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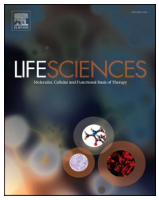

Chronic intranasal URB597 treatment reverts short-term memory deficits in a rat model of metabolic syndrome

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ABSTRACT

Aims: Metabolic syndrome (MetS) is characterized by several metabolic alterations that may increase the risk of memory alterations. While metabolic consequences of MetS are well documented, its memory impact remains underexplored. This study aimed at investigating the progression of MetS-associated impairments and evaluating the therapeutic potential of URB597, a fatty-acid amide hydrolase inhibitor, that increases the N-acylethanolamine levels.

Materials and methods: In Experiment 1, male Sprague-Dawley rats were fed a control (CTRL), high-fat (HF), high-carbohydrate (HC), or combined HF/HC diet for 12 weeks to identify the most effective model of MetS-induced metabolic and memory changes. In Experiment 2, rats received intranasal URB597 (0.1 mg/kg) for 10 weeks following the HF/HC diet to assess its therapeutic impact. Body weight, body mass index (BMI), and triglycerides were measured; memory function was assessed using the Object Recognition, Morris Water Maze, and Y-maze tasks.

Key findings: Results from Experiment 1 showed that the HF/HC diet induced metabolic dysfunctions and impairments in both recognition and long-term spatial memory, while short-term spatial memory remained intact. In Experiment 2, the prolonged diet reproduced the same metabolic and memory deficits observed in Experiment 1, and URB597 treatment reversed recognition memory impairments but did not improve spatial memory performance, suggesting a domain-specific vulnerability to MetS and to the treatment response.

Significance: These findings highlight memory deficits associated with MetS and point to N-acylethanolamine signaling as a potential modulatory pathway, with URB597 serving as a pharmacological tool to investigate its therapeutic relevance.

1. Introduction

Metabolic syndrome (MetS) is a clinical condition characterized by the coexistence of multiple metabolic risk factors, including abdominal obesity, hyperglycemia, dyslipidemia, and hypertension, which significantly increase the risk of developing cardiovascular diseases and type 2 diabetes [1]. Among these consequences, the impact of MetS on brain health has emerged as particularly concerning, with evidence showing that it contributes to cognitive deficits and an increase risk of neurological disorders [2–6]. For instance, individuals with MetS are more likely to develop mild cognitive impairment and dementia (e.g., Alzheimer's disease) [7]. These effects are primarily driven by chronic low-grade inflammation, impaired insulin signaling, and oxidative stress, which together disrupt synaptic plasticity and neurogenesis, two key

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processes for learning and memory. Additionally, MetS-related vascular dysfunction reduces cerebral blood flow, leading to white matter lesions and microvascular damage, further exacerbating neuronal decline [8]. At preclinical level, particularly in rats, MetS is commonly induced through high-fat and high-sugar diets to investigate the underlying molecular and physiological mechanisms [9,10]. Consistent with this approach, studies in rat models have shown that exposure to a hypercaloric diet is associated with memory impairments across multiple domains. Specifically, short-term spatial memory deficits in the Object Location (OL) test [11], short- and long- term recognition memory impairments in the Object Recognition (OR) test [12], and long-term spatial memory deficits in the Morris Water Maze (MWM) task [13] have been reported. Considering the complex pathophysiology of MetS-associated memory deficits, novel therapeutic approaches targeting multiple pathways simultaneously are needed. In this context, bioactive fatty acid amides, such as N-acylethanolamines (NAEs), which are involved in various physiological and pathological processes [14], could represent promising candidates.

Among the NAEs, arachidonoylethanolamide (anandamide, AEA), palmitoylethanolamide (PEA), and oleoylethanolamide (OEA) are the most extensively studied due to their distinct roles in inflammation, neuroprotection, and energy homeostasis [15,16]. AEA is a partial agonist of cannabinoid receptors type 1 (CB1) and 2 (CB2), it interacts with transient receptor potential vanilloid 1 (TRPV1) and, at high doses, also engages peroxisome proliferator-activated receptors (PPARs), contributing to its broad pharmacological effects [17–19]. Functionally, AEA exerts analgesic, anxiolytic, and antidepressant effects [20–22], while also promoting neuroprotection, memory enhancement, and food intake regulation via CB1 receptor activation in the brain [23–27]. In contrast, OEA primarily acts as a satiety signal and plays a key role in metabolic regulation, particularly glucose metabolism [28–31]. Additionally, it has gained attention for its memory-enhancing effects [32,33]. PEA, on the other hand, is recognized for its analgesic, anti-inflammatory, and neuroprotective properties [34–36]. Unlike AEA, both OEA and PEA do not bind to CB1 or CB2 receptors, but exert their effects through PPAR-α activation [28,34,37] and interactions with TRPV1 receptors [38,39].

The NAEs share a common degradation pathway mediated by fatty acid amide hydrolase (FAAH) [40]. A widely used strategy to increase their level has been the inhibition of the enzymes responsible for their breakdown. URB597 irreversibly carbamylates the catalytic serine nucleophile of FAAH [41], leading to a non-specific increase in endogenous NAEs levels, underscoring its therapeutic potential. Our and other studies research, have demonstrated that URB597 improves memory and exhibits neuroprotective effects across various animal models [17,25,42–47]. Interestingly, chronic administration of URB597 has been shown to restore redox balance in the brain of hypertensive rats [48] and in a rat model of type 2 diabetes [20]. Furthermore, Wang et al. (2021) [49] also reported the beneficial effects of URB597 in a vascular dementia model, highlighting its role in mitigating vascular dysfunction and oxidative stress.

Currently, available treatments primarily target the metabolic alterations of MetS, while no approved therapies specifically address the cognitive deficits frequently comorbid with this condition. In this study, we first established a MetS model in male rats and confirmed the development of both metabolic dysfunctions and associated memory impairments. To investigate potential therapeutic effects, we chronically administered URB597 via intranasal (i.n.) delivery, an innovative and non-invasive method enabling direct and efficient delivery to the central nervous system, as previously demonstrated [50].

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats at postnatal day (PND) 21, weighing approximately 60 g, were purchased from Charles River Laboratories (Calco, Italy). They were housed in pairs in a temperature-controlled environment (21 ± 1 °C) with a 12-h light/dark cycle (lights on from 7:00 a.m. to 7:00 p.m.), with free access to food and water and appropriate environmental enrichment. The experiments began at PND 28 and consisted of two phases with two different groups of animals (Experiment 1 and Experiment 2). All procedures involving animal care or treatments were performed in compliance with the ARRIVE guidelines, the Directive 2010/63/EU of the European Parliament, the D. L. 26/2014 and were approved by the Italian Ministry of Health (authorization number: 266/2023-PR project number: D6507.21).

2.2. Experimental design

Experiment 1 (see Fig. 1a for details): this experiment aimed to test different types of diets to identify the one that best induces MetS symptoms, including serum alterations, weight gain and memory deficits. The diet (Piccioni Srl, Milan, Italy) was administered for 12 weeks and the groups of animals consisted in:

- Control (CTRL) (n = 9): standard normocaloric diet and tap water ad libitum;
- High carbohydrate (HC) (n = 9): standard diet and 20% *w/v* sucrose solution ad libitum;
- High fat (HF) (n = 9): diet with 60% kcal from fat (lard) and tap water ad libitum;
- HF/HC (n = 10): combined high-fat diet with 60% kcal from fat and 20% w/v sucrose solution ad libitum.

Experiment 2 (see Fig. 1b for details): using the experimental MetS model developed in Experiment 1, we evaluated chronic i.n. treatment with URB597, an indirect agonist of NAEs receptors, at a dose of 0.1 mg/kg (volume of 50 μL/Kg) to treat MetS-induced disturbances [45,50]. To better mimic the chronic nature of the pathology in humans, we therefore used the diet that had induced the most significant alterations in Experiment 1 and extended its duration to 20 weeks, allowing for a 10-week pharmacological intervention. URB597 treatment was initiated after 10 weeks of diet, when metabolic and cognitive alterations were fully established, to assess its therapeutic efficacy in reversing existing deficits. This design thus reflects clinically relevant treatment scenarios while modeling the progressive nature of MetS. The animals were then randomized into the following groups, according to the type of diet and treatment (URB597 or vehicle, VEH): CTRL-VEH (n = 12), CTRL-URB597 (n = 13), HF/HC-VEH (n = 12), HF/HC-URB597 (n = 15).

For both the experiments to evaluate zoometric parameters, body weight (g), body mass index (BMI) [weight (g) / nose-to-anus length^2 (cm^2)] and the body mass gain (Δ = bodyweight at the end of the diet or treatment - body weight at the beginning of diet or treatment) [51], along with blood levels of triglycerides, cholesterol, and glucose were measured. Moreover, memory deficits were assessed by subjecting rats to behavioral tests, such as OR, MWM and Y-maze tasks.

2.3. Drugs

The FAAH inhibitor URB597 (0.1 mg/kg) was dissolved in a VEH containing 5% polyethylene glycol, 5% Tween80 and 90% saline solution [46]. All drugs were freshly prepared on the day of the experiment and administered every other day for 10 weeks, through i.n. route in a volume of 50 μL/kg, by using a micropipette (Pipetman P-200, Gilson Inc., Milan, Italy). All animals were habituated to i.n. administration with saline solution (0.9%) for 2 days before starting the treatment.

2.4. Serum analysis

Blood samples were collected from ad libitum-fed animals via tail cut and stored at −80 °C until processing. Then the serum concentrations of

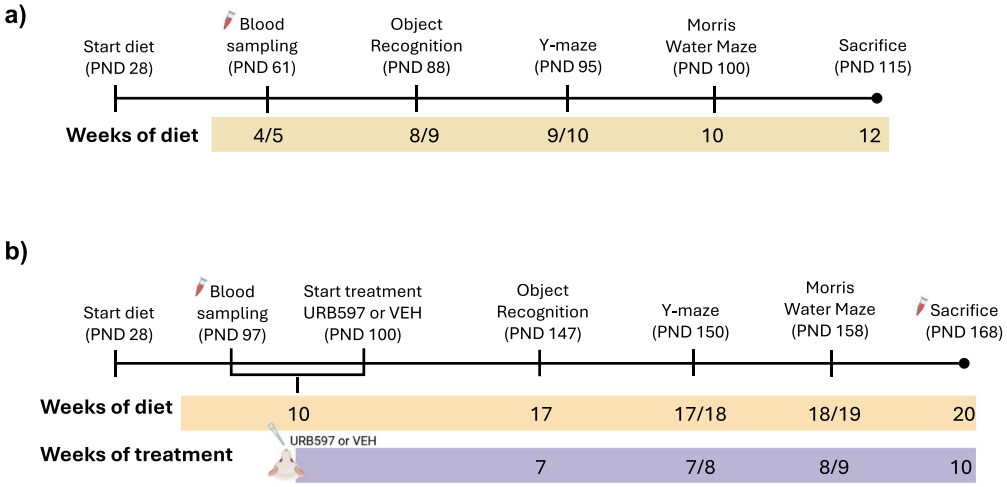

Fig. 1. Timeline of Experiment 1 (a) and Experiment 2 (b).

glucose, total cholesterol and triglycerides were determined following the instructions provided by the respective assay kits: MAK263, MAK043 and MAK266 (SIGMA-ALDRICH, Milan, Italy).

2.5. Behavioral test

2.5.1. OR

We used a slightly modified version of a previously described protocol [52]. The behavioral testing was conducted in a grey open-field arena (40 × 40 × 40 cm) with the floor covered by sawdust, located in a low-light environment. The stimuli used as objects were transparent glass vials and white glass light bulbs. For the habituation phase, animals were allowed to freely explore the empty arena twice per day (morning and afternoon) for 3 min across three consecutive days. During the training phase, rats were individually introduced into the arena from the side opposite to the objects and permitted to explore two identical objects (A1 and A2) for a total duration of 6 min. To prevent olfactory cue interference, the sawdust was mixed and all objects were thoroughly cleaned with 70% ethanol between trials. Animal behavior was monitored using a video-recording system mounted above the arena. Object exploration was operationally defined as directing the snout toward the object at a distance of less than 1 cm and/or making nasal contact; behaviors such as climbing, sitting on, or circling the object were excluded from the analysis. The cumulative time spent investigating both objects was taken as an index of object exploration. Short-term memory performance was assessed 1 h following the training session. During the test phase, one replica of the previously explored object (A3) and one novel object (B) were positioned in the same locations used during training. Object identity and spatial arrangement were counterbalanced across animals to control for inherent object or side preferences. Each rat was allowed to explore the arena for 6 min, during which behavior was continuously recorded. Videos were analyzed by a trained observer who was unaware of treatment condition. We measured locomotor activity as the number of crossings and vertical activity (number of rearings + wall rearings), as well as the time spent exploring each object and the total exploration time. A discrimination index was calculated to assess cognitive performance, defined as the difference in time exploring the novel and familiar object, expressed as the ratio of the total time spent exploring both objects (i.e., [time novel − time familiar / time novel + time familiar] × 100). Animals that explored for less than 10 s were excluded from the statistical analysis [53].

2.5.2. Y-maze

To evaluate short-term spatial memory, Y-maze test was performed according to the protocol previously described [54]. The Y-maze was composed of three black plastic arms arranged in a Y-shaped configuration, each arm measuring 50 cm in length, 10 cm in width, and 30 cm in height. All arms, designated as the "start," "other," and "novel" arms, were identical in appearance. This paradigm takes advantage of the innate preference of rodents for exploring unfamiliar environments and uses spatial cues to evaluate spatial memory performance. During the acquisition phase, rats were introduced into the start arm and allowed to explore the maze for 5 min while access to one arm (the novel arm) was blocked. Following a 2-h intertrial interval, animals were reintroduced into the maze for the test phase (5 min), starting again from the same start arm, with all three arms freely accessible. The percentage of the time spent in the novel arm was calculated as: (time spent in novel arm / time spent in all the three arms) × 100. Animals that climbed over walls or remained immobile were excluded from the statistics.

2.5.3. MWM

The experiments were performed according to the procedure previously described [35,55]. Spatial learning was assessed using a circular water maze consisting of a tank 1.83 m in diameter and 0.58 m in height, filled with water maintained at 23–24 °C to a depth of 20 cm. The apparatus was located in a testing room containing multiple prominent distal visual cues positioned around the maze. During the acquisition phase, a rectangular escape platform (20 × 25 cm) was submerged 2.5 cm below the water surface and positioned in a constant location, approximately 25 cm from the pool wall. Animals underwent spatial training consisting of four trials per day across three consecutive days. For each trial, rats were released into the pool facing the wall from one of four predetermined starting points and allowed to swim freely until locating the hidden platform. On the first training day, animals that did not reach the platform within 60 s were gently guided to it. After mounting the platform, rats remained there for 10 s and were then transferred to a holding cage for a 25-s intertrial interval. Escape latency, defined as the time required to locate the platform, was measured for each trial. Memory retention was assessed 24 h after the last training session with a 60 s free-swim probe trial (with no platform) and a new starting position was used. During the probe test, time spent in the target and opposite quadrants was measured. Training and probe trials were both videotaped, and an automated tracking system (Smart, Panlab, Barcelona, Spain) was used to record the swim path of each subject and calculate the behavioral parameters.

2.6. Statistical analysis

Statistical analysis was performed using GraphPad Prism 8.0 software. Data are expressed as mean ± SEM. In the Experiment 1, the body

weight, BMI and acquisition during MWM were analyzed with a repeated measures ANOVA (RM ANOVA). In all the other cases, data were analyzed with one (diet as variable) or two-way ANOVA (diet and quadrant as variables in the MWM). In the Experiment 2, the body weight, BMI and acquisition during MWM were analyzed with a RM ANOVA. In all the other cases, data were analyzed with two-way (diet and treatment as variables) or three-way ANOVA (diet, treatment and quadrant as variables in the MWM). A one-sample *t*-test against 0 was performed on the discrimination index (%) in the OR test for both Experiments 1 and 2, and one-sample t-test against 15 s for the MWM test. Tukey-Kramer post-hoc tests were performed to control for significant differences between groups when appropriate. A probability level of <0.05 was accepted as statistically significant.

3. Results

3.1. Experiment 1

3.1.1. Exposure to a HF/HC diet caused biometric and biochemical alterations typical of MetS

We investigated which diet or combination of diets could most effectively induce metabolic alterations resembling those observed in MetS.

As shown in Fig. 2a, RM ANOVA for the body weight revealed significant effects of the diet ($F_{(3,33)} = 14.380$, $p < 0.001$), weeks of diet ($F_{(12,396)} = 2263.000$, $p < 0.001$), and interaction between these two factors ($F_{(36,396)} = 18.900$, $p < 0.001$). Tukey post hoc analysis indicated that a significant increase in body weight in HF/HC rats compared to the CTRL group first emerged after 5 weeks of diet ($p < 0.05$) and was maintained from the 6th to the 12th week ($p < 0.001$). We also found that a significant increase in body weight in HF rats compared to those on a normal diet first emerged at the 5th week ($p < 0.05$), persisted at the 6th week ($p < 0.01$), and was maintained from the 7th to the 12th week ($p < 0.001$).

One-way ANOVA for the increase of body weight (Δ) demonstrated a significant effect of the diet ($F_{(3,33)} = 23.200$, $p < 0.0001$) (Fig. 2b). The post hoc analysis indicated that HF and HF/HC groups showed a higher increase of body weight gain versus the CTRL group ($p < 0.0001$).

The RM ANOVA for the BMI demonstrated significant effects of the diet ($F_{(3,33)} = 7.659$, $p < 0.001$) and week of diet ($F_{(1,33)} = 5.444$, $p = 0.026$), but not of the interaction diet x week of diet ($F_{(3,33)} = 0.274$, $p = 0.844$) (Fig. 2c). Tukey post hoc analyses revealed an increased BMI in HF ($p < 0.05$) and HF/HC ($p < 0.01$) vs CTRL groups at the 7th week of diet. Notably, such effects remained until the 10th week of diet only when animals received the HF/HC type of diet ($p < 0.01$). Moreover, one-way ANOVA revealed a significant effect of the diet for the triglycerides level ($F_{(3,12)} = 5.591$, $p = 0.012$) (Fig. 2d) and for glucose ($F_{(3,23)} = 5.043$, $p = 0.008$) (Fig. 2e). The post hoc test showed that the HF/HC group had increased only serum triglyceride levels ($p < 0.05$). No effect for total cholesterol levels ($F_{(3,24)} = 0.117$, $p = 0.949$) (Fig. 2f) was found.

Taken together, these results suggest that HF and HF/HC animals developed biometric and biochemical alterations typical of MetS, with the HF/HC diet producing particularly pronounced effects.

3.1.2. Exposure to hypercaloric diets affected the short-term recognition memory

Here we aimed to evaluate whether exposure to a hypercaloric diet mimicking MetS could induce memory deficits in rats, with a specific focus on identifying the most affected domains. Firstly, we assessed potential alterations on short-term recognition memory by subjecting rats to the OR task. Our results showed that during both the training and testing phases, total exploration time was similar across groups, with no significant differences (training: $F_{(3,31)} = 1.906$, $p = 0.149$; test: $F_{(3,31)} = 2.408$; $p = 0.086$) (Fig. 3a–b), and no effect of the diet on the

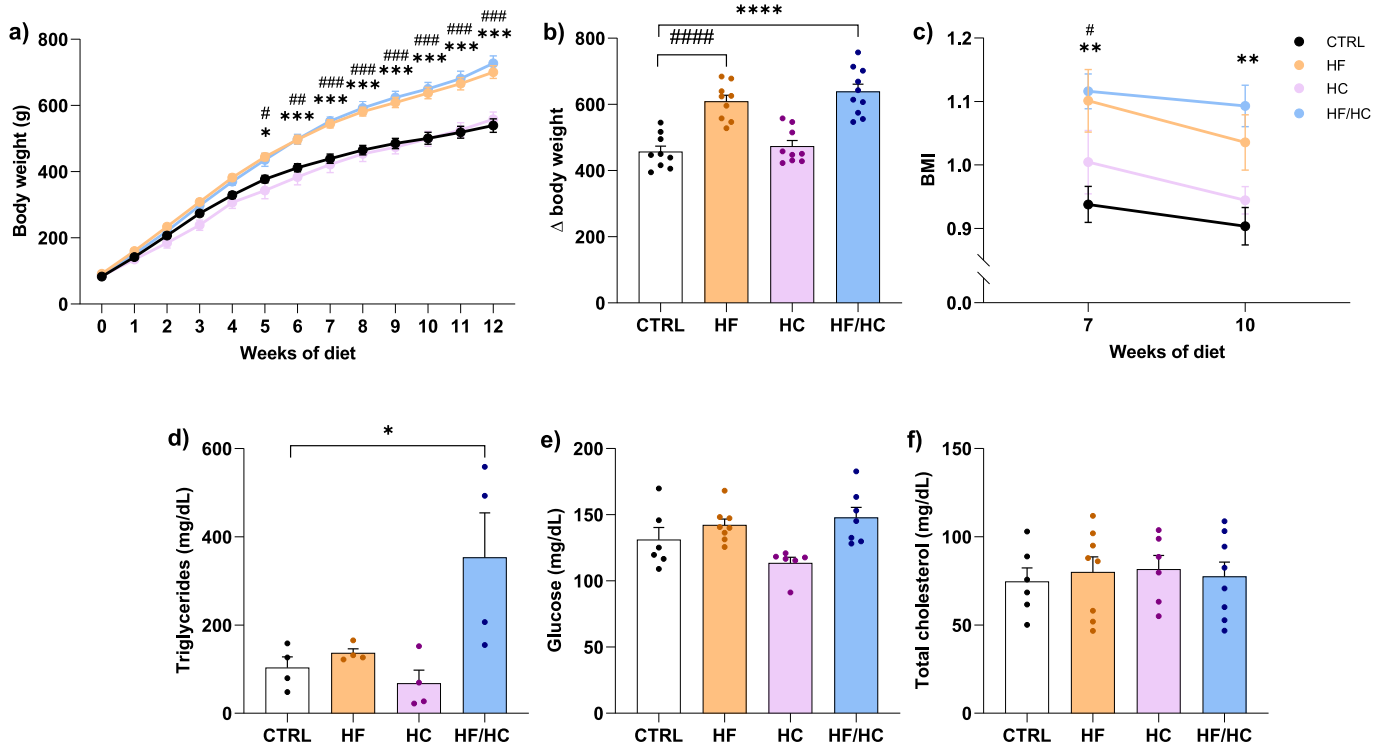

Fig. 2. Effect of hypercaloric diets on biometric and biochemical parameters. The HF and HF/HC diets induced significant differences in body weight (a) starting from the 5th week of administration, as well as in weight gain (b) and BMI (c). Moreover, the HF/HC group showed an increase of triglycerides (mg/dL) in the serum (d), but no alterations in glucose (mg/dL) (e) and total cholesterol (mg/dL) (f) levels in the serum. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; ****, $p < 0.0001$ HF/HC vs CTRL; #, $p < 0.05$; ##, $p < 0.01$; ###, $p < 0.001$; ####, $p < 0.0001$ for HF vs CTRL (for panels (a–c), CTRL, HF, HC, HF/HC groups: n = 4–6; for panels (d–f), CTRL = 9, HF = 9, HC = 9, HF/HC = 10).

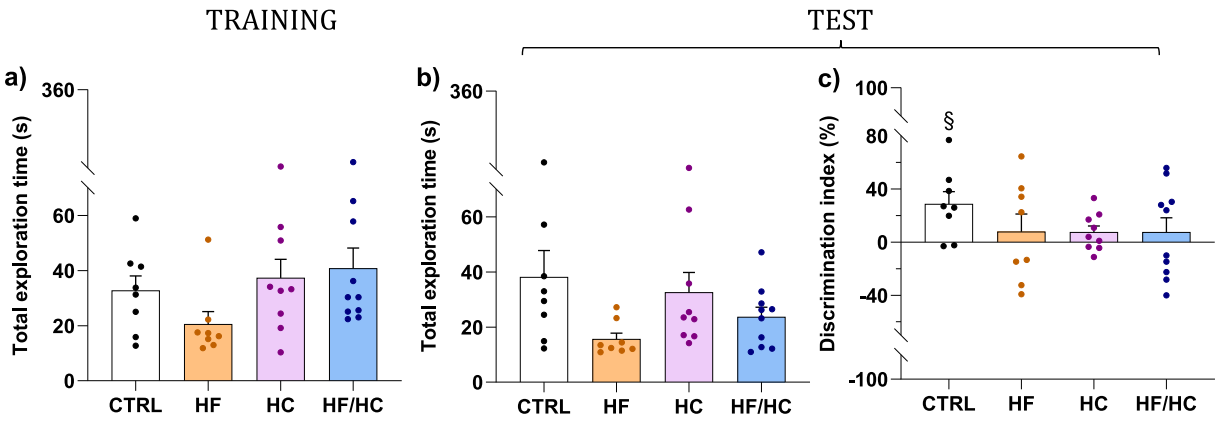

Fig. 3. Effect of hypercaloric diets on the short-term recognition memory in the OR task. All the groups showed no differences in the total exploration time (s) of the objects during the training (a) and during the test (b). Only the CTRL group discriminated between the new and old object (c), indicating the hypercaloric diets induced short-term memory deficits. §, $p < 0.05$ one-sample *t*-test vs 0 (CTRL group, n = 8; HF group, n = 8; HC group, n = 9; HF/HC group, n = 10).

discrimination index (test session) was found ($F_{(3,31)} = 1.049$, $p = 0.385$) (Fig. 3c). Moreover, we did not find any effect of the diet in locomotor activity during the training session (crossings: $F_{(3,31)} = 0.402$, $p = 0.753$; vertical activity: $F_{(3,31)} = 1.052$, $p = 0.384$) or during the test session (crossings $F_{(3,31)} = 0.616$, $p = 0.610$; vertical activity: $F_{(3,31)} = 0.802$, $p = 0.503$) (Table S1). Notably, a one-sample *t*-test against 0 revealed significance only in the CTRL group ($t_7 = 3.096$, $p = 0.017$), indicating that only these animals successfully discriminated the novel object, whereas HF, HC and HF/HC groups did not.

3.1.3. The hypercaloric diets did not cause short-term spatial memory alterations

We evaluated short-term spatial memory using the Y-maze test in animals subjected to different diets. In the Y-maze test, one-way ANOVA did not reveal any effect for the time spent (%) in the novel arm ($F_{(3,29)} = 0.487$, $p = 0.693$) (Supplementary Fig. 1a; Fig. S1a) and for the total entries in arms (locomotory activity) ($F_{(3,29)} = 1.184$, $p = 0.333$) (Fig. S1b). These results indicate that, in our model, high-calorie diets did not induce alterations in short-term spatial memory or locomotor activity in this task.

3.1.4. The HF/HC diet induced long-term spatial memory deficits

We evaluated whether exposure to hypercaloric diets affected long-term spatial memory using the MWM test. As shown in Fig. 4a, RM ANOVA for escape latency during spatial training revealed a significant effect of the training day ($F_{(2,66)} = 70.750$, $p < 0.001$), confirming that the groups progressively learned to locate the platform across the training sessions (no other statistical difference were found). Two-way ANOVA showed a significant effect for the quadrant ($F_{(1,66)} = 117.800$, $p < 0.001$), no effect for the diet ($F_{(3,66)} = 0.744$, $p = 0.530$), but an effect for the interaction quadrant x diet ($F_{(3,66)} = 6.309$, $p < 0.001$) (Fig. 4b). Tukey post hoc analysis revealed that all groups, except for the HF/HC, discriminated the target and opposite quadrants ($p < 0.001$; i.e., more time spent in the target vs opposite quadrant), indicating that the HF/HC group exhibited spatial memory retrieval deficits. Moreover, a one-sample *t*-test against 15 revealed a significant effect only in the CTRL group ($t_8 = 2.343$, $p = 0.046$), indicating that this group performed above chance level in the MWM test.

3.2. Experiment 2

Based on the findings from Experiment 1, we identified the HF/HC diet as the most effective in reproducing the metabolic and behavioral alterations commonly observed in MetS. The effects of URB597 were therefore tested on the alterations induced by this diet. To better mimic the progressive nature of MetS and the gradual emergence of memory impairments, we extended the HF/HC diet to a total duration of 20 weeks. This longer exposure allows the development of more robust and translationally relevant deficits, and provides an adequate window for a 10-week pharmacological treatment, which started after 10 weeks of diet (see Fig. 1b).

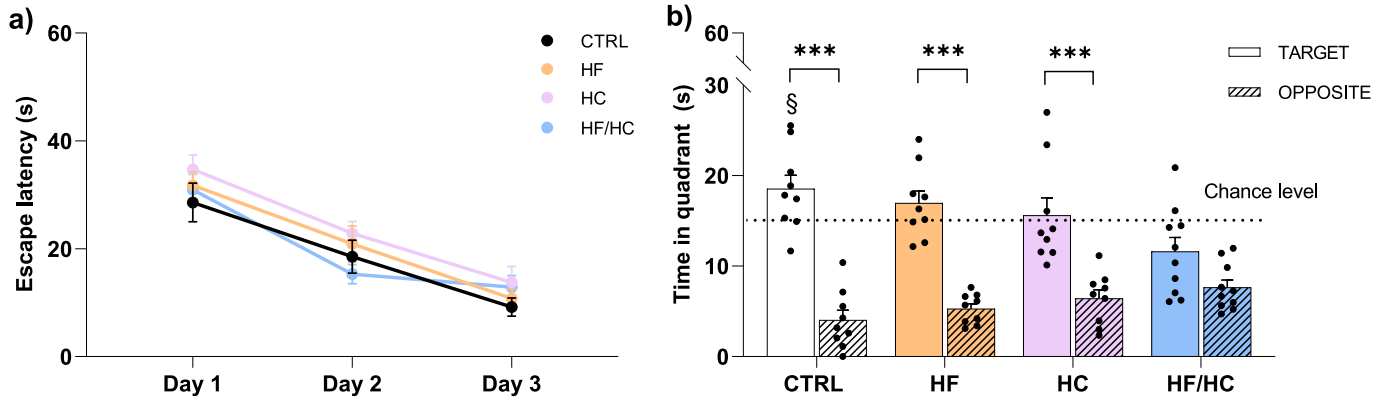

Fig. 4. Effect of hypercaloric diets on the long-term spatial memory in the MWM task. All the groups progressively learned to locate the platform across the training sessions (a). During the probe, the HF/HC group only did not discriminate between target and opposite quadrant (b), indicating an impairment of spatial memory. ***, $p < 0.001$; §, $p < 0.05$ one-sample *t*-test vs 15 (CTRL group, n = 9; HF group, n = 9; HC group, n = 9; HF/HC group, n = 10).

3.2.1. HF/HC diet-induced biometric and biochemical alterations were not reverted by chronic URB597 treatment

We aimed at investigating whether biometric and biochemical parameters altered by the HF/HC diet could be restored by chronic treatment (i.n.) with URB597. Regarding the biometric parameters (Fig. 5a), our results for the body weight showed significant effects of the diet ($F_{(1,48)} = 34.740$, $p < 0.0001$), week of treatment ($F_{(9,432)} = 437.400$, $p < 0.0001$), and interaction week of treatment × diet ($F_{(9,432)} = 24.740$, $p < 0.0001$). Post hoc analysis indicated that HF/HC-VEH rats had a significantly higher body weight compared to CTRL-VEH rats, with differences emerging at the 4th week of treatment and becoming progressively more pronounced through the 9th week ($p < 0.05$ to $p < 0.001$). HF/HC-URB597 rats exhibited an increased body weight compared to CTRL-URB597 rats, starting from the 3rd week and intensifying over time until the 9th week ($p < 0.05$ to $p < 0.001$). No differences were found between HF/HC-VEH and HF/HC-URB597 group, indicating that the diet increased the body weight, but that URB597 did not revert such effect.

Two-way ANOVA for the body weight gain (Δ) demonstrated a significant effect of the diet ($F_{(1,48)} = 32.800$, $p < 0.001$), and no significant effect of the treatment ($F_{(1,48)} = 0.759$, $p = 0.388$) or interaction between these two factors ($F_{(1,48)} = 0.014$, $p = 0.907$) (Fig. 5b). The post hoc analysis revealed that the diet induced an increase body weight gain in both HF/HC-URB597 vs CTRL-URB597 ($P < 0.0001$) and HF/HC-VEH vs CTRL-VEH ($p < 0.01$), but that URB597 did not show any reversal effect.

RM ANOVA for the BMI (Fig. 5c) demonstrated significant effects of the diet ($F_{(1,48)} = 30.440$, $p < 0.0001$) and week of treatment ($F_{(1,48)} = 6.176$, $p = 0.016$), but no significant effects of the interactions. Tukey post hoc analysis highlighted that HF/HC-VEH rats had a higher BMI comparing to CTRL-VEH before starting the treatment (i.e., 10 weeks of diet and 0 weeks of treatment; $p < 0.01$), and after 7 weeks of treatment (i.e., 17 weeks of diet; $p < 0.05$). We also found an increased BMI in HF/HC-URB597 vs CTRL-URB597 rats after 7 weeks of treatment (i.e., 17 weeks of diet; $p < 0.05$) and no differences vs HF/HC-VEH, indicating that the pharmacological treatment was not effective to counteract these alterations.

All these results demonstrated that a prolonged HF/HC diet reproduced biometric alterations, but that URB597 did not revert these effects.

RM ANOVA for the level of triglycerides showed a significant effect of the diet ($F_{(1,38)} = 18.970$, $p < 0.001$) and a significant interaction between week of treatment and diet ($F_{(1,36)} = 4.605$, $p = 0.039$) (Fig. 5d). The post hoc analysis revealed that both HF/HC -VEH and -URB597 groups exhibited higher triglyceride levels after 10 weeks of diet, and that URB597 had no effect on these metabolic parameters ($p < 0.05$). No differences were found after 20 weeks of diet.

RM ANOVA for glucose levels showed an effect of the diet ($F_{(1,20)} = 4.848$, $p = 0.040$), week of treatment ($F_{(1,20)} = 5.460$, $p = 0.030$), week of treatment x treatment ($F_{(1,20)} = 5.030$, $p = 0.036$), and week of treatment x diet x treatment ($F_{(1,20)} = 5.840$, $p = 0.025$) (Fig. 5e). RM ANOVA for total cholesterol show no effect for the diet ($F_{(1,20)} = 3.806$, $p = 0.065$), and no effect for the treatment ($F_{(1,20)} = 0.553$, $p = 0.466$), or the timepoint ($F_{(1,20)} = 0.500$, $p = 0.488$) (Fig. 5f).

These results demonstrated that the diet induces alterations only in triglycerides (post hoc $p < 0.05$), but not in glucose and cholesterol levels, despite a main effect of diet on glucose in the ANOVA. Treatment with URB597 has no effect on any of these metabolic parameters.

3.2.2. Chronic URB697 treatment counteracted short-term recognition memory deficits caused by the HF/HC diet

To evaluate whether URB597 treatment had an effect on short-term recognition memory, we subjected rats to the OR test. Two-way ANOVA

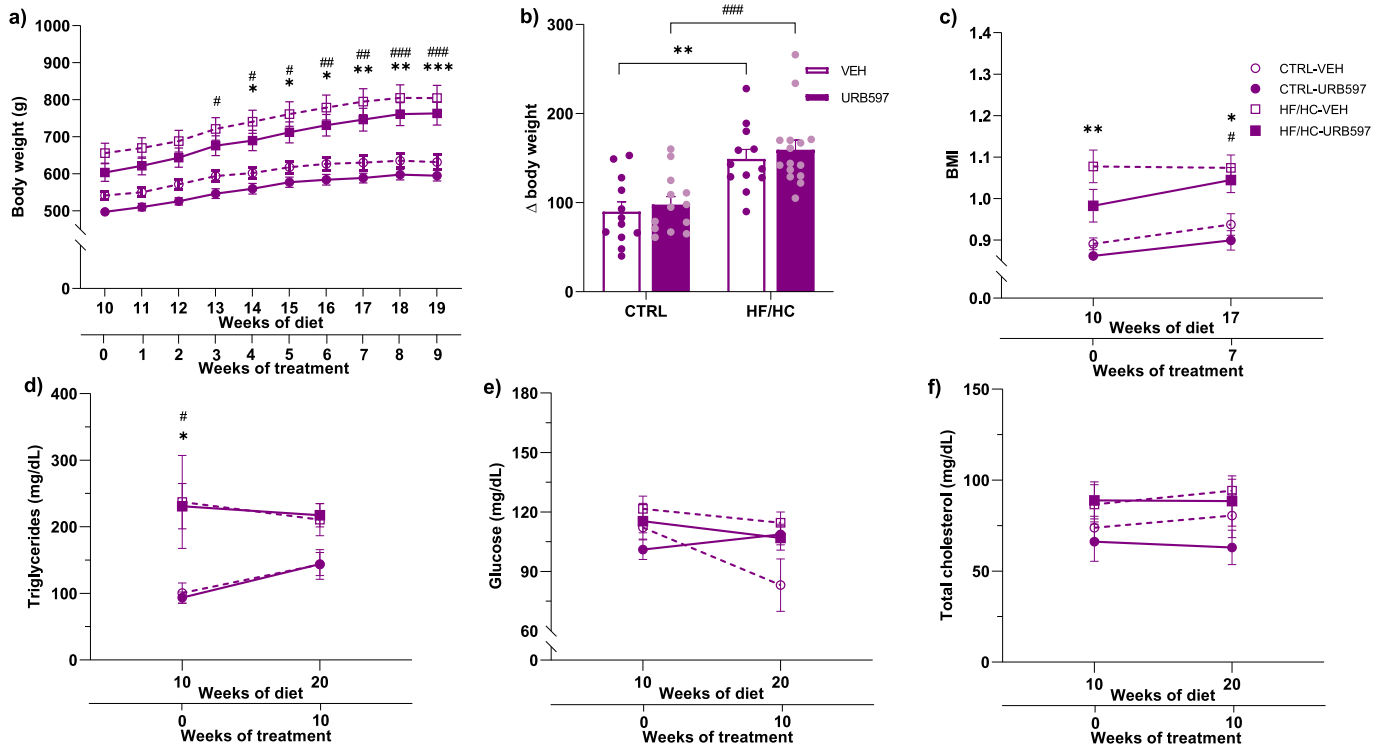

Fig. 5. Effect of chronic URB597 treatment on biometric and biochemical parameters in animals exposed to a HF/HC diet. The HF/HC diet induced differences in body weight (a), weight gain (b) and BMI (c) compared to the corresponding CTRL group, while URB597 had no effect on these biometric parameters. After 10 weeks of diet, the HF/HC diet induced an increase in triglycerides (d), but not in glucose (e) or cholesterol (f). Moreover, URB597 did not showed efficacy on any of these parameters in the serum of the animals. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$ for HF/HC-VEH vs CTRL-VEH; #, $p < 0.05$; ##, $p < 0.01$; ###, $p < 0.001$ for HF/HC-URB597 vs CTRL-URB597 (for panels (a–c)), CTRL-VEH = 6–11; CTRL-URB597 = 6–11; HF/HC-VEH = 6–9; HF/HC-URB597 = 6–11; for panels (d–f), CTRL-VEH = 12; CTRL-URB597 = 13; HF/HC-VEH = 12; HF/HC-URB597 = 15.

showed that during both the training and testing phases, total exploration time was similar across groups, with no significant differences of the diet (training: $F_{(1,38)} = 0.384$; $p = 0.539$; test: $F_{(1,38)} = 0.112$; $p = 0.739$), treatment (training: $F_{(1,38)} = 0.181$; $p = 0.673$; test: $F_{(1,38)} = 0.009$; $p = 0.924$) or interaction (training: $F_{(1,38)} = 0.009$, $p = 0.924$; test: $F_{(1,38)} = 0.406$, $p = 0.528$) (Fig. 6a–b). Moreover, we did not find any effect of diet or treatment on locomotor activity during the training session (crossings: $F_{(1,38)} = 0.560$, $p = 0.459$; vertical activity: $F_{(1,38)} = 3.158$, $p = 0.084$), while during the test session an effect of diet, but not of treatment, was observed on vertical activity ($F_{(1,38)} = 4.242$, $p = 0.046$), although post hoc comparisons revealed no significant differences between groups (crossings: $F_{(1,38)} = 0.218$, $p = 0.644$) (Table S2). Interestingly, for the discrimination index (%), we found significant effects of the diet ($F_{(1,38)} = 15.760$, $p < 0.001$) and treatment ($F_{(1,38)} = 9.756$, $p = 0.003$), and a trend toward significance for the interaction between these two factors ($F_{(1,38)} = 3.367$, $p = 0.074$) (Fig. 6c). Tukey post hoc analysis revealed that the HF/HC-VEH group did not discriminate the novel from the familiar object comparing to the CTRL-VEH group ($p < 0.01$) and that URB597 reversed this deficit (HF/HC-URB597 vs HF/HC-VEH $p < 0.05$; one-sample *t*-test vs. 0: CTRL-VEH $t_8 = 5.938$, $p < 0.001$ 0.0003; CTRL-URB597 $t_9 = 5.365$, $p < 0.001$; HF/HC-VEH $t_{10} = 1.737$, $p = 0.113$; HF/HC-URB597 $t_{11} = 2.895$, $p = 0.015$).

These results demonstrated that, firstly, the prolonged diet reproduced the recognition memory deficits found in Experiment 1, and secondly, that chronic i.n. treatment with URB597 reversed these deficits.

3.2.3. *Exposure to the HF/HC diet did not induce short-term spatial memory alterations, and treatment with URB597 had no effects*

We investigated whether prolonging the diet and URB597 treatment had effects on short-term spatial-like memory using the Y-maze test. Two-way ANOVA for the time spent in the novel arm (%) showed no significant effect for the diet ($F_{(1,46)} = 0.362$, $p = 0.550$), treatment ($F_{(1,46)} = 0.308$, $p = 0.581$), or interaction between these two factors ($F_{(1,46)} = 0.062$, $p = 0.805$) (Fig. S2a). Two-way ANOVA for the total entries in arms (locomotory activity) showed no significant effect for the diet ($F_{(1,46)} = 0.113$, $p = 0.738$), treatment ($F_{(1,46)} = 0.113$, $p = 0.738$), or interaction between these two factors ($F_{(1,46)} = 0.376$, $p = 0.543$) (Fig. S2b). These results show that the HF/HC diet did not induce short-term spatial memory deficits, even when prolonged, and that URB597 had no effect on it.

3.2.4. *Long-term spatial memory deficits induced by the HF/HC diet were not reverted by chronic URB597 treatment*

Through the MWM test, we investigated whether long-term spatial memory deficits could be reproduced with a long-term HF/HC diet and whether chronic i.n. URB597 treatment could reverse them. RM ANOVA for the escape latency during the spatial training revealed an effect of the day ($F_{(2,96)} = 60.050$, $p < 0.0001$) (Fig. 7a), confirming that the two groups progressively learned to locate the platform across the training sessions (no other statistical difference were found). Two-way ANOVA for the time spent in the quadrants during the probe test showed a significant effect of the quadrant ($F_{(1,96)} = 23.980$, $p < 0.0001$), no significant effects of the diet ($F_{(1,96)} = 1.191$, $p = 0.278$) or treatment ($F_{(1,96)} = 0.887$, $p = 0.349$), but a significant effect of the interaction quadrant x diet ($F_{(1,96)} = 9.150$, $p = 0.003$) (Fig. 7b). The post hoc analysis indicated that only CTRL-VEH and CTRL-URB597 groups were able to discriminate between the target and the opposite quadrant ($p < 0.05$).

These results suggested that a prolonged HF/HC diet induced long-term spatial memory deficits (as in the Experiment 1), but that URB597 treatment was not effective in reversing them. Moreover, a one-sample *t*-test against 15 revealed a significant effect in the CTRL-VEH ($t_{11} = 2.777$, $p = 0.018$) and CTRL-URB597 ($t_{12} = 2.953$, $p = 0.012$) groups, indicating that these groups performed above chance level in the MWM test.

4. Discussion

The present findings showed that the HF/HC diet induces marked metabolic alterations together with measurable impairments in memory performance. In this context, chronic i.n. administration of URB597, by augmenting NAE tone, effectively reversed the MetS-induced deficit in short-term recognition memory, while its effects did not extend to the long-term spatial domain.

Metabolic alterations associated with MetS can predispose individuals to cardiovascular diseases and diabetes [56], but they can also contribute to cognitive and memory impairments [6,57,58]. However, there is no clear consensus on the relationships between MetS and cognitive health [6,57,59]. Given the multifactorial nature of MetS, identifying an experimental model that reliably captures its human pathophysiology remains challenging.

Exposure to CTRL, HF, HC, or combined (HF/HC) diet, revealed that both the HF and combined (HF/HC) diets resulted in increased body weight and BMI but, only the HF/HC diet induced a rise in triglyceride levels, indicating that this combined regimen was the most effective in

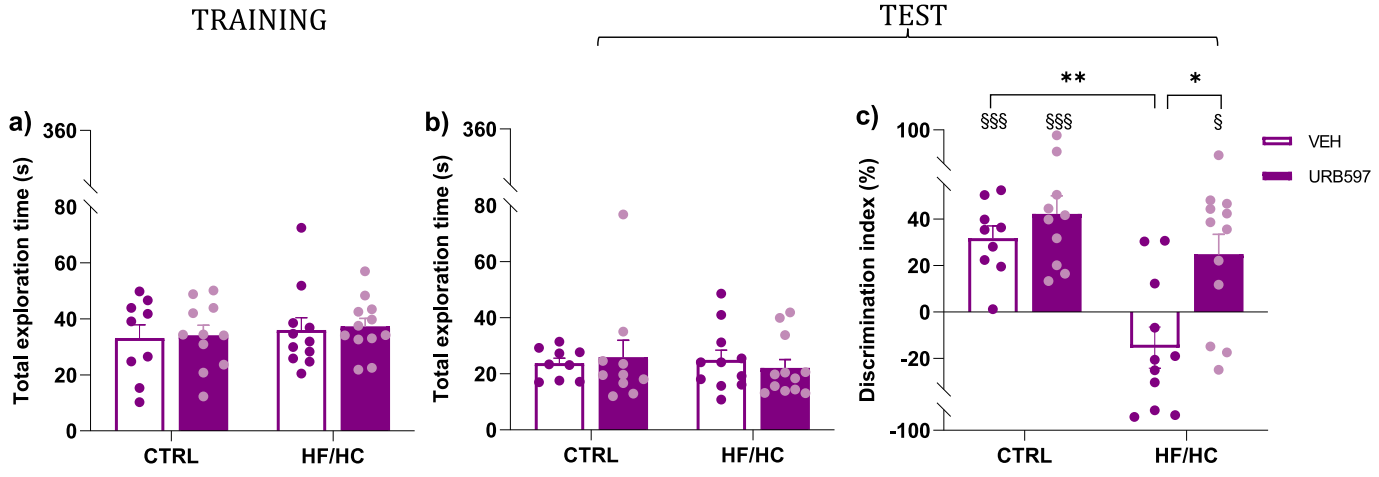

Fig. 6. Effect of chronic URB597 treatment on the short-term OR memory in animals exposed to a hypercaloric diet. All the groups did not show differences in the total exploration time during the training (a) and during the test (b). The HF/HC diet induced a decrease in the discrimination index (%), indicating a deficit in the short-term recognition memory, which was reverted by the chronic i.n. treatment with URB597 (c). *, $p < 0.05$; **$p < 0.01$; §, $p < 0.05$; §§§, $p < 0.001$ vs 0 (CTRL-VEH group, n = 9; CTRL-URB597 group, n = 10; HF/HC-VEH group, n = 11; HF/HC-URB597 group, n = 12).

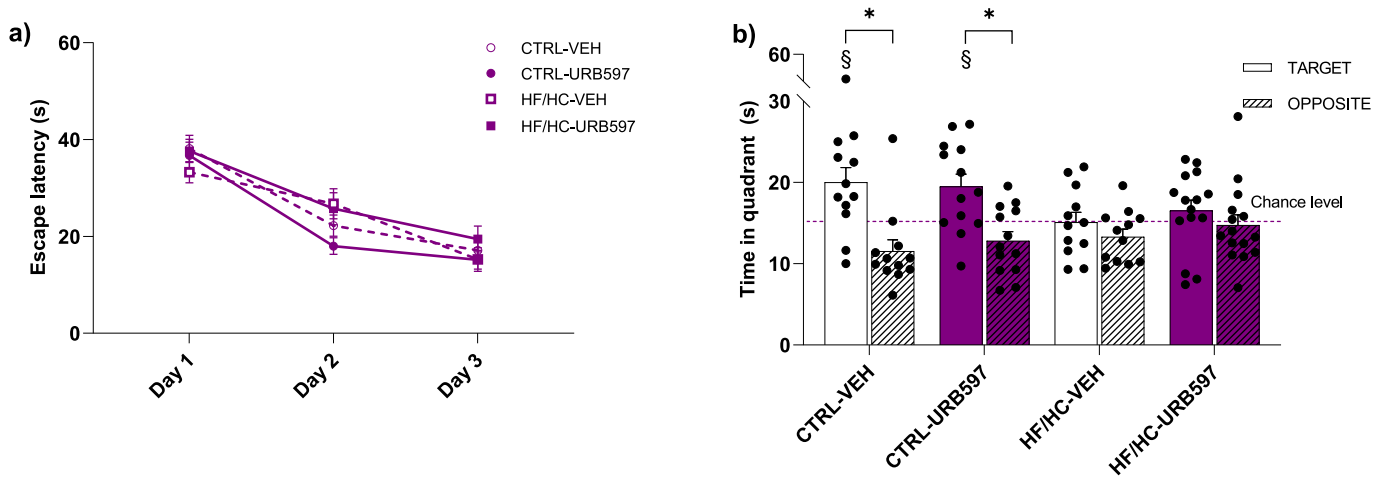

Fig. 7. Effect of chronic URB597 treatment on the long-term spatial memory in animals exposed to a hypercaloric diet. All the groups progressively learned to locate the platform across the training sessions (a). The HF/HC-VEH group showed spatial memory deficits tested 24 h after the last training session and it was not reverted by the URB597 treatment (b). *, $p < 0.05$; §, $p < 0.05$ one-sample *t*-test vs 15 (CTRL-VEH group, n = 12; CTRL-URB597 group, n = 13; HF/HC-VEH group, n = 12; HF/HC-URB597 group, n = 15).

triggering marked biochemical alterations. Metabolic dysfunction induced by hypercaloric diets may affect cognitive performance through several neurobiological mechanisms. Hypercaloric diets have been shown to promote oxidative stress, neuroinflammation, and insulin resistance in brain regions involved in memory processing, including the hippocampus and perirhinal cortex, ultimately disrupting synaptic plasticity and impairing both spatial and recognition memory processes [54,60]. At first glance, the absence of changes in glucose or cholesterol levels may seem inconsistent. Nevertheless, our findings are in line with previous reports showing that Sprague–Dawley rats fed a sucrose-rich diet do not necessarily exhibit weight gain or alterations in fasting glucose [61]. This apparent discrepancy may be explained by direct central neurotoxic effects, independent of peripheral metabolism. Dietary manipulation, particularly carbohydrate-enriched diets, can rapidly induce alterations in the central nervous system (e.g., neuroinflammation, oxidative stress, and brain insulin resistance). These effects may occur independently of, or even precede, peripheral metabolic changes. The HC diet may exert direct neurotoxic effects that impair recognition memory even when systemic metabolic parameters remain comparable to controls. In addition, several studies have noted that rodents can develop a form of resistance to cholesterol changes when exposed to HF diets, which may limit the detectability of hypercholesterolemia in this model [62,63].

A review by Brown and Panchal [64] highlighted that the dietary regimen most closely reproducing the metabolic criteria of human MetS in rats is the combined HF/HC diet. However, the authors also emphasized the need for additional studies to better characterize the associated memory alterations in both humans and animal models. Some studies have found a strong effect of hypercaloric diets on recognition memory [65–67], others suggest that recognition memory, compared to spatial memory, may be less sensitive to the deleterious effects of the diet [68]. This could depend on various factors, including the composition of the diet and/or the duration of its administration [60,69,70]. In our study, animals exposed to a hypercaloric diet exhibited a mild impairment in recognition memory after 8 weeks. Regarding long-term spatial memory, HF/HC animals showed impaired discrimination between the target and opposite quadrants, indicating a deficit in coarse spatial memory. In contrast, platform crossings and escape latency were not significantly altered, a dissociation suggesting that quadrant occupancy reflects general spatial bias whereas platform crossings capture fine spatial precision and may be less sensitive to subtle impairments. From a translational perspective, this pattern may reflect a selective impairment in allocentric navigation strategies, while more procedural or egocentric strategies remain relatively preserved, as reported in human virtual MWM studies [71,72]. These findings suggest that long-term spatial memory may be particularly sensitive to the early effects of a hypercaloric diet. This interpretation is consistent with the well-established vulnerability of the hippocampus - crucial for spatial navigation [73] - to metabolic disturbances [74–76]. High-caloric diets can induce neuroinflammation, oxidative stress, and insulin resistance, all of which detrimentally affect hippocampal function [77]. Studies have demonstrated that rodents consuming such diets exhibit significant deficits in hippocampal-dependent tasks, including spatial memory assessments [11,78,79]. In humans, habitual intake of HF and high-sugar diets correlates with poorer performance in spatial memory tasks, suggesting a similar underlying mechanism [80–83]. Interestingly, short-term spatial memory assessed in the Y-maze was preserved in our model. This pattern underscores the need to better elucidate the neurobiological mechanisms underlying MetS-related memory alterations and the temporal progression of metabolic damage in the brain, particularly in light of the differential vulnerability of distinct regions. Unlike long-term memory, which requires prolonged synaptic modifications, short-term spatial memory depends on transient neural activation and short-lived synaptic changes [84], probably making it less susceptible to early metabolic dysfunction. It is also possible that metabolic disturbances gradually impair hippocampal synaptic plasticity, leading to deficits primarily in tasks that require memory retention over longer time intervals, such as the MWM [85,86]. The pattern observed in Experiment 1, where long-term spatial memory was altered, whereas the short-term one remained preserved, suggests that early metabolic insults may not be sufficient to fully disrupt multiple memory domains. Importantly, the Experiment 1 allowed us to compare different hypercaloric regimens (HF, HC, and their combination) and to identify the HF/HC diet as the most effective in inducing the metabolic and behavioral alterations relevant to MetS.

Thus, in Experiment 2 we adopted a more prolonged regimen (20 weeks), which allowed us to model the chronic nature of MetS and provided a 10-week window for therapeutic intervention. By initiating URB597 treatment after 10 weeks of diet—when deficits were already established—we tested a therapeutic reversal paradigm with greater translational relevance for clinical populations.

Our results showed that prolonged exposure to the HF/HC diet produced biometric and memory alterations similar to those observed in Experiment 1, without further exacerbation with longer diet duration. Although the HF/HC diet increased triglyceride levels after 10 weeks of diet exposure (before treatment initiation), this effect was not

maintained after 20 weeks (following 10 weeks of treatment). A blunted triglyceride response at later stages has been reported in other models and may reflect a metabolic adaptation to sustained hypercaloric intake [87], combined with the physiological rise in triglycerides that accompanies aging [88,89]. Moreover, hypertriglyceridemia shows substantial inter-individual variability in rodents, and increases are not consistently observed in Sprague–Dawley rats even under robust hypercaloric protocols [90]. Thus, the absence of a further increase at 20 weeks is consistent with previous observations and supports the notion that triglycerides may not be a reliable late-stage marker of metabolic burden in this strain.

Thus, here we aimed to investigate whether treatment with URB597 could reverse MetS-related memory impairments once they had emerged. URB597 irreversibly inhibits the FAAH enzyme, which breaks down NAEs such as AEA, OEA, and PEA, resulting in an increased tone of these bioactive lipids [41]. Importantly, Giacovazzo et al. (2019) [50] demonstrated that i.n. administration of URB597 produces a robust inhibition of FAAH activity in the brain, achieving levels comparable to those obtained with parenteral delivery, without significantly affecting systemic NAE levels.

Beyond its pharmacodynamic efficacy, i.n. administration offers several advantages that make it particularly suitable for chronic conditions such as MetS. This route enables non-invasive and repeated delivery directly to the central nervous system, avoids first-pass hepatic metabolism, and can improve the bioavailability of lipid-based compounds—features that are especially relevant for FAAH inhibitors [91,92]. In the present study, we demonstrated that URB597 reversed recognition memory deficits induced by MetS, whereas it did not improve spatial memory deficits. We hypothesize that the neuroprotective and anti-inflammatory effects of this compound as well as its role in improving memory [17,20,45,48], may have contributed to reversing the recognition memory deficits. Specifically, the selective efficacy of URB597 on recognition memory may involve multiple mechanisms. The OR task relies on both the perirhinal cortex and the hippocampus, with the perirhinal cortex playing a dominant role [93]. In contrast, spatial memory is primarily hippocampus-dependent and is more vulnerable to extensive hippocampal dysfunction. For example, a study by Broadbent and colleagues (2004) [94] found that OR memory remained intact after lesions to the dorsal hippocampus that damaged 50–75% of the hippocampal volume, with impairment occurring only after larger lesions affecting 75–100% of the hippocampal volume. This indicates that spatial memory performance requires a larger portion of hippocampal integrity compared to recognition memory [95]. We therefore speculate that, in our model, prolonged HF/HC diet primarily affects the perirhinal cortex and hippocampal circuits in a manner that compromises recognition memory and long-term spatial memory. This differential circuit vulnerability may also explain why URB597 was effective in reversing recognition memory deficits but did not improve long-term spatial memory or alter short-term spatial memory performance. For instance, Jankovic et al. (2022) [96] reported that chronic administration of URB597 improved short-term recognition memory in stressed male rats tested in the OR test. Specifically, URB597 has been shown to modulate catecholaminergic signaling within the medial prefrontal cortex, by restoring β_2-adrenergic and dopamine type 1 (D1) receptor expression, thereby promoting long-term potentiation and positively influencing working memory, as well as memory consolidation and retrieval. These findings suggest that the beneficial effects of URB597 on recognition memory may involve, at least in part, modulation of catecholaminergic pathways within prefrontal circuits sensitive to endocannabinoid and stress-related signaling. Another potential mechanism, highlighted by Zer-Aviv and Akirav (2016) [97], suggests that the effects of URB597 are primarily mediated by prefrontal rather than hippocampal circuits, through normalization of stress-induced CB1 receptor upregulation. Beyond CB1 receptor signaling, URB597 may exert additional effects through elevated AEA acting at CB2 receptors expressed on microglia [98], therefore contributing to anti-inflammatory actions, as well as through increased OEA and PEA levels that activate PPARα and PPARγ, regulators of genes involved in synaptic plasticity and neuroinflammation. However, these remain speculative, as the present study did not assess the involvement of specific brain regions; therefore, future investigations are needed to clarify the neural substrates underlying these effects.

Overall, this study provides the first evidence that enhancing endocannabinoid tone can restore recognition memory once deficits have emerged. Given the treatment resistance observed in advanced MetS, it is crucial to identify the 'point of no return' in metabolic and cognitive decline. These findings underscore the need for early interventions, combining pharmacological strategies with public health initiatives to prevent irreversible impairments.

5. Limitations

This study has several important limitations. First, the use of only male rats limits generalizability, as sex differences influence both metabolic syndrome and cognitive outcomes. Given the difficulty of modeling metabolic syndrome in females, males were chosen to minimize animal use in line with the 3Rs and reduce potential confounding variables.

Second, the lack of neuroinflammatory or mechanistic measures restricts interpretation. Third, the fixed timing of treatment initiation may not correspond to the most effective therapeutic window. Finally, food intake and glucose and insulin tolerance tests were not assessed in this study and will be addressed in a follow-up study.

CRediT authorship contribution statement

Benedetta Di Cesare: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Giulia Federica Mancini:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Martina Parente:** Methodology, Investigation, Formal analysis. **Edoardo Pisa:** Methodology, Investigation, Formal analysis, Data curation. **Luca Romanelli:** Validation, Methodology, Investigation, Formal analysis, Data curation. **Clemens Zwergel:** Methodology, Investigation, Formal analysis. **Antonello Mai:** Validation, Methodology, Investigation, Data curation. **Maria Morena:** Validation, Supervision, Formal analysis, Data curation, Conceptualization. **Valentina Pallottini:** Validation, Formal analysis, Data curation, Conceptualization. **Caterina Scuderi:** Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Simone Macrì:** Writing – review & editing, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Patrizia Campolongo:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization.

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Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lfs.2026.124445.

Data availability

Data will be made available on request.

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