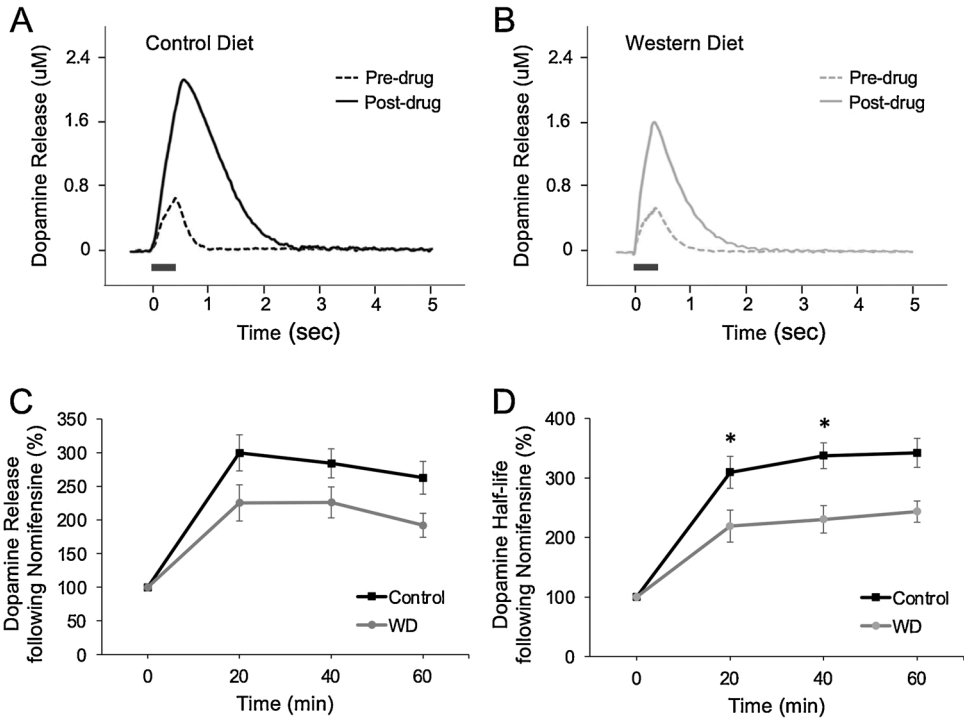

Fig. 3. Diet-induced changes in phasic dopamine transmission following DAT inhibition. Example responses depict stimulation-evoked dopamine release before and after administration of the dopamine transporter inhibitor nomifensine in mice on the control diet (A) and Western Diet (WD) (B). Dotted and solid lines indicate example responses before and 20 min after nomifensine, respectively. Means ± SEM of percent change in dopamine release (C) and half-life (D) show a reduced dopaminergic response to nomifensine in the WD mice compared to mice on the control diet.

synaptic mechanisms, of which the present study assessed DAT functioning, dopamine autoreceptor functioning, and neuronal supply of dopamine. DAT functioning is often assessed by the speed with which dopamine is cleared from the synapse (*i.e.* dopamine reuptake rates or synaptic dopamine half-life). In the NAc specifically, Geiger et al. [28] found that high-fat diets increased the time needed for synaptic dopamine clearance, which would suggest reduced DAT functioning. However, the present results showed no differences in dopamine half-life between diet groups, indicating that the WD did not alter DAT functioning. These findings mirror those of Jones et al. [12] indicating that altered DAT functioning in the NAc is likely not a factor contributing to decreased extracellular dopamine release of WD mice. Previous studies studies do suggest that our results may have differed if dopamine recordings and DAT assessments had been done in different regions of the striatum [12,14,29,30]. Several studies indicate that longterm exposure to a high-fat diet leads to decreases in NAc D2 receptors, which often act as dopamine autoreceptors and regulate dopamine release [10,30]. High-fat diet has also been shown to reduce D2 autoreceptor inhibition of spontaneous neuron firing in the VTA [31]; however, the current results showed no difference between diet groups in dopamine autoreceptor functioning. Our findings, which parallel those of Fordahl et al. [15], suggest that the WD altered dopamine release *via* a mechanism other than autoreceptors. For example, diet has shown to alter the composition of membrane lipids, thus influencing neurotransmitter release and receptor functioning [32]. Additional mechanisms to explore include VMAT2 functioning, TH levels, insulin production and receptor populations, and interactions with glutamate receptors, all of which have been shown to be influenced by diet and/or fat consumption [10,11,13,15].

During dopamine recordings, mice were systemically administered nomifensine, a DAT inhibitor. Nomifensine increased dopamine release and dopamine half-life in both diet groups; however, this dopaminergic response was attenuated in WD mice. These results support behavioral findings that high-fat diets reduce reinforcing effects of psychostimulants such as cocaine and amphetamine, which act at least in part by inhibiting DAT [6,7]. Given that we did not observe diet-induced differences in the baseline half-life of synaptic dopamine, this attenuated response to nomifensine in WD mice is likely not due to impaired DAT functioning but more likely related to the observed decrease in baseline dopamine release in WD mice. Several disorders, including ADHD, narcolepsy, and depression, are treated with DAT inhibitors. The present findings and others suggest that diet may alter the efficacy of these medications [33,34]. These findings cannot distinguish the effects of diet from potential obesity effects (as the WD mice gained more weight than the controls); however, previous studies have concluded that obesity is not associated with an altered reinforcing effect of psychostimulants [35,36].

In conclusion, the current study further demonstrates that diet can alter mesolimbic dopamine functioning. Mice on the WD displayed decreased baseline dopamine release in the NAc and a decreased dopaminergic response to a DAT inhibitor. In this study, male mice were placed on either the WD or control diet for 12 weeks, which spanned across late adolescence into adulthood. Several critical factors that may impact the generalizability of these results and cross-comparisions with other studies. Such factors include variations in the nutritional breakdown of the diet, the duration of the diet, the developmental period of diet exposure, and sex/hormones [10,11,15,29]. Carlin et al. [11] showed that in both sexes basal dopamine levels were reduced following a high fat diet, but that only the female mice displayed a diet-induced increase in DAT mRNA expression. Thus, it is possible that current findings may have been similar and potentially more pronounced in female mice. Overall, an increased understanding of diet-related influences on mesolimbic dopamine functioning may help identify potential risk factors and improve treatments for dopamine-related disorders such as ADHD, addiction, and depression.

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CRediT authorship contribution statement

Mary K. Estes: Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Resources, Validation, Visualization, Writing - original draft, Writing - review & editing. **Jasric J. Bland:** Formal analysis, Investigation, Resources, Writing - original draft, Visualization, Funding acquisition. **Kenya K. Ector:** Formal analysis, Investigation, Resources, Writing - original draft, Visualization. **Melissa J. Puppa:** Conceptualization, Methodology, Resources, Validation. **Douglas W. Powell:** Conceptualization, Methodology, Resources, Software, Validation, Writing - review & editing. **Deranda B. Lester:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - review & editing.

Declaration of Competing Interest

None.

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