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Neuroprotective effect of transient receptor potential Vanilloid 1 agonist capsaicin in Alzheimer's disease model induced with okadaic acid

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ABSTRACT

Background: The presence of Transient Receptor Potential Vanilloid 1 (TRPV1) channels was detected in many regions of the human and rat brain, including the cortex and hippocampus. TRPV1 channels have functions such as the modulation of synaptic transmission and plasticity and the regulation of cognitive functions. Previous studies conducted with TRPV1 agonists and antagonists show that this channel is associated with the neurodegenerative process. In the present study, the purpose was to investigate the effects of capsaicin, which is a TRPV1 agonist, and capsazepine, a TRPV1 antagonist, in the Alzheimer's Disease (AD) model that was induced by intracerebroventricular (ICV) administration of okadaic acid (OKA).

Methods: The AD-like experimental model was created with bilateral ICV OKA injection. Intraperitoneal capsaicin and capsazepine injections were administered to the treatment groups for 13 days and histological and immunohistochemical examinations were performed from the cortex and hippocampal CA3 regions of the brain. The Morris Water Maze Test was used for spatial memory measurement.

Results: ICV OKA administration increased the levels of caspase-3, phosphorylated-tau-(ser396), Aβ, TNF-α, and IL1-β, from the cortex and hippocampal CA3 regions of the brain and decreased the phosphorylated-Glycogen synthase kinase-3 beta-(ser9) levels. In addition, the OKA administration corrupted the spatial memory. The TRPV1 agonist capsaicin reversed the pathological changes induced by ICV OKA administration, but not the TRPV1 antagonist capsazepine.

Conclusions: It was found in the study that the administration of the TRPV1 agonist capsaicin reduced neurodegeneration, neuroinflammation, and deterioration in spatial memory in the AD model induced by OKA.

1. Introduction

Dementia is a progressive neurodegenerative disease of the Central Nervous System and is characterized by the deterioration of cognitive functions such as memory, learning, recall, orientation, language functions, perception, decision-making, planning, and personality. It also affects the activities of the individual in daily life and may result in mortality. Alzheimer's Disease (AD), which is the most common type of dementia, accounts for 50–80% of all dementia cases [1]. It is estimated that the number of AD cases will reach 100 million by the year 2050 [2].

Neurofibrillary Tangles (NFT) and Amyloid Beta (Aβ) plaque formation and neuroinflammation accompany cognitive dysfunction in the pathophysiology of AD [3]. Aβ exerts neurotoxic effects by causing deterioration in neuronal synaptic activity, excitotoxicity, tau hyperphosphorylation, and oxidative stress [4]. The formation of NFT occurs when the structure of the tau protein is disrupted in neurons clumping in the cell as a double helix [5]. The main reason for NFT formation in AD is the hyperphosphorylation of the tau proteins. The phosphorylation level of the tau proteins is kept in balance by various enzymes under physiological conditions. The inactivity of the Protein Phosphatase 1 (PP1) and Protein Phosphatase 2A (PP2A), which are among the enzymes providing this balance, causes hyperphosphorylated tau formation and

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result in NFT formation [6].

Okadaic Acid (OKA) is a selective and potent PP1 and PP2A inhibitor that causes *in vivo* and *in vitro* tau hyperphosphorylation. It was reported previously that the levels of PP1 and PP2A enzymes, which are common in the brain, are decreased in AD [7]. OKA, which is administered intracerebroventricularly (ICV), is used widely in AD research since it mimics AD with its effects. Many *in vivo* studies reported that tau hyperphosphorylation occurs with one single local injection of OKA into the hippocampus or with the administration as ICV (as in AD) [8]. It was also reported that cognitive function deterioration and neuroinflammation in the brain and increased amounts of Aβ were observed in OKA-administered rats [9–11]. It was shown that OKA causes increased intracellular calcium (Ca^{+2}) levels and changes the expression of proteins associated with Ca^{+2} signaling [12].

Ca^{2+} plays roles in many processes such as neuronal excitability, neurotransmitter release, cell proliferation, and death [13]. Intracellular Ca^{2+} dysregulation is a pathological condition in neurodegenerative diseases such as AD [14]. Transient Receptor Potential Vanilloid 1 (TRPV1) channels are Ca^{+2}-permeable nonselective cation channels. TRPV1 channels have various endogenous and exogenous agonists called vanilloids. Capsaicin (CAP), resiniferatoxin, harmful heat (>43 °C), oxidative stress, low pH (<5), and various endogenous lipids are channel-activating agonists, which bind to specific binding sites on the channel, activating the channel, and in this way, the passage of Ca^{+2} ions into the cell occurs [15–18]. The presence of TRPV1 channels in the Central Nervous System in humans and rats was detected in the cerebral cortex, striatum, hippocampus, amygdala, thalamus, hypothalamus, cerebellum, locus ceruleus, and cochlear nucleus [19]. The presence of TRPV1 in different cells such as neurons, astrocytes, and pericytes in the Central Nervous System was also demonstrated previously [20]. TRPV1 channels have functions such as synaptic transmission, modulation of plasticity, and regulation of cognitive functions [21]. Studies conducted with TRPV1 agonists and antagonists show that this channel is associated with the neurodegenerative process. The wide distribution of TRPV1 channels in the brain, their effects on neuroinflammation, modulation of intracellular Ca^{2+}, and stimulation by oxidative stress [22] suggest that they may also have roles in AD. As a matter of fact, it has been determined that TRPV1 channels are associated with AD pathology in studies conducted in genetic Alzheimer's disease models [23–25]. Although the most common form of AD is sporadic AD, limited research is available on the effect of TRPV1 channels in the experimental model of sporadic AD. In the present study, the purpose was to investigate the effects of TRPV1 agonist CAP and TRPV1 antagonist Capsazepine (CPZ) in an AD model that was induced by ICV-injected OKA.

2. Materials and methods

2.1. Animals

All the procedures applied to animals in the present study were performed according to the experimental protocol approved by the Inonu University Medical Faculty Experimental Animal Research Ethics Committee. The rats were obtained from Inonu University Experimental Animals Production and Research Center. A total of 60 male Sprague-Dawley rats, 8 months old and weighing 250–350 g, were divided randomly into 6 groups with 10 rats in each. All the animals taken into single cages before the experiment were kept in single cages until they were sacrificed. The rats were housed in a ventilated room at a temperature of 20–22 °C, with 12-hour light and 12-hour dark periods. The rats were fed *ad libitum* standard pellet rat chow and drank tap water.

2.2. Surgical administrations

The rats other than those in the control group were anesthetized with 70 mg/kg ketamine and 8 mg/kg xylazine intraperitoneally (IP). The scalp area where the incision would be made was shaved and cleaned with a povidone-iodine solution. After the animals were fixed to the stereotactic device (Rodent Stereotaxic Instruments, Harvard Apparatus, US), the scalp was cut from the midline with a scalpel to reveal the bone structure [26]. Dental burr holes were drilled in the skull on both sides over the lateral ventricles by using the stereotaxic coordinates (0.8 mm posterior to the bregma, 1.4 mm lateral to the sagittal suture, and 4.8 mm beneath the surface of the brain) [26,27].

2.3. Experimental groups

The Control Group: No surgical procedure or injection was performed in the control group. The animals were decapitated at the end of the learning experiment.

The Sham Group: Artificial Cerebrospinal Fluid (aCSF) was injected into the lateral ventricles of the rats bilaterally (ICV 5 μl). IP vehicle injection was performed on the animals in the Sham Group for 13 days.

The OKA Group: A total of 200 ng OKA (Santa Cruz Biotechnology, Texas, USA) that was dissolved in 5 μl aCSF was administered ICV bilaterally to rats [28].

OKA + CAP: A total of 200 ng OKA that was dissolved in aCSF in a volume of 5 μl was administered to the rats ICV bilaterally. Then, CAP (Santa Cruz Biotechnology, Texas, USA) was dissolved in Dimethyl Sulfoxide (DMSO) and diluted with 99% phosphate buffer and 1 mg/kg CAP was injected IP for 13 days [23].

The OKA + CPZ: A total of 200 ng OKA that was dissolved in aCSF in 5 μl volume was administered to the rats ICV bilaterally. Then, CPZ (Santa Cruz Biotechnology, Texas, USA) was dissolved in DMSO, diluted with 99% phosphate buffer, and a 1 mg/kg CPZ injection was given IP for 13 days [23].

OKA + CAP + CPZ: A total of 200 ng OKA that was dissolved in aCSF in a volume of 5 μl was administered to the rats as bilateral ICV. Then, 1 mg/kg CAP and CPZ injections were administered IP for 13 days.

2.4. Morris water maze test

All the rats were taken to the Morris Water Maze (MWM) Test 14 days after the surgery to measure their spatial memory. The MWM was designed by Richard G. Morris to measure spatial memory in rodents [29]. The water tank, which was 60 cm in height and 150 cm in diameter, was filled with water until a height of 40 cm. The temperature of the water was maintained at 26 ± 2℃. The tank was divided into 4 virtually equal quadrants (northwest, northeast, southeast, and southwest). The northwest quadrant was set as the target quadrant. A platform that had a diameter of 10 cm was placed on the target quadrant 1–2 cm below the water surface and 30 cm from the edge of the pool. To prevent the rats from seeing the platform when released into the water, the water in the pool was dyed black with a non-toxic paint (Mixol, Germany).

In the first 4 days, which included the trial test, the animals were released into the water in the tank from four different directions, 4 times at 20-minute intervals each day. The rats were allowed to swim for 120 s to find the hidden platform. The animals, which could not locate the hidden platform in 120 s, were left on the platform for 30 s to learn visual cues around them. The Escape Latency Times of the rats were measured during the learning period that lasted for 4 days. In the probe trial test on the 5th day, the platform in the tank was removed and the animals, which were released into the water from one direction, were allowed to swim for 120 s. The time spent by the rats in the target quadrant (i.e. the quadrant where a platform was placed) was measured. A computerized video camera system (Ethovision, Noldus) was used to record the movements of the animals in the MWM.

2.5. Histopathological examination

At the end of the MWM Test, the anesthetized rats were decapitated. The brain tissues of the rats were removed and placed in a 10%

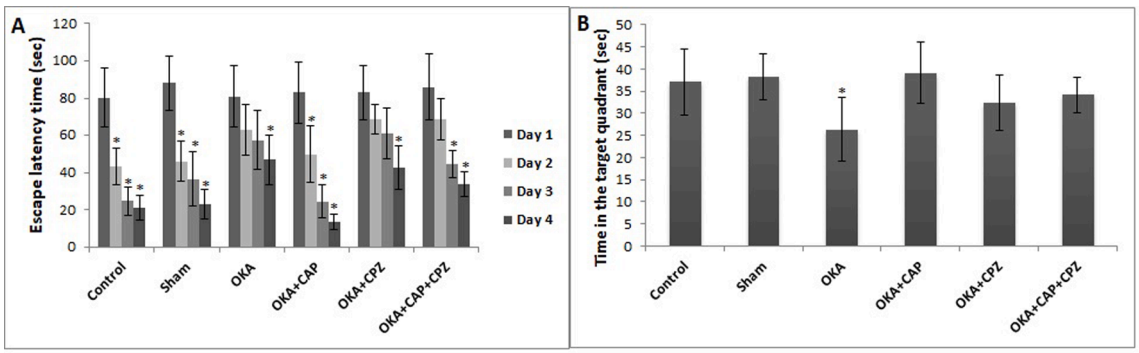

Fig. 1. Effect of TRPV1 agonist capsaicin and TRPV1 antagonist capsazepine on okadaic acid-induced impairment of spatial memory. Capsaisin significantly reduced the latency time significantly on OKA-induced spatial memory impairment in rats. *p < 0.05 different from day (A). Capsaisin application increased the time spent in the target quadrant. *p < 0.05 different from control, sham, OKA+CAP groups. (B). Data expressed as mean ± SD.

formaldehyde solution. Particular attention was paid to the speedy execution of this process. Then, tissue tracking and paraffin embedding were performed. Sections of 5 μm thickness were taken from paraffin blocks, stained with Hematoxylin&Eosin [30], and analyzed under a light microscope (Olympus BX53; Olympus, Tokyo, Japan). The histopathological score was given according to necrotic cell, and pycnotic nucleus damage and frequency. Scoring was done as follows: 0: no damage, 1: there is little damage, 2: there is moderate damage, 3: there is severe damage [30].

2.6. Immunohistochemistry analysis

The Avidin-Biotin-Peroxidase Method was applied immunohistochemically to determine the immunoreactivity of the caspase-3, p-tau-(ser396), Aβ, phosphorylated glycogen synthase kinase-3 beta-(ser-9) (p-GSK-3β-(ser9)), tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) (Santa Cruz Biotechnology, Texas, USA) in the cortex and hippocampus CA3 regions of the brain. Then, 5 μm-thick sections that were taken from paraffin blocks were kept in an oven at 60 °C for 1 night and passed through xylene and decreasing grade alcohol series treated with citrate buffer for antigen retrieval after washing with distilled water. Hydrogen Peroxide was applied after washing with Phosphate-Buffered Saline (PBS). The subsequent operations were performed by using the Large Volume Detection System Kit. Then, a serum block was applied for 5 min. After the serum block, caspase-3, p-tau-(ser396), Aβ, p-GSK-3β-(ser9), TNF-α, IL-1β, and H2AX were applied overnight at + 4 °C as Primary Antibodies. After the administration of the primary antibodies, secondary streptavidin-HRP and DAB chromogen with biotin

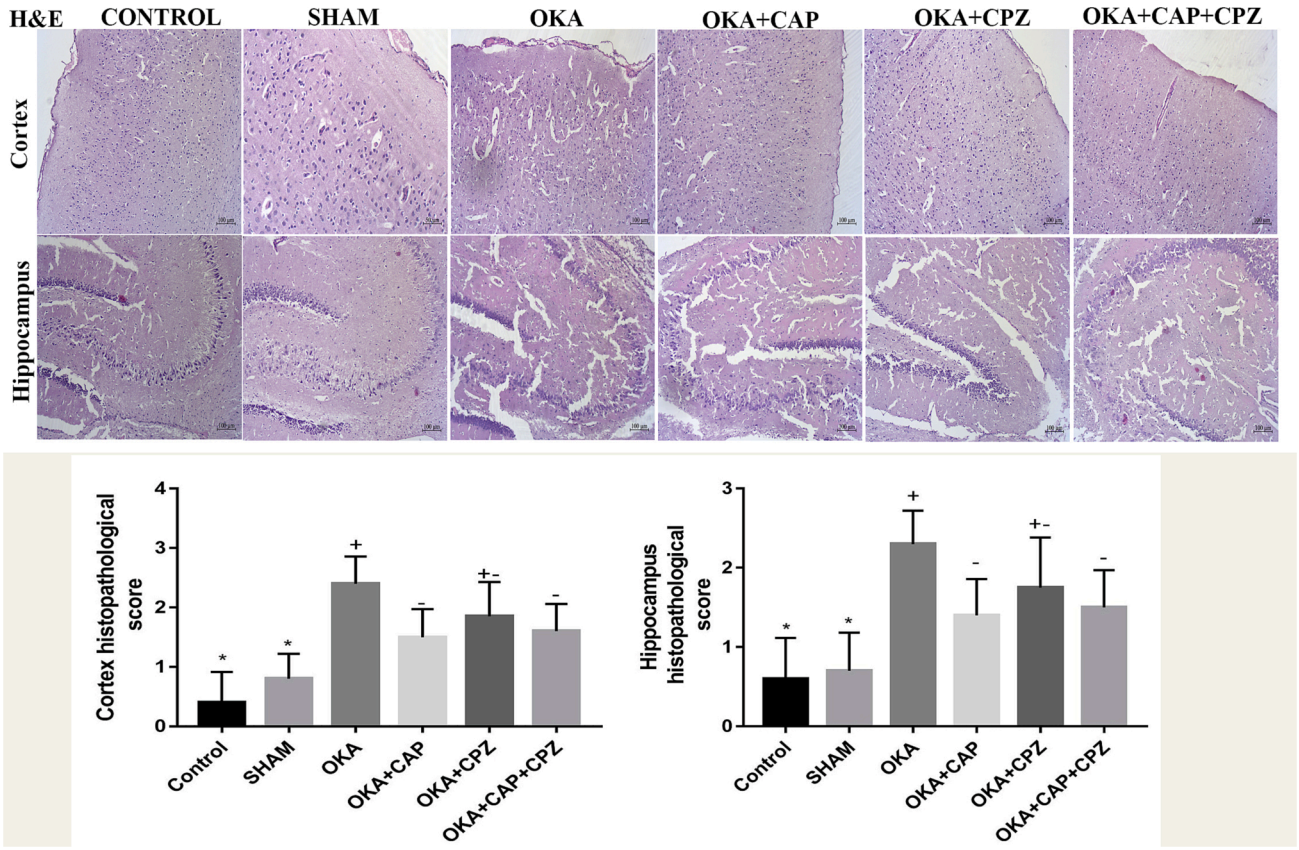

Fig. 2. H&E staining images of the cortex and hippocampus CA3 region. X400. Histopathological score results of the cortex and hippocampus CA3 region. All data are expressed as the mean ± SD. There is no significant difference among groups with same symbol (*,+,-). Data expressed as mean ± SD.

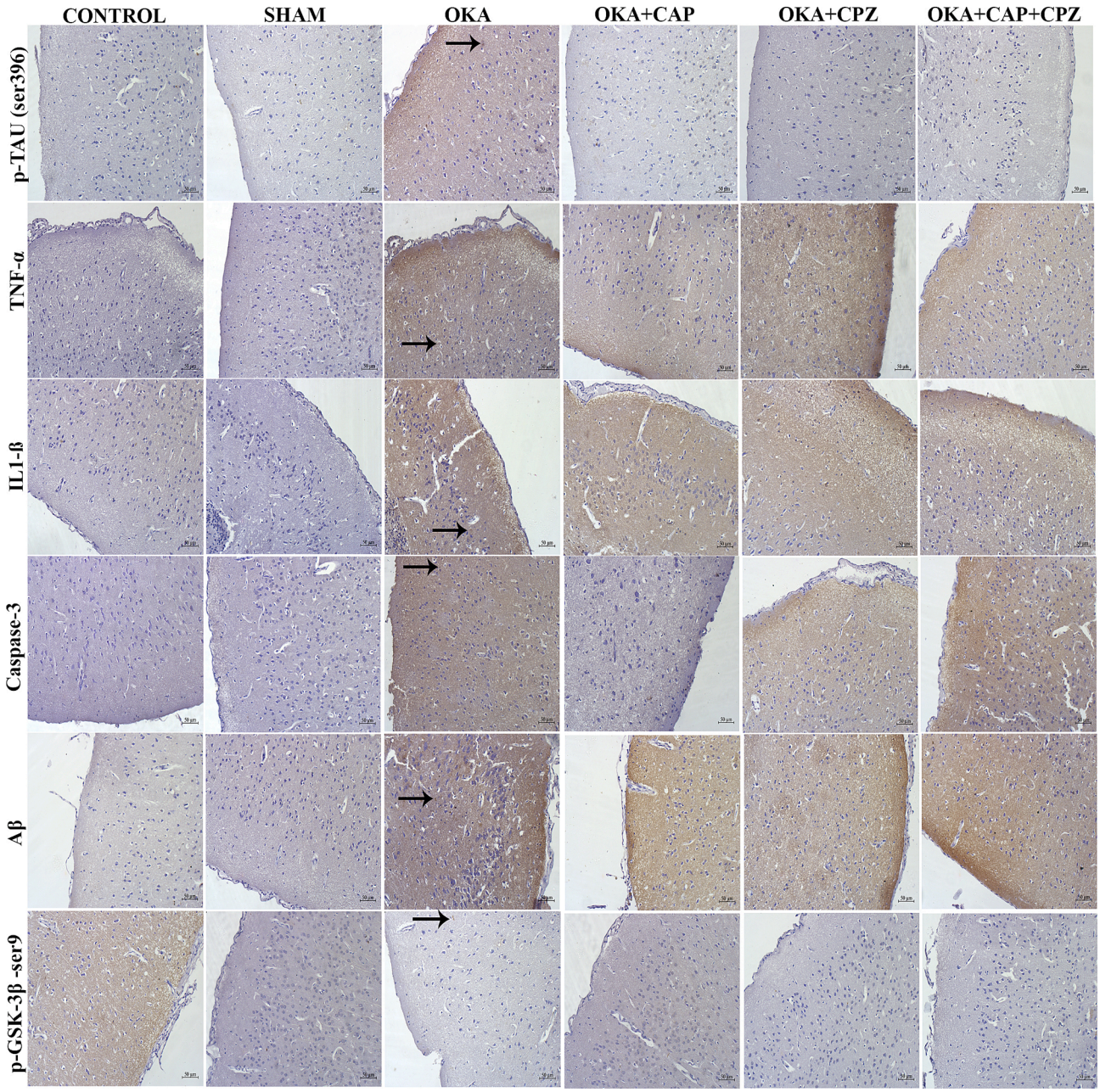

Fig. 3. Immunohistochemistry images of cerebral cortex p-tau-(ser396), TNF-α, IL1-β, caspase-3, Aβ, and p-GSK-3β-(ser9). X200.

were applied, and counterstaining was performed with Gill Hematoxylin. Finally, the sections were passed through a gradually increasing alcohol series and xylene and closed with Entellan. Scoring was performed after measuring immunoreactivity from 10 different areas on the images taken from the slides. Scoring was done as follows; "0: No staining, 1: Little staining, 2: Moderate staining, and 3: Severe staining" [30].

2.7. Statistical analysis

The SPSS 22 Package Program was used for the statistical analysis of the MWM Test data for the evaluation of spatial memory. The Shapiro-Wilk Test was used to understand whether the data showed homogeneous distribution. The One-Way ANOVA Test was used to evaluate the data on the 5th day of the MWM Test (Probe Trial Test) and the Post-Hoc Tukey Test was used to make multiple comparisons between the groups. Repeated measurements ANOVA Test was used in the statistical analysis of the data (the Trial Test) of the first 4 days of the MWM Test. Statistical analyzes for histological data were performed by using the GraphPad Prism version 7.00 for Mac (GraphPad Software, La Jolla, CA). D'Agostino Pearson's Omnibus Test was used to identify the normal distribution of the data. In the case of the normal distribution, quantitative variables were compared using the One-Way Analysis of Variance and Tukey's Post-Hoc test. Values were expressed as mean ± standard deviation (SD). A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. The results of the Morris water maze test

When the escape latency times were evaluated in the first four days of the MWM test in the trial test (Fig. 1A), it was found that the escape latency times were significantly shorter on the second, third, and fourth days in the Control, Sham, and OKA + CAP groups compared to the first

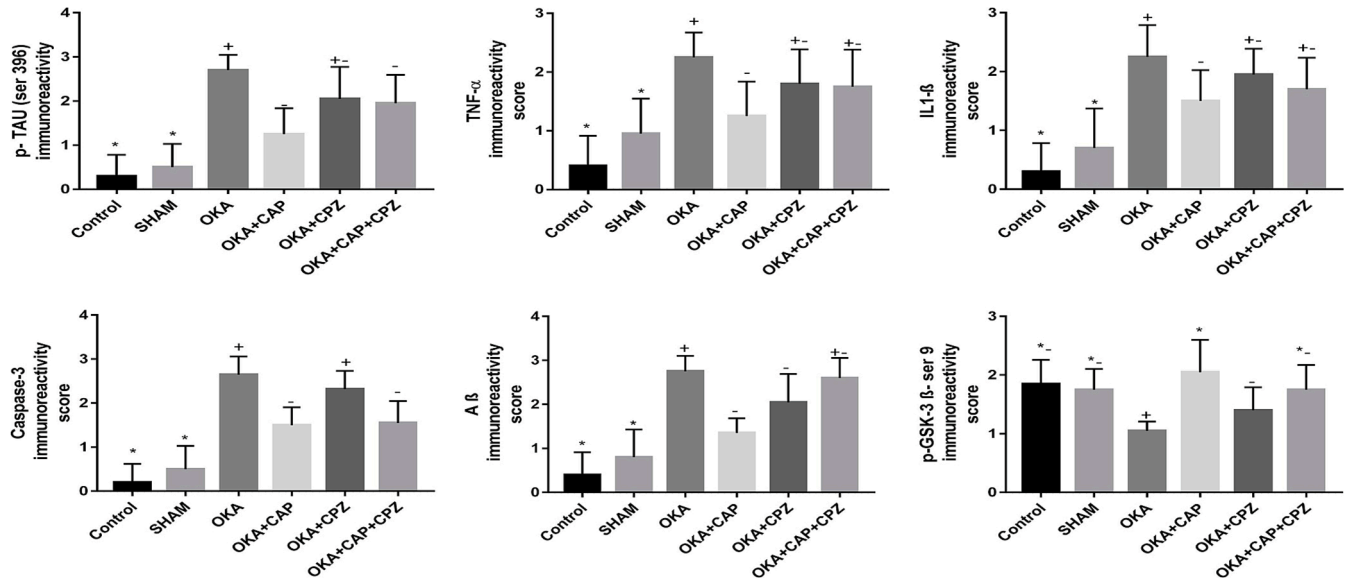

Fig. 4. Capsaicin administration decreased OKA-induced p-tau-(ser396), TNF-α, IL1-β, caspase-3, Aβ immunoreactivity levels and increased p-GSK-3β-(ser9) immunoreactivity levels in the cerebral cortex. All data are expressed as the mean ± SD. There is no significant difference among groups with same symbol (*,+,-).

day ($p < 0.05$). The escape latency times decreased at statistically significant levels only on the fourth day in the OKA and OKA + CPZ groups compared to the first day ($p < 0.05$). The escape latency times decreased at statistically significant levels on the third and fourth days in the OKA + CAP + CPZ group compared to the first day ($p < 0.05$).

It was found in the probe trial test on the fifth day of the MWM test (Fig. 1B) that the time spent in the target quadrant in the OKA Group decreased at a significant level compared to the Control and Sham groups ($p < 0.05$). The time spent in the target quadrant increased significantly in the OKA + CAP group compared to the OKA group ($p < 0.05$).

3.2. Histopathological findings

Hematoxylin&Eosin staining images are given in Fig. 2 and graphics are given in Fig. 2. Histopathological damage in the cortex and hippocampus tissue of the OKA Group increased at a significant level compared to Control and Sham groups ($p < 0.05$). Histopathological damage in cortex and hippocampus tissues was reduced at a significant level in OKA + CAP, and OKA + CAP + CPZ groups compared to the OKA Group ($p < 0.05$).

3.3. Immunohistochemical findings

3.3.1. Cerebral cortex immunohistochemical findings

Immunohistochemical findings in the cerebral cortex are given in Figs. 3-4. The immunoreactivity of p-tau-(ser396), TNF-α, IL-1β, caspase-3, and Aβ in the cerebral cortex region increased at significant levels in the OKA group compared to the Control and Sham groups ($p < 0.05$). The p-GSK-3β-(ser9) immunoreactivity showed a statistically significant decrease in the OKA Group compared to the Control and Sham groups ($p < 0.05$). In the OKA + CAP group, p-tau-(ser396), TNF-α, IL-1β, Caspase-3, and Aβ immunoreactivities were decreased at significant levels compared to the OKA group ($p < 0.05$). The p-GSK-3β-(ser9) immunoreactivity was increased at a significant level in the OKA + CAP group compared to the OKA group ($p < 0.05$). Caspase-3 and p-tau-(ser396) levels were significantly decreased in the OKA + CAP + CPZ group compared to the OKA group, while p-GSK-3β-(ser9) levels were significantly increased ($p < 0.05$).

Aβ immunoreactivity was decreased in the OKA + CPZ Group at a statistically significant level compared to the OKA Group, and the p-GSK-3β-(ser9) levels were significantly decreased ($p < 0.05$).

3.3.2. Hippocampus immunohistochemical findings

Immunohistochemical findings of the hippocampus are given in Figs. 5-6. p-tau-(ser396), TNF-α, IL-1β, Caspase-3, and Aβ immunoreactivity in the hippocampus CA3 region increased in the OKA group at a statistically significant level compared to the Control and Sham groups ($p < 0.05$). The p-GSK-3β-(ser9) immunoreactivity showed a statistically significant decrease in the OKA group compared to the Control and Sham groups ($p < 0.05$). Although p-tau-(ser396), TNF-α, IL-1β, caspase-3, and Aβ immunoreactivities showed a significant decrease in the OKA + CAP group compared to the OKA group, and the p-GSK-3β-(ser9) immunoreactivity increased at a statistically significant level ($p < 0.05$). TNF-α, IL-1β, and Aβ levels were significantly decreased in the OKA + CAP + CPZ group compared to the OKA group and p-GSK-3β-(ser9) levels were increased at statistically significant levels ($p < 0.05$).

Aβ immunoreactivity was decreased in the OKA + CPZ group at a statistically significant level compared to the OKA group ($p < 0.05$).

4. Discussion

AD, which is the most common cause of dementia, is a progressive neurodegenerative disease. It is estimated that the prevalence of AD will increase approximately 2–3 times by 2050 on a worldwide scale [31]. AD, which progressively leads to mental, behavioral, and functional decline and loss of learning ability, poses great emotional and financial burdens on the patient's family and society [32]. Although various drugs are used for AD, these drugs cannot prevent the progression of the disease. Intracellular NFT and extracellular Aβ accumulation, neuroinflammation, and cholinergic nerve loss are prominent in the pathology of the disease [33]. Genetic AD accounts for approximately 5–10% of all cases, and sporadic AD for approximately 90–95%. For this reason, studies on sporadic AD have great importance [34]. ICV OKA administration, which is among the experimental animal models employed to understand the pathophysiology of AD and to conduct studies for the development of new treatments, is a sporadic AD model [35]. OKA, which is a selective inhibitor of PP1 and PP2A enzymes, can cross the cell membrane easily. The inhibition of PP1 and PP2A causes hyperphosphorylation of tau proteins in neurons. It is already known that the level and activity of PP1 and PP2A in the brain are low in AD [36]. One of the tau protein regions dephosphorylated by protein phosphatases is

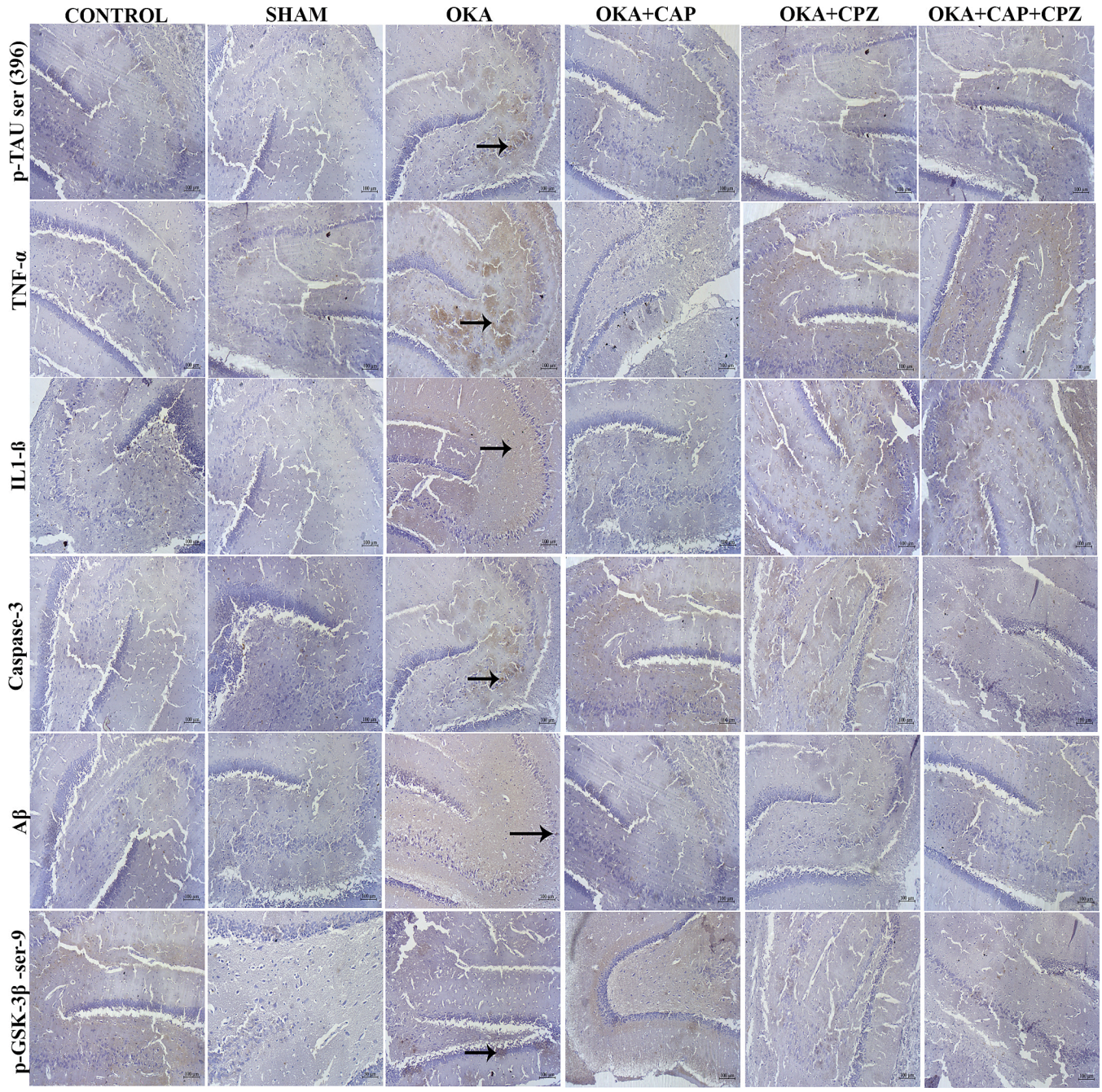

Fig. 5. Immunohistochemistry images of the hippocampus CA3 region p-tau-(ser396), TNF-α, IL1-β, caspase-3, Aβ, and p-GSK-3β-(ser9). X200.

ser396 [37]. Tau hyperphosphorylation was accompanied by impaired memory formation, increased microglial activation in the brain, neuroinflammation, oxidative stress, and increased Aβ accumulation in many experimental studies in which ICV OKA was used [8–11,38]. In the present study, caspase-3, p-tau-(ser396), Aβ, TNF-α, IL-1β levels, and histopathological damage increased, and p-GSK-3β-(ser9) levels decreased in the cortex and hippocampus CA3 regions of the brains of the rats in the OKA Group. Also, according to the results of the MWM Test, the spatial memory of the rats was impaired in the OKA Group.

Ca^{2+} modulates many neuronal processes, including synaptic plasticity and apoptosis. The intracellular Ca^{2+} dysregulation reveals the characteristics of AD, including Aβ accumulation, tau hyperphosphorylation, and neuron death [39]. It was shown previously that TRPV1 channels, which are Ca^{+2} permeable non-selective cation channels, exist in many regions of the brain, including the cortex and hippocampus [20]. In previous studies, it was reported that TRPV1 agonist CAP increases NMDA-receptor-dependent Long-Term Potentiation (LTP) in the CA1 region of the hippocampus reducing Long-Term Depression (LTD). It was also reported to regulate GABAergic activity [40]. TRPV1 channels have functions regarding the regulation of neurogenesis, synaptic transmission, plasticity, and cognitive functions [21,41].

In a study conducted by Kim et al. in a 3xTg-AD mice model, TRPV1 deficiency was shown to improve cognitive functions and decrease Aβ and phosphorylated tau levels [24]. In their study conducted on 3xTg transgenic mice, Wang et al. reported that TRPV1 activation with CAP reduced phosphorylated tau(ser396), Aβ levels, and memory impairment [25]. In the Sucrose-Induced AD model, the TRPV1 agonist rutaecarpine was reported to decrease memory impairment, synaptic plasticity, and tau hyperphosphorylation and increase GSK3-β-(ser9)

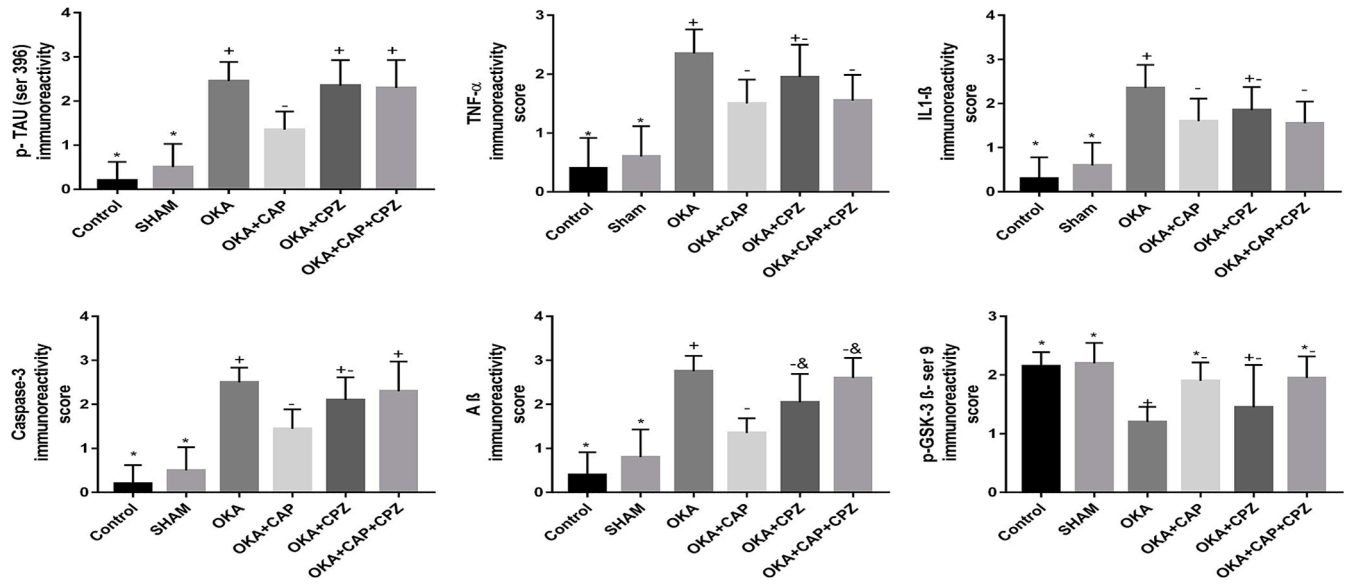

Fig. 6. Capsaicin administration decreased OKA-induced p-tau-(ser396), TNF-α, IL1-β, caspase-3, Aβ immunoreactivity levels and increased p-GSK-3β-(ser9) immunoreactivity levels in hippocampus CA3 regions. All data are expressed as the mean ± SD. There is no significant difference among groups with same symbol (*,+,-,&).

levels [42]. In their study, Xu et al. showed that CAP administration decreased the p-tau-(ser396) levels in the hippocampus and increased the p-GSK3-β-(ser9) levels in rats with experimental diabetes [43]. In the study of Du et al., it was shown that TRPV1 level decreased in brain tissue in the APP23/PS45 genetic AD model, and the activation of TRPV1 with CAP improved LTP, cognitive and synaptic deterioration in the hippocampus CA1 region [23]. In another study, mice, to which ICV Aβ was applied, were treated with CAP and CPZ, and the disruption of synapses and LTP in the hippocampal CA1 region was found to have reduced in CAP-treated mice [44]. The hippocampus is known to play a critical role in learning and memory. The most important regions of the hippocampus involved in learning and memory formation are CA1, CA3, and the dentate gyrus [45].

The MWM Test is used in AD research to evaluate spatial memory formation in rodents [46]. In the present study, ICV OKA administration impaired spatial memory formation. The impairment in spatial memory, which occurred with the ICV OKA administration, improved in the CAP group. The administration of the CPZ failed to correct the spatial memory corruption.

Caspase-3, which plays key roles in neuronal apoptosis, was shown to be associated with neuronal damage in many neurodegenerative diseases such as AD [47,48].

The accumulation of Aβ causes the formation of neuritic plaque, which is characteristic of AD pathology. The accumulation of Aβ causes tau hyperphosphorylation in AD, and tau hyperphosphorylation causes Aβ accumulation [49].

As a large protein, tau protein maintains the structure of microtubules, which have important functions such as maintaining the shape of neurons and axonal transport. The activity of the tau protein, which is located between microtubules providing their stability, is determined by the level of phosphorylation. The phosphorylation level of tau proteins should be in balance. The kinases and phosphatase enzymes in the cell maintain this balance. The tau protein is phosphorylated from many sites under abnormal conditions, which causes the structure of microtubules to deteriorate. The disruption of the structure of microtubules causes NFT formation and neuron damage in the cell [6]. GSK3β is a serine protein kinase that is involved in cell signaling in glucose metabolism and regulation of cell proliferation. GSK3β is an important molecule in the development of AD and is involved in the formation of double-helix filament NFT. The phosphorylation of GSK3β at the serine 9 site inhibits its activity at significant levels. Unlike the serine region, Tyr216 phosphorylation of GSK3β increases its activity [7,50]. In the present study, TRPV1 agonist CAP decreased the already-increased Caspase-3, Aβ, and p-tau(ser396) levels and histopathological damage in the cortex and hippocampus CA3 regions with ICV OKA administration. Also, TRPV1 agonist CAP increased the already-decreased GSK3β-(ser9) level in the cortex and hippocampus CA3 region with ICV OKA administration.

Neuroinflammation is associated with neurodegenerative diseases such as AD, multiple sclerosis, Parkinson's Disease, and amyotrophic lateral sclerosis. In clinical and experimental studies conducted previously on AD, it was reported that the production of cytokines such as TNF-α and IL-1β increases in the brain. Like microglia, astrocytes are cells releasing proinflammatory cytokines. Neuroinflammation is a process that increases neuronal damage further [51]. It was reported in a study that was conducted in a genetic AD model that CAP administration reduced neuroinflammation by decreasing TNF-α, and IL-1β levels in the brain [52]. In the present study, CAP administration decreased TNF-α and IL-1β levels in the cortex and hippocampus CA3 regions. In our current study, when we evaluated the data obtained by MWM test, histopathological and immunohistochemical examinations, we found that there were similar findings between the CPZ group and the OKA group. These data show us that activation of TRPV1 channels rather than inhibition is more effective on preventing neurogeneration.

5. Conclusions

Despite all the advances in medicine, the definitive treatment of AD has not been found yet. The drugs used for treatment purposes are aimed at slowing the progression of the disease and its symptoms [53,54]. The pathology of AD is complex and many fundamental questions remain unanswered. A better understanding of the underlying biology contributing to neurodegeneration is needed urgently. Especially Aβ and tau remain the predominant targets in therapeutic research on AD [55]. In the present study, an AD-like experimental model that aimed to generate hyperphosphorylated tau was used. TRPV1 channels modulating intracellular Ca^{2+} levels have important roles in the nervous system in physiological and pathological conditions [22]. TRPV1 agonist CAP decreased the neurodegeneration by correcting the changed TNF-α, IL-1β, caspase-3, Aβ, p-Tau (ser396), and p-GSK-3β (ser9) levels

in cortex and hippocampus CA3 regions with ICV OKA administration. Also, CAP fixed the spatial memory, which was impaired by the OKA administration. The TRPV1 agonist CAP might be a new therapeutic agent for neurodegenerative diseases such as AD associated with tau hyperphosphorylation; however, further studies to be conducted on the subject are needed.

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.

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