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Effect of Telmisartan on Hippocampal Alterations Induced by Streptozocin in Male Rats

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Abstract:
Introduction: Basic experiments suggest that telmisartan, is unique among angiotensin receptor blockers in which it has a role in neural injury, neuroinflammation, and cognitive function by activating peroxisome proliferator activating receptor gamma (PPAR-γ). The aim of the study is to investigate the potential effect of telmisartan on the hippocampal immunohistochemical markers of male rats' dementia model induced by streptozocin intracerebroventricularly (ICV). **Materials and methods:** Hippocampal alterations was induced by administering streptozocin (3 mg/kg ICV) and concomitantly treated with telmisartan (3mg/kg p.o) for 4 weeks in wistar albino male rats. Biochemical parameters include MDA, GSH, TNF-α and IL-1β in brain tissue were estimated. In addition immunohistochemistry for detection of Glial fibrillary acidic protein (GFAP) and neuronal nitric oxide synthase (nNOS) expression were also estimated.**Results:** Administration of streptozocin(STZ) was significantly increased oxidative stress and neuroinflammation of the rat's brain. Concomitant used of telmisartan significantly attenuate oxidative stress and neuroinflammation. **Conclusion:** Telmisartan has beneficial effects against oxidative stress and neuroinflammation in brain tissue of rats submitted to STZ ICV.
Keywords: Telmisartan, hippocampus, oxidative stress, inflammation.

1. Introduction

The hippocampus is an area of the brain that is involved in short and long term memory [1, 2]. The loss of neurons or axonal degeneration secondary to ischemia can result in deficits of the hippocampus spatial memory [3]. Prolonged circulatory deficits induce irreversible changes in the brain tissue inflicting the damage and death of neural cells [4]. Ischemia is primarily occurs as a result of oxygen and energy substrates loss, for example, glucose. In contrast to glucose, which has some alternatives, oxygen has no substitute as the final electron acceptor in the oxidative phosphorylation pathway, which is why its loss dramatically decreases ATP production and causes an electron leakage generating reactive oxygen species (ROS). Persisting glycolysis leads to intracellular acidification further impairing cell functions [5]. Many possible risk factors and pathological alterations have been used in the elaboration of *in vitro* and *in vivo* models of this alteration in rodents, including intracerebral infusion of streptozotocin (STZ) [6]. Telmisartan, a unique angiotensin receptor blocker (ARB) with peroxisome proliferators activated receptor gamma (PPAR-γ) stimulating activity, protects against cognitive decline partly because of PPAR-γ activation [7]. Activation of PPAR-γ protects rat hippocampal neurons against A beta-induced neurodegeneration, by preventing the excitotoxic rise in bulk-free Ca^{2+}. In addition, activation of PPAR gamma results in the modulation of Wnt signaling components, including the inhibition of glycogen synthase kinase-3beta (GSK-3beta) and an increase of the cytoplasmic and nuclear beta-catenin levels [8]. The current study was designed to investigate the effect of telmisartan on immunohistochemical markers in the hippocampus of male rats dementia model induced by intracerebroventricularly (ICV) infusion of streptozocin(STZ).

2. Material and method

Experimental protocol

The study included 36 wistar albino male rats weighing (200-250 gm); they were obtained from the animal house of the College of Pharmacy/Al-Mustansiriya University. The animals were maintained at controlled temperature (25±2 ˚C) with light schedule 12-12 hour's light/dark cycles, allowed free access to water, and fed standard rat chow *add libitum*. Telmisartan tablets were provided by Boehringer Ingelheim pharmaceutical company, Germany, while streptozocin was provided by Abcam, UK. Animals were allocated randomly into 3 groups and treated as follows:

Group 1: includes 12 rats received saline orally for 4 weeks and served as negative controls. Group 2: includes 12 rats injected 3 mg/kg as a single dose of streptozocin ICV followed by oral saline for 4 weeks, and served as positive control. Group 3: includes 12 rats injected 3 mg/kg streptozocin ICV as a single dose followed by oral dose of 3 mg/kg telmisartan for 4 weeks. At the end of treatment period, all rats were sacrificed under anesthesia by intraperitoneal injection of 100 mg/kg thiopental (24 hours after the last administration of telmisartan and saline). Craniotomies were performed to obtain brains for the assessment of tissue damage.

Preparation of samples and analysis

After sacrificing the animals, brains were excised from each animal immediately, and the hippocampus tissues

obtained according to a rat brain atlas, placed in 10% formalin buffer solution for 24 hours at room temperature, blotted with filter paper and accurately weighed, followed by dehydration step, by immersing it in a gradually increasing concentration of alcohol. Brain tissues were kept in xylene for one hour under a temperature of 60˚C, and then embedding it in paraffin wax. A rotary microtome was used to cut sections at 5 µm in thickness, which sequentially mounted onto microscope slides, and stained with hematoxylin and eosin [9].

Preparation of tissue homogenates

A 10% (w/v) brain tissue was prepared in phosphate buffer at 4˚C, using metal head tissue homogenizer which adjusted at set 3 for one minute. The homogenate was then centrifuged at 10,000 g for 15 minutes and the supernatant formed was used for the biochemical estimations. All samples were kept frozen at (-18˚C) unless analyzed immediately.

Biochemical assays

Brain tissue homogenate malondialdehyde (MDA) and glutathione (GSH) assay

The product of lipid peroxidation malondialdehyde (MDA) level was measured in tissue homogenates depending on the formation of pink chromophor because of the reaction between (MDA) and thiobarbituric acid (TBA), which can be measured spectrophotometrically according to the method of Buege and Aust [10]. Glutathione (GSH) levels were determined according to the method of Elman [11], in which 0.5 ml of 4% sulphosalcylic acid was added to the equal volume of tissue homogenate for precipitation of protein.

Estimation of TNF-α and IL-1β levels in brain tissue

The quantification of TNF-α and IL-1β was completed with the help and instructions provided by Ray Biotech. Inc. Quantikine rat TNF-α, IL-1β immunoassay kits. The assays employ the sandwich enzyme immunoassay technique [12].

Immunohistochemistry for detection of Glial fibrillary acidic protein (GFAP) and neuronal nitric oxide synthase (nNOS) expression in paraffin –embedded sections:

The sections were processed by using paraffin embedded blocks which were sectioned at 5 µm for detection GFAP and nNOS using a commercially available kit. The sections were positioned on a positively charged slide. They were deparafinized and rehydrated through a descending alcohol series followed by distilled water. The sections were incubated with sodium citrate buffer in humidity heat chamber for antigen retrieval. Subsequently, the endogenous peroxidase activity was inactivated with hydrogen peroxide. The non specific bindings were blocked with a protein blocking reagent. Slides were examined, after staining with eosin and hematoxylin. Scoring of GFAP expression was done for percentage of staining intensity per field as following (157):0 = none, 1 =< 5%, 2 =5-25%, 3 = 25-75% and 4 =75-100% [13]. The immunostaining for neuronal nitric oxide synthase (nNOS) was graded in five classes according to the percentage of stained tissue [14]: 0= when the staining was absent, 1= when the percentage of stained tissue varied from 1%-25%, 2= when the percentage of stained tissue varied from 26%-50%, 3= when the percentage of stained tissue varied from 51%-75% and 4= when the percentage of stained tissue was superior to 75%.

Statistical analysis

The data were expressed as mean ± standard error of the mean (SEM) and statistically analyzed by using unpaired student t-test and analysis of variance (ANOVA). P-values less than 0.05 were considered significant for all data presented in the results.

3. Results

Effect of telmisartan on MDA and GSH levels in brain tissue of rats treated by STZ

Administration of 3 mg/ kg STZ ICV resulted in a significant elevation ($p< 0.05$) of MDA level and a significant($p< 0.05$) reduction of GSH level in brain tissue of rats treated with saline for 4 weeks when compared with group one(table 1). Meanwhile, daily oral administration of telmisartan(3mg/ kg) for 4 weeks resulted in a significant($p< 0.05$) reduction of MDA level and a significant($p< 0.05$) elevation of GSH level in brain tissue of rats in group 3 when compared with those animals in group 2, but still these values are significantly($p< 0.05$) different when compared with values of group 1(table 1).

Effect of telmisartan on TNF-α and IL-1β levels in brain tissue of rats treated by STZ

A significant ($p< 0.05$) decrease in TNF-α and IL-1β were recorded in rats given a single dose of STZ ICV when compared with group 1, meanwhile group 3 in which oral administration of telmisartan(3 mg/kg) concomitantly after STZ ICV significantly($p< 0.05$) reduced TNF-α and IL-1β when compared with group 2, but still significantly higher ($p< 0.05$) when compared with group 1 (table 1).

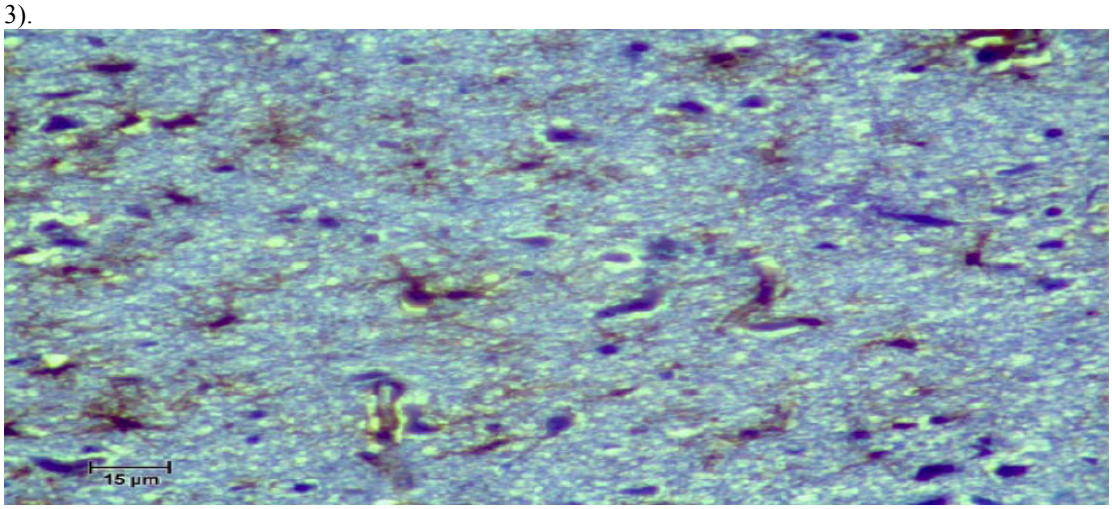
Table 1: The effect of 3 mg/kg telmisartan on biochemical parameters in brain tissue homogenate of rats treated by STZ

Treatment groups	MDA nmol/gm tissue	GSH µmol/gm tissue	TNF-α pg/ gm tissue	IL-1β pg/ gm tissue
Normal saline group n= 12	43.5± 1.88[a]	10.45±0.13[a]	11.96±0.98 [a]	4.76±0.66 [a]
STZ(3 mg/ kg) n= 12	92.87±2.57[b]	4.82±0.37 [b]	69.1±3.41 [b]	26.32±1.49 [b]
STZ(3 mg/ kg) + telmisartan(3mg/kg) n= 12	57.62±3.05[c]	6.69±0.24 [c]	31.27±3.27 [c]	18.33±1.15 [c]

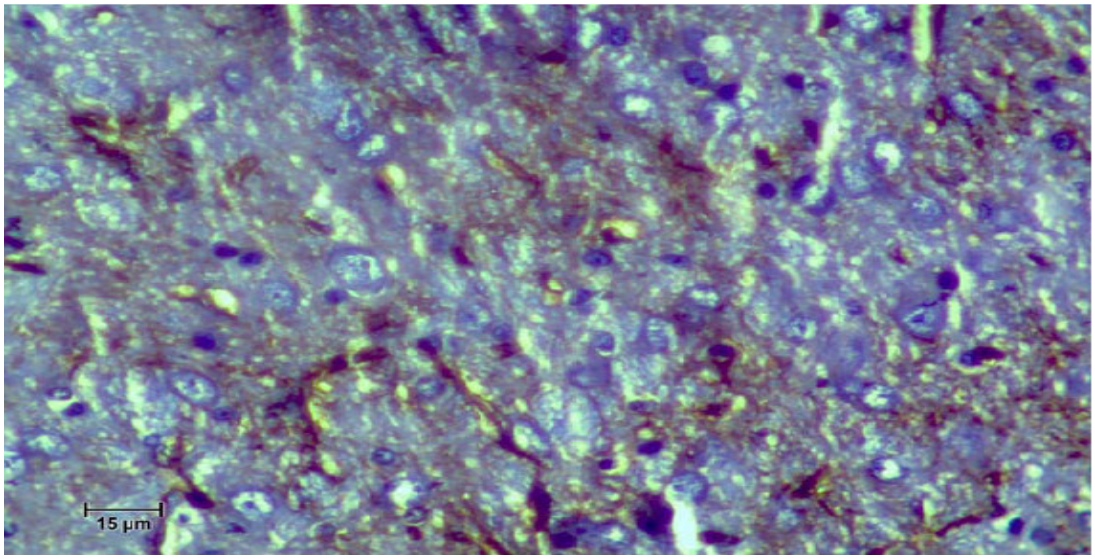
Data were expressed as mean ± SEM; n= number of animals, values with non identical superscripts (a,b,c) within the brain tissue were considered significantly different($p<0.05$)

Effects of telmisartan on glial fibrillary acidic protein (GFAP)

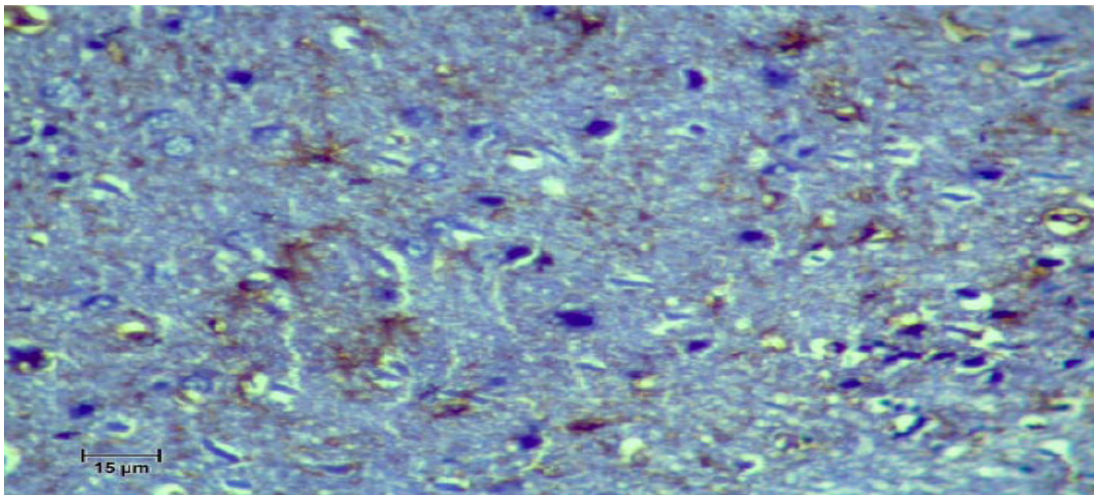
Analysis of data statistically revealed a significant difference ($p<0.05$) among the groups. Administration of STZ followed by saline for 4 weeks in group 2 showed a significant ($p<0.05$) elevation in GFAP when compared with group 1. Furthermore, concomitant use of telmisartan (3 mg/kg p.o) showed significant ($p<0.05$) reduction when compared with group 2 but still significantly elevated when compared with group 1(table 2 and figures 1, 2 and 3).



(Figure 1): Immunohistochemical staining for hippocampus expressions of GFAP marker in the group one (saline group). (Scale bar at left lower corner represents 15µm (400 x)



(Figure 2): Immunohistochemical staining for hippocampus expressions of GFAP marker in the group administered 3mg/kg streptozocin. (scale bar at left lower corner represents 15µm(400x))



(Figure 3): Immunohistochemical staining for hippocampus expressions of GFAP marker in the group administered 3mg/kg streptozocin with 3 mg/ kg telmisartan (Scale bar at left lower corner represents 15µm (400x))

(Table 2): The effect of 3 mg/kg telmisartan on GFAP in hippocampus of rats treated by STZ

Treatment groups	GFAP	nNOS
Normal saline group n= 12	1.97 ± 0.15^{a}	1.87 ± 0.22^{a}
STZ(3 mg/ kg) n= 12	4.12 ± 0.21^{b}	3.44 ± 0.15^{b}
STZ(3 mg/ kg) + telmisartan(3mg/kg) n= 12	2.29 ± 0.12^{c}	1.92 ± 0.8^{a}

Data were expressed as mean ± SEM; n= number of animals, values with non identical superscripts (a,b,c) within the brain tissue were considered significantly different($p<0.05$)

Effects of telmisartan on neuronal nitric oxide synthase (nNOS) in the hippocampus of rats treated by STZ

Table 3 showed that nNOS was significantly ($p<0.05$) reduced after the administration of STZ ICV when compared with control group; however administration of telmisartan orally in a dose of 3mg/kg for 4 weeks was concerned with significant ($p<0.05$) elevation in the level of nNOS when compared with STZ treated group, nevertheless that comparison with group 1 was not significantly different ($p>0.05$) (table 2 and figures 4, 5, 6).

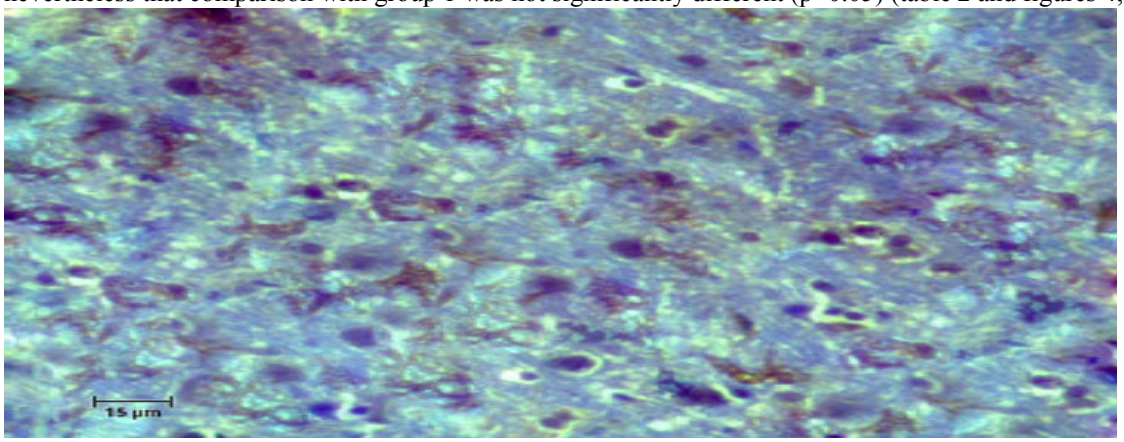


Figure 4: Immunohistochemical staining for hippocampus expressions of nNOS marker in the control (Scale bar at left lower corner represents 15µm (400x))

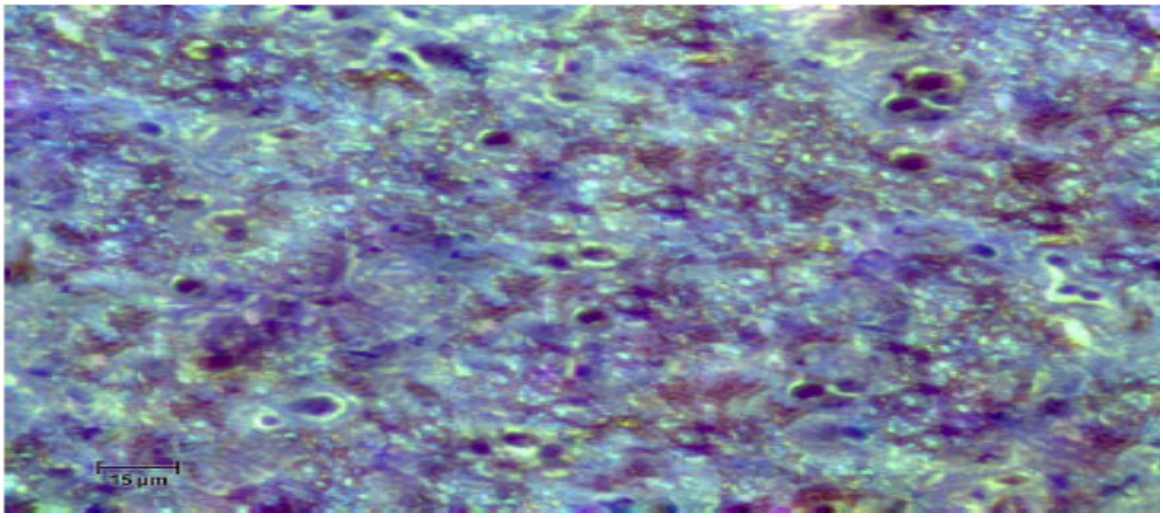


Figure 5: Immunohistochemical staining for hippocampus expressions of nNOS marker in STZ treated group (Scale bar at left lower corner represents 15µm (400x))

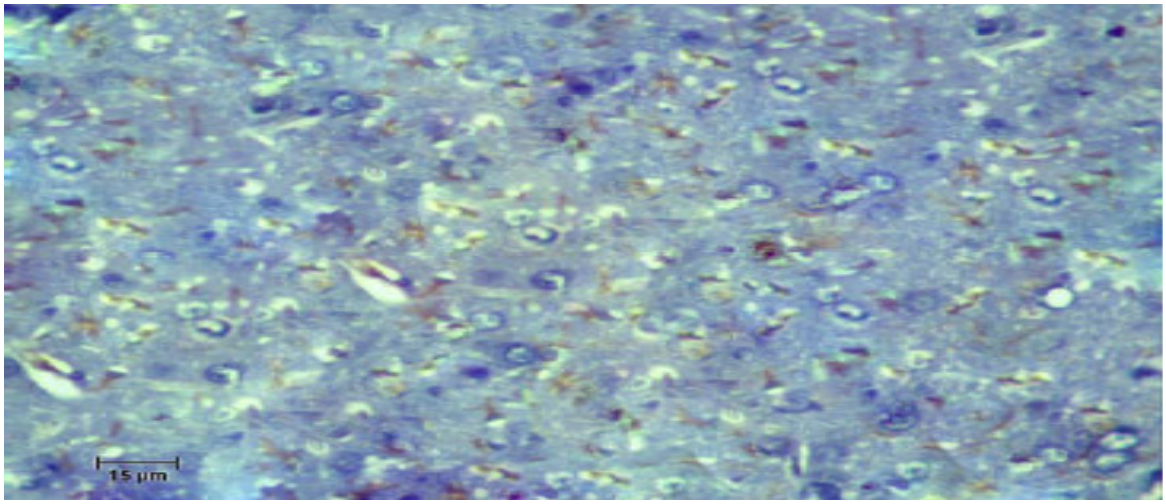


Figure 6: Immunohistochemical staining for hippocampus expressions of nNOS marker in STZ + telmisartan treated group (Scale bar at left lower corner represents 15µm (400x))

Discussion

Streptozocin induced many possible risk factors and pathological alterations have been used in the elaboration of *in vitro* and *in vivo* models of dementia in rodents, including intracerebral infusion of streptozotocin (STZ) [14]. STZ ICV produced impairment in cognition which concerned with a significant increase in brain myeloperoxidase activity, AChE activity, nitrite/nitrate levels and TBARS levels along with depletion of GSH levels [15]. In the current study STZ ICV was associated with significant elevation of oxidative stress and neuroinflammatory mediators including TNF-α and IL-1β in brain tissue homogenates which are in line with the previous studies [16, 17]. STZ ICV in rats causes desensitization of insulin receptors (IRs) and biochemical changes similar to that of Alzheimer dementia or aged brain [18, 19]. In brain tissue insulin controls the breakdown of glucose via IRs in brain which yields acetyl coenzyme A (acetyl CoA), glutamate and adenosine triphosphate (ATP) which required for normal structure and function of neurons [20]. The main constituent of acetylcholine synthesis is acetyl CoA, in which acetylcholine plays a vital role in the learning and memory processes. Insulin receptors IRs are concerned with memory functions and may get alterations due to oxidative stress induced by STZ result in myelin damage and dementia [20]. In addition, it has been reported that ICV STZ, causes an increase in inflammation by up regulation of some genes in brain tissue especially those encoding neurotrophic factor, glial cell derived neurotrophic factor and integrin-alpha-M, in which these findings agreed with the current study which report that inflammatory mediators TNF-α and IL-1β are elevated in brain tissue by administration of STZ ICV [21]. Furthermore, the up regulation of inducible nitric oxide synthase (iNOS) and concomitant increase in oxidative stress with administering STZ ICV leading to the formation of peroxynitrite, a powerful pro-oxidant [22].

In the current study the administration of telmisartan concomitantly with STZ was concerned with a significant reduction in oxidative stress and neuro-inflammation when compared STZ treated group only, but still reported that 4 weeks of telmisartan treatment was not enough to improve the results near that of group one (negative control), except nNOS level in brain tissue which became non significant ($p>0.05$) different when compared with group one. Telmisartan attenuated the damage effect of ICV STZ, as well as the histopathalogical changes. It has been reported that rennin angiotensin aldosterone system (RAS) in the CNS may contribute to the disease process of CNS disorders including Alzheimer disease, probably via neuronal death and memory dysfunctions [23]. Previous studies and literatures reported that high levels of angiotensin II contribute to oxidative stress, neuroinflammation and inhibit acetylcholine release in rats and humans [24, 25, 26, and 27].Furthermore, it has been reported that stimulation of RAS causes activation of inflammatory cytokines that concerned with neuroinflammation and incidence of dementia[28].Thus, administration of ARBs like telmisartan in the current study may reduce the inhibitory action on acetylcholine release and thereby increase acetylcholine concentration as well as reduce the activation of inflammatory cytokines, in which this agree with other previous studies[29, 30]. Previous studies have been reported that telmisartan has agonistic activity at peroxisome proliferator activated receptor gamma (PPAR-γ) [31, 32]. Agonistic effects at PPAR-γ exert a neuroprotective and antioxidant effects in ischemia and intracerebral hemorrhage, since deficiency of neuronal PPAR-γ has been reported with cerebral damage after cerebral ischemia [33, 34, 35 and 36]. In addition, studies have also demonstrated that agonistic effects at PPAR-γ are concerned with anti-inflammatory properties which are due to negative regulation of the expression of pro-inflammatory molecules such as IL-1b and TNF-α which are in line with the current study [37, 38]. PPAR-γ considered as a novel target to manage decline in cognition in patients with Alzheimer dementia via reducing spatial memory impairment, Aβ aggregates, Aβ oligomers, astrocytic and microglia activation [39].

Conclusion

According to the results of the current study and the pharmacological actions of telmisartan mentioned above, one can conclude that telmisartan provide beneficial effects by improving oxidative stress and neuroinflammation induced by STZ ICV in rats.

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