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A brief physical activity protects against ischemic stroke

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Abstract:

With restricted therapeutic opportunities, stroke remains a relevant, critical disease necessitating study. Due to the unique aspect of ischemic strokes, finding approaches to maintain the vigor of the cerebral vasculature, such as increased angiogenesis, may protect against stroke. Ischemic strokes are caused by disruptions in blood movement in the brain, resulting in a torrent of harmful cerebrovasculature modifications. In an investigation by Pianta *et al.*, Sprague-Dawley rats have been separated into those that undergo exercise prior to middle cerebral artery occlusion (MCAO) and those that were not exposed to physical activity preceding MCAO. The outcomes and results of the current study gave new insights into the capacity of exercise to help prevent ischemic strokes or mitigate poststroke effects. The data collected from the study suggested that rats that went through a short bout of exercise before MCAO presented superior motor performance, more active cells in the peri-infarct region, and reduced infarct sizes. When compared to the control group, the rats that went through exercise also had heightened angiogenesis and improved neuroprotection. Thus, a brief bout of physical activity preceding a stroke may provide neuroprotection by enhancing the strength of the cerebrovasculature in the brain. This notion that even an instant of physical exercise before a stroke is induced can help dampen the effects of ischemic stroke, which could lead to future techniques in preventing the ischemic stroke so that it never happens at all.

Keywords:

Angiogenesis, cerebral blood flow, cerebrovasculature, exercise, ischemic stroke, middle cerebral artery occlusion, neuroprotection, physical activity

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Introduction: Novel Techniques to Counteract Ischemic Stroke

Stroke is one of the most harmful and dangerous diseases in the contemporary world, and the enigmatic nature of the disease has yet to be unraveled. There have been numerous scientific discoveries made by researchers, but the lack of substantial new information has caused strokes to continue to torment humans and to remain one of the leading causes of death in the world.^[1] A vast monetary weight is dropped on the US annually due to strokes. In addition, the Food and Drug Administration (FDA) has solely permitted

one type of medication for usage, tissue plasminogen activator (tPA), which has a restricted time frame due to the antagonistic effects out of this specific time frame.^[2] Furthermore, tPA therapy assists merely 5% of ischemic stroke patients who are treated within a 4.5-h window.^[3] Mechanical thrombectomy has some issues as well, due to the ineffectiveness of the method on most patients within a 6–24-h time interval^[4–6] and the shortage of medical professionals who can administer this particular technique.^[7,8] Due to the lack of effective treatments, studies on unique stroke treatments are justified.^[9]

One treatment that may prevent strokes in the elderly is constant bodily exercises or movement because aerobic activity increases cardiovascular ability, intellectual performance, memory,

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and mobility.^[10,11] Moreover, physical activity has many neuroprotective mechanisms – including neuroprotective and regenerative processes – and helps stimulate and sustain cerebrovascular liveliness and structure and cerebral blood movement post stroke during reperfusion.^[12] Vascularization is key to stroke rehabilitation.^[13,14] The positive consequences of exercise on stroke have been evaluated in multiple animal models.^[15] The severity of exercise can also help determine the size of the infarct post middle cerebral artery occlusion (MCAO).^[16] Exercise can also promote cerebral vasculature angiogenesis due to the amplified amount of growth factors such as vascular endothelial growth factor (VEGF) and insulin-like growth factor.^[17-20] Altogether, exercise prior to stroke advances functional effects of the body during poststroke recovery.

Some studies, however, negate the functional advantages of physical activity in stroke. Performing exercise early in the poststroke period can cause serious damage to brain tissue and induce cell apoptosis.^[21] However, light-to-intermediate amounts of physical activity prior to stroke can in fact reduce stroke severity.^[22-24] Exercise can be thought as a minor stressor^[25,26] and thus increases pathological function and exerts neuroprotection.^[27,28] Therefore, discovering new ideas and ways to uphold the brain's vasculature can help impede stroke.

The study by Pianta *et al.* aimed to find the connection between physical activity and stroke aftermath. Although long and intense physical exercise for patients at risk of stroke could be detrimental, short bouts of exercise may succor in neuroprotection of the patient. The investigators tested for the effects of exercise before stroke stimulation and portrayed cerebral blood flow (CBF) and associated motor functions *in vivo*.^[9] This study aimed to observe disease-preventing physical activity and how it may augment angiogenesis and reinforce cerebral vasculature. These effects may provide neuroprotection against stroke.

The Effects of a Short Bout of Physical Activity before Middle Cerebral Artery Occlusion

With restricted therapeutic opportunities, stroke remains a relevant, critical disease warranting study. Finding approaches to maintain the vigor of the cerebral vasculature, such as increased angiogenesis, may protect against stroke due to the unique aspect of ischemic strokes. Ischemic strokes are caused by disruptions in blood flow in the brain, resulting in a torrent of harmful cerebrovasculature modifications. The study portrayed CBF and associated motor functions *in vivo* and tested

for the effects of exercise before stroke stimulation.^[9] There were three groups of mature Sprague-Dawley rats that were subjected to testing in this study. One group of rats was exposed to a lone short fit of physical activity (30–60 min on the exercise wheel), and then a stroke was induced on them using a temporary MCAO.^[9] One group of rats was not exposed to exercise but still was subjected to MCAO which signified the control. Another group of rats was not subjected to MCAO at all. Blood movement in the brain was assessed at three different times during the study. CBF was measured using a laser Doppler prior to and during MCAO and during reperfusion. Behaviors of the groups of rats were then examined after the stroke using the elevated body swing test. Rats that went through exercise before being subjected to MCAO portrayed normal changes in CBF but presented superior motor performance when related to the rats in the control group.^[9] Stroke rats that went through short bouts of exercise before MCAO also had more active cells in the peri-infarct region and a decreasing infarct size.^[9] When compared to the control group, heightened amounts of angiogenesis/endothelial markers such as Ang-2, VEGF receptor-2 (VEGER2), VEGF, and endothelial precursor cell indicator CD34+ were discovered in the exercise stroke rats, through the processes of immunofluorescence and Western blot analysis.^[9] Thus, exercise before a stroke may provide neuroprotection by enhancing the strength of the network of blood vessels in the brain. In addition, some plausible future methods of enhancing neuroprotection and preventing ischemic strokes are the usage of cannabinoids, sirtuin proteins, and ischemic preconditioning (ICP).

Exercise Prior to Stroke Enhances Neuroprotection

The study results concluded that physical activity, such as using the exercise wheel before the stroke, allowed improved neuroprotection for the rats against the disease.^[9] The enhanced neuroprotection may result from the augmented angiogenesis in the brain. Stroke animals that went through exercise presented heightened physical performance and less histopathological shortages.^[9] Overall, heightened amounts of angiogenesis/endothelial markers such as VEGF, VEGFR-2, and Ang-2 were discovered in the exercise stroke rats near the infarct in their brains.^[9]

The outcomes of this study complemented those of past studies that have shown how treadmill activity promotes angiogenesis in ischemic stroke animals.^[29,30] Largely, these studies have all exhibited improvements in strengthening of cerebrovasculature, motor functioning, infarct volumes, and the number of extant neurons near the infarct. Enhanced angiogenesis,

psychological function, blood–brain barrier stability, and reduction of infarct sizes were caused by 8 weeks of medium-to-high magnitude treadmill exercise preceding MCAO.^[31] This information reflects the rise in Ang-2, VEGFR2, and VEGF in the corpus striatum and the decline in the peri-infarct areas of the exercise stroke groups in the current study.^[9] Treadmill exercise also portrayed considerably raised brain VEGF expression and diminished brain infarct size at 14-day postischemic stroke.^[32] Treadmill exercise has also been shown to induce neurogenesis, synaptogenesis, and neurotrophin signaling pathways, thus stimulating efforts at neuroprotection.^[33] In addition, the high-intensity physical activity groups in the treadmill studies demonstrated the most significant reduction in infarct size, and largest surge in the indicators of angiogenesis,^[11] similar to the results of the exercise group that was exposed to the highest physical activity in the present study.

Brief Bouts of Exercise before Middle Cerebral Artery Occlusion May Improve Neuroprotection But Not Neurological Function

Despite these similarities, compared to the past studies, the exercise groups in the contemporary study did not display any advancements in neurological performance compared to the nonexercise stroke group.^[9] The reasoning behind this discrepancy may be caused by the difference between the amount of exercise in the present study and the Rezaei's study. This variation could suggest that short bouts of exercise before stroke induction may not be enough to avert neurological shortfalls post ischemic stroke. The explanation behind these inconsistencies could also be from the distinct functional metrics used to evaluate neurological function between the two studies. Moreover, 3 weeks of 30-min periods of physical activity per day preceding ischemic stroke incites angiogenesis; raises brain-derived neurotrophic factor and midkine expression; diminishes infarct sizes, neuronal apoptosis, and oxidative damage; and augments motor performance but not neurological function.^[34] The same outcome was determined in the current study, and it is likely that the advantages brought upon by physical activity in the present study were also due to the same reasons as suggested by the Otsuka study.^[9] The Otsuka study also implies that 3 weeks of physical activity per day previous to induced stroke is not adequate to stimulate neurological advancements and that a longer period could. However, a 30–60-min bout of physical activity directly prior to MCAO may cause neurological improvements that could help against ischemic stroke.^[9]

The Timing between the Start of Physical Activity and the Stroke Induction is Critical to Neuroprotection

While the discoveries in the current study are accordant with those of previous studies,^[29–31,34–36] such as on angiogenesis and stroke, the study by Pianta *et al.* displays the unique idea that even an instance of physical activity preceding MCAO could be enough to enhance angiogenesis and increase neuroprotection. Nevertheless, lengthier and recurrent exercise before stroke may bestow more advantages such as enhanced neurological performance.^[31] Nonetheless, the timing between the commencement of a recent spurt of physical activity and the generation of the ischemic stroke might be the most essential feature of exercise-induced assistances against stroke. The present study spreads the range of the discoveries found in Rezaei's and Terashi's study (examined the consequences of regularity of exercise) and looks at the length and the difference between 30- and 60-min periods of exercise, therefore, illuminating the benefits of 60-min exercise prior to MCAO.^[9] Thus, the current investigation fortifies the position that preconditioning physical activity is helpful for stroke. Preconditioning physical activity-stimulated neuroprotection in preclinical stroke models is most likely facilitated through its capability to augment cerebral vasculature and blood–brain barrier integrity and foster neurogenesis.^[37] The present investigation is also the first to observe how exercise affects inflammation in the periphery succeeding stroke, given that stroke stimulates inflammation in the spleen.^[38,39] The study results suggest that a lone period of physical activity prior to MCAO can decrease inflammation in the spleen post ischemic stroke.^[9]

Exercise Preceding Middle Cerebral Artery Occlusion May Not Affect Cerebral Blood Flow

A few restrictions of the present study include the deficiency of physical activity-induced effects on CBF and the lack of supplementary exercise limitations. Exercise did not produce any functional alterations in CBF during MCAO compared to the nonphysical activity stroke group despite the enhanced angiogenesis.^[9] It is likely that changes in CBF by the mechanism of angiogenesis might not have been captured during the chosen times post-MCAO, implying that acute and chronic evaluations of CBF might be necessary to completely expose the effects physical activity has on stroke. It is possible that the laser Doppler may not be perceptive enough to identify minute alterations in CBF and that the laser speckle technique may be necessary.

Longer, Constant, and Moderate Exercise Can Optimally Improve Neuroprotection

In addition, lengthier or quicker amounts of physical activity, the application of both pre-MCAO and post-MCAO exercise routines, or the association between compulsory and spontaneous exercise sessions were all variables that were not examined.^[9] The patterns in the data from the study advocate that the 60-min exercise group received the most benefits and that longer periods of exercise before MCAO could improve neuroprotection.^[9] Moreover, shortages of exercise could possibly hinder neurogenesis and improvements in cerebrovasculature.^[40] It is likely that nonpermissive stem cell microenvironments could be produced by deficiencies in physical activity.^[41] Although exercise stimulates neurogenesis, it may not be best to implicate physical activity regimens that are too high in intensity.^[22-24] Despite the support that physical activity post stroke revealed neuroprotective results,^[29,30,35,36] exercise can also be dangerous contingent on the specific time.^[21,42,43] The worth of these other exercise-linked elements should be looked into further in order to develop more exercise-based treatments for stroke.

Parameters for using physical activity to defend against stroke can be found from this study data. Longer periods of exercise are connected to improved neuroprotection, and small-to-medium amounts of physical activity preceding strokes in humans can lower stroke severity.^[22,23] Due to the minimum of 40 min of aerobic physical activity for 3–4 days a week suggested by contemporary US standards to prevent stroke^[44] and the current investigation's data regarding the 60-min exercise group, it is probable that shorter 20–30-min exercise routines are less competent at decreasing stroke severity than lengthier periods of physical activity such as 40–60-min moderate intensity sessions.^[9] Although the data from the present study show that longer exercise durations prior to stroke diminish stroke severity, additional research must be made before the conclusions from these data can transit to humans. Frequent exercise is also suggested to protect against stroke alongside longer durations of physical activity prior to stroke. For example, one of the most effective ways to decrease the neuronal apoptosis following strokes in rats is exercising >3 times/week.^[45] Furthermore, constant, long-term physical activity preceding MCAO enhances the neuroprotection and maintenance of pathological function.^[31] Thus, it is conjectured that physical activity every day can be vital to not only avoid a stroke,^[44] but also maintain and augment neuroprotection if an ischemic stroke actually occurs.

Overall, the results from the current investigation displayed that physical activity can be used to prevent

strokes and mitigate the effects of ischemic strokes.^[9] The outcomes of the study also revealed that exercise can lessen the motor and histopathological deficiencies that supplement an ischemic stroke.^[9] The perceived rise in angiogenesis was caused by exercise-stimulated neuroprotection, and the current study has shown that a lone, short bout of physical activity can prompt these neuroprotective assistances. In the dangerous event of an ischemic stroke, even a moderate intensity period of physical activity may minimize cerebral tissue damage in total.

Alternative Treatments for Ischemic Stroke

The current investigation revealed that a short bout of exercise before stroke may be sufficient to limit the effects of the ischemic insult. New and distinctive techniques of how to prevent and control the severity of ischemic strokes have been warranted, as the FDA has only approved one drug, tPA, for ischemic strokes. The National Institute of Neurological Disorders and Stroke determined that a patient would attain improved neurological recuperation and have less signs of disadvantages if he/she was treated with tPA within a 3-h window, after the beginning of indications of stroke.^[46] Although tPA has saved many lives, it accompanies a large number of limitations and restrictions. Such limitations include that tPA had to be given early after the first sign of symptoms, could possibly trigger uninhibited bleeding in the brain, and frequently was unsuccessful in separating large blood clots.^[46] Thus, new methods of thrombolysis or novel practices must be made to prevent or mitigate the effects of ischemic stroke because tPA has not completely solved the mystery. In the current study, we investigated the effects of exercise directly before the induction of stroke on animals. Other studies have also conducted research on ischemic stroke and have proposed other ideas on inhibiting or lessening the outcomes of stroke such as the use of cannabinoids, sirtuin proteins, and ICP. These studies have examined new techniques to enhance neuroprotection and neurogenesis to try to prevent ischemic stroke.

Uncomplicated therapeutic cannabis products can serve as effectual neuroprotectants as portrayed by contemporary investigations and inquiries.^[47] For example, a remedial, mouth spray including both tetrahydrocannabinol and nonpsychoactive cannabidiol (CBD), Savitex[®], has been discovered to reduce the spasms that accompany multiple sclerosis.^[47] Another current study also revealed that Epidiolex[®], a nonpsychoactive CBD formulation, is reliable and efficient in reducing seizures in Lennox–Gastaut syndrome.^[47] The use of cannabinoids may be another novel treatment in lessening the effects of ischemic stroke, similar to the functions of the present study. CBD could provide

poststroke neuroprotection as displayed in a 2015 meta-analysis that inspected 34 preclinical studies investigating CBD.^[47] According to their data, the authors were able to deduce that cannabinoids were capable of decreasing infarct size and enhancing practical effects in investigational stroke, with activity at both cannabinoid (CB) 1 and CB2 receptors linked with optimistic results.^[47] This investigation and that of other studies have subsidized to the hopefulness relating to the conceivable applicability of cannabinoids in the handling of stroke patients.

Another study examined the function of the sirtuin proteins, Sirt1 in particular, in enhancing neuroprotection and preventing ischemic stroke. The results of ischemic damage can possibly be guided by the genetic control of Sirt1 expression.^[48] When compared to their wild-type equivalents, mice which did not display Sirt1 presented greater infarct sizes succeeding permanent MCAO (pMCAO).^[48] In addition, the functional concentrations of Sirt1 are moderated by ischemic damage. For instance, up until 7 days after pMCAO, Sirt1 increased in the peri-infarct zone in mice. In another line of support, ischemic stroke effects can be moderated by the stimulation or suppression of Sirt1 with pharmacological agents.^[48] Treatment with the Sirt1 activator at different intervals of time succeeding pMCAO decreased infarct size, whereas the application of sirtuin inhibitor sirtinol enlarged infarct size.^[48] Similar to the effects of angiogenesis on infarct size post stroke, this study had parallel results to the present investigation. The triggering and upregulation of Sirt1 were connected to several other endogenous or exogenous compounds that could possibly stimulate ischemic tolerance.^[48] Systematically, multiple sources of evidence locate distinct signaling pathways, all controlled in some way by Sirt1, that prompt neuroprotection from ischemic strokes.^[48] The applications of this study are mostly for poststroke benefits which are similar to the investigations of Tang *et al.*; Gao *et al.*; Chen *et al.*, 2019; and Xie *et al.* that supported that exercise post stroke revealed neuroprotective results.

IPC is an area of exploration that continually displays potential in emerging treatments for ischemic strokes. The general concept of IPC can be described as resistance to possible future ischemic occurrences brought upon by exposures to nonsevere ischemic events that can stimulate adaptive alterations.^[49] These sublethal ischemic insults stimulate adaptive modifications that supply resistance to potential ischemic events.^[49] IPC normally results in amplified gene expression and cellular metabolism throughout either the activities of a preconditioning molecular mimetic or, temporary ischemic occurrences small in potency.^[49] The mitochondrion is a critical focal point

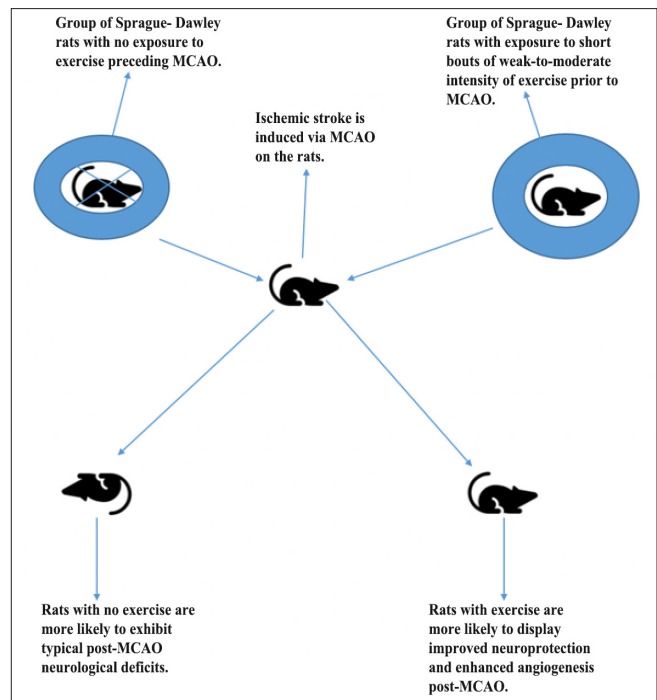


Figure 1: Exercise and neuroprotection. A short bout of exercise may promote neuroprotection against stroke

of such alterations in gene expression and metabolism. The activation of 5' adenosine monophosphate-activated protein kinase (AMPK), a principal manager of cellular metabolism, can be caused by the consequences on mitochondria by IPC.^[49] Through communication with mitochondria and the preservation of metabolic homeostasis, AMPK stimulation has been displayed to participate in IPC neuroprotection.^[49] Resveratrol and metformin-IPC mimetics have also been revealed to provide neuroprotection through mitochondrial outcomes and AMPK stimulation.^[49] Both IPC and the present investigation of exercise have possibly found new ways to counteract the effects of ischemic stroke or prevent them altogether [Figure 1]. The studies reveal novel techniques to increase neuroprotection in the brain and thus, these methods will conceivably reduce the severity of ischemic strokes.

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Conflicts of interest

There are no conflicts of interest.

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