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Effect of Adiponectin on Acute Experimental Cerebral Ischemia/Reperfusion Injury

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ABSTRACT

AIM: To examine the effect of adiponectin administration on acute brain injury in an experimental model of cerebral ischemia/reperfusion (I/R) in rats.

MATERIAL and METHODS: The study animals were divided into the following four groups: group I, sham (did not undergo surgical intervention and did not receive drugs); group II, the I/R model (received the intervention, but did not receive drugs); group III (I/R-adiponectin) (the I/R model was used, and the animals were treated with 5 mg/kg adiponectin peritoneally 30 minutes after the ischemia); and group IV (I/R-tirofiban)(the I/R model was used, and the animals were treated with 0.5 mg/kg tirofiban peritoneally 30 minutes after the ischemia).

RESULTS: Tumor necrosis factor-α (TNF-α) and interleukin (IL)-1β levels were statistically higher in the I/R group (group II) than in other groups. In the post-hoc (Tukey) test analysis, groups I, III, and IV had significantly lower TNF-α and IL-1β levels after treatment with both tirofiban and adiponectin than group II. No statistically significant difference was found between groups III and IV in terms of TNF-α levels. However, the decreased IL-1β level was more pronounced in group IV (tirofiban) than in other groups. The mean neurologic deficit scores were statistically significantly different among the groups. In the post-hoc (Tukey) test analysis, neurologic deficit scores were statistically significantly lower in groups III and IV than in group II.

CONCLUSION: Adiponectin has anti-inflammatory and cerebral protective effects in experimental cerebral I/R injury.

KEYWORDS: Rat, Ischemia, Reperfusion, Adiponectin, Tirofiban

ABBREVIATIONS: I/R: Ischemia/reperfusion, **TNF-α:** Tumor necrosis factor-α, **IL:** Interleukin, **GP:** Glycoprotein

INTRODUCTION

Stroke remains the second major cause of death worldwide (1). The most effective treatment for ischemic stroke in the first 4.5-hour (h) acute time window is intravenous thrombolytic reperfusion with recombinant tissue plasminogen activator or clot retrieval with endovascular interventions in patients with appropriate indications (3). Although significant developments have been made in the treatment of ischemic stroke, a low percentage of patients still receive these treatments. Accordingly, for the remainder of the unfortunate large populations that exceed the significantly narrow therapeutic time window, more effective drugs and methods need to be investigated.

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Adipose tissue is known as an active endocrine organ because it synthesizes bioactive molecules called adipokines (21). Adipokines have an important role in inflammation, immunity, insulin sensitivity, and vascular homeostasis (10). Impairment in adipokine production has been associated with increased inflammation and endothelial dysfunction (12). Adipokines are also involved in the pathogenesis of metabolic syndrome (21). Although several in-vivo and in-vitro studies have been conducted to evaluate the role of adipokines on cardiovascular system pathologies, their effects on brain damage have not been fully demonstrated (11,15,21).

Adiponectin is the most produced among the adipokines. It has important effects on both adipose tissue and other tissues. It has cardioprotective and anti-inflammatory effects in ischemia/reperfusion (I/R) syndrome (4,6,8). In addition to reducing insulin resistance, adiponectin has demonstrated potent anti-inflammatory effects in in-vivo and in-vitro studies (28). Adiponectin reduces apoptosis and necrosis in the I/R syndrome of heart, brain, hepatic, and renal tissues. However, the molecular details of these protective effects of adiponectin have not been fully elucidated (4).

Adiponectin reduces insulin resistance and has anti-inflammatory and cardioprotective properties (25). In obesity, many pro-inflammatory adipokines are over produced with increased adipose tissue, whereas adiponectin, which has anti-inflammatory properties, decreases. This leads to obesity-related metabolic disorders and cardiovascular diseases (13,25). Dysfunctional adipose tissue results in obesity, insulin resistance, hypertension, and cardiovascular diseases. Adipose tissue in obesity triggers the infiltration of macrophages and lymphocytes. These changes lead to increased pro-inflammatory adipokines that cause endothelial dysfunction and vascular inflammation. Adiponectin ensures protection against vascular dysfunction caused by lipid dysmetabolism, obesity, and diabetes (13,19,20).

Microglia are the first cells to respond actively to cerebral ischemia. These cells increase pro-inflammatory cytokines, such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α, at the site of ischemia and initiate the inflammatory response and contribute to apoptosis (24). Tirofiban is a selective, non-peptide glycoprotein (GP) IIb/IIIa receptor inhibitor. It inhibits fibrinogen-dependent platelet aggregation and subsequent platelet formation reversibly and has anti-apoptotic effects (9).

The role of adiponectin in cerebral ischemia has not been adequately investigated and understood. This study aimed to investigate the effect of adiponectin administration on acute brain injury in a cerebral I/R model in rats.

MATERIAL and METHODS

Ethics

All experimental procedures were approved by the Ethics Committee of Kutahya University of Health Sciences (23.10.2020-No: 2020.10.01). All experimental procedures were performed following ethical principles. We have made every effort to minimize the suffering to which the animals were exposed and the number of animals used.

Materials

Rat TNF-α and IL1 beta enzyme-linked immunosorbent assay kits (BioVision, Inc. Headquarters: 155 South Milpitas Blvd. Milpitas, California 95035) were used for measuring the serum levels.

To measure the TNF-α and IL-1β levels of all the study groups, 2-mL blood samples were obtained into ethylenediamine tetraacetic acid tubes. All samples were centrifuged at 1000 g for 15 min, and the serum was separated. Subsequently, the sera were stored at –20°C until required for the assay. Standard dilutions were prepared. A standard dilution series (100 µL) and each sample were added to the wells, which were covered with a plate coater and incubated at 37°C for 1 h. After incubation, the liquid in each well was removed. Detection Reagent A working solution (100 µL) was added to each well, which was covered with a plate coater and incubated at 37°C for 1 h. Detection Reagent B working solution (100 µL) was added to each well, which was covered with a plate coater and incubated at 37°C for 30 min. After incubation, each well was washed five times. Substrate solution (90 µL) was added to each well, and the wells were covered with a plate coater and incubated for 10–20 min at 37°C. Samples were measured at 450 nm using a ChoraMate microplate reader to obtain the results.

Animals

In our study, we used 40 Wistar albino female rats with an average mass of 250–300 g, aged 6 to 8 weeks. The rats were observed during the study in an environment with a suitable temperature (21 ± 2°C) and humidity (60 ± 5%). We monitored the rats in this environment for a week before initiating the study to ensure their adaptation to the environment.

Establishment of the Cerebral I/R Model

In this study, an experimental animal model of cerebral I/R was established (2). Anesthesia was achieved by intraperitoneally administering 90 mg/kg of ketamine hydrochloride and 15 mg/kg of xylazine before the surgical procedure. Subsequently, study animals were placed in the supine position, and the neck region was shaved and cleaned first with an antiseptic solution and then with 70% alcohol. After local surgical area cleaning, an approximately 3-cm cervical midline incision was made to expose the left common carotid artery to provide middle cerebral artery I/R. The common carotid artery was reached by advancing with superficial micro-dissection (Figure 1). Subsequently, the internal and external carotid arteries were reached. The internal carotid artery lumen was entered with a 4-0 monofilament nylon suture, the suture was advanced, and the middle cerebral artery was occluded. After 60 min of ischemia, the suture was removed, and reperfusion was achieved. Moreover, the surgical procedure was terminated by suturing the incision. After the ischemia model was applied, the study animals were followed up in the reperfusion phase for 23 h. We divided 40 study animals into four groups (Table I). Group 1, sham, did not undergo surgical intervention and did not receive drugs. None of the rats died in the sham group (n=10). In group II, the I/R model was applied, but the animals did not receive drugs. In the I/R group, two of the rats died

Table I. Comparison of the Mean TNF-α and IL-1β Levels Between The Groups

	Group I, n=10 (Sham)	Group II, n=8 (Cerebral I/R)	Group III, n=8 (Cerebral I/R-Adiponectin	Group IV, n=7 (Serebral I/R-Tirofiban)	p
TNF-α (pg/ml) Mean±SD	55.6 ± 17.2	394.6 ± 52.7	204.8 ± 57.6	155.1 ± 47.7	**<0.001***
IL-1β (pg/ml) Mean±SD	3215.00 ± 1526.22	40475.00 ± 3562.82	26283.33 ± 4610.71	13916.66 ± 4250.49	**<0.001***

***SD:** Standard deviation, **pg/ml:** Picograms/millilitre, **I/R:** Ischemia/reperfusion. One-way ANOVA tests were used; ***:** p <0.05.*

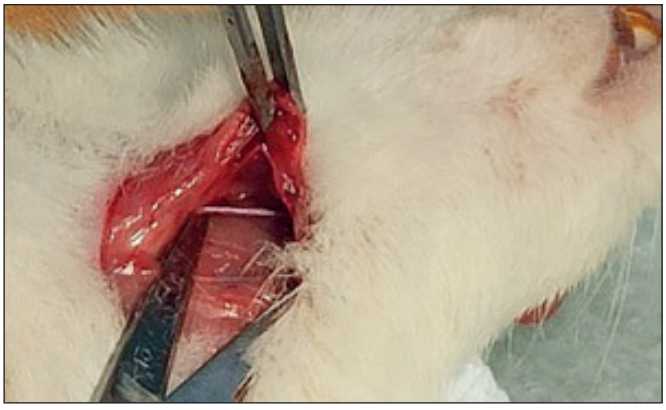

Figure 1: Surgical procedure of ischemia/reperfusion model. The study animals were placed in the supine position. A cervical median line incision of approximately 3 cm was made to provide middle cerebral artery ischemia and reperfusion. The common carotid artery was exposed by advancing with superficial microdissection.

after carotid occlusion operation, and the mortality rate was 20% (n=8). In group III, the I/R model was applied, and 30 min after the ischemia, the animals were peritoneally treated with 5 mg/kg adiponectin. In the I/R group treated with adiponectin, two of the rats died after carotid occlusion operation, and the mortality rate was 20% (n=8). In group IV, the I/R model was applied, and 30 min after the ischemia, the animals were peritoneally treated with 0.5 mg/kg tirofiban. In the I/R group treated with tirofiban, three of the rats died after carotid occlusion operation, and the mortality rate was 30% (n=7).

Observations

Twenty-four hours after the reperfusion, the behavioral responses developed were assessed neurologically just before sacrificing. Motor and behavioral changes were evaluated by scoring between 0 and 4 points (5). The scoring assessment was performed as follows: 0 points, no deficit; 1 point, loss of stretch and flexion of the opposite paw; 2 points, turning to the side of the loss of stretch while walking and circling; 3 points, later oversion toward the left when walking; and 4 points, loss of walking and decreased level of consciousness.

After the procedure, 2-mL blood samples were taken from the study animals in each group to determine the levels of IL-1β and TNF-α. The study animals were sedated with similar anesthetic agents and decapitated at the end of the 24th hour.

Statistical Analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences software package (version 24.0; IBM Corp, Armonk, NY, USA). Data are expressed as mean ± standard deviation. Nonparametric data were compared using the Mann–Whitney U test. One-way analysis of variance was used to compare more than two groups, and then, the analysis was performed using the Tukey test. P<0.05 was considered statistically significant.

RESULTS

TNF-α levels were significantly higher in group II (I/R group) than in other groups (p<0.001). In the post-hoc (Tukey) test analysis, TNF-α levels were significantly lower in groups I, III, and IV after treatment with both tirofiban and adiponectin than in group II (I/R) (p<0.001). No statistically significant difference was found between groups III (adiponectin) and IV (tirofiban) (p=0.28) (Figure 2). The level of IL-1β was significantly higher in group II (I/R group) than in the other groups (p<0.001). In the post-hoc (Tukey test) evaluation, IL-1β levels significantly decreased after treatment with adiponectin and tirofiban (p<0.001). This decrease was more pronounced in group IV (tirofiban) than in the other groups (Figure 3).

The results of TNF-α and IL-1β of the groups and the statistical analysis are shown in Table I. The mean neurologic deficit scores of groups II (I/R), III (treated with adiponectin), and IV (treated with tirofiban) were 2.71 ± 0.75, 1.62 ± 0.51, and 1.57 ± 0.78, respectively. The mean neurologic deficit scores were statistically significantly different among the groups (p=0.008). In the post-hoc (Tukey) test analysis, neurologic deficit scores were statistically significantly decreased in groups III (treated with adiponectin) (p=0.017) and IV (treated with tirofiban) (p=0.015). However, no significant difference was found between groups III and IV (p=0.87) (Table II).

DISCUSSION

In previous studies, adiponectin effectively prevented experimental I/R injury (5,18,26,27). The expression of TNF-α-induced endothelial adhesion molecules, transformation of macrophages to foam cells, TNF-α production in macrophages and adipose tissue, and smooth muscle cell proliferation are inhibited by adiponectin. In addition, adiponectin has

Table II: Comparison of the Neurological Deficit Scores of the Groups

	Group II, n=8 (Cerebral I/R)	Group III, n=8 (Cerebral I/R- Adiponectin	Group IV, n=7 (Serebral I/R- Tirofiban	P
Neurological deficit score (Mean ± SD)	2.71 + 0.75	1.62 ± 0.51	1.57 ± 0.78	0.008*

***SD:** Standard deviation, **I/R:** Ischemia/reperfusion. ***:** p <0.05.*

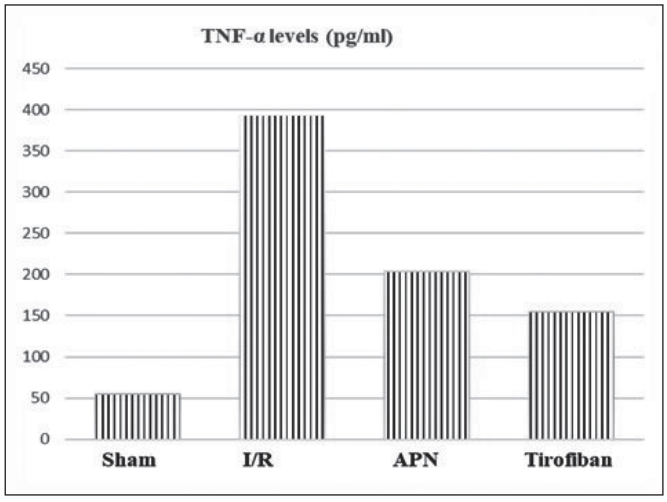

Figure 2: TNF-α levels were significantly higher in the ischemia/reperfusion group (group II) (p<0.001).TNF-α levels were significantly decreased after treatment with both tirofiban and adiponectin compared to theischemia/reperfusion group (p<0.001). **Sham:** group I; **I/R:** group II (ischemia/reperfusion); **ADP:** group III (cerebral I/R-adiponectin); **tirofiban:** group IV(cerebral I/R-tirofiban).

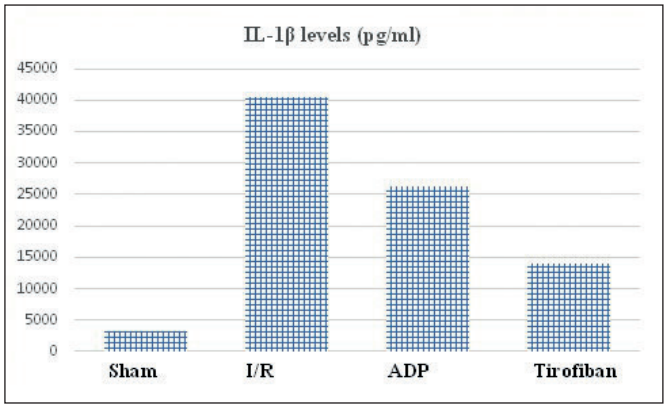

Figure 3: IL-1β levels were significantly higher in the ischemia/reperfusion group (group II) (p<0.001). IL-1β levels were significantly decreased after treatment with both tirofiban and adiponectin compared to theischemia/reperfusion group (p<0.001). **Sham:** group I; **I/R:** group II (ischemia/reperfusion); **ADP:** group III (cerebral I/R-adiponectin); **tirofiban:** group IV (cerebral I/R-tirofiban).

antiapoptotic and antioxidant effects, which play a role in its cardioprotective effects (29). In this study, we focused on the anti-inflammatory effect of adiponectin in brain injury due to experimental cerebral acute ischemia and its effect on functional recovery of neurologic deficits.

Oxidative stress and apoptosis have important roles in ischemic stroke because they lead to neurologic deficits and pathogenesis. The pro-inflammatory process has an important role in the complex pathogenesis of acute cerebral ischemia (14,22). Adiponectin has anti-inflammatory effects and improves oxidative stress (14). Inflammation plays an important role in the progression of cerebral injury after I/R injury (5). IL-1β and TNF-α are pro-inflammatory cytokines that are increased in ischemia (5,17,24). In this study, increased levels of serum IL-1β and TNF-α were shown in non-treated rats that experienced I/R injury. Serum levels of IL-1β and TNF-α were lower in rats treated with adiponectin than in the non-treated I/R group. This finding was similar in the rats treated with tirofiban. This indicated that adiponectin had anti-inflammatory effects on cerebral I/R injury. These findings emphasize the beneficial effects of adiponectin in cerebrovascular disorders.

The main known functions of adiponectin include anti-inflammatory, antioxidant, and antiatherogenic effects (8). Adiponectin levels in healthy brains are significantly low. In cases of acute cerebral ischemia, circulating adiponectin can enter the brain due to blood–brain barrier damage (5). In contrast, circulating adiponectin was temporarily reduced in patients with the acute phase of ischemic stroke (23). A recent study conducted by Bai et al. verified the protective effect of exogenous adiponectin pretreatment on acute cerebral ischemic injury (2). However, the effect of exogenous adiponectin treatment after acute cerebral ischemic injury was investigated in few studies. Based on the importance of oxidative stress and inflammatory reactions in the ischemic cerebrovascular disease pathogenesis, adiponectin was suggested for use as a potential treatment agent due to its anti-inflammatory and anti-oxidative effects (30). Liu et al. reported the beneficial effects of adiponectin due to its antioxidant and anti-inflammatory functions when used before cerebral ischemia. The authors suggested that adiponectin could be a potential therapeutic target (16). According to the results of these studies, we focused on the anti-inflammatory effect of adiponectin and hypothesized that its cerebral protective and therapeutic effects were related to its anti-inflammatory effect.

Tirofiban is a selective, low-molecular-weight, non-peptide thrombocyte GP IIb/IIIa receptor inhibitor. It prevents fibrinogen-dependent binding to thrombocytes reversibly and sub-

sequent formation of thrombi by preventing the final step of thrombocyte activation (31). Tirofiban reduced disability and provided rapid functional independence in patients with acute stroke without increasing the risk of complications (32). The present study showed that adiponectin administration effectively reduced neurologic deficits similar to tirofiban in cerebral ischemia/post-reperfusion brain injury in rats. This may indicate that adiponectin has a strong neuroprotective effect. According to the human study of Efstathiou et al., hypoadiponectinemia increased mortality in patients with ischemic stroke and had a negative correlation between adiponectin levels and infarct size (7). These results suggest that adiponectin has an important role in stroke and that its therapeutic effects should be investigated.

CONCLUSION

In conclusion, adiponectin inhibits the cerebral expression of IL-1β and TNF-α, which play important roles in brain injury caused by I/R. Adiponectin reduces neurologic dysfunction due to brain damage caused by I/R with its anti-inflammatory effects. Therefore, adiponectin may be an important therapeutic target in the treatment of cerebral ischemic injury.

AUTHORSHIP CONTRIBUTION

Study conception and design: NE, MC, HEA, GA

Data collection: NE, MC, HEA, FAA

Analysis and interpretation of results: NE, MC ,HEA, FAA, SCK

Draft manuscript preparation: NE, MC

Critical revision of the article: NE, GA, SCK

Other (study supervision, fundings, materials, etc...): MC, GA, SCK, FAA

All authors (NE, MC, GA, FAA, HEA, SCK) reviewed the results and approved the final version of the manuscript.

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