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Significance of Suppression of Cerebral Gluconeogenesis in the Protective Value of Exercise Post Conditioning Towards Ischemic Injury in Rats

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Abstract

The practice of exercise before a stroke lowers neurovascular damage and improves functional results. In order to determine the extent to which regulation of gluconeogenesis was related to how much brain damage post-stroke exercise training (PostE) prevented, this research set out to investigate these questions. Middle Cerebral Artery (MCA) blockage for 72 hours ensued by 24 hours of resuscitation in young rats. After 24 hours after a reperfusion PostE's treadmill exercise was started. Infarct quantity, neurological deficits at one and three days after reperfusion as well as apoptosis of cells was used to gauge the extent of the brain injury. Oxaloacetate (OAA), glucose, lactate, pyretic acid, phosphoenolpyruvate (PEP), and ROS were quantified by ELISA, and immunofluorescence was used to the critical enzyme phosphoenolpyruvate carboxykinase (PCK)-1/2's site and production. By using Western blot, we were able to identify upstream pathways such as forehead 3-kinase (PI3K)/Akt, p-PI3K/Akt, transcription factor (FoxO1), and all of them. Additionally, immunofluorescence was used to find p-FoxO1 expressed in the cytoplasm. PostE is superior to non-exercise control. Subsequently one and three days, there were smaller brain infarction sizes, neurological problems, and cell death. On both days, OAA was higher in postE groups and lower affects the expression of tissue PCKs, PEP, pyretic acid, lactate, ROS, glucose. The workout environment also drastically reduced PCK-1/2 expressions. Additionally, PostE dramatically increased the expression of phosphorylated PI3K, AKT, and FoxO1 proteins at one and three days. In this work, PostE suppressed gluconeogenesis and decreased brain damage after stroke in conjunction with increased PI3K/AKT/FoxO1 signalling. These findings imply that FoxO1 control of gluconeogenesis is a factor in post-stroke brain protection.

Keywords: phosphoenolpyruvate carboxykinase (PCK)**,** Endoplasmic retinal (ER), ischemia/reperfusion (I/R), microscopic endothelial cells (MEC)

Introduction

A stroke, among the two largest reasons for death worldwide, kills approximately 5.5 million individuals annually. Endoplasmic retinal (ER) strain is implicated in physiological reactions, both short- and long-term, to cerebral ischemia (1). Numerous cardiovascular conditions may lead to brain ischemia/reperfusion (I/R) damage. Heart failure, low blood pressure, and bypass surgery on the coronary arteries are major causes of global cerebral ischemia (2). Despite the procedure and thrombus removal are critical for reducing ischemic neuronal damage, reperfusion injury to the penumbra may still cause significant harm to neurons, glia, and blood vessels (3). A preliminary investigation of Dysgenic's (DG) neuroprotective role against traces of brain injury in a STZ-induced type 2 diabetes Zebra fish model, with the goal of examining its glucose-regulating effect (4). To get precise, scientists postulated that a

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rise in blood pH would decrease the effects of oxidative stress and acidity generated from the stimulation of hyperglycolysis and gluconeogenesis in ischemia/reperfusion injury. These results could contribute to novel therapeutic approaches for reducing brain tissue loss after an ischemic stroke (5). In contrast, restoration after ischemia may cause serious brain failure referred to as cerebral IR damage, therefore early blood supply or reperfusion is the most efficient means of treating cerebral ischemia (6). The neurovascular device's microscopic endothelial cells (MECs) in the brain respond quickly and actively to ischemia, setting in motion critical events that contribute to further harm. There has been a lot of research looking at the functions and processes of cerebral MECs in ischemic brain damage because of how important they represent (7). Ischemic post-conditioning, additionally referred to as ischemic preparation, has been explored extensively to reduce brain tissue loss caused by stroke. Excluding for among novel study proving its usefulness in ischemia damage, it has not been widely studied (8). They demonstrate that ischemic post conditioning protects against cerebral I/R injury through its neuroprotective properties, which operate through lowering apoptotic and preventing respiration in damaged brain cells (9). Emerging and potential therapies that target key cellular processes occurring during ischemia and reperfusion that contribute to acute (10). The reduction of the effects of oxidative stress and apoptosis may underlie the beneficial benefits of a substance called extract and exercise. Either stevia on its own or in tandem with physical activity provides a greater more health benefits compared to employ out individually **(**11**).** Considering a protein called expression was directly associated with IPO's protective effects it was stands to reason that obesity drop and additionally inhibition in diabetes mellitus contribute to I/R damage worsening and insufficient efficacy (12). Gastrointestinal ischemia is a leading cause of death and disability, and IIRI is a syndrome that occurs inevitably in these cases. Clinical therapy is complicated by the gradual emergence of symptoms throughout the perinatal period and the lack of targeted therapies (13). Ischemic sensitivity can potentially be induced by either remote preconditioning or post conditioning. These findings indicate that distant preconditioning, including distant early and late post conditioning, protects the spinal cord from damage. After the commencement of spinal cord ischemia, remote ischemic conditioning is carried out on a different region (14). Development into transmembrane protectors is required to develop better therapies for IR damage, because the mitochondrial outer membrane permeabilization (MOMP) and the breakdown of mitochondrial membrane phospholipids are critical intermediate stages on the road to cell death (15).

Cardiovascular risk variables can potentially effectively lowered with exercise training. Both in animal models and people, exercise training has been shown to reduce the heart's susceptibility to IR (16). Through the process of the PI3K/Akt2 indicate process, which is adversely mediated through MicroRNA-124, as a protective mechanism, could possess a preventative impact. There is still a need for further in-depth research on the viability of IPostC's use in medicine (17). The processes through which exercise provides cardio protection are quite similar to those by which remote ischemic conditioning does so. Nonetheless, its possible function in diabetic individuals' myocardial protection is limited

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undetermined (18). Cardiovascular disease, hypertension, and hematopoietic difficulties have all been linked to an increased risk of myocardial ischemia in clinical and experimental studies of Anabolic steroids inappropriate use (19). Cerebral ischemia is a significant health concern that has the potential to end in death and disability (20). Although there have been potential pharmacological strategies for defending the heart against that have been shown in experimental investigations, there are difficulties in using these discoveries in reality (21). Cerebral ischemia-reperfusion damage could become reduced by infliximab and leflunomide immunotherapy instead of by ischemic post conditioning. Although postconditioning therapy for brain damage has been shown to have therapeutic benefits, the effectiveness of postconditioning depends on the duration that the recurrences have become (22). The context of decision, these findings indicate that the compound pinocembrin, when administered at the start of or before to restoration in externally injected rat and in person mouse strains, has strong protective effects on cardiac I/R damage by increasing glycolsis (23).

Materials and Methods

The National Capital Medical University Animal Ethics Committee provided its institutional authorization regarding the study we performed. According to the national institutes of health's guide for the care and use of laboratory animals. Three groups of adult Sprague-Dawley rats were randomly assigned. Middle cerebral artery occlusion (MCAO) control without PostE, MCAO, and with PostE, MCAO. Mice were sacrificed Morphological and molecular analysis at Posted 1 and 3 days examination after being given PostE 24 hours after ischemia. Western blotting and Immunofluorescence experiments were simply performed on contra lateral ischemic hemispheric.

Focal cerebral ischemia and reperfusion

Ischemic animal groups were treated with right MCAO for 2 hours. Rats were first sedated employing a precision vaporizer and 3% isoflurane to maintain the sedative effect that had been calibrated to ensure accurate dosing. The middle cerebral artery (MCA) was occluded from the right common carotid artery to the right internal carotid artery using a 4-0 poly-L-lysine-coated nylon suture. Throughout the operation, clinicians kept a close eye on the patient's temperature PCO_2, PO_2 at the core and cerebral circulation.

PostE program

Each rat were exposed to MCAO, and then exercise control group or an exercise group for post-stroke or a non-exercise cohort. They previously presented an experiment in which rats ran at a modest pace of 12 meters per minute on a treadmill device. Every day, the rats spent 30 minutes on a treadmill. During the activity phase, three rats shared a conventional cage for the same amount of hours.

Cerebral infarct volume and neurological deficit

Infarct quantity and neurological condition were determined from one to three days after PostE. Since discussed before sodium 2, 3, 5-triphenyltetrazolium chloride was used to dye

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brain slices from rats that were only two millimetres thickness. Through comparing the ratio of infarct size to contralaterall brain volume, the infarct area may be calculated. Neurological impairments were scored using modified scales twenty-four hours after reperfusion to determine the extent of MCAO. Low-scoring rats weren't involved in the next experiment.

Tunel

During PostE, the demise of cells was assessed using the Tunel test either 1 or 3 days later. They had been put to sleep, perfused with saline, and then their brains were frozen and sectioned using 4% par formaldehyde. Fragmentation of genome was measured using a commercial Tunel detection kit in accordance with manufacturer guidelines according to a fluorescent microscope. The Tunel procedure index was determined by counting the percentage of cells that showed positive staining.

ELISA

They initially stated the preparation for industrial immunoassays utilizing enzymes for use in the retinal reading detection of OAA, PEP, pyretic acid, lactate, reactive oxygen species (ROS), and glucose.

Immunofluorescence

Prior to reported and nuclear protein that is unique to neurons Fluorescent and confocal microscopes developed by Panasonic were used to examine the illustrations**.**

Protein expression

Enzymes in the ischemic brain were isolated and probed with a primary antibody PCK-1 overnight at 4°C in a western blot analysis, as we briefly detailed above. The rats were euthanized either one or three days following exercise. The main antibodies have been treated for 1 h at room temperature with the corresponding IgG-HRP additional antibody. Regarding protein gels, monoclonal antibody (MA) was utilized as a standard.

Statistical analysis

The Statistical Package for served to examine the study's data. One-way analysis of variance (ANOVA) was used to compare various groups to each other. The least significant difference test for post hoc comparisons produced a p value of $p < .05.$

Results

Brain infarction and neurological defects

Cerebral volume of infarct was clearly seen on the transit training center pictures from ischemia/reperfusion animals. PostE greatly reduced infarction. Cerebral disabilities have been observed in the ischemia/reperfusion group on both the 5 and 12-point scales. PostE led to a dramatic drop in both the 5- and 12-point ratings.

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Tunel

Significant apoptosis destruction of cells was caused by ischemia/reperfusion in the ischemic brain. The amount of cell death increased. Represents the (Figure 1A) 24 hours and (Figure 1B) 72 hours compared to the stroke group; cell death was significantly decreased after PostE protocols on days 1 and 3, respectively.

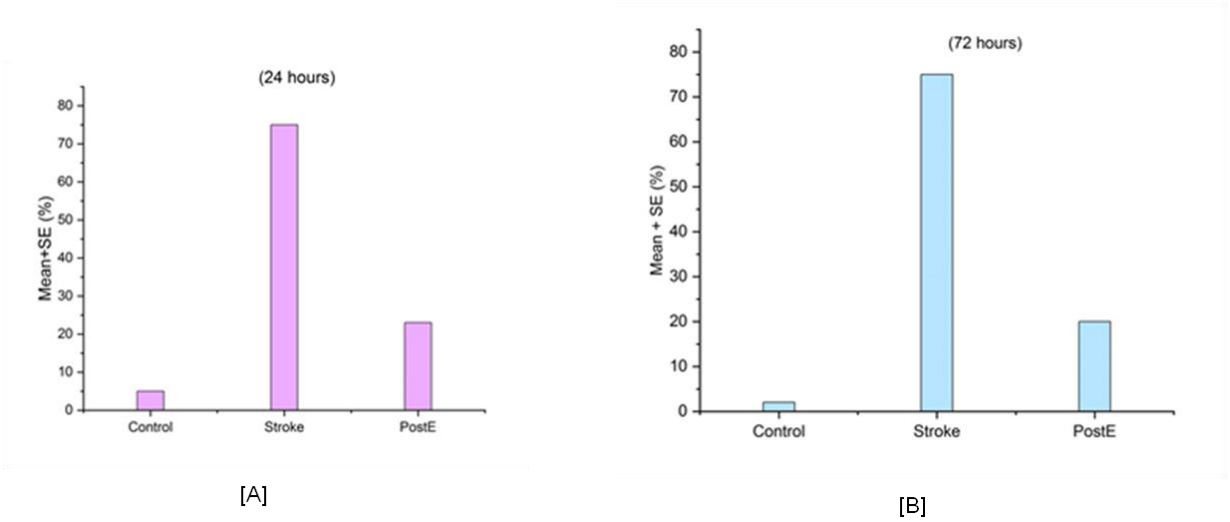

Figure (1): Compared to the stroke group, cell death was significantly decreased after PostE protocols on days 1 and 3, respectively [A] 24 hours [B] 72 hours

For detection of apoptotic cell death, the TUNEL test is widely used. Suppressing cerebral gluconeogenesis is an important factor when evaluating the protective benefits of exercise post-conditioning on ischemia damage in rats.

Gluconeogenesis

Concentrations of oxaloacetate (OAA), phosphoenolpyruvate, pyruvic acid, lactate, reactive oxygen species (ROS), and glucose were measured at 1 and 3 days represents the (Figure 2) gluconeogenesis and glucose levels. Compared to the MCAO-only rats, PostE significantly increased levels. When comparing ischemia/reperfusion and control rats, there was a striking decrease in OAA and an increase in PEP, pyruvic acid, lactate, reactive oxygen species, and glucose. Represents the (Figure 2A) OAA and decreased levels of restored by PostE, (Figure 2B) represents the show that PEP,(Figure 2C) pyruvic acid, (Figure 2D) lactate, and (Figure 2E) ROS (Figure 2F) glucose levels were all reduced from the elevated values seen in the stroke group. These findings show that PostE inhibited gluconeogenesis in response to ischemia.

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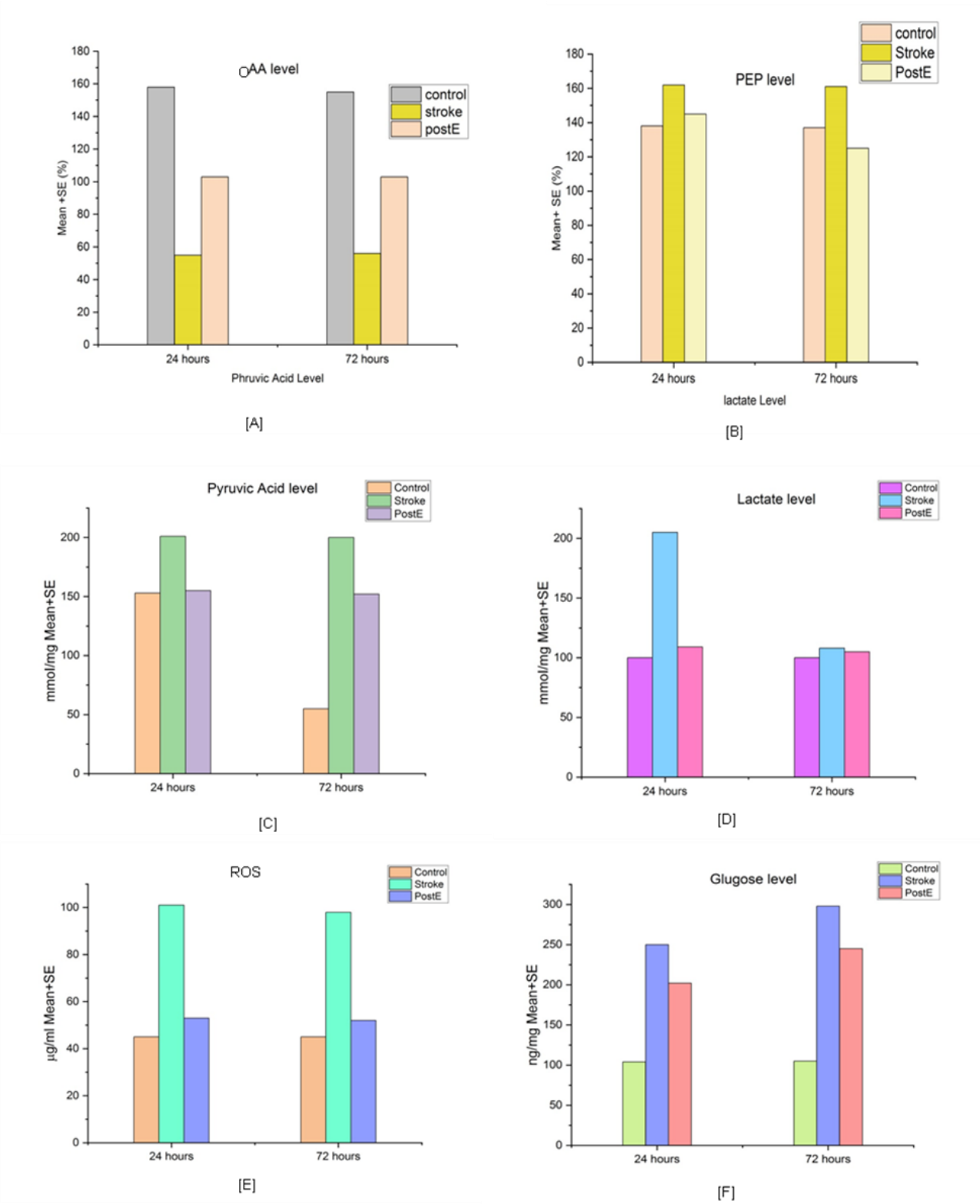

Figure (2): Gluconeogenesis and glucose levels. Compared to the MCAO-only rats, PostE significantly increased levels of [A] QAA [B] PEP [C] pyruvic acid [D] lactate [E] ROS [F] glucose

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The complicated metabolism processes involved in establishing neurological protective effects are highlighted by the importance of inhibiting cerebral gluconeogenesis in the protective benefit of exercise following conditioning. Exercise following conditioning may enhance outcomes and give therapeutic effects in the setting of ischemia damage by regulating glucose metabolism in the brain. There needs to be further investigation into the processes at play and the possible therapeutic implementation from these observations.

Expression of PCKs

I/R injury greatly upregulated PCK-1 and PCK-2 protein expression. Stroke-induced increases in PCK-1. Represents the (Figure 3A) expression of PCKs compared to the MCAO-only rats; PostE reduced protein expressions of PCK-1. Represents the (Figure 3B) PCK-2 PostE versus stroke expression was significantly attenuated by PostE double immunofluorescence labelling of confocal images reveals consistent patterns of PCK expression in neurons. Both PCK1 and PCK2 expression levels in neurons were shown to be elevated after stroke represents the (Figure 4) expression of PCK-1 on neurons Quantification of the fluorescence images show the increasing expression of PCK-1 in neurons after stroke (Figure 4A) PCK-1 24 hours (Figure 4B) pck-1 72 hours. Represents the (Figure 5) expression of PCK-2 on neuron quantification of the fluorescence images show the increasing expression of PCK-2 in neurons after stroke shows that PCK-1 and PCK-2 cellular expressions were reduced after PostE treatment. These data imply that PostE suppressed the expression of critical enzymes in the gluconeogenetic pathway, most notably in synapses after stroke (Figure 5A) PCK-2 24 hours (Figure 5B) PCK-2 72 hours.

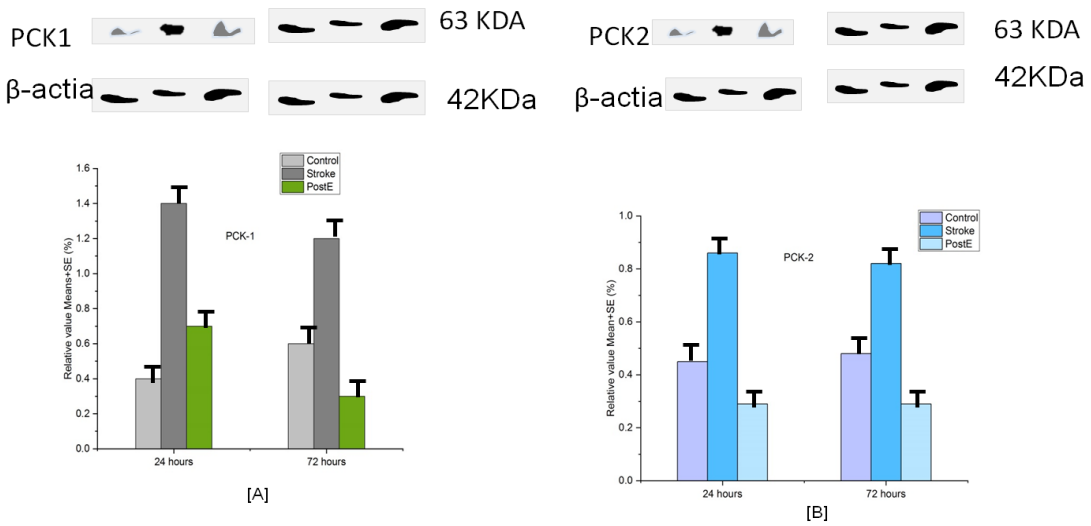

Figure (3): Expression of PCKs. Compared to the MCAO-only rats, PostE reduced protein expressions of [A] PCK-1 [B] PCK-2

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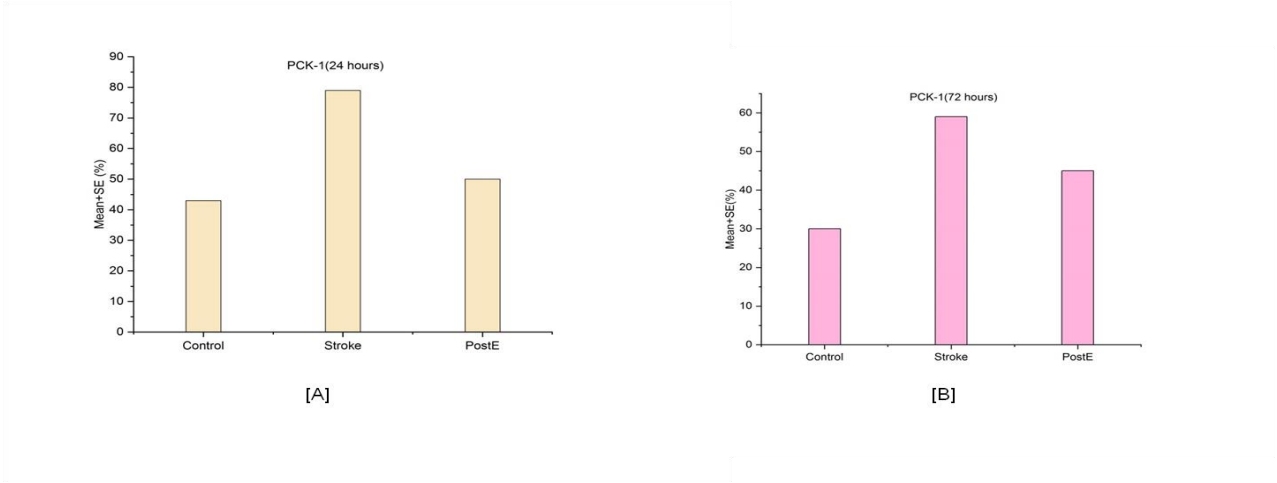

Figure (4): Expression of PCK-1 on neurons [A] pck-1 24 hours [B] pck-1 72 hours

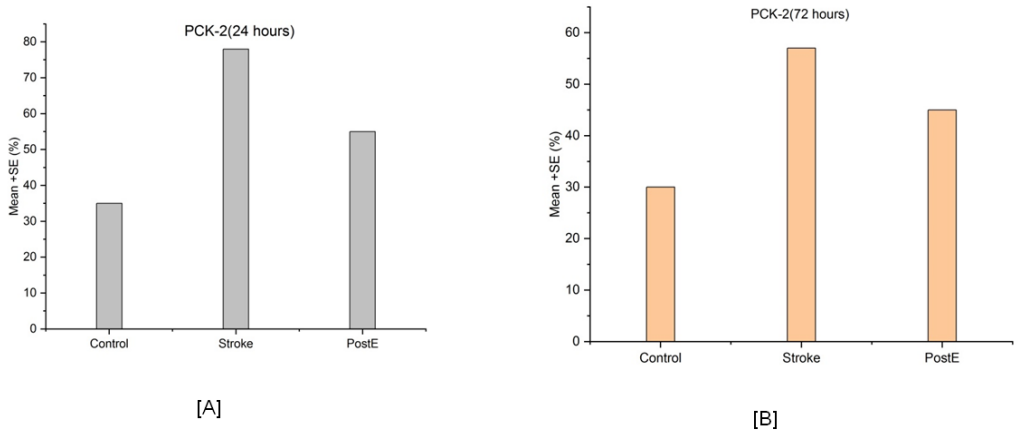

Figure (5): Expression of PCK-2 on neurons [A] pck-2 24 hours [B] pck-2 72 hours

In rats, exercise post-conditioning protects against ischemic injury by increasing the expression of PGC-1 and pyruvate carboxylic kinases (PCKs), two transcriptional coactivators involved in regulating cell-based.

Phosphorylation of PI3K/AKT/FoxO1 and total

Absolute FoxO1 was identified to be significantly higher in the MCAO rats compared to the control rats, whereas phosphorylation of PI3K/AKT/FoxO1 was found to be significantly lower. Shows that PostE once again caused FoxO1 and AKT expression to switch roles. P-FoxO1 shows that PostE boosted expression of p-FoxO1, whereas Figure 6d shows that of p-AKT, and shows that of p-PI3K. Post-stroke gluconeogenesis was reduced, most likely due to PostE's ability to stimulate phosphorylation of the PI3K/AKT/FoxO1 signalling axis. Represents the (Figure 6A) is FoxO1, (Figure 6B) is p-FoxO1, (Figure 6C) is AKT, (Figure 6D) is p-AKT, (Figure 6E) is PI3K, and (Figure 6F) is p-PI3K.

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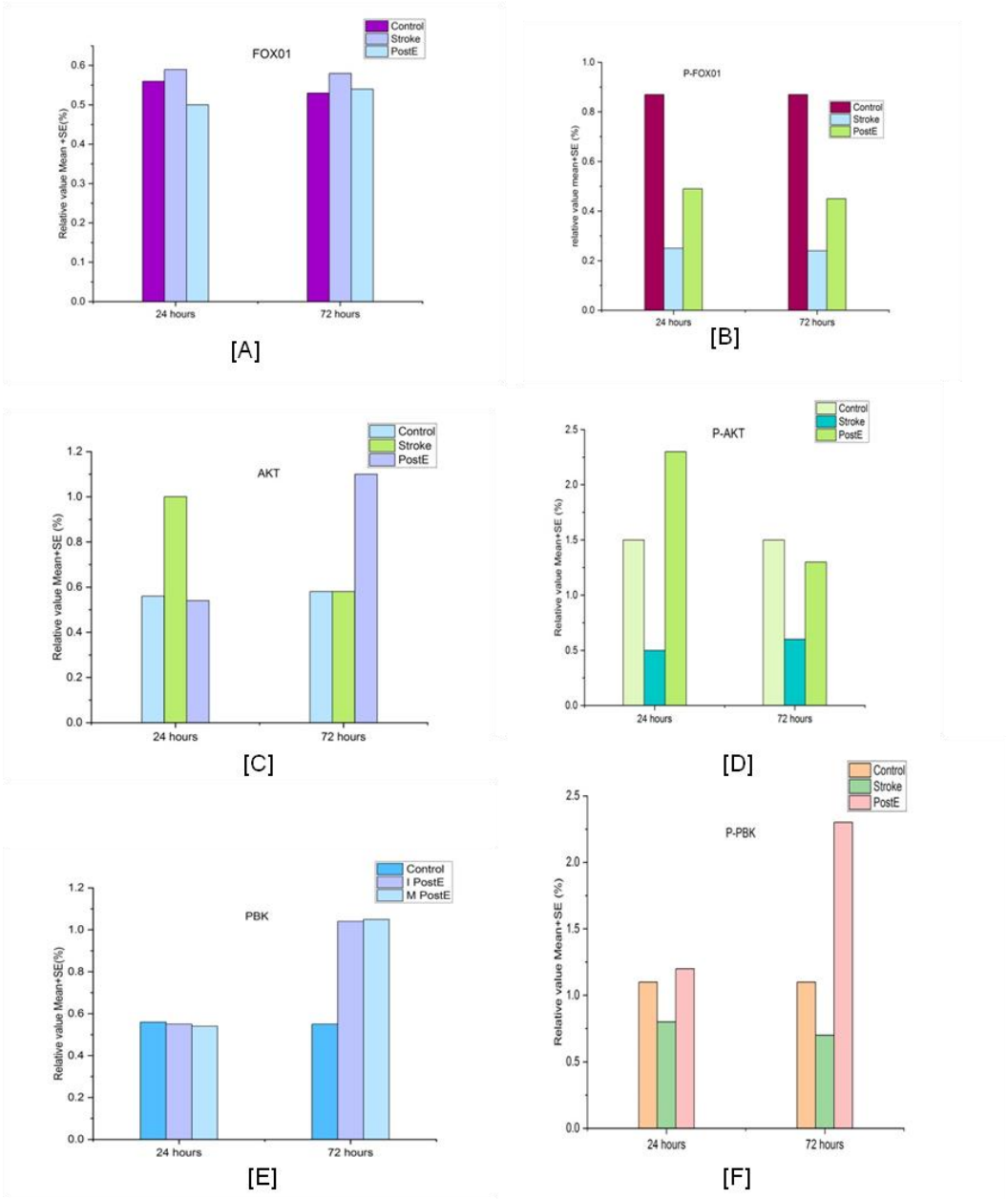

Figure (6): [A] FoxO1, [B] p-FoxO1, [C] AKT, [D] p-AKT, [E] PI3K, and [F] p-PI3K

Improve rats, inhibiting cerebral gluconeogenesis aids in glucose homeostasis, lowers the likelihood of ischemia damage, and avoids excessive energy use. Therefore, the importance of PI3K/AKT/FoxO1 phosphorylation and total FoxO1 expression in mediating the beneficial effects of exercise post-conditioning via the reduction of cerebral gluconeogenesis has been highlighted.

f. Cytoplasm expression of p-FoxO1

P-FoxO1 is shown to be expressed in the cytoplasm of neurons by fluorescent pictures cytoplasm expression of p-FoxO1 was dramatically decreased after ischemia/reperfusion in

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comparison to control rats. Represents the (Figure 7) shows that PostE restored cytoplasm p-FoxO1 expression, indicating that PostE promotes FoxO1 cytoplasm expression (Figure 7A) P-pox01 24hours (Figure 7B) P-FOX01 24hours.

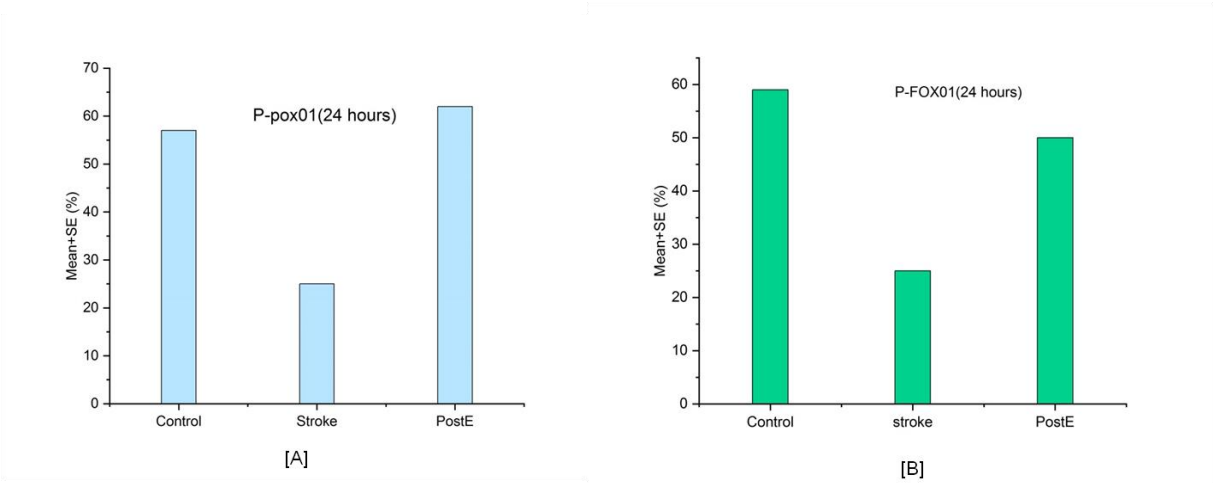

Figure (7): Quantification of the fluorescence images demonstrate increasing cytoplasm expression of p-FoxO1 in neurons after PostE in comparison to the stroke group [A] P-pox01 24 hours [B] p-Fox01 72 hours

Preventative benefits of exercise post-conditioning against ischemia damage in rats are associated with the down regulation of cerebral gluconeogenesis, which is mediated by cytoplasm production of phosphorylated Forkhead box protein O1 (p-FoxO1). FoxO1 is a transcription factor that functions in several ways inside cells, notably in the regulation of glucose homeostasis. Phosphorylated FoxO1 (p-FoxO1) is prevented from accessing the nucleus and stimulating gene transcription because it is sequestered in the cytoplasm. The down regulation of cytoplasm p-FoxO1 is critical for proper brain gluconeogenesis.

Discussion

The cognitive impairment associated with an ischemic stroke was shown to be mitigated by post-conditioning exercise in this research. One and three day neurological effects are reduced as well as infarct size and apoptotic cell death by postconditioning exercise. Neuronal gluconeogenesis was reduced, and PI3K/AKT/FoxO1 signalling were activated, all of which contributed to a reduction in brain damage (24). They identified a correlation between PI3K/AKT/FoxO1 signals and gluconeogenesis after ischemia and reperfusion damage, while this study didn't investigate the potential cause-and-effect interaction of the two processes. Defensive responses of cells, such the inhibition of oxidative stress-induced autophagy, respectively a process called and inflammation, most presumably underlie the processes of ischemia and exercise conditioning (25). Exercising prior to an ischemia event has been associated to a reduction in brain damage and an improvement in functional results, suggesting a neuroprotective impact. Similarly to exercise preconditioning, our evidence shows that exercise conditioning after a stroke may have a protective impact on the brain (26). Myocardial infarction patients who engage in post-ischemic exercise find improvements in their antioxidant activity the state. They speculated that cardiac damage

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http://www.veterinaria.org
Article Received: 06 April 2023; Revised: 24 May 2023; Accepted: 13 June 2023

caused by ischemia may be reduced via post-intervention exercise training. Brain-derived neurotrophic factor (BDNF) production was induced by post-stroke exercise, and endoplasmic reticulum stress was attenuated, both of which led to neuroplasticity and recovery from functional impairment. Decreased digestion of glucose has been proven to cause ischemic damage. In the presence of ischemia, anaerobic glycolysis takes over as the predominant source of ATP because mitochondrial oxidative phosphorylation and ATP generation are impaired (27). The brain requires a steady supply of ATP, which cannot be supplied by anaerobic glycolysis alone since doing so results in acidosis and reactive oxygen species (ROS). Recovery produces a reduction in ATP production due in part to oxidative fail to function properly. During ischemia, more substrate for energy generation is needed; hence gluconeogenesis is anticipated to rise. Increased glucose production for ATP synthesis results from the up regulation of gluconeogenesis under normal conditions. Nonetheless, gluconeogenesis can additionally decrease ATP supplies since it is an ATP-dependent activity. Reduced gluconeogenesis increases PEP activity, which in turn increases lactic acidosis and reactive oxygen species generation. It is widely recognized that these activities lead to cell death due to the interruption of glucose production due to a shortage of ATP. Through initiating the decarboxylation process and subsequent phosphorylation of OAA to create the pension plan, phosphoenolpyruvate carboxykinase (PCK) performs an important part in glucose metabolism (28). Previous studies indicate that exercise instruction lowers cardiac private carbohydrates and gluconeogenesis, demonstrating that exercise post-conditioning may have a defensive impact. During exercise post-conditioning, the current research demonstrated significant increases in OAA and decreases in PEP and glucose. This confirms previous research showing that hypothermia therapy after a stroke may reduce glucose levels to sham levels while also mediating OAA and PEP. Furthermore, exercise post-conditioning resulted in a significant attenuation of PCK1/2 expression. Gluconeogenesis' rate-limiting enzyme has also been shown to decline in the liver in response to exercise. These outcomes imply that post-exercise conditioning may inhibit gluconeogenesis, protecting brain tissue from injury. The present study demonstrated that PCK activation in neurons promoted gluconeogenesis. Their prior investigations showed that PCKs are present in glia and neurons, and our new work confirmed that PCK expression is elevated in the aftermath of ischemic stroke (29).

The enzyme phosphate activation is thought to play a role in the transition from glycolysis to gluconeogenesis, although the fundamental mechanism that drives the change is additionally unresolved. Although enabled, FoxO1, a member of the forehead relatives of transcribed regulators, causes neurons to become more susceptible to apoptosis. Should FoxO1 is activated, it moves from the cytoplasm to the nucleus, where it activates its target genes. FoxO1 are thought is inactivated and forced to be released into the cytoplasm after being phosphorylated. FoxO1 has been shown to control gluconeogenesis in the hepatic system. FoxO1 raises hepatic glucose through binding to the promoter of PCK1, a gene that encodes a crucial rate-limiting gluconeogenic enzyme. FoxO1 regulates PCK promoter-containing report gene expression, based on findings in hepatic tissues. Throughout the insatiable PEP

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cycle, FoxO1 controls PCK transcriptional. Consistent with prior findings, we found that post-conditioning with exercise reduced FoxO1 activity after stroke by shifting its localization from the nucleus to the cytoplasm (30). A consensus FoxO1 binding site has been shown to trigger apoptotic factors including Fast, TNF-in FoxO1-mediated apoptosis. The putative influence of FoxO1 on brain gluconeogenesis is further supported by evidence that activation or phosphorylation of FoxO1 induces the production of hepatic gluconeogenesis. Significantly increasing the Fox signalling process, conditioned has been shown to protect neurons from ischemia-induced damage. The SIRT1/FoxO1 signalling pathway has been shown to generate neurological protection in rats with global cerebral ischemia after ischemic pre- or post-conditioning. Furthermore, it has been shown that ischemia conditioning may reduce hepatic gluconeogenesis and increase glucose absorption in diabetic rodents by means of a brain-liver neurocircuit. Reduced renal ischemia/reperfusion damage was achieved by reduced gluconeogenesis and hyperglycemias after a period of renal ischemic preconditioning. Therapeutic effects of exercise on Alzheimer's disease have been linked to reduced brain damage, increased Bcl-2 expression, and decreased expression of caspase-3 and BAX in response to cerebral ischemia. This data demonstrates that neuron death is attenuated by exercise post-conditioning through FoxO1-mediated gluconeogenesis. Further research is needed to determine the cause and effect connection between FoxO1 and gluconeogenesis, when has been suggested in this present investigation. These findings indicate that the PI3K/AKT/FoxO1 pathway may play a role in controlling gluconeogenesis in the brain. According in the most recent findings, the PI3K/AKT/FoxO1 pathways govern gluconeogenesis; however, they did not investigate the regulation of these signalling pathways. The potential regulating mechanism would be the subject of Future studies. Post-stroke exercise training mitigates infarct size via reducing the PI3K/Akt axis and raising phosphorylated FoxO1 levels. Previous research suggested that irisin inhibits gluconeogenesis via PCK signals regulated by PI3K/Akt/FoxO1.

Conclusion

They showed that PostE after stroke protects neurons by lowering gluconeogenesis and regulating PI3K/AKT/FoxO1 signalling. The influence of FoxO1 on brain gluconeogenesis is further supported by evidence that activation or phosphorylation of FoxO1 induces the production of hepatic gluconeogenesis. Significantly increasing the Fox signalling process, conditioned has been shown to protect neurons from ischemia-induced damage. The SIRT1/FoxO1 signalling pathway has been shown to generate neurological protection in rats with global cerebral ischemia after ischemic pre- or post-conditioning. Furthermore, it has been shown that ischemia conditioning may reduce hepatic gluconeogenesis and increase glucose absorption in diabetic rodents by means of a brain-liver neurocircuit. Reduced renal ischemia/reperfusion damage was achieved by reduced gluconeogenesis and hyperglycemias after a period of renal ischemic preconditioning.

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