High-fat diet-induced dopaminergic dysregulation induces REM sleep fragmentation and ADHD-like behaviors

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Highlights

- High-fat diets (HFD) reduce wakefulness and increase REM sleep with fragmentation.
- HFD increased anxiety, hyperactivity, anhedonia, and impaired memory.
- HFD group showed decreased mRNA levels of dopamine-related genes in the circuit.
- Downregulated dopamine system and behavioral deficits are reminiscent of ADHD.

Psychiatry Research

High-fat diet-induced dopaminergic dysregulation induces REM sleep fragmentation and ADHD-like behaviors

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Keywords

High-fat diet; REM sleep; Dopamine; Attention deficit hyperactivity (ADHD)

ABSTRACT

Consumption of a high-fat diet (HFD) has been associated with reduced wakefulness and various behavioral deficits, including anxiety, depression, and anhedonia. The dopaminergic system, which plays a crucial role in sleep and ADHD, is known to be vulnerable to chronic HFD. However, the association between HFD-induced behavioral and molecular changes remains unclear. Therefore, we investigated the effects of a HFD on the dopaminergic system and its association with behavioral deficits in male mice. The mice were divided into normal diet and HFD groups and were analyzed for sleep patterns, behavior tests, and transcription levels of dopamine-related genes in the brain. The HFD group showed decreased wakefulness, increased REM sleep with fragmented patterns, decreased time spent in the center zone of the open field test, shorter immobile time in the tail suspension test, impaired visuospatial memory, and reduced sucrose preference. Additionally, the HFD group had decreased mRNA levels of D1R, COMT, and DAT in the nucleus accumbens, which negatively correlated with REM sleep proportion and REM sleep bout count. The results suggest that HFD-induced behavioral deficits were resemblance to ADHD-like behavioral phenotypes and disturbs REM sleep by dysregulating the dopaminergic system.

Main texts:

1. Introduction

The consumption of a high-fat diet (HFD) has been linked to an increased risk of various diseases, including obesity and metabolic syndrome, which encompasses conditions such as Type II diabetes, hyperlipidemia, hypercholesterolemia, and hypertension (Furukawa et al., 2004). Notably, in children and adolescents, HFD consumption is one of the major contributing factors to global obesity (Moreno et al., 2010; Ogden et al., 2010). Besides obesity and an increased risk of metabolic syndrome, HFD has been associated with deficits in cognitive functions (Elias et al., 2003; Kerwin et al., 2011) and psychiatric conditions such as anxiety-like and depressive behaviors (de Noronha et al., 2017; Dong et al., 2004; Milaneschi et al., 2017). Several studies have demonstrated that a diet rich in fatty foods reduces hippocampus volume, worsens cognitive function, attention, and psychomotor efficiency, and induces depression and anxiety in humans (Jacka et al., 2015). Furthermore, diet-induced obesity has been linked to cognitive deficits, elevated inflammation, accelerated brain aging, and increased risks of neurodegenerative disorders (Leigh and Morris, 2020). Thus, these findings suggest that HFD might affect neurobiology and lead to psychiatric problems.

Obese individuals often report sleep problems, such as excessive daytime sleepiness, sleep-disordered breathing, and sleep apnea (Flegal et al., 2002; Resta et al., 2003; Vgontzas et al., 1998; Vgontzas et al., 1997). In humans, HFD has been associated with increased human sleepiness (Wells et al., 1997) and elevated sleep-promoting inflammatory cytokines (Bastard et al., 2002). These findings suggest that HFD may influence sleep-wake regulation in humans, potentially affecting overall health and well-being.

In animal studies, mice fed an HFD exhibit decreased wakefulness and increased nonrapid eye movement (NREM) sleep (Jenkins et al., 2006), while rats fed with HFD have elevated amounts of rapid eye movement (REM) sleep (Luppi et al., 2014). Although there is evidence that HFD can affect sleep-wake regulation, these findings primarily focused on the duration of sleep stages and the underlying mechanisms remain unclear. A connection has been established between the regulation of sleep and food intake, two fundamental behaviors closely related to metabolism. Since sleep and feeding are directly regulated by orexin (Sakurai et al., 1998), HFD may affect sleep by increasing leptin levels and inhibiting wake-promoting orexinergic neurons (Sakurai, 2014). This association between sleep and feeding regulation underscores the importance of investigating the effects of HFD on sleep-wake regulation.

One potential mechanism involves the interaction of sleep and feeding with the dopaminergic system.

Sleep and feeding are also affected by dopaminergic neurons in the ventral tegmental area (VTA) (Eban-Rothschild et al., 2016), which play an essential role in the neural circuitry underlying emotion, reward, and addictive processes. The dopaminergic neurons in VTA innervate the nucleus accumbens (NAc) and prefrontal cortex (PFC). Food reward and other reward-seeking behavior are mediated by dopamine in the neural circuitry underlying reward and addiction processes (Fibiger and Phillips, 1988).

The consumption of high-fat foods can impair rewarding properties, and the impaired reward system overrides homeostatic satiety signals (Reyes, 2012). In rodents, chronic consumption of HFD attenuates the response to sucrose and decreases mesolimbic dopamine turnover in NAc (Davis et al., 2008). Chronic exposure to HFD has been shown to reduce basal dopamine levels and dopamine release in response to food or amphetamine (Geiger et al., 2009a).

Repeated exposure to addictive substances, including HFD, facilitates adaptive changes in the mesolimbic dopaminergic pathway, which is critical for regulating motivation and organizing emotional and contextual behaviors (Nestler and Carlezon, 2006; Steketee and Kalivas, 2011). Long-term consumption of HFD results in increased dopamine release, leading to adaptions and reward hypofunction (Carlin et al., 2013). Deficits of mesolimbic dopamine neurotransmission were exhibited in a dietary obesity rat model (Geiger et al., 2009b). Obese individuals have shown blunted activation in reward regions (Stice et al., 2008) and downregulation of the dopamine receptor in imaging studies (Wang et al., 2001). HFD impaired dopamine reuptake by attenuating signaling in the NAc (Fordahl and Jones, 2017). These findings suggest a potential relationship between dopamine, HFD, and sleep disruption, which may be further explored in the context of HFD-induced behavioral deficit and dopaminergic changes.

Recent studies demonstrate that the dopamine system is vulnerable to HFD consumption, particularly due to the impact of HFD on dopaminergic signaling pathways, neurotransmitter release, and receptor expression (Naneix et al., 2017). This vulnerability within the dopamine system could explain the deficits observed in reward-related processes in obesity, as alternations in the dopaminergic system can lead to disruptions in the neural circuitry underlying reward and addiction processes (Naneix et al., 2017). ADHD is a heterogeneous neurodevelopmental psychiatric disorder and is defined by three core clinical symptoms including hyperactivity, inattention, and impulsivity (Faraone et al., 2006). Furthermore, ADHD patients experience poor academic performance, anxiety, and depression (Champ et al., 2021). Anxiety, memory impairment, and a low hedonic tone have been observed as the most common comorbid clinical feature of

ADHD (Gaddi et al., 1991; Katzman et al., 2017; Rhodes et al., 2012; Skodzik et al., 2017; Sternat et al., 2018), which may result from a hypoactivation of the reward pathway (Pornpattananangkul et al., 2019).

ADHD is associated with the brain reward cascade, especially in the dopamine system, and defects in dopamine metabolism have long been implicated in the etiology of ADHD (Blum et al., 2008). Studies on neuroimaging suggest that ADHD is associated with a dysfunctional reward system, as evidenced by lower dopaminergic neuron responsiveness and a decrease in synaptic dopamine markers (Stark et al., 2011). On the other hand, HFD consumption leads to impaired learning/memory functions, depression, and anhedonia (Ajayi et al., 2021; Hassan et al., 2022; Kaczmarczyk et al., 2013; Tsai et al., 2022), and these behavioral characteristics were similar to those in attention-deficit hyperactivity disorder (ADHD). However, an integrated understanding of HFD-induced behavioral phenotypes and their neurobiological mechanisms remains unknown, highlighting the need for research to elucidate these relationships. Therefore, we hypothesize that the consumption of an HFD during adolescence may increase the vulnerability to behavioral deficits and dopaminergic dysregulation, resulting in ADHD-like symptoms. Our study aims to investigate the molecular, neurophysiological, and behavioral changes caused by HFD in an animal model.

2. Materials and methods

2.1. Animals

Experiments were carried out with male C57BL/6J (000664, Jackson Laboratory, Bar Harbor, ME, USA) mice at four weeks. Mice were randomly assigned to two groups, including normal diet (ND; n=9) and high-fat diet (HFD; n=13) groups. ND (RodFee, DBL, Eumseong, Korea) consisted of 68% carbohydrates, 22% proteins, and 10% fats in terms of caloric content, whereas the HFD (D12492, Research Diets, New Brunswick, NJ, USA) consisted of 20% carbohydrates, 20% proteins, and 60 % fats. All mice were given food and water *ad libitum* with constant 55 ± 5% humidity and 20 ± 2 °C temperature under a 12-h:12-h light/dark cycle (lights on 7 AM). Before behavioral tests, mice undergo an induction period of at least two months to induce each diet effect. All animal protocols were approved by the ethics committee at Gwangju Institute of Science and Technology, following Institutional Animal Care and Use Committee guidelines (GIST-2021-110).

2.2. Stereotaxic Surgery

After behavioral tests, we conducted stereotaxic surgery for implanting electrodes. During surgery, mice were placed in a stereotaxic instrument (51730, Stoelting Co., Chicago, IL, USA) and anesthetized with isoflurane (4% induction, 1-2.5% maintenance) delivered by a precision vaporizer (Classic T3 Anesthetic Vaporizer; 72-6468INT, Harvard Apparatus, Cambridge, MA, USA) in a mixture of 25% oxygen and 75% nitrogen. Ketoprofen was injected intramuscularly at a dose of 5 mg/kg body weight. To record the frontal and parietal cortex electroencephalograms (EEG), we implanted screw electrodes on the skull (AP 1.0 mm and ML 1.0 mm and AP -3.5 mm and ML 1.0 mm from bregma) and soldered the other ends to a headmount (Cat. No. 8402, Pinnacle Technology, Lawrence, KS, USA). The electrodes for electromyography (EMG) were inserted into the nuchal muscle. All electrodes were fixed to the skull with dental cement. We allowed the recovery period at least 1 week before the sleep recordings.

2.3. Sleep recording and analysis

For habituation with EEG cables and the recording chamber environment, the mice were placed into the recording chamber 12 hours before recording. The 3-channel mouse preamplifier (Cat. No. 8202, Pinnacle Technology, Lawrence, KS, USA) was connected to mice headmount and commutators (Cat. No. 8204, Pinnacle Technology, Lawrence, KS, USA). EEG/EMG and synchronized video were recorded in a sound-attenuated condition for 24 hours. The HFD and ND groups maintained their given chows during the recording. The sleep-wake states were manually socred at every 10-second epoch to categorize into three stages: wake (high EMG, low EEG amplitude, and high EEG power density in 6.0-9.0 Hz theta range), NREM (low EMG, higher EEG amplitude compare to wake and high EEG power density in 0.5-4.0 Hz delta range), and REM (low EMG, low EEG amplitude, high EEG power in theta range) based on standard criteria (Huber et al., 2000), using Sirenia Sleep Pro software (Pinnacle Technology, Lawrence, KS, USA).

2.4. Assessment of circadian wheel-running activity

Mice were singly housed in running wheel cages. Wheel revolutions were recorded using the Clocklab software (Actimetics, Evanston, IL, USA), with sampling epochs of 1 min. After one week of habituation to wheel cages, wheel revolutions were recorded in 24 h light/dark (12-h:12-h light/dark cycle; lights on 7 AM) for seven days and then in constant darkness (DD) for 16 days. Data were analyzed using ClockLab software. The

circadian period and amplitude were the chi-squared periodogram's peak values for seven days in LD or 14 days in DD. Activity bouts were defined as periods during which activity never reached less than one count per minute (bout threshold) for longer than 18 min (maximum gap length) at a time. The actogram of wheel activity presented data from 7 days LD and 16 days DD by a double-plotted method.

2.5. Behavioral test

We used standard behavioral test protocols to conduct the following five behavioral tests: open field test (OFT), novel place recognition (NPR) test, elevated plus maze (EPM) test, tail suspension test (TST), and sucrose preference test (SPT) (Can et al., 2012; Denninger et al., 2018; Kang et al., 2022; Komada et al., 2008; Liu et al., 2018; Seibenhener and Wooten, 2015). On five consecutive days during the dark cycle (between 19 and 24 pm), the OFT, NPR, EPM, and TST were conducted in a soundproof room separate from the home cage. After these four tests, we conducted the SPT of mice in their home cage for six days.

On the first day of testing, mice were tested for locomotor function and anxiety levels via OFT. The experiment was conducted in an open-topped square container with a volume of 40 cm^3 under red light (~50 lux). The mice were allowed to explore freely in the empty test area for 10 minutes before returning to their home cages.

Over the next two days, the NPR test was conducted to examine the hippocampus-dependent spatial memory (Denninger et al., 2018). On the second day of testing (acquisition trial), mice were permitted to explore two identical objects (Object A and Object A') which were each placed at locations symmetrical to the visual cue in a square arena for 10 min. After 24 h, on the third day of testing (test trial), one of the objects was relocated to a novel location, and mice explored the two objects in the familiar location and novel location for 10 min. The discrimination index indicates a relative preference for the novel location based on the following equation.

$$\text{Discrimination index} = \frac{Time\ spent\ in\ novel\ location - Time\ in\ familiar\ location}{Time\ spent\ in\ novel\ location + Time\ in\ familiar\ location}$$

The EPM test was carried out on the fourth day of testing to evaluate anxiety-like behavior in mice based on their natural aversion to open and elevated areas as well as their natural, spontaneous exploration of novel environments (Komada et al., 2008). The test area was composed of four arms (25 cm long x 5 cm wide)

connected by a center zone (5 x 5 cm) elevated 50 cm above the floor and illuminated with 300 lux. There were two arms with walls (16 cm high, closed arms), and the other arms did not have any walls (open arms). Mice were placed on open arms with their heads facing toward the center zone and allowed to explore freely for 5 min.

On the fifth day of testing, the TST was performed to measure hyperactive-like behavior (Can et al., 2012; Commons et al., 2017). Mice tails were individually suspended 8 cm above the floor in a chamber (21 cm x 15 cm length x 38 cm high) with a plastic cylinder (4 cm length, 1 cm diameter) and tape to avoid mice climbing. The immobility time was video-recorded under dim red light for 6 min. We recorded and analyzed the behavioral tests using a video tracking system, Smart 3 (Panlab, Harvard Apparatus, Barcelona, Spain).

The final behavioral test, SPT, was performed to evaluate anhedonic-like behaviors (Liu et al., 2018). We exposed mice to two bottles for three days for habituation, followed by three days for testing. Mice were habituated to two bottles containing tap water for three days in the habituation period. During the test period, mice were acclimatized to drinking from two bottles filled with 1% (w/v) sucrose solution or tap water for three days of testing. The bottles were rearranged daily, and the volume of the solutions was measured. The sucrose preference (%) was defined as a percentage of the volume of sucrose intake over the sum of the sucrose intake and the tap water intake.

2.6. Brain tissue preparation

Mice were sacrificed under deep anesthesia using isoflurane at the age of 36-42 weeks. The brain was harvested and dissected by using a mice brain matrix (14-0100, 15-30 g Mice, Coronal, 1 mm, Shenzhen Leiyea Biotechnology, Guangdong, China). Tissue biopsies using a 1mm inner diameter biopsy punch were extracted from 1-mm brain slices corresponding to the dopaminergic midbrain (+0.64 mm to +1.00 mm interaural; -3.16 mm to -2.80 mm Bregma), involving ventral tegmental area (VTA) and slice (+4.78 mm to +5.74 mm interaural; 0.98 mm to 1.94 mm Bregma), including prefrontal cortex (PFC) and nucleus accumbens (NAc), as described previously in Paxinos and Franklin's mouse brain atlas. Micro punches were taken of the VTA, NAc, and PFC in 1 ml RNA later (RNA later^{TM} Soln., Invitrogen, Waltham, MA, USA) and quick-frozen on dry ice and stored at -80 °C until further processing.

2.7. Quantitative Reverse Transcriptase PCR (qRT-PCR)

Total RNA was extracted from tissue punches of PFC, NAc, and VTA with TRI reagent (TR118, Molecular Research Center, Ohio, USA) following the manufacturer's instructions. RNA (1.5 μg) was reverse transcribed into cDNA with oligo(dT)18 primers (RT200, TOPscriptTM RT DryMIX (dT18 plus), Enzynomics, Daejeon, Korea). The oligomer containing a reverse transcription tube was incubated at 50 °C for 60 minutes, followed by 5 minutes at 95 °C for inactivation. A cDNA sample (1 μL) was then used as a template for qPCR in each well and amplified with the primers. We conducted qPCR using TOPreal qPCR 2x PreMIX (RT5015, Enzynomics, Daejeon, Korea) for 40 cycles, with each cycle consisting of 15 seconds of annealing at 60°C and 30 seconds of elongation at 72°C. The 2-ΔΔCt method was used to calculate the fold change in the gene expression to measure the differentially expressed genes in each group.

GAPDH: GGAGAAACCTGCCAAGTATG, CATACCAGGAAATGAGCTTGAC

D1R: GGGCCCTACTACGAATAATG, CATAGTCCAATATGACCGATAAG

D2R: GCTCAGGAGCTGGAAATGGAGAT, CTTCCTGCGGCTCATCGTCTT

COMT: GCTGCTGTCTCATTGGGTCTC, CGAACTCAAACCAACCAATAGCC

TH: GGTATACGCCACGCTGAAGG, TAGCCACAGTACCGTTCCAGA

DAT: CTTCTCCTCTGGCTTCGTTGT, CAGGGTAGATGATGAAGATCAACC

2.8. Quantification and statistical analysis

All data were analyzed with GraphPad Prism version 9 (GraphPad Software, Inc., La Jolla, California). Group comparisons were done by Student's t-tests or two-way repeated-measures ANOVA with Bonferroni's multiple comparisons test. Correlation analyses were conducted by a two-tailed Spearman correlation analysis. Statistical significance level was set at 0.05.

3. Results

3.1. HFD altered the sleep-wake behaviors in mice

We assessed whether chronic exposure to an HFD after one month would affect behavioral phenotypes and the dopaminergic system. The experimental procedure of this study is schematically illustrated in Figure 1A. HFD group demonstrated reduced wakefulness during the 24-hour period compared to the ND group (Fig. 1B). The HFD group showed a longer REM sleep duration than the ND group ($p < 0.05$; Fig. 1D), whereas the duration of NREM did not differ between the two groups (Fig. 1C). In activity-rest circadian

rhythm analyses, HFD consumption did not affect the circadian period, wheel activity level, and movement bouts in both 24-hr light/dark (LD) and constant darkness (DD) conditions (Fig. S1-S4).

We analyzed the duration of each vigilance in 24-hour and 12-hour periods of light/dark. A decrease in wakefulness was observed over 24 hours in HFD compared with ND (61.18% vs 56.86%, $p < 0.05$; Fig. 1E). HFD group revealed an increasing trend in NREM sleep ($p = 0.1142$; Fig. 1F), but spent more time in REM sleep during the 24 h light/dark cycle (4.82% vs 6.49%, $p < 0.05$; Fig. 1G). REM duration was increased during the light period, but not in the dark period (10.73% vs 7.646%, $p < 0.05$; Fig. 1H and 2.25% vs 2.00%, $p = 0.6563$; 1I), whereas there were no significant changes in wake and NREM durations during 12 h periods of light and dark (Fig. S5A-S5D). In bout analyses, HFD group had more frequent and shorter REM bouts (48.00 vs 67.92, $p < 0.05$; Fig. 1J and 1.38 min vs 1.28 min, $p < 0.05$; 1K). In the analysis of the frontal and parietal EEG, the power spectra showed different trends of overall patterns, but NREM delta, REM theta, and WAKE theta power were not significantly different between HFD and ND groups (Fig. S6).

3.2. Increased anxiety in mice with HFD

Anxiety and locomotion were examined by OFT in mice with HFD. Although the HFD group showed an increase in body weight compared to the ND group (Fig. S7A), the locomotor function did not differ between the two groups (Fig. 2A). In addition, there are no differences in the mean speed of locomotion within the whole maze or center zone between two groups (Fig. 2B and 2C, respectively). Activity in the central zone of OFT represents anxious behaviors in mice. The HFD group presented less distance and time explored in the center zone than the ND group (17.05% vs 11.48%, $p<0.05$ and 14.96% vs 9.345%, $p<0.05$, respectively; Fig. 2D and 2E). In addition, mice fed with HFD spent less time in the center zone over the course of the entire test period than the ND group (Fig. 2F). Representative trajectories revealed that the ND group explored the arena without distinct avoidance of center zone, whereas the HFD group showed a pattern of avoiding the center zone and preferring the outer zone (Fig. 2G and 2H). Furthermore, in the EPM test, the HFD group spend more time with longer travel distances in closed arms than the ND group (Fig. S8A-S7E).

3.3. Deficits in spatial memory in mice with HFD

To assess visuospatial memory, we conducted the NPR test. Briefly, two identical objects were symmetrically placed from the visual cue at two separate points in the NPR arena. Then a mouse was introduced

to the center of the arena to explore the arena freely for 10 minutes and returned to the home cage (*Acquisition trial* in Fig. 3A). After 24 hours, one object was moved to a novel location (N) while the other remained in the familiar location (F), and the mouse was allowed again for free exploration in the NPR arena for 10 minutes (*Test trial* in Fig. 3A). Representative trajectories and 2D heatmap plots showed that the ND group preferred the novel location to the familiar location, whereas the HFD group presented an exploration pattern similarly distributed in the novel and familiar locations (Fig. 3B). Indeed, quantification analysis confirmed that the HFD group showed the similar interaction times in both familiar and novel locations ($P>0.05$), while the ND group spent a longer interaction time in the novel location (63.13% vs YY 36.87%, $P<0.05$; Fig. 3C). The discrimination index (DI) in the test phase revealed the HFD group showed a DI with no significant difference from zero, whereas the ND group had a DI greater than zero ($P<0.05$; Fig. 3D).

3.4. Hyperactivity and anhedonia in the HFD group

The tail suspension test (TST) and sucrose preference test (SPT) were used to examine the effects of HFD on the emotional state of mice. The total duration of immobility was shorter in the HFD group compared to the ND group (Fig. 4A). In addition, the HFD group exhibited more immobility episodes (Fig. 4B) and a shorter mean duration of immobility (Fig. 4C). Conversely, active episodes were longer and more frequent in HFD group than in ND group (Fig. 4D and 4E). On the other hand, in SPT a reward-based test to measure pleasure-seeking behavior (Eltokhi et al., 2021), the HFD group displayed a significantly weaker preference for sucrose than the ND group (70.88% vs 60.53%, $p<0.05$; Fig. 4F).

3.5. HFD reduced brain dopaminergic system markers

To determine whether behavioral deficits and an altered sleep-wake cycle are related to the brain dopaminergic system, we quantified transcriptional level of genes related to dopamine synthesis and metabolism in VTA, PFC, and NAc (Fig. 5A), including dopamine receptor 1 (D1R), dopamine receptor 2 (D2R), catechol-O-methyltransferase (COMT), dopamine transporter (DAT), and tyrosine hydroxylase (TH). The mRNA expression level of COMT in VTA regions of the HFD group was lower than that of the ND group (Fig. 5B). In the PFC region, the HFD group exhibited lower mRNA levels of COMT and D1R genes (Fig. 5C and 5D). Furthermore, there were significantly lower mRNA levels of DAT, COMT, and D1R genes in the NAc region of

the HFD group compared to the ND group (Fig. 5E-5G). The transcriptional levels of TH, D2R, and DAT genes did not differ in the three brain regions between the HFD and ND groups (Fig. S9A-S8E).

3.6. Correlation between sleep and dopaminergic system

We analyzed the correlation between sleep parameters and mRNA levels of dopamine-related genes in the PFC, VTA, and NAc (Fig. 6 and S9). In the PFC regions, the mRNA levels of DAT, D1R, and COMT genes were negatively correlated to REM sleep parameters (Fig. 6A). In addition, the transcriptional levels of genes related to the dopamine system were correlated to REM sleep bout length (Fig. S10A-S9D). Scatter plots were generated only for variables with a statistically significant p-value between mRNA levels and sleep parameters (Fig. 6B-6F). DAT and D1R mRNA levels in the PFC were negatively correlated with REM bout count and length, respectively (Fig. 6B and 6C). COMT was also negatively correlated to REM bout count (Fig. 6D) and REM duration (Fig. 6E).

4. Discussion

We found that long-term HFD consumption during adolescence and young adult periods led to behavioral dysfunction and altered sleep patterns with alterations in dopaminergic system. HFD caused decreased wakefulness and increased REM sleep. Despite longer total REM sleep duration, REM sleep bouts appeared more frequently with shorter REM bout length, indicating fragmentation of REM sleep. HFD also resulted in anxiety, memory impairment, anhedonia-like behavior, and hyperactivity, which are similar to the symptomatology of ADHD. These behavioral phenotypes were associated with transcriptional changes in genes related to the dopamine system. To the best of our knowledge, this report is the first demonstration that HFD impairs REM sleep regulation via dopaminergic dysregulation and is associated with ADHD-like behaviors.

4.1. Nutritional consideration of normal diet and HFD

In this study, we compared the effects of HFD to ND. The ND was based on the NIH-41 open formula, consisting of 68% carbohydrates, 22% proteins, and 10% fats in terms of caloric content. On the other hand, the HFD was composed of 20% carbohydrates, 20% proteins, and 60% fats. Although the fat content in the HFD is increased and the carbohydrate proportion is decreased, it is not the same as the ketogenic diet (KD), which

typically consists of a much lower carbohydrate proportion (5-10%), higher fat content (70-80%), and a similar protein composition (10-20%) compared to our HFD (Masood et al., 2023). Therefore, we believe that the effects of HFD are unlikely to coincide with the potential beneficial effects of ketosis.

4.2. Sleep-wake behaviors altered by HFD

We found that male mice with HFD showed decreased wakefulness and altered transcription of dopamine-related genes. Dopamine has a role in sleep-wake regulation as a wake-promoting neuromodulator (Eban-Rothschild et al., 2018). HFD-induced dopaminergic dysregulation lowered wake-promoting effects and led to decreased wakefulness. HFD intake causes a high level of leptin and leptin resistance (Handjieva-Darlenska and Boyadjieva, 2009), and since leptin inhibits wake-promoting orexin neurons (Inutsuka and Yamanaka, 2013; Sakurai, 2014), it is plausible to hypothesize that HFD may decrease wakefulness by inhibiting orexin neurons. There is a possibility that HFD caused shorter wakefulness and longer total REM sleep due to dopaminergic dysfunction. We also observed that dopamine-related genes, including DAT, D1R, and COMT, were negatively correlated with the count and length of REM sleep bouts and total REM sleep duration in the HFD group. A decrease in transcriptional levels of dopamine-related genes was associated with increased REM sleep amounts and a more fragmented pattern of REM sleep.

Our findings are also consistent with a previous report that activation of VTA neurons induces an increase in wakefulness and a decrease in REM and NREM sleep (Sun et al., 2017). Previous research has shown that a regulatory mechanism of REM sleep involves medial septum projections to the VTA, which implicates the role of the dopaminergic system in REM sleep regulation (Boyce et al., 2016). The chemogenetic inhibition of TH-positive neurons in VTA resulted in reduced wakefulness and increased REM and NREM sleep, similar to the sleep-wake patterns observed in our data (Eban-Rothschild et al., 2016).

Reduced dopamine function results in a higher cholinergic tone based on the monoamine-acetylcholine balance hypothesis in the regulation of the sleep-wake cycle (Vakalopoulos, 2014). HFD-induced dopaminergic dysregulation may lead to elevated levels of acetylcholine, which promotes REM sleep. Decreased wakefulness and increased REM sleep with fragmentation resembled the reported characteristics of sleep in patients with ADHD (Cortese et al., 2009; Diaz-Roman et al., 2018; Sadeh et al., 2006). Moreover, the mice with HFD in our experiment showed abnormal behaviors because REM sleep was fragmented and the

normal functions of REM sleep, such as memory consolidation (Lee et al., 2016), depressive symptoms (Palagini et al., 2013; Pesonen et al., 2019), and anxiety (Grubac et al., 2019), were impaired. These behavioral changes resembled ADHD-like symptoms. Consequently, we speculated that the abnormalities in the dopaminergic system play a pivotal role in sleep and behavioral deficits in HFD-fed mice, ultimately leading to the development of ADHD-like behavioral phenotypes.

4.3. Behavioral deficits induced by HFD

We found that anxious behavior in the HFD group manifested as decreased activity in the center zone of OFT. Mesolimbic, mesocortical, and nigrostriatal dopaminergic systems modulate anxiety (Zarrindast and Khakpai, 2015). Dopamine receptor subtype 3 knockout mice showed anxiety-like behaviors with more thigmotaxis at OFT and lower time spent in the light part of the light/dark exploration test (Moraga-Amaro et al., 2014). In addition, optogenetic inhibition of VTA dopaminergic neurons projecting to the interpeduncular nucleus elicited anxiety (DeGroot et al., 2020). Therefore, decreased transcriptional levels of genes related to the dopaminergic system in HFD group may have contributed to an increased level of anxiety.

Epidemiological studies have demonstrated that ADHD is linked to impairments in working memory and visuospatial short-term memory, particularly in children (Kofler et al., 2020). Memory function was also negatively affected by HFD. Reportedly, HFD consumption affects learning and memory by changing hormone state, BDNF release, inflammatory pathways, and BBB dysfunction (Cordner and Tamashiro, 2015; Stouffer et al., 2015). Hippocampal neurogenesis and inflammation were inhibited by HFD during the juvenile period (Boitard et al., 2014). In addition, HFD reduces the effects of insulin, enhancing long-term hippocampal potentiation (Izumi et al., 2003) and modulating synaptic plasticity (van der Heide et al., 2005; Wang et al., 2020) by insulin resistance (Koch et al., 2014; Williams et al., 2014). Therefore, memory impairment in HFD group might be mediated either directly by insults in the hippocampus or indirectly by the attenuation of insulin action.

Furthermore, the HFD group showed hyperactive behaviors and anhedonia. Although the TST is conventionally used as a measure of depressive-like behavior, the increased activity pattern with shorter lengths of immobile episodes and total immobile time in HFD group was consistent with a previous report that suggests hyperactivity (Karth et al., 2019). The changes in immobile episodes in our data can be interpreted as a hyperactive state (Commons et al., 2017) because the mice with HFD showed more escaping behaviors from the

stressful situations of tail suspension. These behavioral phenotypes of HFD group might be associated with down-regulated dopamine-related genes, including D1R, COMT, and DAT, which have been implicated in hyperactivity (Giros et al., 1996; Perona et al., 2008). In addition, the animals receiving HFD presented anhedonia with decreased D1R in the NAc (Arcego et al., 2020). While the reduced preference for sucrose solution in SPT is often interpreted as a sign of a depressive state, we should interpret the finding of decreased sucrose preference in SPT with caution. In clinical investigations, patients with ADHD present more anhedonia than normal control (Sternat et al., 2018). Given the TST results supporting the hyperactive state, anhedonic behavior in HFD group can be interpreted as a sign of ADHD-like behaviors rather than depression.

4.4. Interaction between HFD and reward system

Long-term consumption of HFD has been shown to cause hypofunction of reward system. In human subjects, bluted activation of dorsal striatum in response to food stimuli has been observed (Stice et al., 2008). Furthermore, a rat model of diet-induced obesity showed a reduced expression of dopamine receptors (Alsio et al., 2010) and alterations of the depressed dopamine release in NAc (Geiger et al., 2009a). These changes may be attributed to the interaction between HFD and the leptin signaling pathway.

TH-positive neurons of the VTA express leptin receptors (Figlewicz et al., 2003), and chronic HFD consumption-induced leptin resistance has been implicated in the defects in the activation of dopaminergic neurons in VTA and, consequently, decreased dopamine release in the mesolimbic pathway (DiLeone, 2009; Fulton et al., 2006; Hommel et al., 2006). This leptin resistance may lead to decreased dopamine release in the mesolimbic pathway, resulting in a hyporesponsive reward system. Additionally, alternations in dopamine signaling have been associated with ADHD-like behaviors in both human and animal studies (Tripp and Wickens, 2009; Volkow et al., 2007). In our study, we reconfirmed that genes related to the dopamine reward system, such as D1R, COMT, and DAT, were downregulated in HFD group. Our findings support the notion that chronic consumption of HFD may contribute to ADHD-like behaviors by inducing a hypodopaminergic state.

The observed transcriptional changes in our experiment can be interpreted as follows: chronic HFD consumption may have induced frequent dopamine release in response to the HFD exposure, leading to a chronic dopamine-depleted state. HFD consumption led to alterations of depressed dopamine release in the nucleus accumbens (Geiger et al., 2009a). This change resembles the alterations in the dopaminergic system

observed in substance use disorder. Consequently, a compensatory mechanism could have been activated, decreasing DAT to increase availability in the synapse and reducing COMT to decrease dopamine metabolism. Although we did not measure dopamine levels in the brain, previous studies have demonstrated that mice with decreased COMT or DAT expression levels exhibit decreased dopamine levels (Gilbert et al., 2006; Kramer et al., 2007). Conversely, frequent dopamine release induced by HFD may have caused a compensatory reduction of the transcription of dopamine receptors (Alsio et al., 2010). Based on the literature, we cautiously suggest that the transcriptional changes we observed in dopamine-related genes may be indicative of an underlying dysregulation in the dopaminergic system.

4.5. ADHD and HFD

ADHD is a heterogeneous neurodevelopmental psychiatric disorder and is defined by three core clinical symptoms including hyperactivity, inattention, and impulsivity (Faraone et al., 2006). Furthermore, ADHD patients experienced poor academic performance, anxiety, and depression (Champ et al., 2021). Anxiety is the most common comorbid clinical feature of ADHD (Gaddi et al., 1991; Katzman et al., 2017) and also found in an animal model (Bouchatta et al., 2020). In addition, memory impairment was frequently reported as a symptom in ADHD patients as poor verbal memory tasks and impaired spatial memory tasks (Rhodes et al., 2012; Skodzik et al., 2017). A low hedonic tone has been observed in ADHD patients (Sternat et al., 2018), which may result from a hypoactivation of reward pathway (Pornpattananangkul et al., 2019) and result in inattention, low concentration, and seeking for external and internal stimuli.

ADHD is associated with the brain reward cascade, especially in the dopamine system, and defects in dopamine metabolism have long been implicated in the etiology of ADHD (Blum et al., 2008). Studies on neuroimaging suggest that ADHD is associated with a dysfunctional reward system, as evidenced by lower dopaminergic neuron responsiveness and a decrease in synaptic dopamine markers (Stark et al., 2011; Volkow et al., 2009). In studies of ADHD in animals, the dopamine system is usually targeted, such as in DAT knockout mice (Perona et al., 2008). A recent study also proposed a neonatal 6-hydroxydopamine lesion model in mice that exhibited selective destruction of dopaminergic neurons and behavioral changes similar to those experienced by ADHD patients (Bouchatta et al., 2020). A recent report suggested that lower COMT activity is associated with an increased risk of ADHD (Abraham et al., 2020). Interestingly, patients with ADHD displayed lower dopaminergic signaling and higher cholinergic tone, which may be associated with decreased wakefulness

and increased REM sleep (Kirov et al., 2016; Vakalopoulos, 2014). In this context, our findings of decreased wakefulness and increased REM sleep with lower transcriptional levels of D1R, COMT, and DAT in the mice with HFD are consistent with clinical manifestation. Downregulated dopamine-related genes and altered behavioral features, including increased anxiety, memory impairment, anhedonia, and hyperactivity, are reminiscent of clinical features in patients with ADHD.

4.6. Behavioral characteristics of HFD-fed mice, resembling inattentive type of ADHD

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) describes the diagnostic criteria for ADHD as a persistent pattern of inattention and/or hyperactivity-impulsivity. This indicates that inattention is a key feature of ADHD, which can be diagnosed even without overt hyperactive behaviors. Additionally, hyperactive behaviors can be situational (Ho et al., 1996). Locomotor activity in the open field test (OFT) is assessed by increased speed or distance traveled in the test arena, a less stressful situation than the tail suspension test (TST). Our high-fat diet (HFD)-fed mice showed hyperactive behavior only under the aversive conditions of the TST, not in the OFT. Consequently, we do not rule out the possibility of hyperactive traits in our HFD-fed mice. Nonetheless, even without clear hyperactivity, we can associate the observed behaviors with ADHD phenotypes.

Our HFD-fed mice exhibited behavioral patterns resembling certain aspects of ADHD. In this regard, previous research is worth mentioning. High-fat diet consumption has been linked more strongly to inattention than hyperactivity-impulsivity traits (Li et al., 2020). The inattentive type of ADHD is often correlated with a higher prevalence of internalizing comorbid disorders, such as anxiety, depression, and self-esteem issues (Baeyens et al., 2006; Willcutt et al., 2012). Our sucrose preference test results revealed no preference for sucrose water in the HFD group, leading us to interpret the HFD-fed mice as experiencing an anhedonia-like state. This state has been suggested as an endophenotype of the inattentive type of ADHD (Meinzer et al., 2012). As such, our HFD-fed mice exhibit behavioral traits more closely related to the inattentive subtype of ADHD, demonstrated by a decreased preference for sucrose, diminished pleasure-seeking behavior, heightened anxiety, and more intense escape behavior under specific aversive conditions.

4.7. *Limitations*

Several limitations should be considered when interpreting the results of this study. First, we focused on measuring transcription levels of genes related to the dopaminergic system to evaluate the impact of a high-fat diet (HFD). We agree that a more comprehensive understanding could have been achieved by quantifying the levels and activities of the corresponding proteins. Although we did not measure dopamine levels in the brain, previous studies have reported decreased dopamine levels when COMT or DAT expression is reduced (Gilbert et al., 2006; Kramer et al., 2007). Based on this evidence, we inferred that mice fed an HFD might exhibit lower dopamine levels. Second, the number of mice was not consistent through the entire study. Some data were excluded from the sleep analysis due to too many artifacts being present in EEG/EMG records. The number of mice in the qRT-PCR data was insufficient as several samples were excluded due to low quality of RNA. In addition, the use of isoflurane anesthesia during sacrifice for qRT-PCR may alter the levels of dopamine and its metabolites (Irifune et al., 1997; Torturo et al., 2019; Votaw et al., 2004). However, because isoflurane was used in both of the experimental groups, we believe the comparisons between the groups are valid. Third, although the 5-choice serial reaction time task is an ideal measure for ADHD-like behavior due to its focus on attention-related aspects, we were unable to implement it in our study. The use of reward food in the task could potentially interfere with the experimental design itself. Forth, due to the experimental design involving two separate batches, the number of mice tested in the sucrose preference test was relatively small, which might affect the generalizability of our findings related to anhedonia. Fifth, we utilized only male mice in our experiment to minimize potential sex-based differences by the estrus cycle in females and other confounding variables (Acharya et al., 2019; Chakraborty et al., 2016; Hases et al., 2020). Given the documented gender differences in ADHD prevalence (Millenet et al., 2018), it is also important to study female subjects but separate investigations are needed. Lastly, it was challenging to distinguish between the direct effect of HFD and the indirect effect via diet-induced obesity on the gene expression and behaviors, because we did not control the total caloric intake and detailed characteristics of fats (whether saturated or unsaturated fat) (Fernandes et al., 2017; St-Onge et al., 2016), which could have potential implications on the observed behavioral outcomes.

5. Conclusion

In our study, we observed a significant influence of HFD on behavior, sleep patterns, and the dopaminergic system, eliciting a resemblance to symptoms typical of ADHD. Behaviorally, HFD induced heightened anxiety, anhedonia-like behaviors, hyperactivity, memory impairment, and altered sleep-wake

behaviors, specifically manifesting as decreased wakefulness and increased REM sleep. Notably, we found the HFD-related increase in REM sleep intertwined with fragmented REM sleep patterns. Additionally, alterations in REM sleep were correlated with the dopamine system, implying that HFD might play an essential role in REM sleep regulation. These behavioral and sleep outcomes are reminiscent of symptoms observed in patients with ADHD and in alignment with the frequently observed dopamine dysfunction in ADHD. Thus, reducing HFD consumption might be a beneficial dietary strategy for patients with ADHD. Further research to elucidate the underlying mechanism of such changes is necessitated.

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Credit authorship contribution statement

Jiseung Kang: Conceptualization, Methodology, Validation, Investigation, Writing, Visualization. Mincheol Park: Investigation. Chang-Myung Oh: Project administration, Supervision, Conceptualization. Tae Kim: Project administration, Supervision, Validation, Conceptualization, Writing. All authors have read and agreed to the published version of the manuscript. Graphics in Figures 1A, 5A, and 7 were created with BioRender.com.

Declaration of Competing Interest

The authors have no relevant financial or non-financial interests to disclose.

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Figure/Table Legends

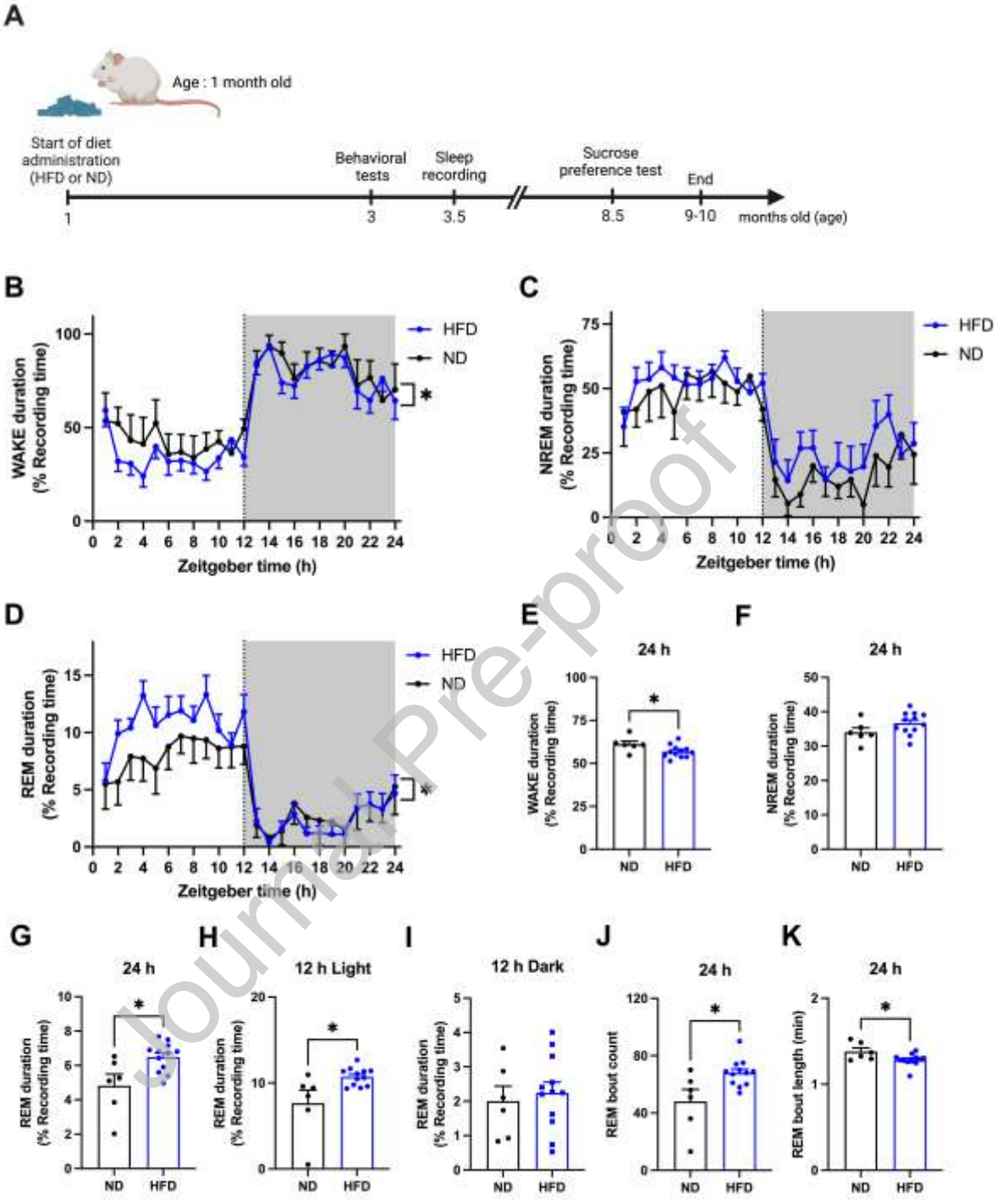

Fig. 1. HFD consumption decreased wakefulness and increased REM sleep in mice. (**A**) The experimental scheme for investigating the effects of high-fat diets on mice induced by a high-fat diet (HFD) or a normal diet (ND). One-month-old mice in HFD (n=12) and ND (n=6) groups were administered high-fat diets and normal diets, respectively. The behavioral test and sleep scoring analysis were conducted two months after the diets were administered. (**B-D**) Comparisons among total durations spent in (**B**) wake, (**C**) NREM, and (**D**) REM during the 1-h period (Two-way ANOVA for diet X time-of-day interactions). (**E-G**) HFD group showed (**E**) less total wake, (**F**) NREM, and (**G**) more REM duration during 24 h light/dark period compared to ND. (**H, I**) In

comparison to ND, (**H**) HFD showed an increase in total REM time during a 12 h light period, (**I**) whereas there is no significant difference in REM duration during the 12 h dark period between the two groups. (**J, K**) HFD group exhibited fragmented REM sleep with (**J**) more REM bout count and (**K**) shorter REM bout length. Black and blue dots indicate the data of individual mice in each group. The data were represented as mean ± SEM. $^{*}p < 0.05$ by Student's t-test or two-way repeated-measures ANOVA with Bonferroni's multiple comparisons tests.

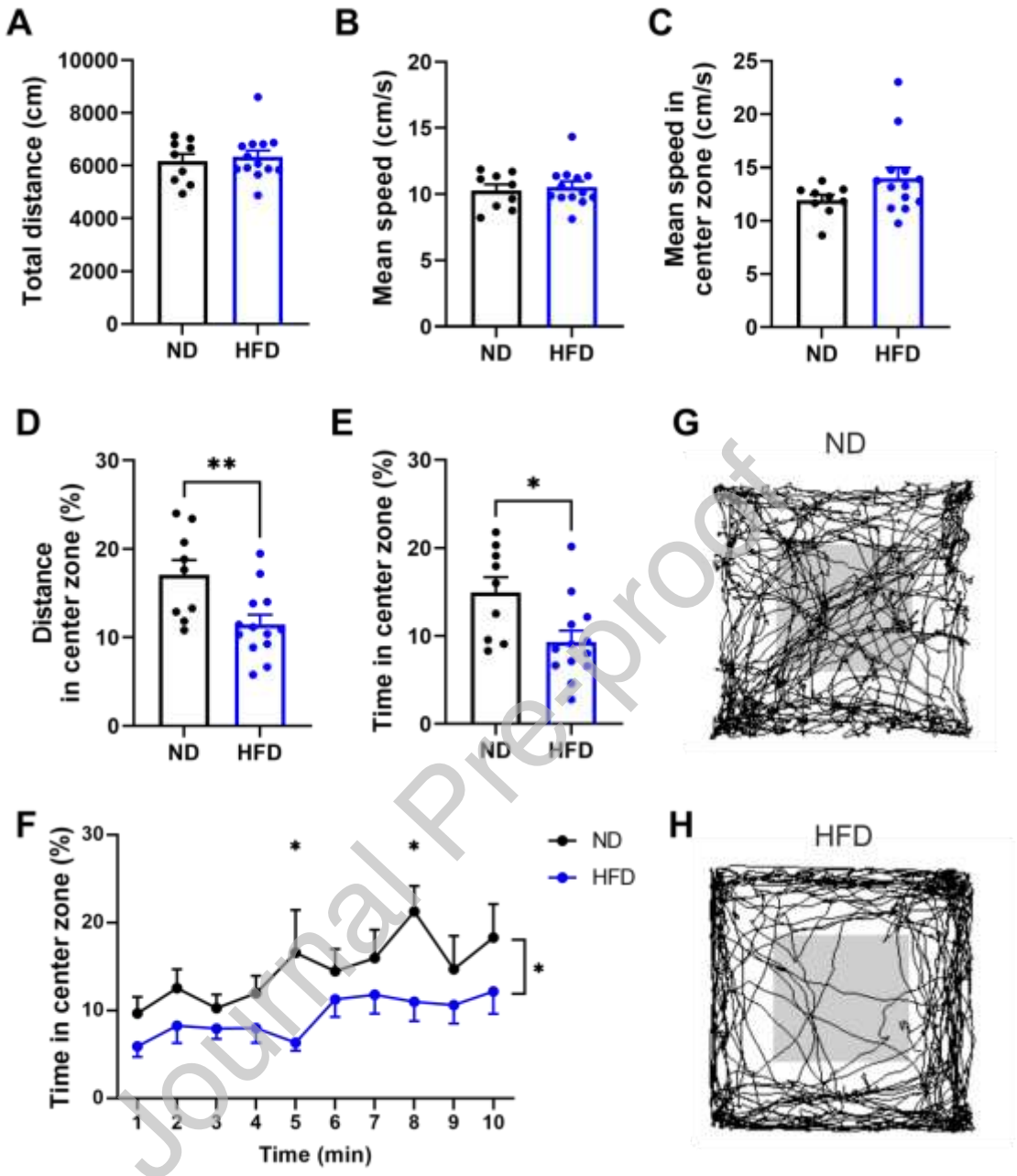

Fig. 2. HFD-induced anxiety-like behaviors in the open field test. (**A**) Both HFD (n=13) and ND (n=9) mice showed similar total distances (cm) in the open field test. (**B, C**) No difference in the mean speed (cm/s) within the total maze (**B**) and in the center zone (**C**) between ND and HFD groups was displayed. (**D**) Percent distance and (**E**) time spent in the center zone throughout the 10 min trial showed lower values in HFD compared to ND. (**F**) Percent time spent in the center zone per minute showed lower levels in the HFD group. (**G, H**) The representative trajectories of (**G**) the ND group and (**H**) the HFD group were exhibited, respectively. Gray-shaded rectangles indicate the center zone of the open field test. Black and blue dots indicate the data of individual mice in each group. The data are represented as mean ± SEM. $^{*}p < 0.05$ and $^{**}p < 0.01$ by Student's t-test or two-way repeated-measures ANOVA with Bonferroni's multiple comparisons tests.

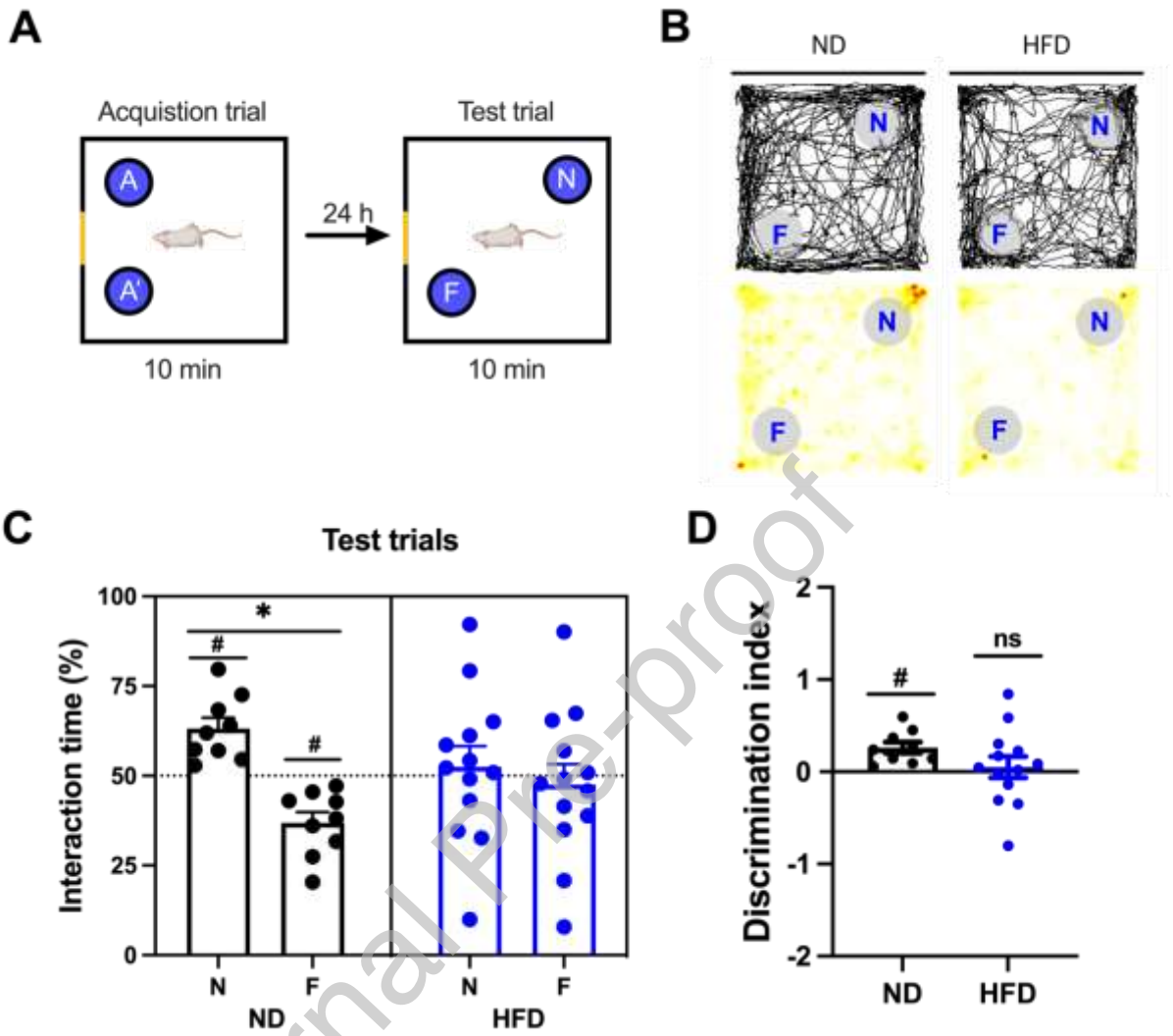

Fig. 3. Mice fed HFD showed deficits in spatial memory during the novel place recognition (NPR) test. (**A**) Schematic diagram of the NPR task. Circles with A and A' denote two identical objects at locations symmetrical to the visual cue (yellow line). Circles with F and N represent familiar and novel locations. See the method section for more detailed procedures. (**B**) The representative trajectories and 2D heatmap plots of mice fed HFD or ND were recorded by a video tracking system, Smart 3. Light gray circles denote the familiar location (F) and novel location (N) in the test trial. It is noted that the ND group spent more time exploring the novel location, whereas the HFD group did not show a preference for the novel location. (**C**) The interaction time in a novel location and familiar location of ND (n=9) and HFD (n=13) groups are illustrated. (**D**) The discrimination index of mice in the ND and HFD groups is shown. Black and blue dots indicate the data of individual mice in each group. The interaction times for each location are expressed as a percentage of the total exploration time and as the statistical difference against a 50% theoretical mean, and the discrimination index is tested against the '0' theoretical mean. The data are presented as the mean ± SEM of each group. $^{\#}p < 0.05$ and $^{\#\#}p < 0.01$ by one sample t-test and $*p < 0.01$ by paired sample t-test.

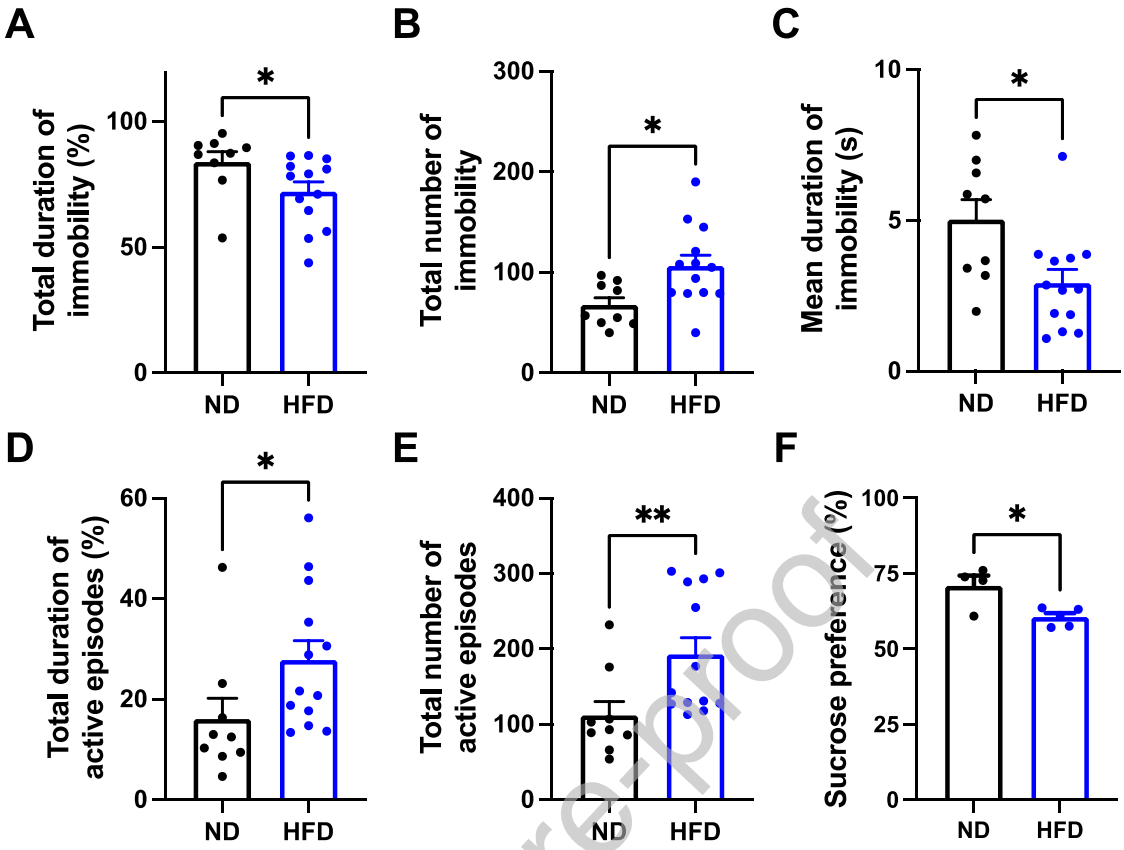

Fig. 4. More active and anhedonic behaviors in mice fed an HFD. (**A-E**) Tail suspension test (n=13 for HFD and n=9 for ND). (**A**) The reduced total duration of immobility, (**B**) the increased total number of immobility, and (**C**) shorter mean duration of immobility (s) in the HFD group were presented. (**D**) Longer total duration of activity and (**E**) increased number of activity episodes were shown. (**F**) Sucrose preference test (n=4 for HFD and n=5 for ND). Black and blue dots indicate the data of individual mice in each group. The data are represented as mean ± SEM. $^{*}p < 0.05$ and $^{**}p < 0.01$ by Student's t-test.

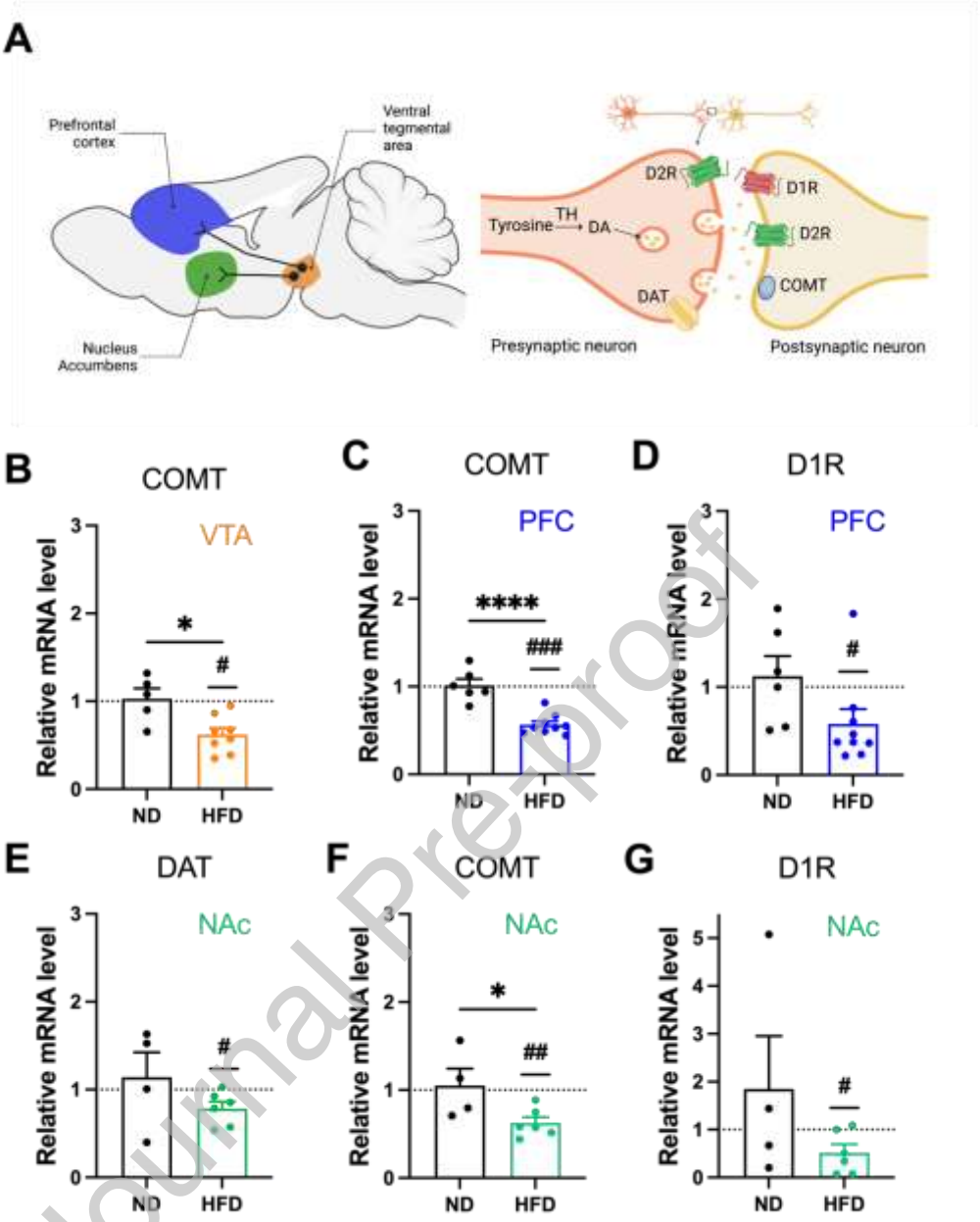

Fig. 5. HFD induced lower gene expression related to the dopaminergic system. (**A**) The dopamine (DA) pathway and DA neurotransmitters in the brain are shown. The dopaminergic neurons are located in the ventral tegmental area (VTA) as the nuclei and VTA DA neurons project to the prefrontal cortex (PFC) and nucleus accumbens (NAc). The right part shows the biosynthesis and metabolism of DA neurotransmitters. See the results section for more detailed procedures. (**B**) The results from qRT-PCR analysis of the mRNA expression of COMT in VTA regions of ND (n=5) and HFD (n=8) groups were shown. (**C, D**) The qRT-PCR results of mRNA expression of (**C**) COMT and (**D**) D1R in the PFC region of ND (n=6) and HFD (n=9) groups are illustrated. (**E-G**) The qRT-PCR results of mRNA expression of (**E**) DAT, (**F**) COMT, and (**G**) D1R in the NAc region of ND (n=4) and HFD (n=6) groups are illustrated. Black and blue dots indicate the data of individual mice in each group. Relative mRNA levels are expressed as $2^{-\Delta\Delta CT}$ values and as the statistical difference against a theoretical mean ($2^{-\Delta\Delta CT}$ =1). The data are represented as mean ± SEM. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$ by two-sample t-test and $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, and $^{\#\#\#}p < 0.001$ by one-sample t-test.

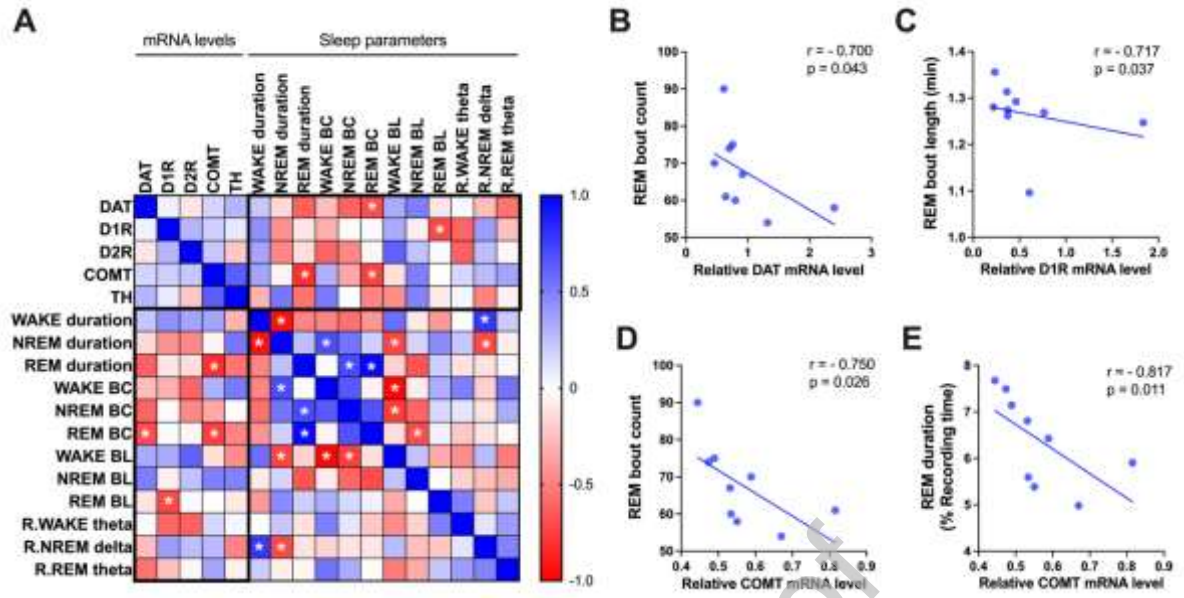

Fig. 6. The transcriptional levels of the dopamine system-related genes were correlated to sleep parameters. (**A**) Correlation matrix plot of each parameter from qRT-PCR of PFC region and sleep analysis (Abbreviations: BC, bout count; BL, bout length; R., Relative). (**B-E**) Correlograms for the sleep parameters and mRNA levels with statistical significance ($P < 0.05$). (**B**) REM bout count number negatively correlated with DAT mRNA levels in the PFC regions of the HFD group (n=9). (**C**) REM bout length negatively correlated with D1R mRNA levels in the PFC of the HFD group. In the HFD group, (**D**) REM bout count and (**E**) REM duration (% recording time) negatively correlated with COMT mRNA levels in the PFC region. As indicated in the color bar, the heatmap matrix shows the Spearman correlation coefficient (r) as the color of each cell (Two-tailed Spearman correlation test; blue indicates positive correlation, red indicates negative correlation). A thick black solid box in the heatmap denotes the correlation between mRNA levels and sleep parameters. The scatter plot with the correlation plot fulfilled statistical significance (*$p < 0.05$) by the Spearman correlation test.

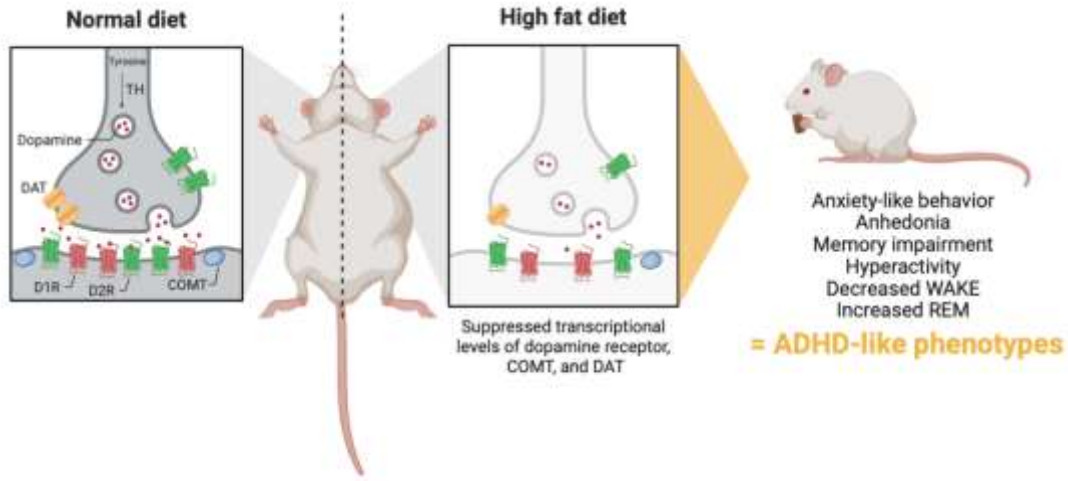

Fig. 7. HFD-induced dopaminergic dysregulation state in mice associated with suppressed transcriptional levels of D1R, COMT, and DAT. Mice fed HFD exhibited ADHD-like behavioral phenotypes with anxiety-like behavior, anhedonia, memory impairment, hyperactivity, and changes in the sleep-wake behaviors.

Credit authorship contribution statement

Jiseung Kang: Conceptualization, Methodology, Validation, Investigation, Writing, Visualization. Mincheol Park: Investigation. Chang-Myung Oh: Project administration, Supervision, Conceptualization. Tae Kim: Project administration, Supervision, Validation, Conceptualization, Writing. All authors have read and agreed to the published version of the manuscript. Graphics in Figures 1A, 5A, and 7 were created with BioRender.com.

Declaration of Competing Interest

The authors have no relevant financial or non-financial interests to disclose.