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Early-life and chronic exposure to high-fat diet alters noradrenergic and glutamatergic neurotransmission in the male rat amygdala and hippocampus under cognitive challenges

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Abstract

Childhood obesity increases the risk of health and cognitive disorders in adulthood. Consuming high-fat diets (HFD) during critical neurodevelopmental periods, like childhood, impairs cognition and memory in humans and animals, affecting the function and connectivity of brain structures related to emotional memory. However, the underlying mechanisms of such phenomena need to be better understood. This study aimed to investigate the neurochemical profile of the amygdala and hippocampus, brain structures involved in emotional memory, during the acquisition of conditioned odor aversion in male rats that consumed a HFD from weaning to adulthood. The rats gained weight, experienced metabolic changes, and reduced insulin sensitivity and glucose tolerance. Rats showed enhanced odor aversion memory, contrary to the expected cognitive impairments. This memory enhancement was accompanied by increased noradrenergic and glutamatergic neurotransmission in the amygdala and

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hippocampus. Importantly, this upregulation was specific to stimuli exposure, as basal neurotransmitter levels remained unaltered by the HFD. Our results suggest that HFD modifies cognitive function by altering neurochemical signaling, in this case, upregulating neurotransmitter levels rendering a stronger memory trace, demonstrating that metabolic dysfunctions do not only trigger exclusively detrimental plasticity processes but also render enhanced plastic effects depending on the type of information.

KEYWORDS
conditioned odor aversion, glutamate, noradrenaline, obesity

1 | INTRODUCTION

The prevalence of obesity in children and adolescents continues to rise worldwide (Di Cesare et al., 2019; GBD 2015 Obesity Collaborators et al., 2017; Sanyaolu et al., 2019). The marked increase in obesity carries an elevated risk of developing metabolic alterations, cardiac diseases, respiratory compromising, cancer, mental disorders, and cognitive deficits (Azhar et al., 2021; Chooi et al., 2019; Halfon et al., 2013; Lauby-Secretan et al., 2016; Quek et al., 2017). Obesity-promoting behaviors have been linked to a variety of factors, including genetics, urbanization, family dynamics, educational settings, and environmental influences (Gibson et al., 2007; Sahoo et al., 2015; Williams et al., 2013; Zhao & Settles, 2014).

Consequences of obesity during adulthood are widely known; likewise, obesity in children and adolescents has a negative impact on the long term, considering that these stages are sensitive periods where visual acuity, language, social behavior, executive and cognitive functioning mature, and develop (Fuhrmann et al., 2015; Selemon, 2013; Spear, 2000). Childhood and adolescence are critical phases characterized by profound changes in brain structure and functionality (Stiles & Jernigan, 2010), including synaptogenesis, neuronal pruning, myelination, and changes in cortical thickness and white matter (Larsen & Luna, 2018; Lebel & Beaulieu, 2011; Tamnes, Østby, Fjell, et al., 2010; Tamnes, Østby, Walhovd, et al., 2010). The macroscopic brain remodeling is accompanied by the maturation of several neurotransmitters systems, including the glutamatergic (Perica et al., 2022), dopaminergic (Reynolds et al., 2018), and noradrenergic systems (Murrin et al., 2007).

At a functional level, adolescents with obesity exhibit a negative correlation between abdominal adiposity and relational memory accuracy (Khan et al., 2015), and they display altered functional connectivity–excessive cortical synchronization (Dubbelink et al., 2008). Moreover, high consumption of hypercaloric diets during adolescence is associated with cognitive underperformance (Nyaradi et al., 2014; Øverby et al., 2013). Hence, evidence suggests that obesity during adolescence is related to cognitive and executive dysfunctions (Mamrot & Hanć, 2019). Comparable results are observed in animal models of juvenile obesity; the consumption of high-fat diets (HFD) at weaning induces alterations in hippocampal plasticity (Hernández-Matias et al., 2021; Karimi et al., 2015; Khazen et al., 2019; Porter et al., 2012; Valladolid-Acebes et al., 2012, 2013), affecting spatial and relational memories (Boitard et al., 2012, 2014; Hernández-Ramírez et al., 2021, 2022).

Significance

Chronic juvenile exposure to high-fat diets is linked to alterations in brain function, including learning and memory. In this study, we report elevated noradrenergic and glutamatergic neurotransmission linked to the enhancement of an aversion memory, highlighting intricate connections between obesogenic diets, neurochemistry, and cognition, implying that metabolic dysfunctions due to consumption of hypercaloric diets can induce both detrimental and enhanced plasticity effects which may impact the overall brain health of individuals.

Regardless of the age of consumption, intake of obesogenic diets is associated with alterations in hippocampal volume (Bauer et al., 2015; Mestre et al., 2017; Widya et al., 2011) and gray matter reduction (Mueller et al., 2012). Juvenile and adult rats that were exposed to obesogenic diets exhibit impairments in water maze performance and recognition memory, associated with a diminished catecholaminergic response within the hippocampus (Hernández-Ramírez et al., 2021). However, obesity is not only associated with memory deficits; juvenile HFD exposure is related to alterations in the amygdala with emotion-related memory enhancement (Boitard et al., 2015). Consumption of hypercaloric diets is related to increased amygdalar activity (Boutelle et al., 2015; Connolly et al., 2013) and volume (Widya et al., 2011), as observed by neuroimaging studies. This increase in amygdalar activity likely promotes the enhancement of aversive-related memories (Boitard et al., 2015). Thus, evidence suggests that the functionality of the hippocampus and amygdala can be influenced by modifiable environmental conditions, such as nutrition and cognitive challenges. In this study, we evaluated the possibility that exposure to HFD starting at weaning may alter different neurotransmitter systems within the hippocampus and amygdala,

affecting emotional processing. Consequently, the study evaluates the impact of long-term HFD consumption—from weaning to adulthood—on metabolism, emotional memory performance, and neurotransmission within the hippocampus and amygdala.

2 | MATERIALS AND METHODS

2.1 | Experimental subjects

All experimental procedures in this study were approved by the Animal Care Committee of the Centro de Investigación y de Estudios Avanzados (CINVESTAV)-IPN Protocol #189-16. Animal experiments were conducted according to the USA-National Institutes of Health guide for the care and use of laboratory animals. Efforts were taken to minimize experimental suffering throughout all procedures.

Sixty-six male 21-day-old Wistar rats were housed in groups of three to four animals per cage in an acclimatized (22° ± 1°C) room under a 12-h light–dark cycle (lights on 06:00 h) with ad libitum access to food and water. Males were used because they exhibit a more pronounced phenotype after high-fat diet exposure. All experimental procedures were conducted during the light portion of the cycle. Animals were assigned randomly to two different groups according to the maintained diet, either the normal diet group (ND $n = 33$, A04, SAFE Diets, France; 2.9 kcal/g; 8% fat; 19% proteins and 73% carbohydrates) or the high-fat diet group (HFD $n = 33$, D12451, Research Diets, New Jersey; 4.7 kcal/g; 45% fat; 20% proteins and 35% carbohydrates), verifying that the initial weight was the same in all groups. Diet regimes began at weaning (P21) and lasted for at least 12 weeks (from weaning to adulthood) and until the behavioral experiments were conducted. Every week, ND and HFD animal's body weight was registered. For the microstructure analysis of licking, a power analysis showed that the sample size of a minimum of 4 has a 90% to detect an effect size of 25% assuming a 5% significance level. For the metabolic and behavioral experiments, sample size was based on previous reports.

2.2 | Surgery

After 10 weeks under ND or HFD, rats were anesthetized under isoflurane (5% induction; 1%–2% maintenance) and mounted on a stereotaxic apparatus. The scalp was shaved, cleaned, and anesthetized locally with .3 mL of lidocaine 2% with epinephrine (PiSA Agropecuaria, México). Rats were implanted unilaterally, counterbalancing the right and left hemispheres, with a microdialysis cannula guide (CMA Microdialysis AB, Sweden) using standard stereotaxic procedures aiming at the ventral hippocampus (VHp; AP − 5.5 mm; L ± 5.3 mm; DV − 6 mm) and the basolateral amygdala (BLA; AP − 3 mm; L ± 5 mm; DV − 7.5 mm) (Paxinos & Watson, 1998). The cannula was fixed to the skull using two stainless steel screws with dental acrylic cement. Animals were allowed to recover from surgery for at least 6 days before behavioral protocols. Animals that lost the cannulae mounting were excluded from further experimental procedures and were euthanized to provide a humane endpoint. These animals are not included on the indicated number within each experimental procedure.

2.3 | Conditioned odor aversion

ND and HFD rats were water deprived for 24 h, and then, they were habituated to drink 30 mL from a graded bottle for 15 min each day between 10 am and 11 am for 4 days. Baseline water consumption was obtained by averaging the intake of the last 3 days. On the fifth day, all rats had access to banana-scented water for 15 min (30 mL, .01% isopentyl acetate; Sigma Aldrich); 30 min later, half of the ND group received an intraperitoneal injection of lithium chloride (LiCl; Sigma Aldrich, .075 M, 7.5 mL/kg), whereas the other half received saline solution (NaCl; Sigma Aldrich, .9%, 7.5 mL/kg). The same was done for the HFD group. Such dose of LiCl fails to induce an effective conditioned aversion in regular conditions (Miranda et al., 2002), but in a juvenile model of diet-induced obesity, it helps us demonstrate any enhancement in the emotional response, preventing a minimum threshold of aversion from masking effects (Boitard et al., 2015). On days 6 and 7, all rats had access to water for 15 min each day to re-establish baseline water intake. On day 8, conditioned odor aversion (COA) long-term memory was evaluated by giving access to the banana-scented water for 15 min, immediately followed by 15 min of water. The percentage of odorized water consumption relative to the basal water consumption was used as a measurement of COA strength. The final number of animals in the statistical analysis is as follows (ND-NaCl $n = 13$, ND-LiCl $n = 20$, HFD-NaCl $n = 15$, HFD-LiCl $n = 18$).

2.4 | Microstructure analysis of licking

A separate group of naïve rats was used for the microstructure analysis of licking during the COA paradigm, with ND and HFD groups treated with NaCl or LiCl. For this experiment, we had four groups: ND-NaCl $n = 5$, ND-LiCl $n = 6$, HFD-NaCl $n = 5$, and HFD-LiCl $n = 4$. The consummatory behavior was analyzed using a microstructure of licking analysis, which involved recording the licking behavior of the rats in an open field box (40 L × 40 W × 40 H cm) equipped with a V-shaped licking port and a photobeam sensor to register individual licks. The licking spout comprised a carefully sanded 20-gauge needle that was glued at the tip of a stainless steel sipper tube. The open field boxes were placed in a ventilated room, and experimental events were controlled and recorded using an acquisition I/O board link to Open Ephys (Buccino et al., 2018) and analyzed with Matlab. Behavioral results were represented as total number of licks and % of licks during the long-term memory tests with respect to the licks during the acquisition. The hedonic reaction to the odor was assessed through the quantification of clusters (sets of licks) and cluster size (mean number of licks in a cluster). Finally, the palatability

index was calculated using the interaction between the number of clusters and cluster size (Clusters × Cluster Size).

2.5 | Microdialysis experiments

To obtain dialysates during the acquisition of COA task, animals were water-deprived for 24 h. Then, rats were habituated individually to the microdialysis chamber for 90 min each day for 4 days. In the behavioral chamber, animals received 30 mL of tap water from a graded bottle for 15 min and the consumption was recorded. Baseline consumption was calculated. On the fourth day, the microdialysis session occurred, the dummy cannula was removed, and a microdialysis probe was inserted (3 mm-CMA12 for VHp or 1 mm-CMA12 for BLA; CMA Microdialysis AB, Sweden). The dialysis probes were attached to the microinfusion pump system with FEP tubbing (CMA Microdialysis AB, Sweden); artificial cerebrospinal fluid (ACSF, 125 mM NaCl, 5 mM KCl, 1.25 mM $NaH_2PO_4H_2O$, 1.5 mM $MgSO_4 \cdot 7H_2O$, 26 mM $NaHCO_3$, 2.5 mM $CaCl_2$, 10 mM glucose) was infused at a rate of 1 μL/min. Following probe insertion, a 40-min stabilization stage was carried out, and samples were collected every 4 min (4 μL/sample) in vials containing 1 μL of an antioxidant mixture (.25 mM ascorbic acid, .27 mM Na_2EDTA, .1 M acetic acid). The first three samples were used as the basal concentration of extracellular neurotransmitters within the VHp and the BLA. After basal samples collection, rats were exposed to scented water (30 mL, .01% isopentyl acetate; Sigma Aldrich) and 30 min later to the visceral stimulus (LiCl; Sigma Aldrich, .075 M, 7.5 mL/kg). Sampling collection continued until 16 samples were obtained and were immediately frozen at −80°C for later analysis. Final number of analyzed animals was ND ($n = 13$) and HFD ($n = 12$).

2.6 | Neurotransmitter analysis

Glutamate, norepinephrine, and dopamine concentrations were determined by micellar electrokinetic chromatography (Guzmán-Ramos et al., 2010). Dialysates were derivatized with 6 μL of 16.58 mM of 3-(2-furoyl) quinoline-2-carboxaldehyde (FQ, Molecular Probes, Invitrogen) in the presence of 2 μL of 25 mM KCN in 10 mM borate buffer (pH 9.2) and 1 μL of an internal standard (.075 mM O-methyl-L-threonine; Sigma-Aldrich). The derivatization reaction occurred in the dark for 15 min at 65°C. Separation and analysis were conducted in a capillary electrophoresis system (Beckman Coulter PACE/MDQ, Glycoprotein System) with laser-induced fluorescence detection (488 nm from an argon ion laser). Samples were separated at 25 kV with a borate buffer (35 mM borates, 25 mM sodium dodecylsulfate, and 15% (v/v) methanol HPLC grade, final pH 9.6). Hydrodynamic injections of samples were performed at .5 psi for 5 s in a 75 μm i.d. capillary (Sciex, Massachusetts). After each sample run, the capillary was flushed with .1 M NaOH, water, and running buffer. The neurotransmitter peaks were identified by matching the migration patterns of the resulting electropherogram from each sample with a spiked sample with each neurotransmitter of interest. The area under the curve values for each neurotransmitter peak was corrected with the area under the curve of the corresponding internal standard peak. Data were analyzed using the Karat System Gold Software (Beckman Coulter). Results are expressed as a percentage of basal concentration (percentage of basal concentration = analyte concentration × 100/mean of the three first samples).

2.7 | Metabolic parameters

After conducting the behavioral and microdialysis experiments, we performed an intraperitoneal glucose tolerance test (IPGTT) to rats from the ND and HFD groups following a 12-h fasting period. To determine blood glucose levels, a small drop of blood was obtained from the tip of the tail by a superficial cut, and it was measured using a commercial glucometer (Accu-Chek Active, Roche). After obtaining a basal measurement (0 min), a glucose solution dissolved in injectable water (2 g/kg) was administered i.p. and blood glucose levels were measured at 15, 30, 60, 120, 150, and 180 min afterwards.

Insulin sensitivity was assessed by performing an intraperitoneal insulin tolerance test (IPITT) in ND and HFD rats after fasting. After determining basal blood glucose levels, we i.p. administered human insulin (.25 I.U./kg, i.p.) (Humulin R, Eli Lilly & Co, Mexico) diluted in saline solution. Blood glucose levels were measured 15, 30, 90, 120, and 150 min after insulin administration.

Finally, all animals were anesthetized with an i.p. sodium pentobarbital injection (40 mg/kg), and epididymal fat was extracted and weighed. Brains were extracted and fixed in 4% paraformaldehyde solution in phosphate-buffered saline for posterior microdialysis probes placement verification. After cryoprotection treatment, coronal sections of 40 μm were cut and stained with cresyl violet. Histological sections were examined under a light microscope. Animals with incorrect cannulae placement were excluded from the analysis.

2.8 | Statistical analysis

Experimental data were plotted and analyzed with GraphPad Prism version 9.5.1 for MacOs, GraphPad Software, San Diego, California, United States. Before analysis, a Kolmogorov–Smirnov normality test was conducted to ensure normal data distribution. Differences in body weight, IPGTT, and IPITT results among the four groups were analyzed employing two-way repeated measures ANOVA, considering group and evaluation time as pivotal factors. After this analysis, Boferroni's multiple comparison test served as post hoc assessment. Comparisons between ND and HFD groups related to epididymal fat, basal plasma glucose levels, and areas under the curves (AUCs) were undertaken through an unpaired Student's *t*-test.

A three-way ANOVA was employed to assess changes in odorized water consumption, incorporating diet, unconditioned stimuli, and time of evaluation as factors; Bonferroni's multiple comparison test was

applied as post hoc analysis. We also used a three-way ANOVA test to evaluate changes induced by COA on parameters related to the microstructure of licking behavior (e.g., number of licks, clusters, and cluster size) and the palatability index, with diet, unconditioned stimuli, and time as factors. Post hoc analysis was conducted using Bonferroni's multiple comparison test. Kruskal–Wallis test was employed to compare percentages of total licks during the LTM among groups since the data did not meet the assumptions of the ANOVA test; a Bonferroni's multiple comparison test was applied as post hoc analysis.

Neurotransmitter basal levels were evaluated using an unpaired Student's *t*-test between ND and HFD groups. Changes in extracellular levels between ND and HFD groups during the CS or the US exposure was also evaluated using an unpaired Student's *t*-test. To assess if any changes were different to the baseline levels, we performed a one-sample *t*-test comparing each neurotransmitter level against its hypothetical baseline value of 100% (basal concentration). All presented data were expressed as the mean ± SEM. The accepted level of significance was a *p*-value ≤ .05.

3 | RESULTS

3.1 | HFD consumption generates overweight and metabolic alterations

After weaning, animals were randomly assigned to ND or HFD groups (Figure 1a). At the beginning of dietary treatments, both groups had similar body weight. By continuing the dietary treatment, differences in weight became evident. A two-way repeated measures ANOVA indicated diet ($F_{(1,38)}=27.8$, $p=.0001$), time ($F_{(12,216)}=811.7$, $p=.001$), and diet × time interaction effects ($F_{(12,216)}=12.55$, $p=.001$). The HFD group gained more weight compared to the ND group subsequently from the sixth week of treatment, according to Bonferroni's multiple comparison test (week 6–7; $p=.049$ and $p=.037$, respectively) (Figure 1b). For the comparison results from the 8th week and on, please refer to Table S1 of the Supplementary material. Similarly, HFD intake led to epididymal fat accumulation compared to ND diet ($t=8.612$, $p=.001$; Figure 1c).

The consumption of HFD resulted in higher fasting blood glucose levels than the ND group (ND 89.94 ± 1.72 mg/dL and HFD 106.4 ± 2.55 mg/dL, $t=5.359$, $p=.001$; Figure 1d). Moreover, we assessed the impact of HFD on glucose uptake and insulin sensitivity. A two-way repeated measures ANOVA indicated statistical differences in IPGTT results for diet ($F_{(1,48)}=33.27$, $p=.001$), minutes ($F_{(6,288)}=199.1$, $p=.001$), and diet × minutes interaction effects ($F_{(6,288)}=4.286$ $p=.0004$). Bonferroni's multiple comparison test exhibited higher levels of blood plasma glucose in HFD than in ND animals at 15 ($p=.0008$), 30 ($p=.001$), 60 ($p=.001$), 120 ($p=.001$), 150 ($p=.0011$), and 180 ($p=.046$) minutes (Figure 1e). We estimated the AUC for IPGTT, used as an index of whole glucose uptake after its systemic administration, which revealed differences in the HFD group compared to the ND group ($t=6.190$, $p=.001$; Figure 1e, inset). Likewise, a two-way ANOVA showed statistical differences in IPITT results. Both diet ($F_{(1,210)}=61.74$, $p=.001$) and minutes ($F_{(6,210)}=24.53$, $p=.001$) effects were observed, but no interaction effect was observed ($F_{(6,210)}=.1584$, $p=.987$). Bonferroni's multiple comparison test displayed higher levels of blood plasma glucose in HFD than ND animals at minute 0 ($p=.0161$), and after the administration of insulin at 15 ($p=.0309$), 30 ($p=.0015$), 60 ($p=.0301$), 120 ($p=.0462$), and 150 ($p=.0206$) minutes (Figure 1f). We then calculated the AUC for IPITT, statistical differences were observed in the HFD group when compared to ND group ($t=3.317$, $p=.0024$; Figure 1f, inset graph). Additionally, we computed the plasma glucose disappearance rate (KITT; Okita et al., 2014). The glucose value KITT was $.693^{*}100/t_{1/2}$, where $t_{1/2}$ was calculated from the linear slope of the plasma glucose concentration. The linear slope model was obtained following insulin injection, specifically during the 15- to 60-min interval of the IPITT curve. Significant differences in KITT were observed through an unpaired *t*-test ($t=5.949$, $p=.0001$). The KITT values for ND animals were 1.614% ± .0365%, while HFD animals exhibited a KITT of 1.346% ± .0222%. These findings underscore the distinction in glucose disappearance rates between the two dietary groups. The results proved that 12 weeks of HFD intake induces weight gain and fat accumulation in rodents. These changes accompany metabolic alterations such as glucose uptake resistance and insulin sensitivity reduction in rodents.

3.2 | HFD consumption enhances an emotion-related memory

In COA experiments (see Figure 2a for protocol timeline), the consumption of a HFD did not alter the water intake during baseline (ND: 10.09 ± .448 mL and HFD: 9.295 ± .387 mL, unpaired Student's *t*-test ($t=1.354$, $p=.180$)). Similarly, there were no significant differences observed in the consumption of scented water during acquisition ($F_{(3,67)}=.1803$ $p=.9094$ among groups; $t=1.210$, $p=.239$, $t=.105$, $p=.917$, $t=.815$, $p=.429$, and $t=.901$, $p=.380$ versus basal consumption for ND-NaCl, HFD-NaCl, ND-LiCl, and HFD-LiCl, respectively; Figure 2b, acquisition), indicating that both groups recognized equally the banana odor. Moreover, a three-way ANOVA (diet, evaluation time, and treatment (LiCl or NaCl)) showed significant differences in the percentage of consumption of scented water—banana odor—in relation to basal water intake among groups. The following significant effects were found: Diet ($F_{(1,197)}=43.38$, $p=.001$), treatment ($F_{(1,197)}=7.88$, $p=.0052$), diet–evaluation time interaction ($F_{(1,197)}=36.39$, $p=.001$), and evaluation time–treatment interaction ($F_{(1,197)}=3.903$, $p=.0496$). However, we did not observe significant effects on evaluation time ($F_{(1,197)}=3.732$, $p=.054$), diet–treatment interaction ($F_{(1,197)}=1.288$, $p=.257$), or evaluation time–treatment–diet ($F_{(1,197)}=1.288$, $p=.257$) (Figure 2b). Bonferroni's multiple comparison analysis revealed that HFD intake from weaning to adulthood maintained unaltered consumption of scented water during the acquisition session ($p=.999$). During the long-term memory evaluation, ND-NaCl and HFD-NaCl had similar consumption levels ($p=.999$). However, some groups had differences in the consumption of scented water after malaise pairing, ND-NaCl differed from

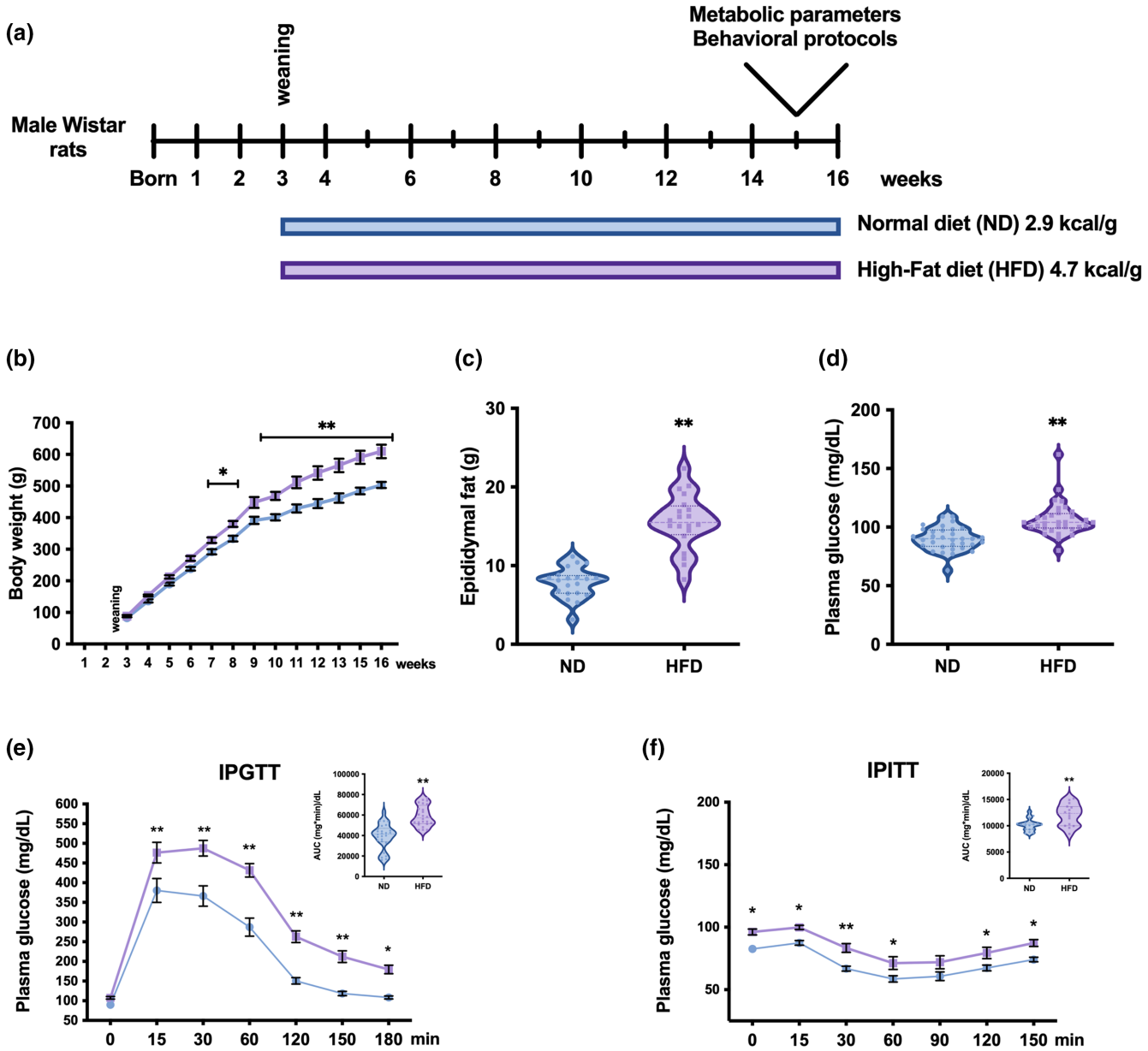

FIGURE 1 Consumption of a high-fat diet from weaning to adulthood generated overweight and metabolic alterations. (a) Schematic representation of the different dietary regimes and experimental procedures. (b) Records of body weight for 13 weeks for normal diet (ND) and high-fat diet (HFD) animals show that HFD intake induces overweight. (c) After dietary regimes, HFD animals accumulated more epididymal fat than ND animals. (d) Fasting plasma glucose levels in ND and HFD animals indicate that blood glucose levels are higher in HFD animals than in ND animals. (e) Intraperitoneal glucose tolerance test (IPGTT) and (f) intraperitoneal insulin tolerance test (IPITT) reveal that HFD animals developed resistance to glucose uptake and insulin insensitivity; inserts in (e) and (f) represent the area under the curve. $^{*}p < .05$ and $^{**}p < .01$ between ND and HFD groups. Two-way ANOVA and Bonferroni's multiple comparison test was utilized for analyzing bodyweight, IPGTT and IPITT curves. Unpaired Student's *t*-test was employed to compare epididymal fat, basal plasma glucose levels, and areas under the curves (AUCs) comparisons. Data are represented as mean ± SEM.

ND-LiCl ($p = .001$) and HFD-LiCl ($p = .001$); HFD-NaCl was different from ND-LiCl ($p = .0085$) and HFD-LiCl ($p = .001$). Importantly, ND-LiCl diverges from HFD-LiCl ($p = .049$). For the complete statistical results of the Bonferroni's multiple comparison, please see Table S9. Thus, HFD intake, from weaning to adulthood, does not alter the consumption of scented water during the acquisition; nevertheless, HFD animals display an enhanced aversion response to scented water after COA.

3.3 | Rats fed with a HFD from weaning to adulthood exhibited a stronger learned hedonically negative palatability

A separate group of naïve rats was used for the microstructure analysis of licking during the COA paradigm, with ND and HFD groups treated with NaCl or LiCl. We analyzed the microstructure of licking to unveil changes in palatability evoked by a banana-scented water

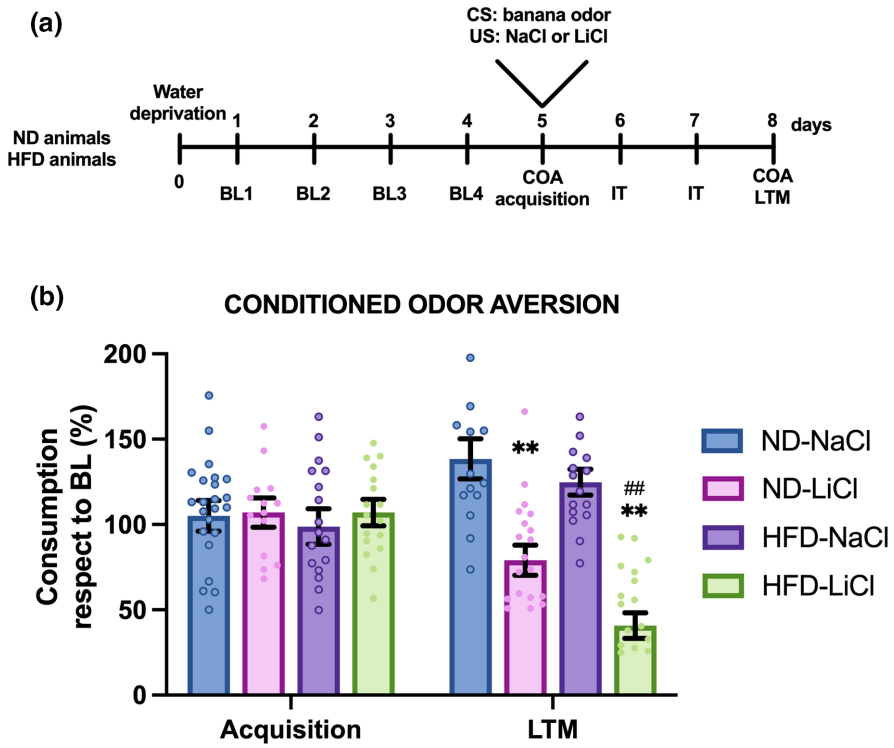

FIGURE 2 Consumption of a high-fat diet from weaning to adulthood enhanced emotional memory. (a) Schematic representation of the conditioned odor aversion protocol. (b) Comparison of banana-scented water consumption as % of the baseline consumption during conditioned odor aversion in high-fat diet (HFD) and normal diet (ND) animals. HFD animals exhibited an enhanced aversive response while maintaining a similar neophobic response compared to ND animals. During acquisition phase, all groups displayed a similar consumption of banana-scented water. Administration of LiCl induced a conditioned odor aversion in both ND and HFD groups during LTM test; however, HFD animals displayed an enhanced aversion compared to ND animals. BL, baseline water consumption; COA, conditioned odor aversion; CS, conditioned stimulus; IT, intertrial session; LTM, long-term memory; US, unconditioned stimulus. $^{**}p < .01$ versus their respective NaCl control group and $^{\#\#}p < .01$ versus ND-LiCl. A three-way ANOVA and Bonferroni's multiple comparison test were used for the analysis. Each dot represents the consumption of an individual rat. Data are represented as mean ± SEM.

solution after the induction of COA. In this study, we defined a cluster as a group of licks that were separated by pauses greater than 500 milliseconds. The size of each cluster was calculated by measuring the time between the first and last lick within that cluster in seconds (Gutierrez et al., 2006).

We observed a significant main effect of treatment and diet on the number of total licks (three-way ANOVA, factor treatment $F_{(1,16)} = 7.346$, $p = .0154$ and factor diet $F_{(1,16)} = 5.701$, $p = .0296$; Figure 3a). We also found a significant interaction between time and treatment $F_{(1,16)} = 4.833$, $p = .043$. A post hoc analysis revealed a significant decrease in the number of total licks between the HFD-LiCl group compared to the ND-NaCl group ($p = .0233$), suggesting that the NFD-LiCl group exhibited a trend to reduce their intake of the water-scented solution. No other comparisons survived significance (See Table S10).

To compare the change of intake from acquisition to LTM, we computed the percentage of total licks relative to Acquisition. A Kruskal-–Wallis test was used (Kruskal–Wallis test, LTM diet–treatment: $\chi^2_{(3,16)} = 8.53$; $p = .0361$), where the post hoc test showed that the HFD-NaCl group was significantly different compared to the HFD-LiCl group ($p = .0309$, see Table S11), indicating that the HFD-LiCl exhibited a stronger reduction in the intake relative to the acquisition day (Figure 3b).

Next, we quantified the number of total clusters during the licking behavior and evaluated the effect induced by COA. A significant main effect of time–treatment interaction was observed on the number of total clusters (three-way ANOVA, factor time–treatment: $F_{(1,16)} = 7.72$, $p = .0134$; Figure 3c). A post hoc analysis revealed that solely the HFD-LiCl group exhibited a significantly reduced number of total clusters compared to the ND-NaCl group during the LTM ($p = .0288$, see Table S12 for complete comparisons).

In addition, the duration of these clusters was quantified and determined as cluster size (Figure 3d). We observed a significant main effect of time (three-way ANOVA, factor time: $F_{(1,841)} = 11.91$, $p = .0006$), treatment ($F_{(1,1142)} = 7.98$, $p = .0048$) and time–diet–treatment interaction ($F_{(1,841)} = 17.06$, $p = .0001$) on the cluster size of the licking behavior. Post hoc analysis showed a significantly higher cluster size of the ND-NaCl group than the ND-LiCl and the HFD-NaCl groups during the acquisition phase ($p = .0208$ and $p = .0076$, respectively). In the LTM test, the cluster size was also significantly different between the ND-LiCl and the HFD-NaCl groups ($p = .0263$) and the HFD-NaCl and the HFD-LiCl groups ($p = .0461$), indicating

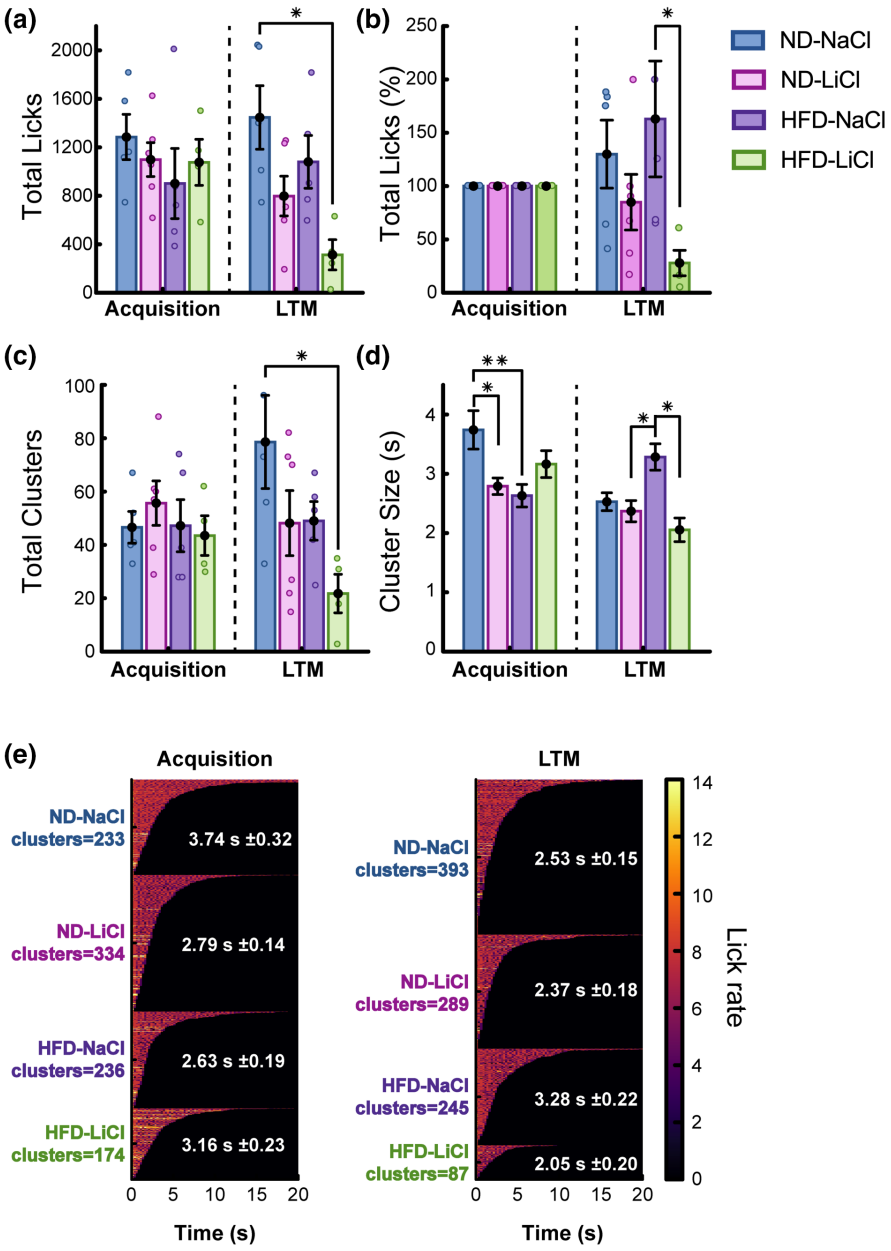

FIGURE 3 Consumption of a high-fat diet from weaning to adulthood induced stronger hedonically negative oromotor responses. A separate group of naïve rats was used for the microstructure analysis of licking during the conditioned odor aversion paradigm, with normal diet (ND) and high-fat diet (HFD) groups treated with NaCl or LiCl. (a) Licking behavior was recorded and analyzed for acquisition and long-term memory (LTM) days. Horizontal bars depict the mean number of licks across groups ± SEM; a vertical dashed line separates bars between acquisition (left) and LTM (right) days. Each dot represents the data of an individual rat. The number of licks was similar across all groups during the COA acquisition day. However, during LTM, HFD rats treated with LiCl had a significant decrease in the number of licks compared to ND-NaCl group. (b) Percentage of change of the licks during LTM relative to the acquisition day. Same representation as in panel a. The HFD-LiCl group showed enhanced aversion to banana-scented water compared to the HFD-NaCl group. (c) Same representation as in panel a, but for the number of clusters during licking behavior. The HFD-LiCl group exhibited fewer clusters compared to the ND-NaCl group during LTM. (d) Mean cluster size across groups. During the acquisition phase, the ND-NaCl group showed larger clusters than ND-LiCl and HFD-NaCl groups; however, during LTM, the HFD-LiCl showed significantly shorter clusters compared to the HFD-NaCl group. (e) Overall licking behavior. Heat maps illustrate the lick rates during acquisition (left panel) and LTM (right panel) days. Clusters are separated by groups and sorted based on cluster size. The plot shows that the HFD-LiCl group exhibited fewer clusters with shorter durations compared to the other groups. Overall, our results suggest that the HFD-LiCl group displayed reduced intake, fragmented licking behavior, and appeared to experience the banana-scented water as more aversive. Data are presented as a mean ± SEM. A three-way ANOVA and Bonferroni's multiple comparison were used to analyze the data of panels a, c, d, and e; panel b was analyzed with a Kruskal–Wallis test and Bonferroni's comparison. $^{*}p < .05$ and $^{**}p < .01$ between the groups connected by dark lines. ND-NaCl = normal diet + i.p. NaCl; ND-LiCl = normal diet + i.p. LiCl; HFD-NaCl = high-fat diet + i.p. NaCl and HFD-LiCl = high-fat diet + i.p. LiCl.

an effect on the hedonic response after COA (for complete comparison results, please see Table S13).

To quantify the reduction of palatability or the enhancement of aversion induced by COA, we calculated a palatability index based on the interaction between the number of total clusters and the mean cluster size for each subject. We observed a significant main effect of treatment on the palatability index (three-way ANOVA, factor treatment LiCl vs. NaCl: $F_{(1,16)} = 6.17$, $p = .0244$; Figure 3e), the post hoc analysis did not reveal any significant differences (for complete comparisons, see Table S14).

To further visualize the licking behavior herein described, heat maps were generated to depict all clusters alongside their respective sizes (Figure 3e). The heat maps indicate that, during the LTM, the HFD-LiCl group exhibited fewer clusters with shorter durations compared to the other groups. Overall, our results show that the HFD-LiCl group displayed reduced intake and appeared to experience the banana-scented water as more aversive.

3.4 | HFD intake induces upregulation in neurotransmission during COA

Glutamatergic, noradrenergic, and dopaminergic extracellular levels were measured with free movement microdialysis within the BLA and VHp in ND and HFD animals (Figure 4a for timeline). Consumption of HFD from weaning to adulthood did not modify the basal extracellular levels of the analyzed neurotransmitters within the VHp or the BLA when compared to their control group of ND: Glutamate ($t = 1.061$, $p = .2929$ for BLA; $t = .5232$, $p = .6042$ for VHp; Figure 4b,e, respectively); norepinephrine ($t = 1.665$, $p = .1010$ for BLA; $t = 1.500$, $p = .1444$ for VHp; Figure 4c,f, respectively); and

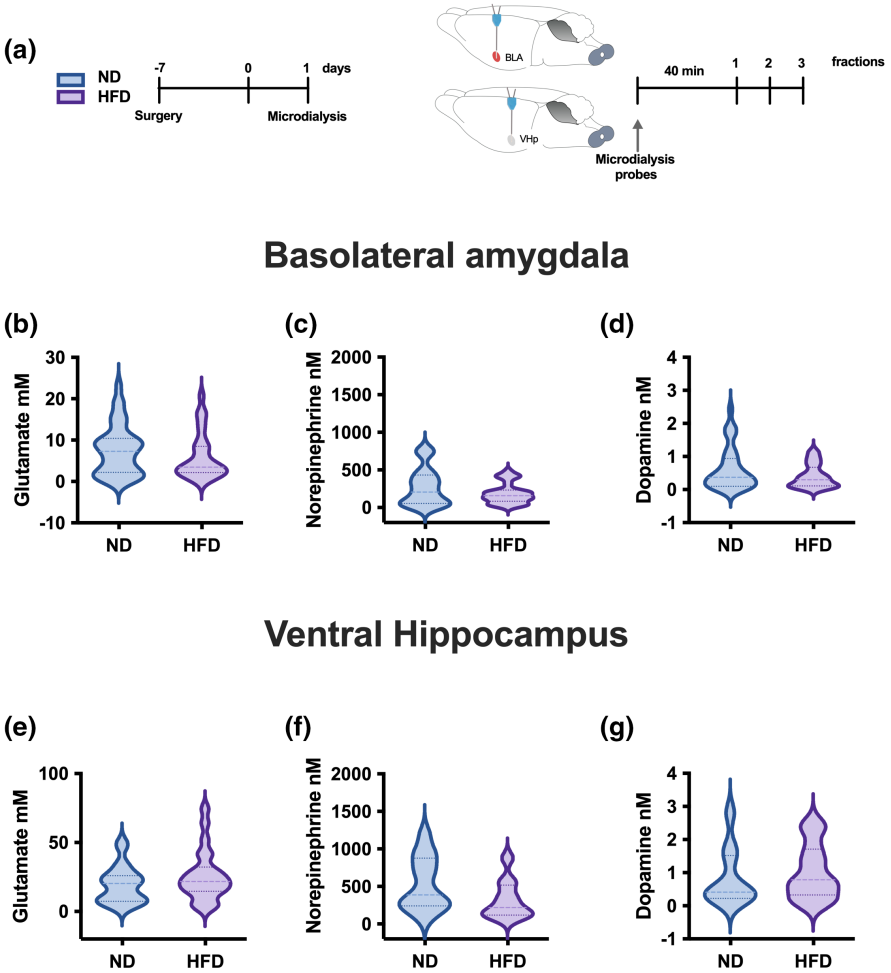

FIGURE 4 Violin plots showing basal neurotransmitter levels in the basolateral amygdala (BLA) and the ventral hippocampus (VHp) remained unaffected by high-fat diet consumption. Vertical dotted lines indicate the interquartile range and medians are indicated by a dashed line. (a) Schematic representation of the microdialysis protocol. Animals underwent stereotaxic surgery, and after surgery recovery, microdialysis probes were inserted into either the BLA or VHp. Following a stabilization period of 40 min, three fractions were collected to determine basal levels neurotransmitters within BLA or VHp. (b) Glutamate basal levels, (c) norepinephrine basal levels, and (d) dopamine basal levels within BLA were similar in the normal diet (ND) and high-fat diet (HFD) groups. (e) Basal glutamate levels, (f) norepinephrine basal levels, and (g) dopamine basal levels within VHp were comparable in ND and HFD groups. mM, millimolar; nM, nanomolar. Neurotransmitters levels were compared between groups using an unpaired Student's *t*-test.

dopamine ($t = 1.667$, $p = .1008$ for BLA; $t = .5294$, $p = .6033$ for VHp; Figure 4d,g, respectively. See Table S15).

The exposure to odor and the gastric malaise agent required for the COA elicited changes in neurotransmission (see Figure 5a for protocol timeline): during exposure to banana-scented water in COA acquisition norepinephrine ($t = .845$, $p = .4032$ for ND and $t = 1.151$, $p = .2603$ for HFD; Figure 5c) and dopamine levels ($t = 1.132$, $p = .2661$ for ND and $t = .070$, $p = .9442$ for HFD; Figure 5d) remained unchanged within the BLA. Conversely, the presentation of banana-scented water induced changes in glutamate in relation to its basal levels ($t = 2.062$, $p = .0474$ for ND and $t = 2.221$, $p = .0343$ for HFD; Figure 5b); however, such glutamate increase was not significantly different between groups, and both ND and HFD groups responded equally to the banana-scented water within the BLA ($t = .4611$, $p = .6464$). Likewise, norepinephrine and dopamine levels were not different between the ND and HFD groups during odor exposure ($t = .5696$, $p = .5709$ and $t = .9892$, $p = .3262$, respectively).

In relation to the administration of a gastric malaise-inducing agent, dopaminergic activity within BLA remained unchanged after LiCl injection ($t = .8384$ $p = .4117$ for ND and $t = .7710$, $p = .4507$ for HFD); such dopaminergic levels were not different between ND and HFD groups ($t = .358$, $p = .7223$; Figure 5g). Nevertheless, LiCl administration increased extracellular glutamatergic levels within the BLA in ND ($t = 2.184$, $p = .0394$ vs. basal levels) and HFD ($t = 3.674$,

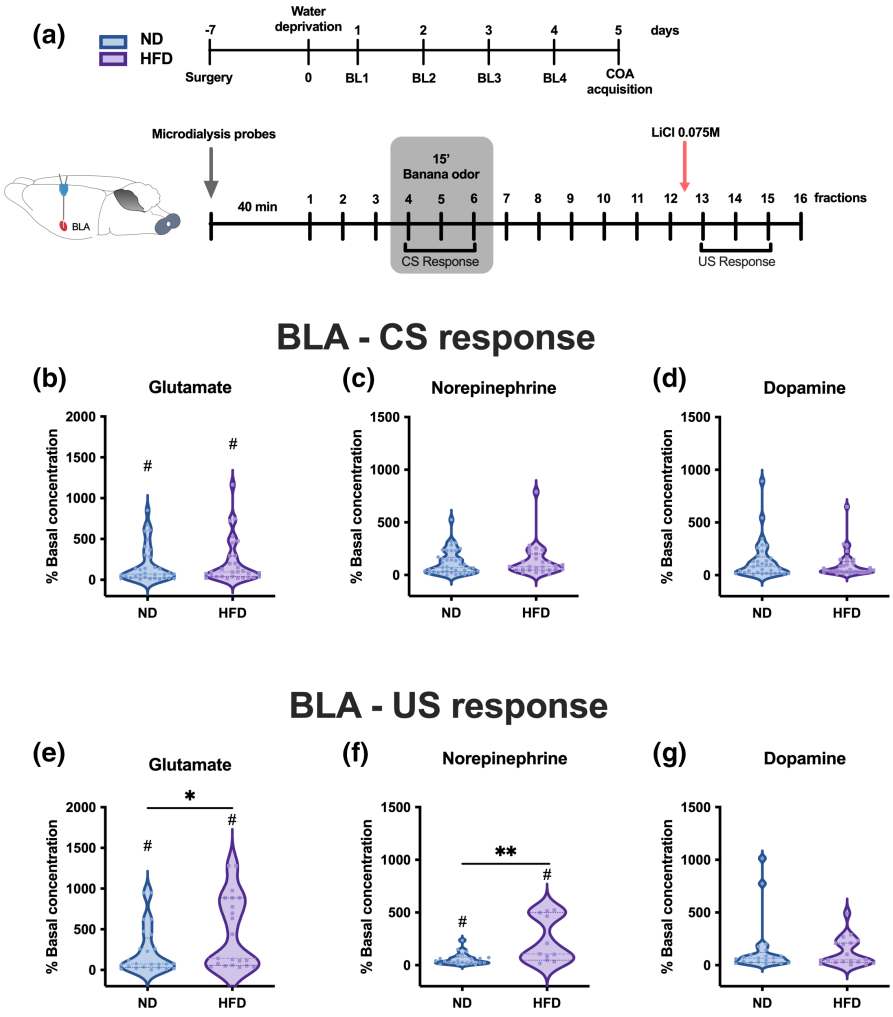

FIGURE 5 Violin plots showing the effect of high-fat diet consumption on glutamatergic and noradrenergic release within the basolateral amygdala (BLA) during conditioned odor aversion (COA) acquisition. Vertical dotted lines indicate the interquartile range and medians are indicated by a dashed line. The dots represent the data of individual rats. (a) Schematic representation of the experimental microdialysis procedures. Following surgery recovery, animals underwent water deprivation to establish baseline water intake. During microdialysis, a probe was inserted into the BLA; after 40-min stabilization period, animals acquired COA. (b) Exposure to scented water induced an elevation in glutamate in both normal diet (ND) and high-fat diet (HFD) animals. (c) Exposure to scented water did not change norepinephrine levels within BLA in any group. (d) Exposure to scented water did not change dopamine levels within BLA in any group. (e) Administration of a low dose of LiCl induced an increase in glutamate levels in both groups; however, HFD animals showed significantly higher glutamatergic response compared to the ND group. (f) LiCl administration decreased the noradrenergic response in ND animals and induced an increase of norepinephrine in HFD animals. (g) LiCl administration did not change dopamine release in any group. CS, conditioned stimulus; US, unconditioned stimulus. $^{*}p < .05$ and $^{**}p < .01$ between groups using an unpaired Student's t-test; and $^{\#}p < .05$ versus the corresponding basal level using one-sample t-test.

$p = .0015$ vs. basal levels) animals. Moreover, statistical differences were observed in the glutamatergic response between ND and HFD groups ($t = 2.047$, $p = .0468$) (Figure 5e). The consumption of HFD also altered the noradrenergic response to LiCl. The control group showed a decrease in its noradrenergic response after administering a low dose of LiCl (ND $t = 2.496$, $p = .0205$ vs. basal levels). Conversely, HFD animals exhibited an augmented noradrenergic response to a low dose of LiCl ($t = 2.349$, $p = .0433$ vs. basal levels; Figure 5f). These changes in noradrenergic levels within the BLA due to LiCl administration were significantly different between ND and HFD groups ($t = 3.987$, $p = .0001$).

Regarding VHp neurochemical responses during the COA protocol (Figure 6a), the presentation of scented water did not evoke changes in the extracellular glutamate ($t = 1.749$, $p = .1081$ for ND and $t = .083$, $p = .9341$ for HFD; Figure 6b); or dopamine ($t = .8473$, $p = .4122$ for ND and $t = 1.949$, $p = .067$ for HFD; Figure 6d) compared to the baseline levels. In contrast, norepinephrine levels increased only in HFD animals after exposure to odorized water ($t = .2342$, $p = .8191$ for ND and $t = 3.447$, $p = .003$ for HFD; $t = 2.150$, $p = .0404$ between ND and HFD groups; Figure 6c. See Table S16).

The neurotransmission response in the hippocampus induced by LiCl was also modified by the consumption of HFD. In the case of dopamine, extracellular levels within VHp were unaltered by LiCl administration ($t = .1502$, $p = .8836$ for ND and $t = 1.109$, $p = .2874$ for HFD; $t = .358$, $p = .7223$ between ND and HFD groups; Figure 6g). Regarding glutamatergic transmission, ND animals did not display

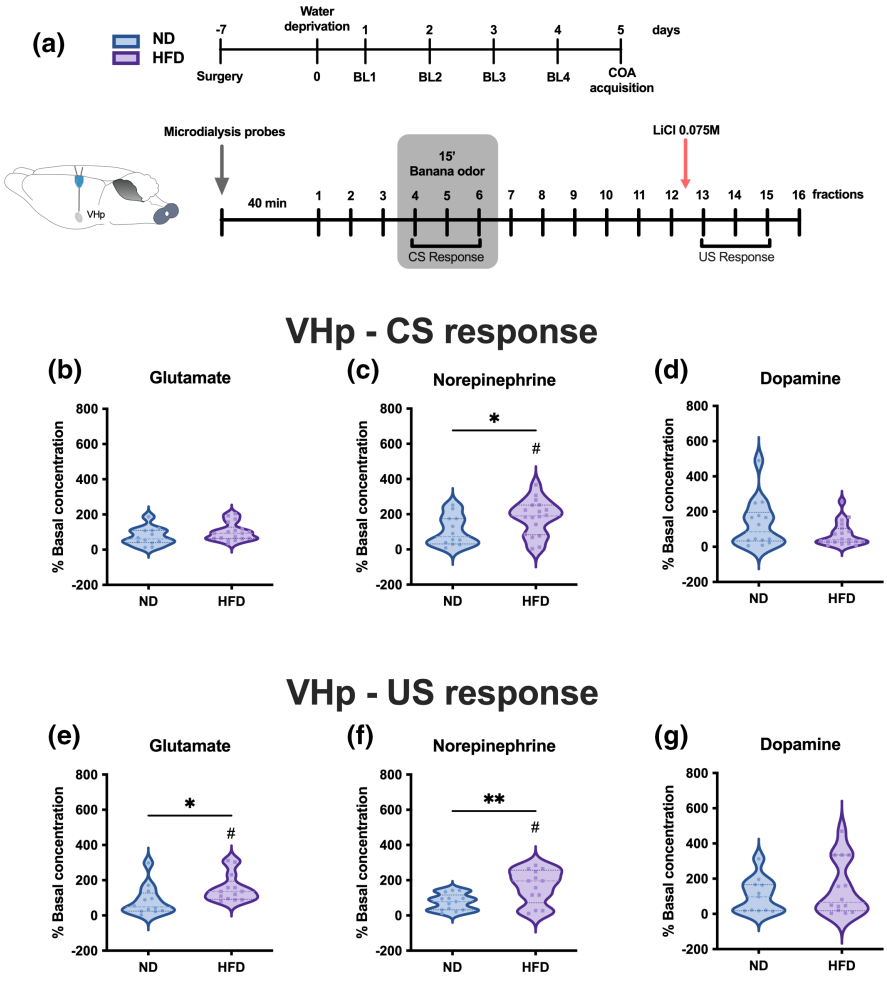

FIGURE 6 Violin plots showing the effect of high-fat diet consumption on glutamatergic and noradrenergic release within the ventral hippocampus (VHp) during conditioned odor aversion (COA) acquisition. Vertical dotted lines indicate the interquartile range and medians are indicated by a dashed line. The dots represent the data of individual rats. (a) Schematic representation of the experimental microdialysis procedures. Following surgery recovery, animals underwent water deprivation to establish baseline water intake. During microdialysis, a probe was inserted into the VHp; after 40 min stabilization period, animals acquired a COA. (b) Exposure to scented water does not alter glutamate levels in normal diet (ND) and high-fat diet (HFD) animals. (c) Exposure to scented water did not change norepinephrine levels in ND animals, while HFD animals exhibit an enhanced response. (d) Banana-scented water did not induce dopamine release in either HFD or ND animals. (e) Administration of a low dose of LiCl increased the glutamatergic response in HFD animals. (f) Administration of LiCl increased the noradrenergic response in HFD animals. (g) Dopamine response remained unaltered after LiCl administration. CS, conditioned stimulus; US, unconditioned stimulus. $^{*}p < .05$ and $^{**}p < .01$ between groups using an unpaired Student's *t*-test, and $^{\#}p < .05$ versus basal levels using one sample *t*-test.

glutamatergic changes after the low-dose administration of LiCl ($t = .6483$, $p = .5314$ vs. basal levels); conversely, HFD animals showed an increased glutamatergic response after LiCl injection within VHp ($t = 2.527$, $p = .0267$ vs. basal levels; $t = 2.204$, $p = .0378$ between ND and HFD groups; Figure 6e). The noradrenergic response associated with LiCl administration in VHp was also altered by the consumption of HFD. ND animals did not display a noradrenergic response after the administration of LiCl ($t = 1.839$, $p = .0907$ vs. basal levels), but the HFD group revealed a heightened noradrenergic response after LiCl injection ($t = 2.375$, $p = .0351$ vs. basal levels; $t = 2.938$, $p = .0072$ between ND and HFD groups; Figure 6f. See Table S17). Hence, the consumption of HFD from weaning to adulthood generates an exacerbated glutamatergic and noradrenergic response within the BLA and the VHp associated with administering a low dose of LiCl.

4 | DISCUSSION

The impact of obesity on cognitive function is a growing concern, particularly under evidence linking early-life exposure to an obesogenic environment to cognitive impairment. This study, aiming to understand neural mechanisms and behavioral outcomes associated with juvenile obesity, investigates how a HFD consumption from weaning to adulthood influences metabolism, hedonic processing of taste, cognitive performance, and neurotransmission in rats. Despite the association of obesity with the risk of cognitive deficits and decreased neurotransmission response, this juvenile obesity model displays behavioral modifications enhancing odor aversive memory during the LTM test. The observed upregulation of the glutamatergic and noradrenergic systems within the BLA and the VHp during stimuli exposure indicates specific links between alterations in neurotransmission and stimulus processing, rather than reflecting a general change in basal neurotransmitter levels. This aligns with prior research highlighting how metabolic changes induced by HFD consumption can modulate neuronal responses to environmental stimuli.

Some studies show that consuming hypercaloric diets during pregnancy increase fear and anxiety responses in the offspring (Bilbo & Tsang, 2010; Peleg-Raibstein et al., 2012; Sullivan et al., 2010). However, the impact of these diets on aversive responses during postnatal development remains inadequately elucidated. Prior research indicates that obesogenic diets are associated with increased amygdalar activation and volume (Boutelle et al., 2015; Widya et al., 2011), contributing to an augmentation of aversive memories, including COA and tone-related fear memory (Boitard et al., 2015). Nonetheless, there is conflicting evidence suggesting subtle alterations in anxiety-related behaviors and a more pronounced influence on depression-like behaviors in prepubertal animals fed with HFD for 8 months (Lorena et al., 2021).

The BLA is a key structure in the formation of aversive memories (McGaugh, 2013) and participates in COA formation (Sevelinges et al., 2009). The VHp is also involved in establishing aversive memories, particularly contextual (Hernández-Matias et al., 2021) and odor aversion memories (Wang et al., 2013). Obesogenic diets are associated with impaired hippocampal activity (Bauer et al., 2015; Hernández-Ramírez et al., 2021; Mestre et al., 2017). Therefore, both the BLA and VHp are involved in the establishment of aversion memories, particularly those associated with odor. The advantage of studying COA is that it allows us to temporally separate the conditioned stimulus from the unconditioned stimulus to evaluate the elicited neurochemical changes independently, as it is a trace conditioning paradigm.

During COA acquisition, exposure to banana-scented water induces an elevated noradrenergic release within the VHp that might be related to the processing of this type of information, as VHp is activated with olfactory information (Kent et al., 2007; Shinohara & Yasoshima, 2021). The pharmacological inactivation of VHp spares odor neophobia but accelerates the attenuation of neophobia (Shinohara & Yasoshima, 2021). Our results indicate that neophobic response is not altered in HFD animals regardless of their major noradrenergic response, but this increase may contribute to the improved establishment of COA. Likewise, we observed enhanced glutamatergic and noradrenergic release within the VHp following administration of hypotonic LiCl. Although excitotoxic lesions of the VHp do not alter conditioned taste aversion acquisition and retrieval (Yamamoto et al., 1995), the activity within VHp is increased during the retrieval of COA (Dardou et al., 2006) and is involved in establishing LiCl-induced conditioned place aversion (Hernández-Matias et al., 2021). Hence, the VHp participates in aversive-related memories, and HFD consumption alters the neurotransmission activity triggered by the administration of an aversive agent, possibly due to anxiety upregulation, as the VHp has been broadly associated with anxiety modulation (for excellent reviews, please see (Fanselow & Dong, 2010; Ghasemi et al., 2022)).

Behavioral data are consistent with previous results where exposure to a HFD enhances odor aversion memory (Boitard et al., 2015; Naneix et al., 2021). COA requires BLA activity (Desgranges et al., 2008). In HFD animals, the administration of LiCl induces an exacerbated glutamatergic and noradrenergic response within the BLA, even with a low dose (.075 M). We have earlier documented that this low dose of LiCl fails to induce a glutamatergic response within the BLA (Miranda et al., 2002). However, the administration of hypertonic LiCl elicits a higher glutamatergic and noradrenergic release within the amygdala (Guzmán-Ramos et al., 2012), similar to the glutamatergic response elicited by LiCl in HFD animals. Thus, even a low dose of the aversive stimulus can elicit an enhanced response from the noradrenergic and glutamatergic systems in HFD animals.

Amygdalar and hippocampal enhanced responses observed during COA acquisition may result from alterations in the hypothalamic–pituitary–adrenal (HPA) axis caused by HFD intake. Obesity is associated with systemic chronic low-grade inflammation, which increases HPA axis activation and cortisol secretion (Pasquali & Vicennati, 2000). Dysregulation of the HPA axis alters cognitive processes by at least two mechanisms: (1) released cortisol crosses the blood–brain barrier and modulates memory

processing by activating glucocorticoid receptors within the brain (Hui et al., 2004). In this regard, administering a glucocorticoid receptor antagonist within BLA mitigates amplified odor aversion memory in HFD animals (Boitard et al., 2015). (2) Activation of the HPA axis modulates neurotransmission through cortisol release and norepinephrine release from the adrenal glands. This norepinephrine binds to adrenergic receptors on the vagus nerve, promoting activation of the nucleus of the solitary tract (Williams et al., 1998) and the locus coeruleus (Wong et al., 2012), increasing noradrenergic levels within several brain structures involved in cognition (Sara, 2009). Also, this increase in norepinephrine levels promotes glutamatergic release (Zhang et al., 2013) within the brain. To summarize, HFD intake may lead to HPA axis hyperactivity caused by chronic low-grade inflammation and alteration in its maturation. This causes upregulation in noradrenergic and glutamatergic release after the presentation of the olfactory stimulus or the aversive stimulus. This increase in neurotransmitters during the processing of stimuli facilitates the formation of an emotion-related memory, such as COA. Therefore, the anxiety disorders observed in adolescents with obesity (Gariepy et al., 2010) are likely because of modifications in the HPA axis. This increased anxiety changes cognition and enhances emotionally arousing memories (McGaugh, 2013).

Moreover, the interaction between these two structures could also explain the observed changes in neurotransmission in VHp and BLA. The BLA sends direct projections to the VHp (Felix-Ortiz et al., 2013; Pikkarainen et al., 1999). These projections are monosynaptic glutamatergic and modulate anxiety-related behaviors. Activation of the BLA projections to the VHp increases anxiogenic behaviors (Felix-Ortiz et al., 2013). Moreover, the presynaptic glutamatergic system (NMDA and AMPA receptors) expressed within hippocampal nerve terminals modulates norepinephrine release (Grilli et al., 2009; Howells & Russell, 2008). In this regard, the consumption of HFDs modifies glutamatergic metabolism and NMDA receptor expression (Valladolid-Acebes et al., 2012). Additionally, hyperinsulinemia, commonly observed in patients with obesity, alters glutamatergic activity by multiple mechanisms, including the augmentation in post-translational modifications, NMDA receptors recruitment, and AMPA receptors endocytosis (Spinelli et al., 2020). Thus, we suggest that neurotransmission alterations observed in our juvenile obesity model are partially caused by modifications in the finely tuned BLA-VHp circuit and the glutamatergic system.

It is important to mention that obesity has been widely associated with neural plasticity and memory impairments in human and animal models. Obesogenic diets reduce hippocampal plasticity (Hernández-Ramírez et al., 2021; Karimi et al., 2015; Porter et al., 2012; Valladolid-Acebes et al., 2012); similarly, consuming hypercaloric diets results in spatial, associative, and recognition memory deficits (Boitard et al., 2012, 2014; Hernández-Ramírez et al., 2021, 2022; Spencer et al., 2017). Moreover, these deficits in plasticity and memory are associated with a diminished catecholaminergic response, at least within the hippocampus. Plasticity and memory impairments are improved after administering a catecholaminergic reuptake inhibitor (Hernández-Ramírez et al., 2021). Prolonged consumption of obesogenic diets decreases catecholaminergic activity in the brain (Carlin et al., 2013; Nguyen et al., 2017); for a review, please see Guzmán-Ramos et al. (2022). Similarly, obesogenic diets have been found to upregulate gene expression associated with neuroinflammation (Lorena et al., 2021). Notably, alterations in neuroinflammation have been associated with changes in the noradrenergic response, mediated by the activation of the locus coeruleus (Borsody & Weiss, 2004), leading to subsequent norepinephrine release. Consequently, obesity has been related to general cognitive deficits caused by a diminished neurotransmission response. However, this does not always occur, our data show memory enhancement and upregulated noradrenergic and glutamatergic responses. Likewise, previous results (Hernández-Ramírez et al., 2021; Nguyen et al., 2017) show that alterations in neurotransmission are not evident under basal conditions; nevertheless, neurotransmission dysregulation becomes clear during stimuli exposure or cognitive challenge. The interpretation of the results above has a sex bias due to the limitation of the study, which used only male rats. This approach was preferred because of the sex asymmetry regarding metabolic homeostasis differentially regulated in males and females (Mauvais-Jarvis, 2015).

From weaning to adulthood, a HFD increased weight and epididymal fat causing glucose intolerance and insulin insensitivity. Although obesity is associated with memory impairments and neurotransmission deficits, this juvenile obesity model exhibited enhanced odor aversion memory and stronger hedonically aversive palatability responses. These behavioral alterations are accompanied by upregulated noradrenergic and glutamatergic systems during aversive-related memory acquisition. The observed alteration in behavior and neurotransmission may result from HFD-induced changes in the hypothalamic–pituitary–adrenal axis, potentially explaining modified responses in the amygdala and hippocampus responses during stimuli exposure. Furthermore, HPA axis dysregulation promotes anxiogenic responses and stress, suggesting that the consumption of hypercaloric diets contributes to stress, thereby interfering with cognitive processes. This interference includes exacerbating emotional memories and impairing executive function and self-regulation, thus initiating a vicious cycle wherein stress induces overeating and the consumption of hypercaloric diets (Tomiyama, 2019). These findings highlight hypercaloric diets' role in neurotransmission dysregulation, influencing mnemonic manifestations depending on brain structures and information type. This study emphasizes the need for further research on the mechanisms and therapeutic targets for obesity-related cognitive impairments.

DECLARATION OF TRANSPARENCY

The authors, reviewers and editors affirm that in accordance to the policies set by the *Journal of Neuroscience Research*, this manuscript presents an accurate and transparent account of the study being

reported and that all critical details describing the methods and results are present.

AUTHOR CONTRIBUTIONS

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Conceptualization and methodology*, D.O-G., G.P-L., R.G., F.B-R. and K. G-R.; *Investigation*, D.O-G., K.G-R., P.S-T., A.H-M., S.H-R., C.I.P. and B.A.; *Formal Analysis*, D.O-G. and B.A.; *Writing-Original Draft*, D.O-G.; *Writing-Reviewing and Editing*, D.O-G., K.G-R., F.B-R., G.P-L., R.G., *Funding Acquisition*, F.B-R., R.G., G.P-L., K.G-R. and OBETEEN consortium.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/jnr.25360.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Transparent Science Questionnaire for Authors

Table S1. Relation of statistical results of analysis for Figure 1b.

Table S2. Relation of statistical results of analysis for Figure 1c.

Table S3. Relation of statistical results of analysis for Figure 1d.

Table S4. Relation of statistical results of analysis for Figure 1e.

Table S5. Relation of statistical results of analysis for Figure 1e (inset).

Table S6. Relation of statistical results of analysis for Figure 1f.

Table S7. Relation of statistical results of analysis for Figure 1f (inset).

Table S8. Relation of statistical results of water intake during baseline monitoring and post-COA training.

Table S9. Relation of statistical results of analysis for Figure 2b.

Table S10. Relation of statistical results of analysis for Figure 3a.

Table S11. Relation of statistical results of analysis for Figure 3b.

Table S12. Relation of statistical results of analysis for Figure 3c.

Table S13. Relation of statistical results of analysis for Figure 3d.

Table S14. Relation of statistical results of analysis for Figure 3e.

Table S15. Relation of statistical results of analysis for Figure 4.

Table S16. Relation of statistical results of analysis for Figure 5.

Table S17. Relation of statistical results of analysis for Figure 6.

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