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Research Paper

Effect of monosodium glutamate-induced obesity on anxiety-like behavior and the possible protective role of L-carnitine

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ABSTRACT

Obesity and excessive weight gain have emerged as significant global health concerns in recent years and are often comorbid with numerous contemporary diseases, including cardiovascular disorders, diabetes, and cognitive impairments. L-carnitine, a vital cofactor in mitochondrial energy metabolism, possesses potent antioxidant and anti-inflammatory properties that merit investigation for mitigating obesity-associated neuronal damage. Consequently, this study investigated the potential neuroprotective effects of L-carnitine on anxiety- and depression-like behaviors in adolescent rats subjected to neonatal monosodium glutamate (MSG) exposure, a model known to induce obesity and associated neurobehavioral alterations. Neonatal rats received MSG (4 g/kg, s.c.) on alternate postnatal days (PND) 2–10. Subsequently, L-carnitine (200 mg/kg) was administered via oral gavage daily from PND 60 to 81 (subchronic treatment). Anxiety- and depression-like behaviors were assessed using the Forced Swim Test (FST), Elevated Plus Maze (EPM), and Open Field Test (OFT). All molecular and histological analyses were conducted in the prefrontal cortex (PFC), a region selected for its susceptibility to excitotoxicity and critical role in emotional regulation. Oxidative stress was evaluated through measurements of total oxidant and antioxidant levels. To elucidate the underlying molecular mechanisms, gene expression analyses focused on neuronal survival and apoptosis (BDNF, Bax, Bcl-2), while immunohistochemical evaluations targeted neuroinflammation and cell death pathways (TNF-α, Caspase-3, IL-1β, and Bcl-2). The findings reveal that neonatal MSG exposure leads to pronounced anxiety- and depression-like behaviors, accompanied by metabolic dysregulation, oxidative stress, neuroinflammation, and apoptosis. Although L-carnitine treatment did not reverse obesity-related metabolic alterations, it exhibited notable sustained anxiolytic effects. The neuroprotective potential of L-carnitine was further supported by its ability to reduce cortical neuroinflammation and neurodegerenative damage through suppression of proinflammatory cytokines and restoration of antioxidant balance. Overall, this study offers valuable insights into the cognitive, genetic, and histological outcomes associated with obesity-related mood disturbances and contributes to understanding the complex biological mechanisms underlying these conditions.

1. Introduction

Obesity, a major global health issue, is characterized by excessive fat accumulation and disruption in energy homeostasis. It is associated with serious complications involving metabolic, hormonal, and cognitive dysfunctions, all of which negatively impact quality of life [1]. A widely used animal model for studying these complications is monosodium glutamate (MSG)-induced obesity. MSG, typically used as a flavor enhancer, causes selective damage to the arcuate, preoptic, and ventromedial regions of the hypothalamus when administered to neonatal experimental animals, leading to neuroendocrine-type obesity [2]. Furthermore, these hypothalamic dysfunctions result in severe metabolic disturbances, including glucose intolerance, hyperinsulinemia, and insulin resistance. However, the neurotoxic effects of

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MSG are not limited to the hypothalamus. It is known that systemic MSG administration induces excitotoxicity in extra-hypothalamic regions rich in glutamate receptors, most notably the hippocampus and the PFC. While the hypothalamus regulates energy balance and the hippocampus controls memory processes, the PFC plays a critical role in the regulation of emotional responses and cognitive flexibility. These regions are highly susceptible to MSG-induced oxidative stress, inflammation, and apoptosis, which are key drivers of behavioral dysfunctions. Therefore, investigating alterations specifically in the PFC, in conjunction with the known impacts on the hypothalamus and hippocampus, is essential for understanding the pathophysiology of anxiety- and depression-like behaviors associated with obesity [3–5]. In this context, MSG exposure can contribute to neurochemical imbalances and behavioral disorders in adulthood. Specifically, disruptions in neurotrophin systems, such as brain-derived neurotrophic factor (BDNF), contribute to the development of anxiety-like behaviors and cognitive deficits [6,7]. MSG-induced neurotoxicity is associated with increased lipid peroxidation and neuronal degeneration [6,8,9]. Considering the relationship between obesity, central nervous system dysfunction, and neuroinflammation, identifying any neuroprotective intervention that could mitigate behavioral disorders following early-life metabolic damage is becoming increasingly important.

Regarding potential therapeutic agents, L-carnitine is a physiologically active, non-essential amino acid primarily found in animal meat and dairy products, though it is also endogenously synthesized in the liver, kidneys, and brain [10–12]. It is known that L-carnitine is indispensable for the mitochondrial β-oxidation of fatty acids and ATP production. Moreover, L-carnitine and its esters can cross the blood-brain barrier, playing critical roles in lipid metabolism, antioxidant defense, and neurotransmission [12]. Possessing strong antioxidant, anti-inflammatory, and anti-apoptotic properties, L-carnitine has demonstrated neuroprotective effects in brain injury models involving hypoxia-ischemia, as well as in neurodegenerative conditions such as Alzheimer's disease, primarily by mitigating oxidative damage and enhancing mitochondrial function [13,14]. Furthermore, supplementation has been reported to alleviate anxiety-like behaviors and improve cognitive function in models of Alzheimer's disease and metabolic syndrome. However, a critical review of these studies reveals methodological and regional differences compared to the present work. Specifically, Tork et al. [12] and Alzoubi et al. [15] primarily investigated histological alterations and antioxidant enzyme activities within the hippocampus (notably the dentate gyrus) following intraperitoneal administration for 4 to 6 weeks. Similarly, da Silva et al. [13] reviewed metabolic effects predominantly in the hypothalamus and hippocampus, noting that oral supplementation protocols typically ranged from weeks to months. Moreover, while Koohpeyma et al. [14] demonstrated the antioxidant efficacy of L-carnitine in MSG-treated rats following a long-term (6-month) oral gavage regimen, their analysis was restricted to testicular tissue, without evaluating the central nervous system. Additionally, Ferreira and McKenna [16] discussed metabolic shifts in the hippocampus and cortex resulting from variable protocols ranging from acute administration to 25 days of supplementation [12–16].

Consequently, the specific neuroprotective efficacy of L-carnitine against MSG-induced inflammation, apoptosis, and anxiety-related pathology in the PFC has not been fully elucidated. To elucidate the molecular mechanisms underlying MSG-induced neurotoxicity and the potential protective effects of L-carnitine, specific markers of neuroplasticity, apoptosis, and inflammation were evaluated. Brain-derived neurotrophic factor (BDNF) is a critical protein for neuronal survival, growth, and synaptic plasticity [6,17]. In the regulation of programmed cell death (apoptosis), Bcl-2 functions as a key anti-apoptotic protein that promotes cell survival [18], whereas Bax acts as a pro-apoptotic effector; the ratio of these two proteins determines cell fate. Caspase-3 serves as the primary executioner enzyme in the apoptotic cascade, leading to neuronal death. Additionally, Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-1 beta (IL-1β) were assessed as major pro-inflammatory cytokines that mediate neuroinflammatory responses in the brain [19]. Accordingly, the present study investigates the impact of neonatal MSG exposure on anxiety- and depression-like behaviors in adolescent rats and evaluates the potential neuroprotective effects of L-Carnitine supplementation.

2. Material and methods

2.1. Animals

This study was carried out with 35 male rat offspring obtained from 12 female Wistar albino pregnant rats provided by Kırşehir Ahi Evran University Experimental Animals Unit. Male rats were specifically selected to avoid the confounding influence of the estrous cycle on behavioral responses and metabolic parameters. Breeding rats were acclimated to the laboratory environment, one week prior to the onset of experiments. Female rats were housed with male rats (F:M = 2:1 per cage) and pregnancy was determined by the presence of a copulation plug (GD0). Subsequently, twelve female Wistar albino rats at gestation day 0 were housed under controlled conditions, with three rats per standard cage. As parturition approached, females with one-day remaining were transferred to individual cages to ensure accurate monitoring. Throughout the study, animals were maintained under standardized laboratory conditions: relative humidity of 50 ± 5%, ambient temperature of 22 ± 2 °C, and a 12 h light/dark cycle (lights on at 07:00). Rats had ad libitum access to standard chow and tap water. The composition of the chow included: crude protein 23.5%, crude fat 3.15%, crude ash 4.91%, crude fiber 4.96%, and added minerals 3.13%. All dams delivered naturally. The number of pups born and their birth weights were recorded. The study protocol was approved by the Kırşehir Ahi Evran University Animal Experiments Ethics Committee (HADYEK approval, dated 24/04/2024, 68429034/22-08-5). All procedures were conducted in accordance with institutional guidelines for animal welfare, with efforts made to minimize animal use and ensure ethical care.

2.2. Experimental procedure

Newborn rats in the MSG group received subcutaneous (s.c.) injections of monosodium glutamate (MSG) at a dose of 4 g/kg body weight, dissolved in normal saline, on alternate days specifically on postnatal days (PND) 2, 4, 6, 8, and 10. In contrast, pups in the sham group were given subcutaneous injections of 0.9% saline at a volume of 0.1 ml on the same PND [20]. The pups remained with their mothers until weaning day, PND21, and then the rats were housed in groups of four in individual cages with a standard diet. On days PN60–81, rats in the carnitine and MSG + Carnitine groups were given L-carnitine at a dose of 200 mg/kg. The rats were randomly divided into five groups ($n = 7$ per group), as follows: Healthy rats (control group), Sham group (given 0,1 mL saline), MSG group (given MSG (s.c) 4 g/kg) [8], Carnitine group (given L-carnitine 200 mg/kg - PN60-81) [14], MSG + Carnitine group (given MSG (s.c) 4 g/kg, PN2-10 and L-carnitine 200 mg/kg PN60-81). MSG (monosodium glutamate, Sigma, Almanya; CAS #:6106-04-3) and Carnitine (L-carnitine, Sigma, Almanya; CAS#: 541-15-1) were acquired from Sigma. The animals' weights were weighed weekly. Blood glucose levels of rats were measured post-fasting on PND59 and PND81 using a BG meter (Accu-Check Active™, Roche).

2.3. LEE index

The Lee index was calculated by measuring the naso-anal length and body weight of the rats on PND 59. The Lee index was used to evaluate the growth performance and the development of obesity in rats. The index was calculated with the following formula: $\sqrt[3]{(\text{Body weight (g)})}/\text{Snout-anus length (cm)}$. A score of ≥ 0.3 was used as the criterion for rats to be considered obese [21].

3. Behavioral tests

3.1. Open field test (OFT)

On PND82, rats were subjected to the open field test. The open field box consisted of a square arena made of matte black Plexiglas, with a base of 60 × 60 cm and walls 40 cm in height. The base of the box was divided into 16 equal squares arranged in a 4 × 4 grid. The four central squares are represented the center zone, while the 12 squares adjacent to the walls are defined as the peripheral zone. Each experimental animal was gently placed at the center of the box and observed for 5 min to explore the environment. OFT were recorded by a video recorder and were analyzed by using the ANY-maze software version 7.4 (Stoelting Co., Wood Dale, IL, USA). More anxious animals typically spend significantly less time in the central area and more time near the walls. Furthermore, the total distance traveled was analyzed as locomotor activity parameters [21].

3.2. Elevated plus maze (EPM)

The Elevated Plus Maze (EPM) was used to assess anxiety-like behavior and was conducted on PND82. A black plexiglas maze (each 50 cm × 10 cm) consists of four plus-shaped arms: two open arms, two enclosed arms (50 cm height), and a central platform (10 cm x10 cm), which was elevated 50 cm above the floor. Rats were placed in one of the open arms facing the center of the apparatus and allowed to explore freely for 5 min. Behavioral tests were recorded by a video recorder and were analyzed by using the ANY-maze software version 7.4 (Stoelting Co., Wood Dale, IL, USA). Time spent in open arms and the number of entries into open arms were recorded to assess anxiety-like behavior. To remove any confounding olfactory cues, the maze was carefully cleaned with 70% ethanol and dried with tissue paper after each test [22].

3.3. Forced swim test (FST)

The forced swim test (FST) was conducted over two days/sessions following the procedure described by Porsolt et al. [23]. On PND83, during the first session, each rat was individually placed in an open cylindrical Plexiglas container (45 cm in height × 20 cm in diameter) filled with 30 cm of water maintained at 25 ± 1 °C, and allowed to swim for 15 min. After the first session, the animals were dried, returned to their home cages, and warmed using a heat lamp. The second session, a 5 min test trial, was conducted 24 h later on PND84. During the second session, rats were reintroduced into the same plexiglas container, and their immobility time was recorded using a video recorder and analyzed with ANY-maze software version 7.4 (Stoelting Co., Wood Dale, IL, USA). A rat was considered immobile when it remained floating without struggling, making only the minimal movements necessary to keep its head above the water surface. The FST protocol was considered for determining the effects on depression-like behavior. Immediately following the FST, the animals were dried and then decapitated on the same day (PND 84) for tissue collection.

3.4. Biochemical and molecular measurement

Following the behavioral tests (PND84), the rats were anesthetized with ketamine (80 mg/kg, i.p.) and xylazine HCl (10 mg/kg, i.p.). After anesthesia, blood samples were collected intracardially, and the animals were subsequently decapitated. The brain tissue was rapidly dissected on a large glass plate placed on ice. The right PFC was fixed in 10% formaldehyde for histopathological evaluation, while the left PFC was stored at −80 °C for biochemical analyses and rt-PCR experiments. The dissection specifically targeted the PFC, corresponding to the anatomical coordinates approximately +2.7 to +4.7 mm anterior to Bregma, according to the rat brain atlas of Paxinos and Watson [24].

3.5. Plasma insulin measurement

Plasma insulin concentrations were determined using a commercially available ELISA kit (Elabscience, catalog no. E-EL-R3034) based on the Competitive-ELISA principle. Briefly, micro-ELISA plates precoated with insulin were incubated with plasma samples and standards. During the reaction, insulin present in the samples competed with the fixed amount of plate-bound insulin for binding sites on the biotinylated detection antibody specific to insulin. After washing to remove excess conjugate and unbound components, avidin conjugated to horseradish peroxidase (HRP) was added to each well and incubated. Subsequently, tetramethylbenzidine (TMB) substrate solution was introduced, and the enzyme-substrate reaction was terminated by the addition of stop solution. The resulting color change was measured spectrophotometrically at 450 nm (±2 nm) (BIO-TEK EL X 800-Aotu strip washer:BIO TEK EL X 50). Insulin concentrations in the samples were calculated by comparing the optical density (OD) values to the standard curve.

3.6. Plasma glucose measurement

Plasma glucose levels were measured using an enzymatic colorimetric assay based on the Trinder reaction (Otto Scientific, catalog no. OttoBC142). In this method, glucose oxidase catalyzes the oxidation of glucose to gluconic acid and hydrogen peroxide. The generated hydrogen peroxide reacts with phenol and 4-aminoantipyrine in the presence of peroxidase to form a red quinoneimine dye. The intensity of the color produced is directly proportional to the glucose concentration and was quantified spectrophotometrically (MINDRAY-BS400). Results were expressed in mg/dL.

3.7. Total antioxidant status (TAS) and total oxidant status (TOS) measurement

To assess total oxidant status (TOS) and total antioxidant status (TAS), 0.1 g of tissue was homogenized in 0.9 mL of 140 mmol KCl buffer (Otto Scientific, Cat. No. OttoC1983). The homogenates were then centrifuged at 7000 rpm for 5 min at 4 °C using a refrigerated centrifuge. The supernatant was collected. According to the manufacturer's instructions, TAS and TOS levels were measured using commercially available colorimetric assay kits (Rel Assay, Cat. No. RL0017 for TAS and RL0024 for TOS).

The TAS assay is based on the ability of antioxidants in the sample to reduce ABTS (2,2′-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)) radicals, with results expressed as mmol Trolox equivalent per liter (mmol Trolox equiv/L). The TOS assay relies on the oxidation of ferrous ion to ferric ion in an acidic medium, forming a colored complex with xylenol orange. The intensity of the color, measured spectrophotometrically, is directly proportional to the total oxidant molecules in the sample. The assay was calibrated using hydrogen peroxide, and the results were expressed as micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 equiv/L).

3.8. Real-time PCR analysis

Quantitative real-time PCR (qRT-PCR) was performed to assess the expression levels of Bax, Bcl-2, and BDNF genes. Primer sequence of specific genes was given in Table 1. Total RNA was isolated according to manufacturers' protocol using RNeasy Mini Kit (Qiagen, Germany) and quantified using a spectrophotometer (Jenway, Genova-Nano, Cole-Parmer, US). Extracted RNA was reverse transcribed to cDNA using Revertaid FS cDNA Synthesis Kit (Thermo Fisher Scientific, US). qPCR analysis was performed using PowerUp SYBR Green Master Mix (Applied Biosystems, USA) in QuantStudio 5 Real Time PCR System, Applied Biosystems instrument with QuantStudio Real Time PCR Software Version 1.2 software. All reactions were performed in triplicate.

Table 1
Primer sequences for real-time PCR assays.

Gene	Forward primers	Reverse primers
β- Actin	5′-ATTCATGGATGATGATATCGCCG-3′	5′-GAGCTAGAAGCATTTGCGGTG-3′
BDNF	5′-GTGATGACCATCCTTTTCCT-3′	5′-CAAATGTGTCATCCAAGGA-3′
Bax	5′-GGATGCGTCCACCAAGAAGCT-3′	5′-TCCGTGTCCACGTCAGCAATC-3′
Bcl-2	5′- CTGTGGATGACTGAGTACCTG-3′	5′-AGCCAGGAGAAATCAAACAGAG-3′

ACT-β was used as houskeeping gene. Comparative CT method ($2^{-\Delta\Delta Ct}$) was performed to analyses the results. For molecular assays, 3 representative tissue samples were randomly selected from each group ($n = 3$).

3.9. Histopathological evaluation

To evaluate histopathological changes, tissue samples from the right prefrontal cortex (PFC) were fixed in 10% neutral buffered formalin for 72 h. Following fixation, tissues were washed under running water to remove the fixative. The samples underwent routine histological processing, which included dehydration through a graded series of ethanol, clearing in xylene, and embedding in paraffin wax. Tissue sections of 5 μm thickness were cut using a rotary microtome and mounted on glass slides. The sections were stained with Hematoxylin & Eosin (H&E) for general morphological assessment and Toluidine Blue (TB) to evaluate neuronal degeneration. Following the staining procedures, the slides were dehydrated, cleared in xylene, and mounted using Entellan covering medium. The prepared slides were examined and photographed under a light microscope (Nikon Eclipse Si, Tokyo, Japan).

3.10. Immunohistochemical evaluation

The approach was carried out to evaluate the expression of proinflammatory indicators IL-1β and TNF-α, apoptosis marker Caspase-3, and antiapoptotic marker Bcl-2 in brain tissue of the right prefrontal cortex (PFC). The avidin-biotin peroxidase assay was applied in immunohistochemical staining. To stain, 5 μm slices of paraffin blocks were cut on polylysine slides. Sections were deparaffinized with xylol, then preserved with a declining alcohol through a graded descending ethanol series to distilled water. Sections were heated in a 600 W microwave oven with 5% citrate buffer (pH 6.0) for antigen retrieval, washed with phosphate buffered saline (PBS), and treated with 3% H_2O_2 to block endogenous peroxidase activity. All subsequent phases used the immunohistochemical staining kit (Thermo Scientific/TS-125-HR, Thermo Fisher Scientific Inc., Waltham, MA, USA), and the treatment was carried out in a condition that prevents tissue drying under humid conditions to prevent tissue drying. To cover the areas outside of the antigenic regions, block serum was injected into PBS-washed sections and let to sit at room temperature for 10 min. After that, the primary antibodies for IL-1β (Proteintech, 26048-1-ap, 1:200), TNF-α (Elabscience, e-ab-68252, 1:100), Caspase3 (Cleaved Caspase-3 proteintech 1:250/ cat no 25128-1-AP) and Bcl-2 (Bcl-2 proteintech 1:400/ cat no 26593-1-AP) were incubated for the entire night at 4 °C. The sections were then incubated using biotinylated secondary antibodies. Following PBS washing, the streptavidin-peroxidase conjunction was applied. The immunoreactivity was then emphasized by AEC (3-amino-9-ethylcarbazole-HA53704, Thermo Scientific, USA). Gill's hematoxylin was employed as a counterstain to enhance nuclear staining. Immunohistochemistry-stained brain sections were seen under a light microscope (Nikon Eclipse Si, Tokyo, Japan), and microscopic pictures of several identified random sites were obtained as digital images from 10 randomly selected, non-overlapping fields within the PFC region per animal. To ensure standardized sampling, the right cortical hemisphere was used for histological evaluation in all animals. The immunoreactivity intensities of the markers found in the images were evaluated using ImageJ software. The color threshold plugin for ImageJ software was used to assess the overall immunoreactivity after color deconvolution (H-AEC separation), background correction, and grayscale conversion. For each marker, a fixed threshold value was applied and the AEC-positive area ratio (%) was calculated. The arithmetic mean of the 10 fields was taken as a single biological value for each animal ($n = 7$ per group) and used for statistical analysis. All image acquisition and analyses were performed in a blinded manner.

3.11. Statistical analysis

Sample Size Determination: The sample size was determined based on an a prior power analysis using G*Power software (version 3.1.9.7). Based on previous studies investigating MSG-induced neurotoxicity, a large effect size (*Cohen's* $f = 0.55$) was anticipated. To achieve a statistical power (1-β) of 0.80 with $\alpha = 0.05$ for a one-way ANOVA involving five groups, the analysis indicated that a minimum sample size of 7 animals per group ($n = 7$) was required. Accordingly, the study was conducted with 35 rats randomly distributed into five groups.

Data Analysis: Behavioral experiments were recorded and analyzed using the ANY-maze software system version 7.4 (Stoelting Co., Wood Dale, IL, USA). All statistical analyses were performed using GraphPad Prism software version 9.1.1. for Windows (San Diego, CA, USA). The normality of the data distribution and the homogeneity of variances were assessed using the Shapiro-Wilk test. A one-way ANOVA followed by Tukey's post hoc test was used to determine whether there were significant differences among the groups. Nonparametric analysis was performed for groups with $n < 5$, as small sample sizes precluded the assumption of normality. Specifically, the Kruskal-Wallis test was used for multiple-group comparisons, followed by the Mann-Whitney U test for post hoc pairwise comparisons. A p-value of less than 0.05 was considered statistically significant. Results are expressed as means ± standard error of the mean (SEM). All behavioral, biochemical, and histopathological analyses were performed using the full study cohort ($n = 7$ per group). For histopathology, technical replicates (multiple fields of view) were averaged to obtain a single value per biological subject. For Real-Time PCR analyses, a representative subset of 3 samples was randomly selected from each group ($n = 3$). No data points were excluded as outliers.

4. Results

4.1. Body weight and obesity parameters

Table 2 presents the mean body weight, body length, Lee index, and BMI values of the experimental groups. Statistical analysis revealed that there were not significant differences in body weight among the groups ($F_{4,30} = 1.003$, $p = 0.422$). However, evaluation of the Lee index at PN59 demonstrated a statistically significant difference between the groups ($F_{4,30} = 50.26$, $^{***}p < 0.001$), with rats in the MSG and MSG + Carnitine group rats exhibiting significantly higher Lee index values compared to the control group rats (***p's < 0.001). Furthermore, comparison of BMI values revealed a statistically significant difference ($F_{4,30} = 9.53$, $p < 0.001$), with MSG and MSG + Carnitine group rats displaying significantly elevated BMI values relative to the control group rats ($^{***}p < 0.001$ and $^{*}p = 0.013$, respectively). These findings underscore the impact of MSG exposure on metabolic parameters, suggesting a potential association with obesity-related indices.

Table 2
Mean ± SEM of changes in body weight, body length, Lee index, BMI, Insulin, Glucose and HOMA-IR.

Parameters	Groups				
	Control	Sham	MSG	Carnitine	MSG+Carnitine
Body Weight (gr)	239.85 ± 3.267	232.28 ± 7.566	253.85 ± 9.010	237.14 ± 3.916	237.14 ± 12.475
Body Length (cm)	22.28 ± 0.2995	21.71 ± 0.2857	20.00 ± 0.4213	22,14 ± 0.1398	20.00 ± 0.4139
Lee's index (gr/cm)	0.28 ± 0.003119	0.28 ± 0.002291	0.32 ± 0.002291***	0.28 ± 0.001007	0,31 ± 0.002199***
BMI (gr/cm^2)	0.484 ± 0.0099	0.492 ± 0.0096	0.635 ± 0.0089***	0.486 ± 0.0068	0.601 ± 0.0473*
Insulin (μU/mL)	9.708 ± 1.850	13.07 ± 3.375	70.72 ± 18.01***	11.94 ± 2.153	61.01 ± 9.343**
Glucose(mg/dL)	103.4 ± 1.938	106.7 ± 2.934	110.3 ± 2.697	103.3 ± 2.974	104.7 ± 2.447
HOMA-IR	2.450 ± 0.4619	3.396 ± 0.8658	18.47 ± 4.363***	3.107 ± 0.5795	15.41 ± 2.258**

#The Lee index was calculated as the cube root of body weight (g) divided by nose-to-anus length (cm), with values above 0.3 classified as obese [Lee index= cube root of body weight (g)/nose-to-anus length (cm)]. The body mass index (BMI) was determined using the formula: body weight (g) divided by the square of nose-to-anus length (cm^2) [(BMI) = body weight (g)/(nose-to-anus length)^2 (cm^2)].
To assess insulin resistance, the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index was calculated using the following formula: HOMA-IR = [Insulin (μU/mL) x Glucose (mg/dL)]/405.

In addition to anthropometric indices, plasma insulin and glucose levels were measured to evaluate metabolic alterations associated with MSG exposure. Statistical analysis revealed a significant difference in plasma insulin concentrations among the groups ($F_{4,30} = 10.41$, $p < 0.001$), with both MSG-treated and MSG + Carnitine-treated rats exhibiting markedly elevated insulin levels compared to control rats (***$p < 0.001$). In contrast, plasma glucose levels did not differ significantly among the groups ($F_{4,30} = 1.234$, $p = 0.318$), indicating that MSG-induced metabolic dysregulation was more pronounced in insulin dynamics rather than basal glucose levels (Table 2).

To further assess insulin resistance, the homeostatic model assessment of insulin resistance (HOMA-IR) index was calculated. Analysis demonstrated a robust increase in HOMA-IR values in MSG and MSG + Carnitine groups compared to controls ($F_{4,30} = 11.74$, ***$p < 0.001$), indicating impaired insulin sensitivity. Notably, co-administration of L-carnitine did not significantly ameliorate the elevation in HOMA-IR, suggesting that its modulatory effect on MSG-induced metabolic dysregulation may be limited in the context of insulin resistance (Table 2).

5. Anxiety and depression-like behaviors

5.1. Open field test findings

Fig. 1 illustrates the total distance travelled (Fig. 1A) and time spent in the central area (Fig. 1B) in open field test of the experimental groups. The one-way ANOVA indicated a statistically significant difference in the total distance traveled among the groups ($F_{4,30} = 11.117$, $p < 0.001$). Post-hoc tukey test revealed that total distance travelled significantly decreased in MSG and MSG + Carnitine group rats than that control group (**$p < 0.01$ and *$p < 0.05$, respectively), sham group (***$p < 0.001$ and **$p < 0.01$, respectively) and Carnitine group (***$p < 0.001$ and **$p < 0.01$, respectively) rats. There was no statistically significant difference observed between the MSG and MSG + Carnitine groups ($p > 0.05$). The one-way ANOVA indicated a statistically significant difference in the center duration among the groups ($F_{4,30} = 6.706$, $p < 0.01$). Post-hoc tukey test revealed that time spent in the central area significantly decreased in MSG group rats than that control group (**$p < 0.01$), sham group (**$p < 0.01$), Carnitine group (*$p < 0,05$) and MSG + Carnitine (*$p < 0,05$) group rats. However, no statistically significant differences were observed among the Control, Sham, Carnitine, and MSG + Carnitine groups in pairwise comparisons for center duration.

5.2. Elevated plus maze findings

Fig. 2 illustrates the entries into the open arms (Fig. 2A) and time spent in open arms (Fig. 2B) in elevated plus maze of the experimental groups. The one-way ANOVA indicated a statistically significant difference for entries into the open arms among the groups ($F_{4,30} = 5.583$, $p = 0.002$). Post-hoc tukey test revealed that entries into the open arms significantly decreased in MSG group rats than control, sham, carnitine and MSG + carnitine group rats (*p's < 0.05). However, no statistically significant differences were observed among the Control, Sham, Carnitine, and MSG + Carnitine groups in pairwise comparisons for the entries into the open arms. The one-way ANOVA indicated a statistically significant difference for time spent in open arms among the groups ($F_{4,30} = 6.154$, $p < 0.001$). Post-hoc tukey test revealed that time spent

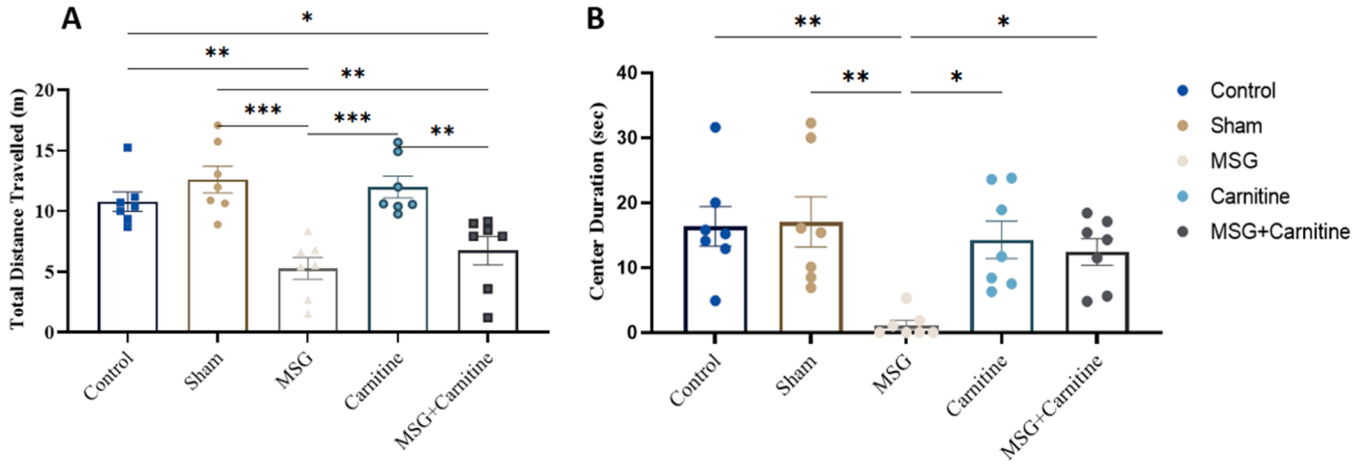

Fig. 1. Assessment of locomotor activity and anxiety-like behavior using the Open Field Test (OFT). (A) Total distance traveled (locomotor activity) and (B) Time spent in the central area (anxiety index) across experimental groups. Data are presented as mean ± SEM, with individual data points overlaid to display distribution. Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test. *p < 0.05, **p < 0.01, ***p < 0.001; $n = 7$ per group.

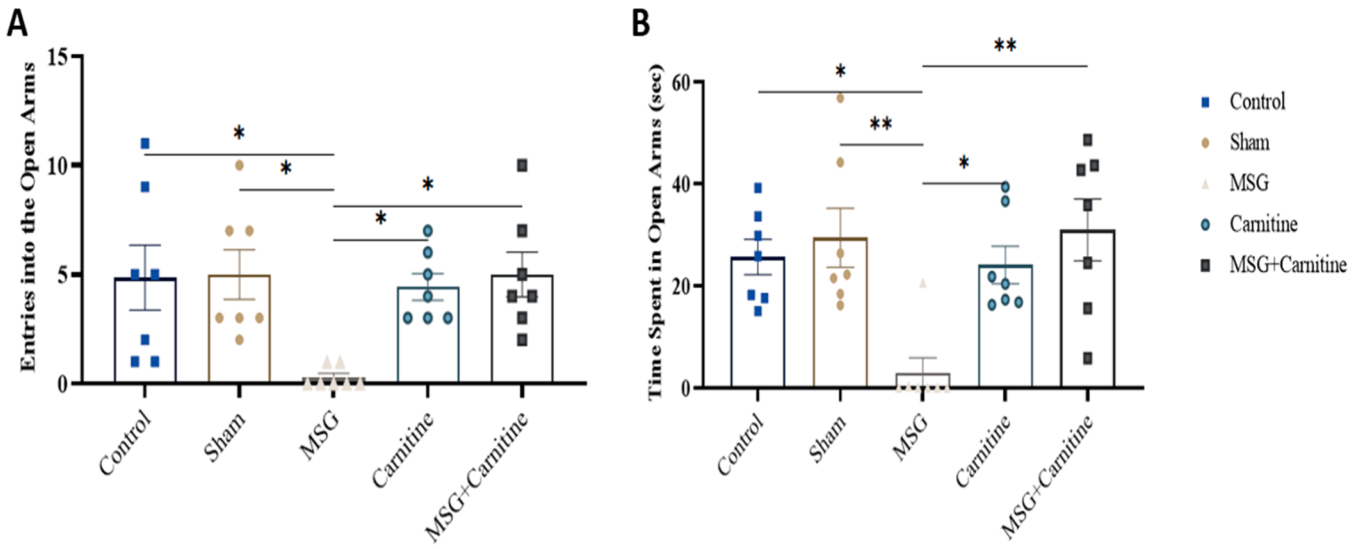

Fig. 2. Assessment of anxiety-like behavior using the Elevated Plus Maze (EPM). (A) Number of entries into open arms and (B) Time spent in open arms across experimental groups. Data are presented as mean ± SEM, with individual data points overlaid to display distribution. Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test. *p < 0.05, **p < 0.01, ***p < 0.001; $n = 7$ per group.

in open arms significantly decreased in MSG group rats than Control, Sham, Carnitine and MSG + Carnitine group rats (*p's < 0.05, **p's < 0,01). However, no statistically significant differences were observed among the Control, Sham, Carnitine, and MSG + Carnitine groups in pairwise comparisons for the time spent in open arms.

5.3. Forced swimming test findings

Fig. 3 illustrates the immobility time in forced swimming tests of the experimental groups. The one-way ANOVA indicated a statistically significant difference for immobility time in FST among the groups ($F_{4,30} = 5.517$, $p = 0.002$). Post-hoc tukey test revealed that immobility time significantly increased in MSG group rats than Control, Sham and Carnitine group rats (*p's < 0.05, **p's < 0,01). However, no statistically significant differences were observed among the Control, Sham, Carnitine, and MSG + Carnitine groups in pairwise comparisons.

5.4. Oxidative stress findings

Fig. 4 illustrates the total oxidant status (TOS, Fig. 4A) and total antioxidant status (TAS, Fig. 4B) of the experimental groups. The one-way ANOVA indicated a statistically significant difference for TOS ($F_{4,30} = 4.598$, $p = 0.005$). Post-hoc tukey test revealed that TOS significantly increased in MSG group rats than Control, Sham, Carnitine and MSG + Carnitine group rats (*p's < 0.05, **p's < 0,01). However, no statistically significant differences were observed among the Control, Sham, Carnitine, and MSG + Carnitine groups in pairwise comparisons. The one-way ANOVA indicated a statistically significant difference for TAS ($F_{4,30} = 4.919$, $p = 0.004$). Post-hoc tukey test revealed that TAS significantly decreased in MSG group rats than Control, Sham and MSG + Carnitine group rats (*p's < 0.05, **p's < 0,01). However, no statistically significant differences were observed among the Control, Sham, Carnitine, and MSG + Carnitine groups in pairwise comparisons.

5.5. Gene expression findings

For the molecular analysis, a representative subset of randomly selected samples ($n = 3$ per group) was utilized. Fig. 5 illustrates the mRNA expression of BDNF, Bax, Bcl-2 and Bax/Bcl-2 ratio of the experimental groups. The Kruskal-Wallis indicated a statistically significant difference for BDNF expression among the groups ($\chi 2$ (4) = 11.433, $p = 0.022$, Fig. 5A). Statistical analysis using the non-parametric

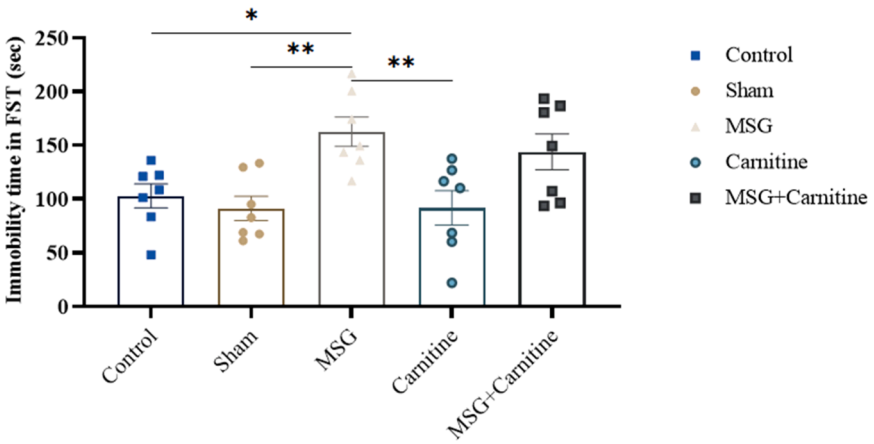

Fig. 3. Assessment of depression-like behavior via the Forced Swim Test (FST). The graph depicts the duration of immobility across experimental groups. Data are presented as mean ± SEM, with individual data points overlaid to display distribution. Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; $n = 7$ per group.

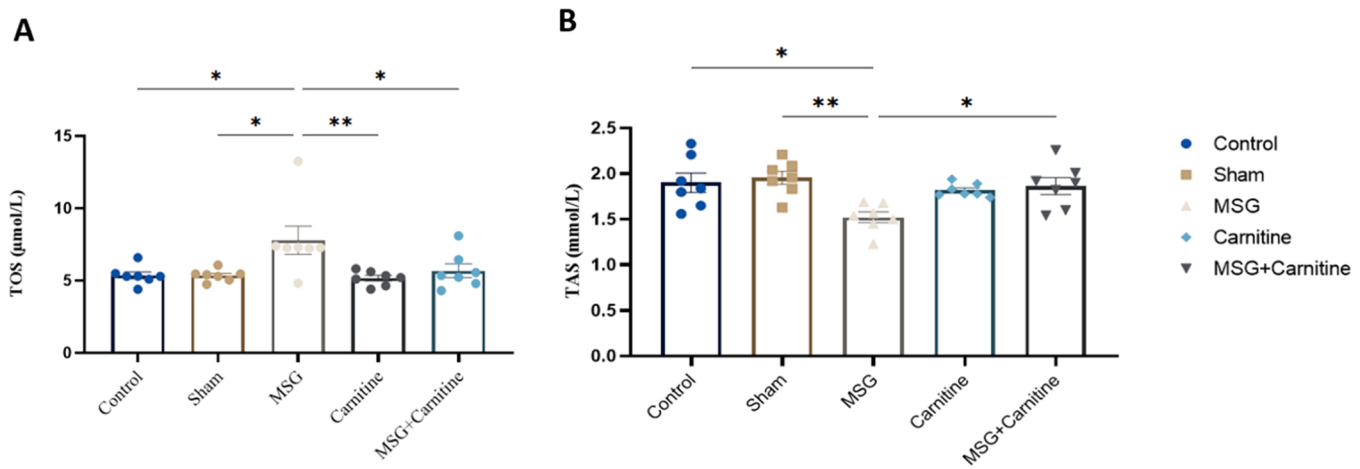

Fig. 4. Evaluation of oxidative stress markers in the prefrontal cortex (PFC). (A) Total Oxidant Status (TOS) and (B) Total Antioxidant Status (TAS) levels across experimental groups. Data are expressed as mean ± SEM, with individual data points overlaid to display distribution. Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; $n = 7$ per group.

Mann-Whitney U test showed that mRNA levels of BDNF were significantly lower in the MSG group compared to both the Control and Sham groups (U = 0.000, Z = −1.964, $p = 0.050$). The group receiving only L-carnitine exhibited BDNF expression levels similar to the control groups and significantly higher than the MSG group (U = 0.000, Z = −1.964, $p = 0.050$; Fig. 5A). These findings indicate that while MSG treatment suppresses BDNF mRNA expression, L-carnitine administration alone does not reduce neurotrophic factor levels and maintains a profile comparable to that of healthy controls. The Kruskal-Wallis indicated a statistically significant difference for Bax expression among the groups ($\chi 2$ (4) = 10.433, $p = 0.034$, Fig. 5B). Regarding Bax mRNA expression, the MSG group and the MSG+Carnitine group showed significantly higher levels compared to the Control, Sham, and Carnitine groups (U = 0.000, Z = −1.964, $p = 0.050$ for all comparisons). While there was no significant difference in Bax expression between the MSG and MSG+Carnitine groups ($p = 0.827$), the persistence of elevated Bax levels in the MSG+Carnitine group indicates that the pro-apoptotic stimulus induced by MSG remained prominent at the transcriptional level despite the treatment. The Kruskal-Wallis indicated a statistically significant difference for Bcl-2 expression among the groups ($\chi 2$ (4) = 12.900, $p = 0.012$, Fig. 5C). The mRNA expression of the anti-apoptotic marker Bcl-2 was evaluated across all experimental groups using the Mann-Whitney U test. Statistical analysis revealed that MSG administration significantly suppressed Bcl-2 mRNA levels compared to the Control, Sham, and Carnitine groups (U = 0.000, Z = −1.964, $p = 0.050$ for each comparison). Similarly, Bcl-2 levels in the MSG+Carnitine group remained significantly lower than those of the healthy control groups (U = 0.000, Z = −1.964, $p = 0.050$). No significant difference was observed between the MSG and MSG+Carnitine groups regarding Bcl-2 mRNA expression ($p = 0.513$). These results indicate that the MSG-induced downregulation of anti-apoptotic signaling was not significantly reversed at the transcriptional level by L-carnitine treatment under the current experimental conditions. The Kruskal-Wallis indicated a statistically significant difference for Bax/Bcl-2 ratio among the groups ($\chi 2$ (4) = 11.633, $p = 0.020$, Fig. 5D). The Bax/Bcl-2 ratio, a key indicator of the apoptotic threshold, was calculated to assess overall neuronal susceptibility to programmed cell death. Statistical analysis revealed that the Bax/Bcl-2 ratio was significantly elevated in the MSG group compared to the Control, Sham, and Carnitine groups (U = 0.000, Z = −1.964, $p = 0.050$), indicating a shift toward a pro-apoptotic state. No significant difference was observed between the MSG and MSG+Carnitine groups regarding Bax/Bcl-2 ratio ($p = 0.513$). Notably, the ratio in the MSG+Carnitine group remained significantly higher than that of the healthy control groups ($p = 0.050$).

5.6. Histopathology findings

Regarding histopathological changes in the brain belonging to rats, it was observed that male brain tissues belonging to the Control, Sham, Carnitine and MSG + Carnitine group had normal histological structure when evaluated under a light microscope. As illustrated in Fig. 6, healthy neurons exhibit well-preserved cellular architecture and structural integrity. In the MSG-treated group, necrotic neurons exhibiting intense eosinophilic staining were observed in the PFC, as well as marked vasodilation in cortical blood vessels.

5.7. Toluidine blue findings

Fig. 7 demonstrates the toluidine blue stained histological section of PFC in rats. We have evaluated toluidine blue staining to show degenerative neurons in PFC. The one-way ANOVA indicated a statistically significant difference for toluidine blue staining ($F_{4,30} = 33.87$, $p < 0.001$). Post-hoc tukey test revealed that MSG led to the significantly increased neurodegeneration than Control, Sham, Carnitine and MSG + Carnitine group rats (***p's < 0.001, Fig. 7B).

5.8. Immunohistochemistry findings

Caspase-3 Reactivity. Fig. 8 demonstrates the immunohistochemically detected Caspase-3 reactivity in the PFC across experimental rat groups. The one-way ANOVA indicated a statistically significant difference for Caspase-3 reactivity among the groups ($F_{4,30} = 17.50$, $p < 0.001$). Post-hoc tukey test revealed that Caspase-3 reactivity significantly increased in MSG group rats than Control, Sham, Carnitine and MSG + Carnitine group rats (***p's < 0.001, Fig. 8B).

Bcl-2 Reactivity. Fig. 9 demonstrates the immunohistochemically detected Bcl-2 reactivity in the PFC across experimental rat groups. The one-way ANOVA indicated a statistically significant difference for Bcl-2 reactivity among the groups ($F_{4,30} = 45.59$, $p < 0.001$). Post-hoc tukey test revealed that Bcl-2 reactivity significantly decreased in MSG group rats than Control, Sham, Carnitine and MSG + Carnitine group rats (***p's < 0.001, Fig. 9B).

IL-1β Reactivity. Fig. 10 demonstrates the immunohistochemically detected IL-1β reactivity in the PFC across experimental rat groups. The one-way ANOVA indicated a statistically significant difference for IL-1β reactivity among the groups ($F_{4,30}$=20.16, $p < 0.001$). Post-hoc tukey test revealed that IL-1β reactivity significantly increased in MSG group rats than Control, Sham, Carnitine and MSG + Carnitine group rats (***$p < 0.001$, Fig. 10B). In addition, Il-1β reactivity significantly increased in

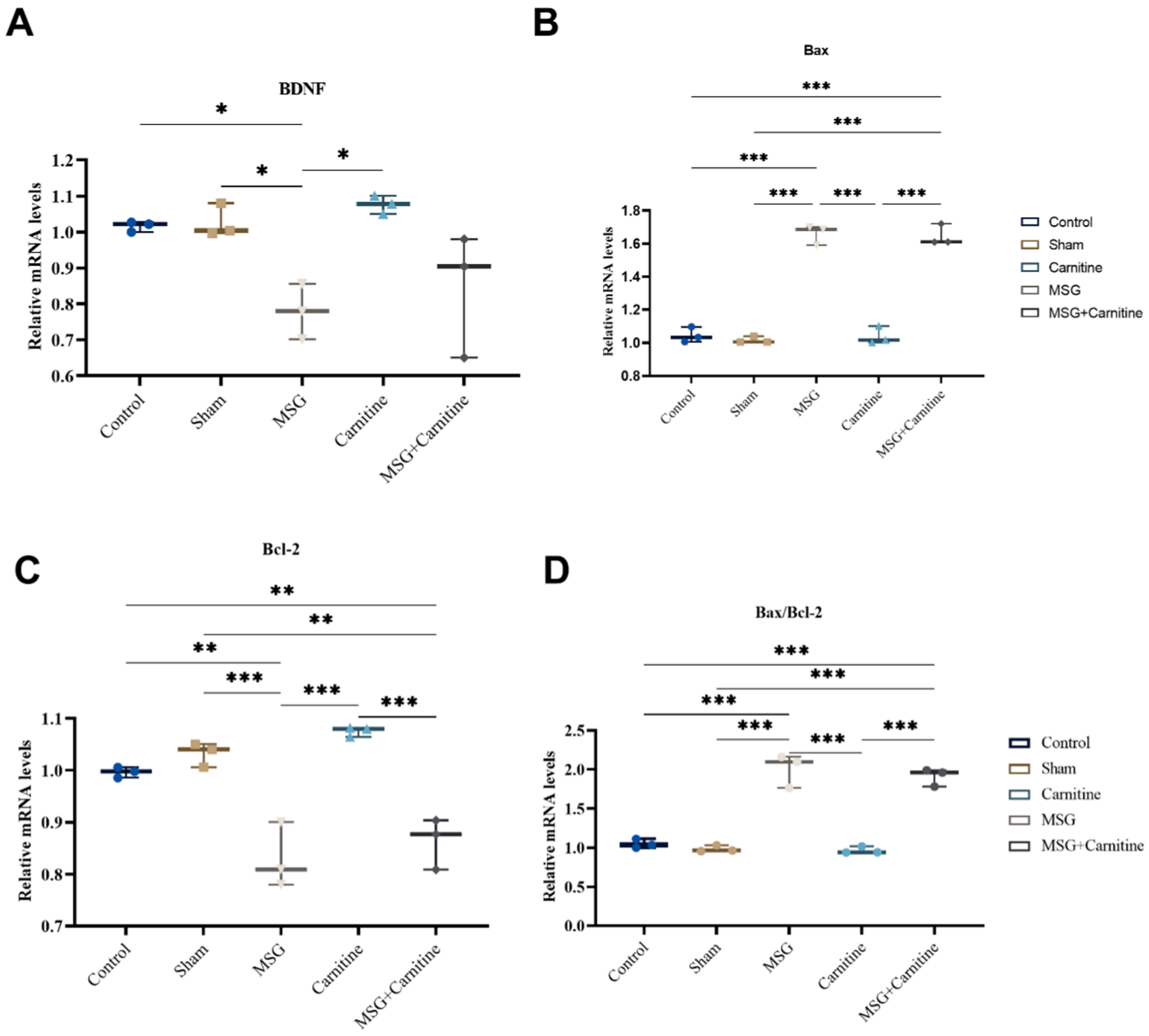

Fig. 5. Relative mRNA expression levels in the prefrontal cortex (PFC). (A) BDNF, (B) Bax, (C) Bcl-2, and (D) Bax/Bcl-2 ratio across experimental groups. Data are expressed as mean ± SEM, with individual data points overlaid to display distribution. Statistical analysis was performed using Kruskal-Wallis followed by Mann-Whitney U test. $^{**}p < 0.01$, $^{***}p < 0.001$; $n = 3$ per group.

MSG + Carnitine group than that carnitine group rats ($^{*}p < 0.05$).

TNF-α Reactivity. Fig. 11 demonstrates the immunohistochemically detected TNF-α reactivity in the PFC across experimental rat groups. The one-way ANOVA indicated a statistically significant difference for TNF-α reactivity among the groups ($F_{4,30} = 17.14$, $p < 0.001$). Post-hoc tukey test revealed that TNF-α reactivity significantly increased in MSG group rats than Control, Sham, Carnitine and MSG + Carnitine group rats ($^{**}p < 0.01$, $^{***}p < 0.001$, respectively, Fig. 10B). In addition, TNF-α reactivity significantly increased in Carnitine and MSG + Carnitine group than that control group rats ($^{*}p < 0.05$, $^{**}p < 0.01$, respectively).

6. Discussion

This study examined the ameliorative effect of L-Carnitine on anxiety- and depression-like behaviors in adolescent rats subjected to neonatal MSG-induced obesity. Beyond the behavioral improvements, L-Carnitine administration reversed alterations in total oxidant and antioxidant levels. Moreover, both histopathological analyses using Toluidine Blue staining and immunohistochemical assessments revealed that L-Carnitine exerted neuroprotective effects by preserving neuronal structures and attenuating apoptotic and proinflammatory responses, as evidenced by reduced caspase-3 activity and decreased levels of IL-1β and TNF-α as well as increased level of Bcl-2. Therefore, the present results emphasize the potential role of L-Carnitine on anxiety- like behaviors due to the obesity induced by MSG.

Neonatal MSG Exposure Alters Body Composition via Hypothalamic Damage: L-Carnitine Fails to Reverse Metabolic Shifts: MSG was administered to neonatal rats at a dose of 4 g/kg body weight on PND 2, 4, 6, 8, and 10 to induce obesity, following established protocols in the literature [6,25]. Our findings revealed that although there were no significant differences in body weight among the groups, both the Lee index and BMI values were significantly elevated in MSG and MSG + Carnitine groups compared to controls. These findings align with previous studies reporting that neonatal MSG exposure disrupts

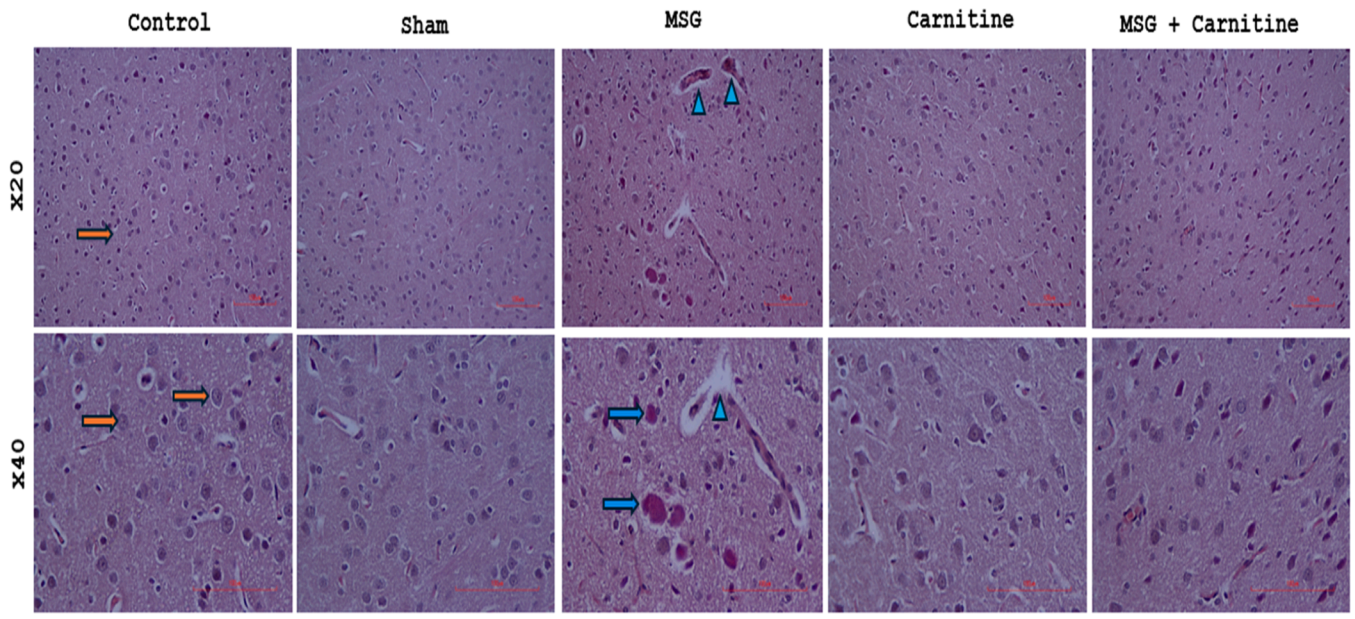

Fig. 6. Histopathological findings in rat prefrontal cortex (PFC) tissue stained with Hematoxylin & Eosin (H&E). Representative photomicrographs showing: (Orange arrow) Healthy neurons with preserved cell structure and integrity in the Control group. (Blue arrow) Necrotic neurons exhibiting eosinophilic staining in the MSG group. (Blue triangle) Vasodilation observed in cortical vessels (MSG group). Images were captured using a Nikon Eclipse Si microscope (Tokyo, Japan) at 20× and 40× magnifications. $n = 7$ per group.

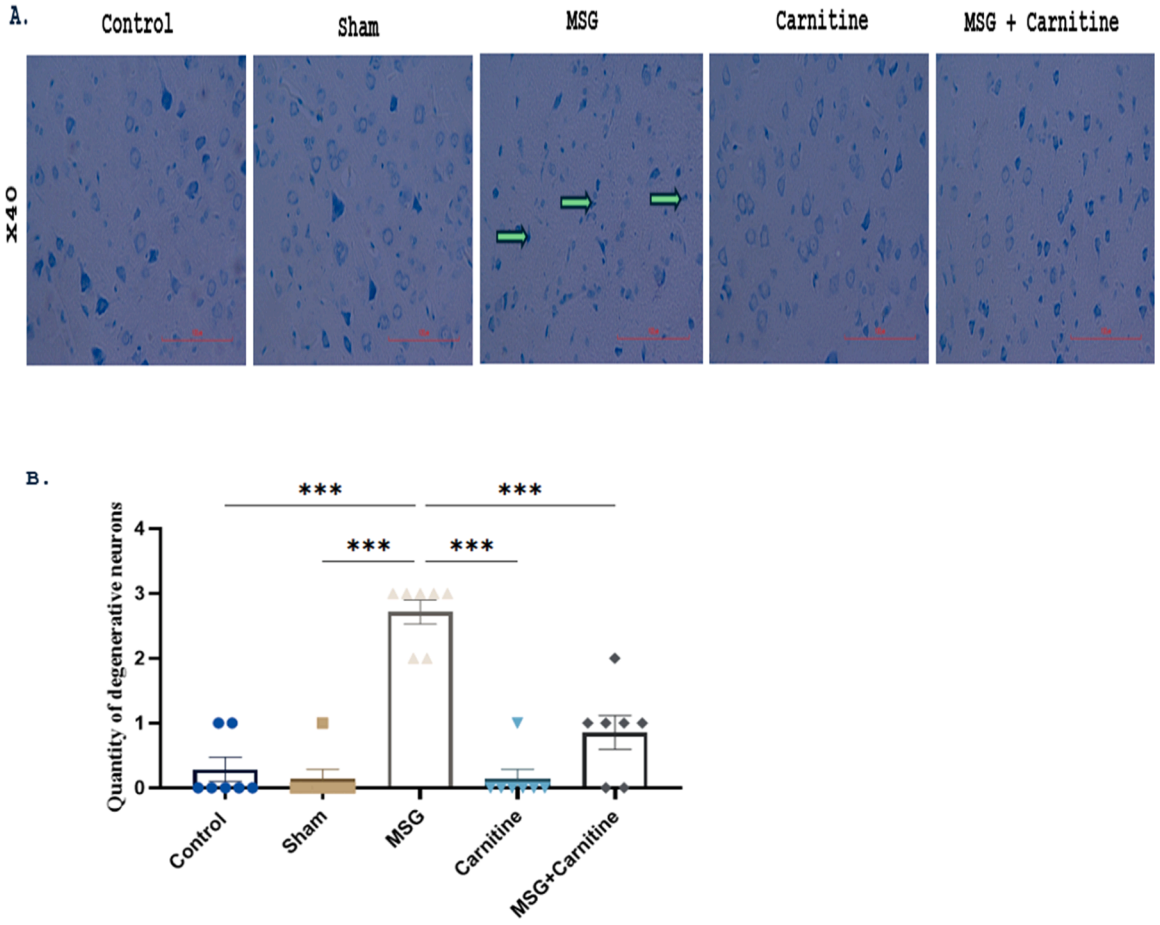

Fig. 7. Histopathological evaluation of the prefrontal cortex (PFC) using Toluidine Blue (TB) staining. (A) Representative photomicrographs of experimental groups (Magnification: 40×), The MSG group of TB stained prefrontal cortex histological section is shown as degenerative neurons (green arrow). (B) Quantitative analysis of neuronal degeneration. Data are presented as mean ± SEM, with individual data points overlaid to display distribution. Statistical comparisons were performed using one-way ANOVA followed by Tukey's post-hoc test. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$; $n = 7$ per group.

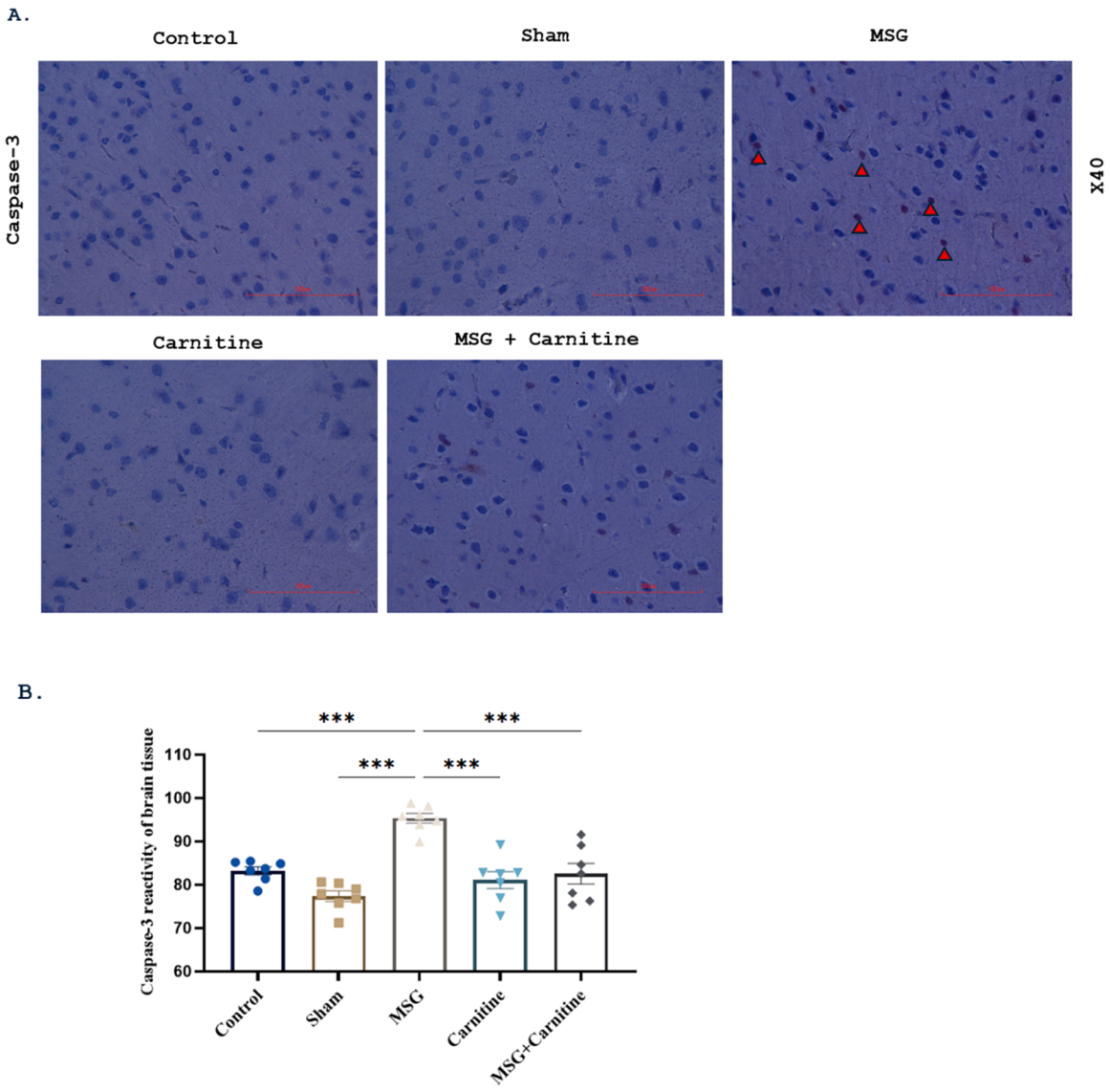

Fig. 8. Immunohistochemical evaluation of Caspase-3 expression in the prefrontal cortex (PFC). (A) Representative photomicrographs of experimental groups (Magnification: 40×) Caspase-3 immunoreactivity shows staining that is particularly intense in the nuclei of neurons (red triangle). (B) Quantitative analysis of Caspase-3 immunoreactivity. Data are presented as mean ± SEM, with individual data points overlaid to display distribution. Statistical comparisons were performed using one-way ANOVA followed by Tukey's post-hoc test. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$; $n = 7$ per group.

hypothalamic regulation of energy balance, leading to increased adiposity without necessarily affecting overall body weight [26]. The hypothalamic arcuate nucleus (ARC), highly vulnerable to excitotoxic damage. The ARC plays a central role in sensing peripheral energy signals such as leptin and insulin, and in regulating feeding behavior and metabolic homeostasis [27]. Neonatal MSG exposure has been shown to cause selective neuronal degeneration in this region, leading to long-term disturbances in energy balance, including hyperphagia, reduced thermogenesis, and increased adiposity [28]. The elevated Lee index and BMI values observed at PN59 suggest that MSG-induced metabolic alterations may manifest more prominently in body composition rather than gross weight gain. Interestingly, the co-administration of L-Carnitine did not prevent the increase in obesity-related indices, indicating that its modulatory effect on MSG-induced metabolic dysregulation may be limited or dose-dependent. These indices are widely used as reliable markers of adiposity in rodent models and are particularly sensitive to changes in body composition rather than absolute weight [29]. The selective increase in Lee index and BMI without a corresponding increase in body weight suggests a shift toward increased visceral fat accumulation, a hallmark of hypothalamic obesity. Similar findings have been reported in previous studies where neonatal MSG administration led to increased adiposity and metabolic dysregulation despite normal or near-normal body weight [30,28]. In addition to anthropometric indices, plasma insulin, glucose, and HOMA-IR values provided further evidence of metabolic disruption [31]. MSG-treated rats exhibited significantly elevated plasma insulin concentrations compared to controls [32], and this increase was also evident in the MSG + Carnitine group, indicating that carnitine co-administration did not normalize hyperinsulinemia. In contrast, plasma glucose levels did not differ significantly among the groups, suggesting that MSG-induced metabolic dysregulation was more pronounced in insulin dynamics rather than basal glucose homeostasis [33]. Importantly, HOMA-IR values were markedly increased in both MSG and MSG + Carnitine groups relative to controls, reflecting impaired insulin sensitivity and the development of insulin resistance [33]. The persistence of elevated HOMA-IR despite carnitine treatment highlights the limited efficacy of L-Carnitine in counteracting MSG-induced alterations in glucose-insulin regulation. These findings reinforce the notion that neonatal MSG

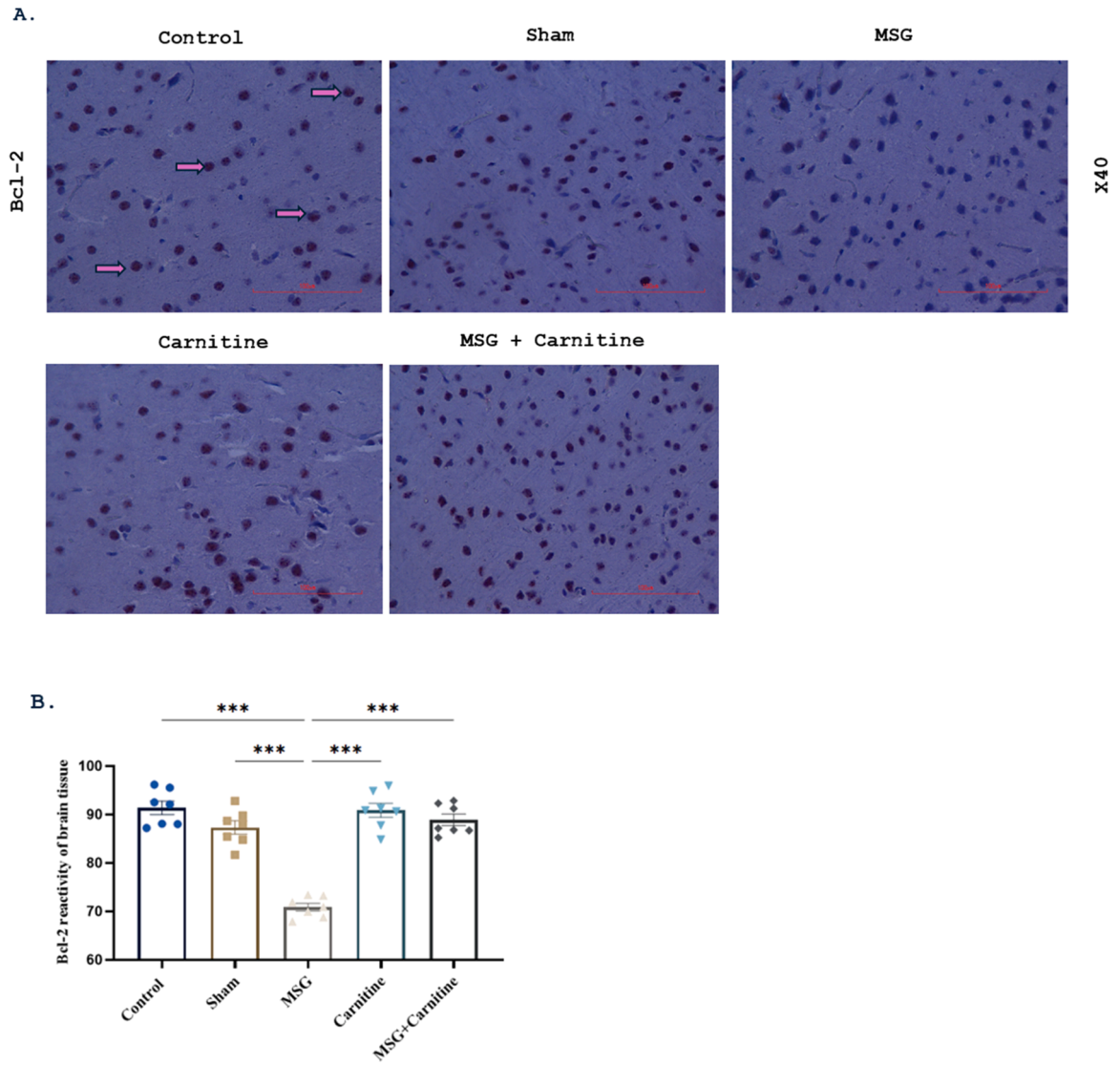

Fig. 9. Immunohistochemical evaluation of Bcl-2 expression in the prefrontal cortex (PFC). (A) Representative photomicrographs of experimental groups (Magnification: 40x), Bcl-2 immunoreactivity is observed in the section as a distinct positive staining in the nuclear localization of a large numberof cells (pink arrow). (B) Quantitative analysis of Bcl-2 immunoreactivity. Data are presented as mean ± SEM, with individual data points overlaid to display distribution. Statistical comparisons were performed using one-way ANOVA followed by Tukey's post-hoc test. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$; $n = 7$ per group.

exposure not only disrupts hypothalamic circuits controlling energy balance but also induces systemic metabolic impairments consistent with obesity-related insulin resistance. These results support the hypothesis that early-life disruption of hypothalamic circuits by MSG can lead to persistent alterations in metabolic regulation and body composition. However, L-Carnitine treatment was insufficient to reverse the alterations in body composition and metabolic parameters induced by MSG-mediated obesity in rats. This finding aligns with previous studies suggesting that while L-Carnitine exhibits antioxidant and anti-apoptotic properties, its protective effects may be limited in the context of MSG-induced systemic toxicity, particularly regarding metabolic and structural changes beyond oxidative stress [18].

L-Carnitine Attenuates MSG-Induced Anxiety and Depression-Like Behaviors in Rats: In the open field test, MSG and MSG + Carnitine-treated rats exhibited significantly reduced total distance traveled compared to control, sham, and carnitine treated rats, indicating a marked decline in spontaneous locomotor activity in MSG induced obesity rats [34]. This reduction aligns with previous findings suggesting that neonatal MSG exposure impairs hypothalamic regulation and dopaminergic signaling, leading to hypoactivity in adulthood [35,36]. The lack of significant difference between MSG and MSG + Carnitine groups for total distance travelled in open field test suggests that carnitine co-administration did not effectively restore locomotor function, possibly due to insufficient modulation of central neurotransmitter systems. Moreover, the time spent in the central area-a commonly used index of anxiety-like behavior-was significantly reduced in MSG-treated rats, consistent with increased thigmotaxis and anxiety-related avoidance behavior [37]. This is also consistent with studies showing that heightened anxiety correlates with reduced exploration of the central area in open field tests [38]. Interestingly, this anxiogenic effect was attenuated in the MSG + Carnitine group, whose center duration did not significantly differ from controls, suggesting a partial anxiolytic effect of L-carnitine. This observation is in line with studies reporting carnitine's neuroprotective and anxiolytic properties via mitochondrial support and antioxidant mechanisms [39]. However, the absence of significant locomotor recovery despite improved center exploration implies that effects of L-Carnitine may be more pronounced on emotional reactivity than on basal motor output.

The elevated plus maze (EPM) is a widely used behavioral assay in rodents to assess anxiety-like behavior based on their natural conflict

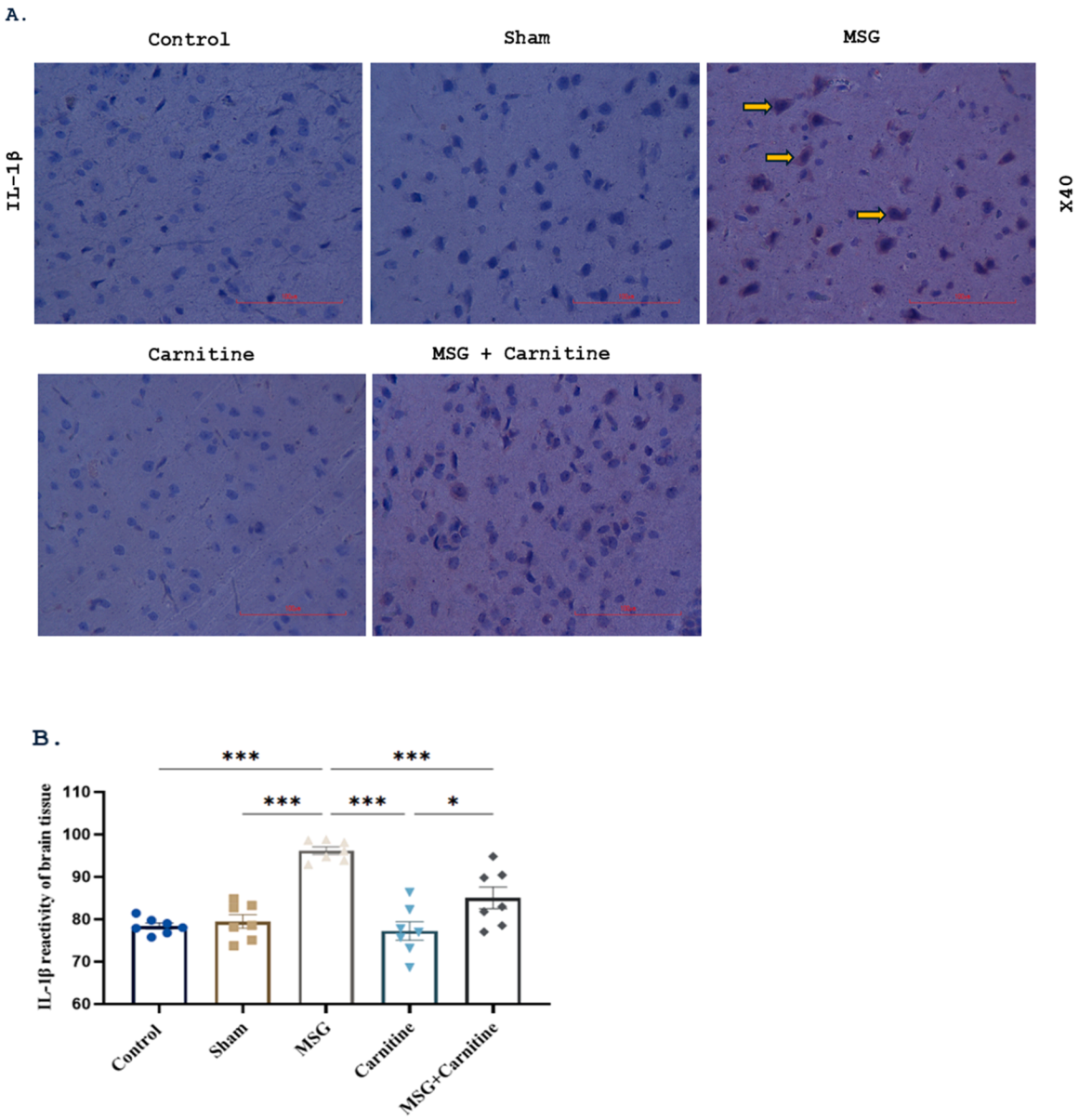

Fig. 10. Immunohistochemical evaluation of IL-1β expression in the prefrontal cortex (PFC). (A) Representative microscopic images of experimental groups (Magnification: 40×), IL-1β immunoreactivity is clearly observed in neurons with cytoplasmic/perinuclear localization (yellow arrow). (B) Quantitative analysis of IL-1β immunoreactivity. Data are presented as mean ± SEM, with individual data points overlaid to display distribution. Statistical comparisons were performed using one-way ANOVA followed by Tukey's post-hoc test. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$; $n = 7$ per group.

between exploration and fear of open, elevated spaces [40]. The most commonly used metrics are "Entries into open arms" and "Time spent in open arms". While, entries into open arms reflects the animal's willingness to explore a potentially threatening environment, time spent in open arms indicates the degree of anxiety or comfort in the exposed area. Our behavioral findings in the elevated plus maze test indicate that MSG administration significantly increases anxiety-like behaviors. The marked reduction in both the number of entries into the open arms and the time spent in the open arms in the MSG group rats compared to all other group rats support the anxiogenic effects of MSG. These results are consistent with previous studies suggesting that MSG induces glutamate-mediated excitotoxicity in the central nervous system, leading to neurochemical imbalances in anxiety-related brain regions such as the amygdala and hypothalamus [25]. On the other hand, carnitine administration appeared to prevent these behavioral impairments; the open arm parameters in the MSG + Carnitine group were comparable to those of the control group, highlighting the anxiolytic potential of carnitine against MSG-induced alterations. This effect may be attributed to carnitine's ability to reduce oxidative stress, support mitochondrial energy metabolism, and suppress neuroinflammation [41]. Additionally, its modulatory influence on GABAergic and glutamatergic systems may further contribute to this protective role [42]. Overall, the findings confirmed the anxiogenic impact of MSG while emphasizing the counterbalancing potential of carnitine and drawing attention to its possible neuroprotective properties.

The forced swimming test (FST), originally developed by Porsolt et al. [23], is a widely accepted behavioral paradigm for evaluating depressive-like behavior and behavioral despair in rodents. In this test, increased immobility time is interpreted as a passive coping strategy and is often used as an indicator of learned helplessness or negative affective states [43,44]. In the present study, MSG administration significantly increased immobility time compared to the Control, Sham, and Carnitine groups, suggesting that MSG may induce depression-like behavior in addition to its anxiogenic effects. This finding aligns with previous

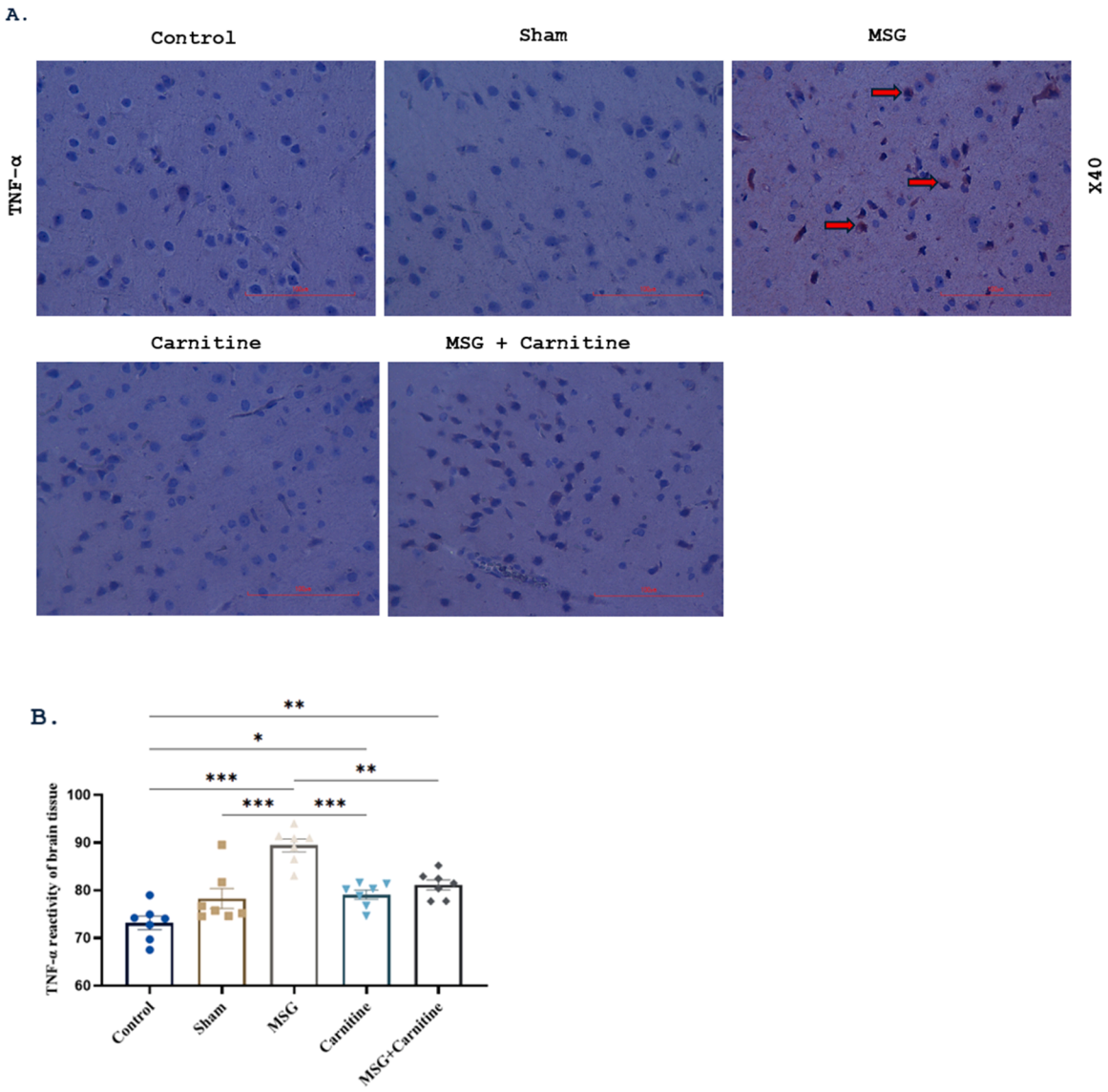

Fig. 11. Immunohistochemical evaluation of TNF-α expression in the prefrontal cortex (PFC). (A) Representative photomicrographs of experimental groups (Magnification: 40×), TNF-α immunoreactivity is observed predominantly in the cytoplasm of glial cells (red arrow). (B) Quantitative analysis of TNF-α immunoreactivity. Data are presented as mean ± SEM, with individual data points overlaid to display distribution. Statistical comparisons were performed using one-way ANOVA followed by Tukey's post-hoc test. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$; $n = 7$ per group.

reports indicating that chronic MSG exposure can disrupt monoaminergic neurotransmission and elevate oxidative stress, both of which are implicated in the pathophysiology of depression [45]. Interestingly, although carnitine administration numerically reduced immobility time in the MSG + Carnitine group compared to the MSG group, this difference did not reach statistical significance. Therefore, while carnitine may exert partial modulatory effects on MSG-induced behavioral despair, the current data do not support a robust protective role under these experimental conditions. This nuanced outcome contrasts with previous reports suggesting carnitine's antidepressant-like properties, which are thought to be mediated through mitochondrial support, antioxidant activity, and modulation of the hypothalamic-pituitary-adrenal (HPA) axis [46,39]. Notably, the lack of significant differences between the MSG + Carnitine and MSG groups implies that carnitine's efficacy may be context-dependent or require different dosing or duration to achieve measurable behavioral rescue. A pertinent point raised regarding our behavioral results is whether the 72 h post-treatment interval allowed for a 'washout' effect or drug withdrawal, particularly in the MSG + Carnitine group. Unlike synthetic psychotropic drugs, L-carnitine is an essential endogenous molecule integrated into the mitochondrial fatty acid oxidation pathway. While its plasma half-life is relatively short, L-carnitine exhibits a significantly slower turnover rate in tissue compartments, including the brain, where it is actively transported and sequestered [41]. Research indicates that supplemental L-carnitine effectively expands the global carnitine pool, and these elevated levels do not abruptly deplete upon cessation of treatment. Instead, they provide a sustained enhancement of mitochondrial bioenergetics and antioxidant capacity that persists for several days [16]. Furthermore, L-carnitine has been shown to exert neuroprotective effects against excitotoxicity by modulating glutamate metabolism and reducing oxidative stress-processes that involve structural and functional cellular recovery rather than transient receptor blockade [16,47,48]. In parallel, our molecular findings demonstrate that the neuroprotective efficacy of L-carnitine persists 72 h post-treatment. However, the manifestation of this recovery in behavioral outputs, specifically the Forced Swim Test (FST), may appear less dramatic than the molecular changes. The FST is a highly sensitive assay reflecting the acute affective state and motivational drive of the animal.

It is plausible that the 72 h interval allowed for a partial attenuation of the acute psycho-stimulatory effects of L-carnitine, while its deeper neuroprotective actions remained intact at the cellular level. Notably, the lack of significant differences between the MSG+Carnitine group and the Control, Sham, and Carnitine-only groups in the FST indicates that L-carnitine successfully preserved baseline affective behavior despite the severe MSG-induced excitotoxic challenge. Therefore, these results should be interpreted as a partial maintenance of behavioral homeostasis 72 h later, rather than a loss of pharmacological impact. These findings suggest that carnitine may exert a modulatory influence on MSG-induced behavioral despair, although the lack of statistically significant improvement in the MSG + Carnitine group indicates that its neuroprotective potential remains inconclusive under the current experimental conditions.

Research indicates that L-carnitine has protective effects against various forms of neurotoxicity and oxidative stress in rats, which are mechanisms implicated in anxiety and depression-like behaviors. In a rat model of Alzheimer's disease, L-carnitine administration improved anxiety-like behavior and cognitive deficits, likely by modulating oxidative-antioxidant balance and reducing neuronal death and plaque accumulation, suggesting its potential to alleviate neurobehavioral symptoms linked to oxidative stress and neurodegeneration [12]. While direct studies on L-carnitine's effects on MSG-induced anxiety and depression-like behaviors are limited, evidence shows that L-carnitine can counteract MSG-induced oxidative stress and tissue damage in other organ systems, such as the reproductive system, by enhancing antioxidant capacity and reducing markers of cellular damage [14]. Additionally, acetyl-L-carnitine, a related compound, has demonstrated dose-dependent reductions in anxiety-like behaviors in rats, further supporting the anxiolytic potential of carnitine derivatives [49]. Collectively, these findings suggest that L-carnitine may ameliorate anxiety and depression-like behaviors induced by MSG in rats, primarily through its antioxidant and neuroprotective properties, although more targeted research is needed to confirm this effect specifically in MSG-induced neurobehavioral models.

A Histopathological and Immunohistochemical Insights: Neuroprotective Effects of L-Carnitine Against MSG-Induced Cortical Inflammation and Neurodegeneration: Histopathological and immunohistochemical analyses revealed pronounced neuroinflammation and neurodegeneration in the PFC of MSG-exposed rats. This was evidenced by elevated immunoreactivity for IL-1β, TNF-α, and Caspase-3, and reduced Bcl-2 expression. Studies in the literature likewise report that MSG exposure induces a consistent neurodegenerative pattern in cortical tissue on H&E sections; specifically, cortical neurons exhibit shrinkage and degeneration accompanied by pyknosis, karyolysis/necrosis, and mild satellitosis findings characteristic of excitotoxic injury and this profile supports our H&E results showing loss of neuronal morphology and degenerative changes in the PFC [50,19]. Additionally, TB staining studies demonstrate that MSG exposure causes pyramidal neurons in the prefrontal cortex to lose their normal contour and adopt a round polygonal degenerative morphology, further corroborating MSG-induced neuronal damage [51]. These findings supported the previous reports indicating that MSG-induced excitotoxicity leads to oxidative stress and neuroinflammation, particularly in regions with immature blood-brain barrier function [19,52]. Although we were unable to measure Bax levels immunohistochemically in our study, L-carnitine administration preserved Bcl-2 immunoreactivity, attenuated histological damage, preserved neuronal morphology, and reduced the expression of proinflammatory and apoptotic markers. In agreement with earlier evidence that L-carnitine mitigates excitotoxic/oxidative histopathological injury in brain tissue by limiting neuronal degeneration, these effects are consistent with studies demonstrating the ability of L-carnitine to suppress NF-κB activation and reduce IL-1β and TNF-α levels, thereby limiting caspase-dependent apoptosis and oxidative damage [53,52]. Furthermore, the preservation of neuronal integrity and the sustained suppression of apoptotic markers observed 72 h after the final treatment suggest that L-carnitine's neuroprotective effects involve lasting structural recovery rather than transient pharmacological modulation [16]. This histopathological evidence supports the notion that the metabolic and anti-inflammatory benefits of L-carnitine provide a resilient defense against MSG-induced excitotoxicity, which persists beyond the immediate administration period [41].

Biomolecular Signatures of MSG-Induced Cortical Injury and the Neuroprotective Role of Carnitine: Following the behavioral assessments, biochemical analyses revealed further evidence of MSG-induced neuropathology and carnitine's restorative effects. In the current study, MSG-induced obesity led to neuronal damage and increased the pro-inflammatory markers, apoptotic markers, and total oxidant levels. Conversely, anti-apoptotic protein levels and antioxidant capacity were found to be decreased. Notably, elevated reactivity of IL-1β, TNF-α, and Caspase-3 indicates neuronal damage and neuroinflammatory responses within the PFC, while reduced Bcl-2 expression reflects a down-regulation of intrinsic cellular survival pathways. Elevated total oxidant levels, coupled with reduced antioxidant capacity, indicate that MSG elicits oxidative stress and disrupts the redox balance of cortical cells. The interplay between TNF-α and IL-1β and oxidative stress has been well-documented, with both cytokines contributing to mitochondrial dysfunction and apoptotic cascades via enhanced reactive oxygen species (ROS) generation [54]. The most striking aspect of the study is that carnitine treatment effectively reversed the observed pathological alterations. Carnitine is known to regulate energy balance by supporting mitochondrial biogenesis and increasing antioxidant capacity [52].

Carnitine administration was found to downregulate IL-1β, TNF-α, and Caspase-3, indicating inhibition of neuroinflammatory and pro-apoptotic signaling pathways in the PFC, while upregulate Bcl-2 expression reflects that cellular survival mechanisms are reactivated. Moreover, Carnitine treatment reestablished endogenous antioxidant defenses, contributing to the restoration of cortical redox homeostasis. These changes reflect a mitigation of cortical neuroinflammation, suppression of apoptotic processes, and re-establishment of redox balance, underscoring Carnitine's neuroprotective capacity within the context of MSG-induced excitotoxicity. Recent studies have demonstrated that L-carnitine exerts anti-inflammatory and antioxidant effects by modulating cytokine expression, enhancing mitochondrial function, and reducing neuronal death in various models of neurotoxicity [53,52,55]. These findings support its therapeutic potential in excitotoxic and neurodegenerative conditions. Importantly, the biochemical restoration observed 72 h after the final dose-characterized by the sustained downregulation of pro-inflammatory cytokines and the upregulation of Bcl-2-indicates that L-carnitine induces a stable shift in the cortical redox and apoptotic environment. Given that protein turnover and the re-establishment of endogenous antioxidant enzymes (such as SOD or GSH) involve complex transcriptional and translational processes, these molecular signatures are unlikely to represent transient pharmacological fluctuations. Instead, they reflect a lasting homeostatic recovery that remains evident even after the systemic clearance of the compound [16]. This persistent biochemical profile reinforces the conclusion that the 72 h post-treatment window successfully captured the sustained neuroprotective efficacy of L-carnitine, rather than a period of declining activity or withdrawal-related rebound.

7. Conclusion

The present study demonstrates that neonatal MSG exposure induces significant anxiety- and depression-like behaviors in adolescent rats, accompanied by metabolic dysregulation, oxidative stress, neuroinflammation, and apoptotic responses. Although L-Carnitine co-administration did not reverse obesity-related metabolic alterations or restore basal locomotor activity, it exerted notable anxiolytic effects, as evidenced by behavioral improvements in the open field and elevated plus maze tests. Furthermore, L-Carnitine mitigated cortical neuroinflammation and apoptotic damage by downregulating pro-

inflammatory cytokines and restoring antioxidant balance, thereby underscoring its neuroprotective potential. However, under the current experimental conditions, L-carnitine did not exhibit a significant antidepressant-like effect or fully restore neurotrophic gene expression.

These findings support the hypothesis that L-Carnitine confers partial protection against MSG-induced neurobehavioral and molecular impairments, likely through its antioxidant and mitochondrial modulatory properties. Future studies should explore dose optimization, long-term efficacy, and molecular mechanisms underlying L-Carnitine's protective effects, as well as its translational relevance for early-life neurotoxicity and metabolic disorders.

8. Limitations

There are certain limitations in the present study that should be considered. First, exclusively male rats were utilized to minimize the confounding variability associated with the estrous cycle, which is known to influence anxiety- and depression-like behaviors. There are certain limitations in the present study that should be considered. First, exclusively male rats were utilized to minimize the confounding variability associated with the estrous cycle, which is known to influence anxiety- and depression-like behaviors. However, this design restricts the generalizability of our findings to females. As emphasized by international funding agencies and the NIH (SABV policy), hormonal variability should be integrated as an essential component of biological variability to increase the translational relevance of preclinical findings. Future studies employing both sexes are warranted to provide a more comprehensive and translatable understanding of L-carnitine's neuroprotective potential.

Second, regarding tissue sampling, we consistently utilized the right PFC for histopathological evaluations and the left PFC for biochemical analyses to maintain methodological standardization and minimize intra-group variability. While this approach eliminates noise arising from anatomical asymmetry, it does not account for potential hemispheric lateralization in emotional processing or neurochemical distribution. Future studies employing both sexes and bilateral cortical analysis are warranted to provide a more comprehensive understanding of L-carnitine's neuroprotective potential.

Third, A methodological point to consider is the timing of tissue collection, which occurred 72 h after the final L-carnitine administration. This interval was a consequence of our experimental design, where behavioral tests (Open Field, Elevated Plus Maze, and Forced Swim Test) were conducted on consecutive days post-treatment to obtain a comprehensive behavioral profile. While our molecular analysis clearly demonstrates sustained neuroprotection-evidenced by the preservation of BDNF and Bcl-2 levels-we acknowledge that the 72 h delay may have particularly influenced the Forced Swim Test (FST) results. The FST is highly sensitive to acute motivational states, and the interval between the final dose and this specific test may have missed the peak behavioral rescue, leading to a lack of statistically significant improvement in immobility time compared to the MSG group. Therefore, the observed stability in other markers suggests that while cellular recovery is long-lasting, the behavioral manifestation in the FST might be more time-sensitive. Furthermore, this delayed assessment was intentionally preferred to differentiate long-term neurobiological stabilization from the transient acute effects often associated with assessments conducted shortly (e.g., 2–6 h) after the final dose, thereby ensuring that our findings reflect sustained recovery rather than immediate pharmacological fluctuations.

Another limitation of this study concerns the extent of metabolic and anthropometric characterization. Obesity and metabolic dysregulation were confirmed through validated anthropometric indices (Lee Index, BMI) and key metabolic markers (fasting glucose, insulin, and HOMA-IR), rather than the direct quantification of visceral white adipose tissue or a full lipid profile. While the significant elevation in HOMA-IR strongly indicates the presence of visceral adiposity and established insulin resistance characteristic of the MSG model, we were unable to evaluate circulating adipokines (e.g., leptin, adiponectin) or lipid fractions due to sample volume and resource constraints. Consequently, although the current data robustly confirm the metabolic syndrome phenotype, future studies incorporating direct adipose tissue weighing and comprehensive peripheral metabolic profiling are warranted to provide a more holistic assessment of body composition and systemic L-carnitine effects.

Disclosure statement

All authors claim that there are no conflicts of interest.

Data accessibility statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the authors used Gemini (Google) in order to improve the fluency and readability. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the published article.

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CRediT authorship contribution statement

Ferhat Pektaş: Supervision, Methodology, Investigation, Conceptualization. **Kübra Tuğçe Kalkan:** Methodology. **Ekin Çelık:** Methodology. **Abdullah Oklaz:** Methodology, Investigation, Data curation. **Mustafa Ağca:** Project administration, Investigation, Funding acquisition. **Burak Tan:** Writing – review & editing, Writing – original draft, Supervision.

Declaration of competing interest

None.

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