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Physical Exercise Improves Cognitive Outcomes in Two Models of Transient Cerebral Ischemia

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Abstract

Background and Purpose—Preclinical studies suggest that exercise can enhance cognition after cerebral ischemia but often employ long training regiments and test cognition during or acutely after training. The cognitive changes may result from enhanced physical fitness and may only provide acute benefit. We sought to determine if a short period of exercise after cerebral ischemia could improve cognitive outcomes when measured days after completion of exercise training in two cerebral ischemia models.

Methods—Focal or global cerebral ischemia was induced in Sprague-Dawley rats. Rats recovered (3–4 days) then were subject to no exercise (0 m/min), mild (6 m/min), moderate (10 m/min), or heavy (15–18 m/min) treadmill exercise (5–6 days). Cognition was tested 8–10 days after last exercise session with hippocampal-dependent contextual fear conditioning.

Results—A short training period of moderate exercise enhanced cognitive function over a week after exercise completion in both models of cerebral ischemia.

Conclusions—Utilization of this exercise paradigm can further the elucidation of exercise-mediated factors involved in cognitive recovery independent of changes in physical fitness.

Keywords

Stroke; Brain Ischemia; Exercise; Cognition

Survivors of stroke will be at an enhanced risk for accelerated cognitive decline, yet there remains no well-accepted therapy for cognitive recovery[1]. Physical exercise (PE) after stroke improves motor functions in patients[2] and animal models.[3] A recent meta-analysis suggested that PE improves cognitive performance in models of acquired brain injuries[4]. However,

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studies that examine the ability of PE to promote cognitive recovery after cerebral ischemia employ weeks of PE training and test cognition during or immediately after the PE period[4]. These study designs cannot distinguish if the effects of PE are due to enhancements in overall animal fitness or an acute effect of exercise intervention. It remains unclear if a short bout of PE after cerebral ischemia has prolonged positive effects.

In this proof-of-concept study, we aimed to determine if a short bout of PE training initiated after cerebral ischemia can improve hippocampal-dependent contextual fear memory tested over a week after the last exercise session.

Materials and Methods

Animal Care and Ischemia Surgeries

All experiments were performed in accordance with the Guide for Care and Use of Laboratory Animals and approved by the University of Miami's Institutional Animal Care and Use Committee. Experimental timeline is indicated in Figure 1. Detailed experimental methods including randomization, blinding, and allocation concealment are in Online Supplement (please see http://stroke.ahajournals.org). Focal cerebral ischemia was achieved with intraluminal suture blockage of the middle cerebral artery for 90 minutes[5, 6]. Global cerebral ischemia was induced with 8-minute asphyxia cardiac arrest[5, 7]. Physiological parameters were maintained within normal ranges during surgeries (Online Supplement).

Subacute Treadmill Exercise

After 3–4 days of recovery, adult (3-month old), male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) were exercised on a treadmill (0.59 mA aversion grid; Columbus Instruments, Columbus, OH) for 5–6 days (Figure 1). A blinded investigator randomized rats to speeds selected based on our experience and other reports[8, 9]: no exercise (0 m/min); mild (6 m/min); moderate (10 m/min); or heavy exercise (15–18 m/min) with sample sizes for each speed: n= 11, n=11, n=10, and n=9 respectively for focal ischemia; and n=10, n=5, n=7, and n=5 respectively for global ischemia. After focal ischemia, heavy exercise was set at 18 m/min. However, rats were unable to run at 18 m/min after global ischemia so 15 m/min was used for heavy exercise. Daily PE consisted of a 2-minute warm-up at 5 m/min then 30 minutes of exercise at designated speed. Rats randomized to the 0 m/min group remained on a stationary treadmill for 30 minutes. Animals that refused to run were excluded from analysis (n=2, global ischemia with heavy exercise).

Contextual Fear Conditioning

Eighteen days after surgery (8–10 days after exercise), hippocampal-dependent contextual fear conditioning was performed[7]. Rats were placed into the operant conditioning chamber (Coulbourn Instruments, Whitehall, PA) for 370 seconds with a 2 second 1.5 mA shock administered at second 340. The following day, rats remained in the chamber for 480 seconds with no shock administered. Amount of time freezing was quantified (FreezeFrame, Coulbourn Instruments) prior to the shock on the first day (Baseline) and for the entire duration on the second day (Contextual). Animals that froze more than 50% on the first day were excluded from further analysis (n=1, global cerebral ischemia with moderate exercise).

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Statistical Analysis

All data are represented as mean ± S.E.M. Sample size calculations are detail in the Online Supplement. Data was analyzed with One-Way ANOVA and comparisons between individual exercise groups quantified with Bonferroni Post-hoc tests. Significance was assessed as $p<0.05$.

Results

At baseline, there were no differences in the amount of time freezing between groups subject to focal ($p=0.6597$, Figure 2A) or global ($p=0.2635$, Figure 2C) cerebral ischemia. Contextual freezing was significantly different among groups ($p=0.0078$ for focal, $p=0.0037$ for global, Figure 2B,D) with animals randomized to no exercise (0 m/min) freezing the least suggesting worse memory. After focal ischemia, rats subjected to moderate exercise (10 m/min) had a significant enhancement in duration of freezing compared to non-exercised rats ($p<0.01$, Figure 2B). Moderate exercise had a similar effect after global cerebral ischemia enhancing contextual fear memory as compared to the non-exercised controls ($p<0.05$, Figure 2D). Heavy exercise (15 m/min) after global cerebral ischemia also enhanced percent time freezing ($p<0.01$).

Discussion

While there is no treatment for cognitive dysfunction after stroke, prolonged PE can improve cognitive recovery after cerebral ischemia in animal models (reviewed in[4]). Using two models of cerebral ischemia and three speeds of treadmill exercise, we show that a brief bout of moderate exercise initiated after cerebral ischemia can enhance memory tested over a week after the last exercise session. This suggests that post-ischemia, exercise-mediated cognitive benefits are unlikely a result of changes in physical fitness or acute exercise effects. While future studies are needed to determine the duration of enhanced fear memory, the fact that this enhancement was evident over a week after the last exercise session suggests it is long lasting. Additionally, our finding that the fastest treadmill speed (18 m/min) was unable to improve cognition is similar to that of others where exercise at 8 m/min, but not 20 m/min, resulted in an acute improvement in spatial memory.[8, 9] Future studies that aim to understand exercise-mediated cognitive improvements after cerebral ischemia should use speeds between 8–15 m/min.

After stroke, there is a period of enhanced plasticity with extensive remodeling occurring in the peri-infarct cortex[10, 11]. Targeted, task-specific motor training can improve motor function and mold this redeveloping motor network[12]. The ability to translate this approach to improving cognitive functioning after stroke has been limited. Several brain regions are involved in cognition necessitating a multi-targeted rehabilitation intervention. Additionally, ischemia-induced enhancement of plasticity may be limited further from the infarct[13]. Here, we tested cognition with hippocampal-dependent contextual fear conditioning[7]. Our previous studies find no gross neuronal loss in the hippocampus after focal ischemia[5] and extensive hippocampal neuronal loss after global ischemia[14]. Despite these injury differences, PE improved hippocampal-dependent cognitive functioning suggesting that PE

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may be a multi-targeted therapy that can improve cognitive centers regardless of ischemic insult.

Summary

In this proof-of-concept study, we find that an early, short bout of moderate exercise in two models of cerebral ischemia promotes an enhancement of cognitive function over a week after the last exercise session. Without the confounding effects of prolonged exercise training on overall fitness or acute effects of recent exercise, our experimental paradigm can be utilized for identification of biomarkers and/or soluble mediators of lasting exercise benefits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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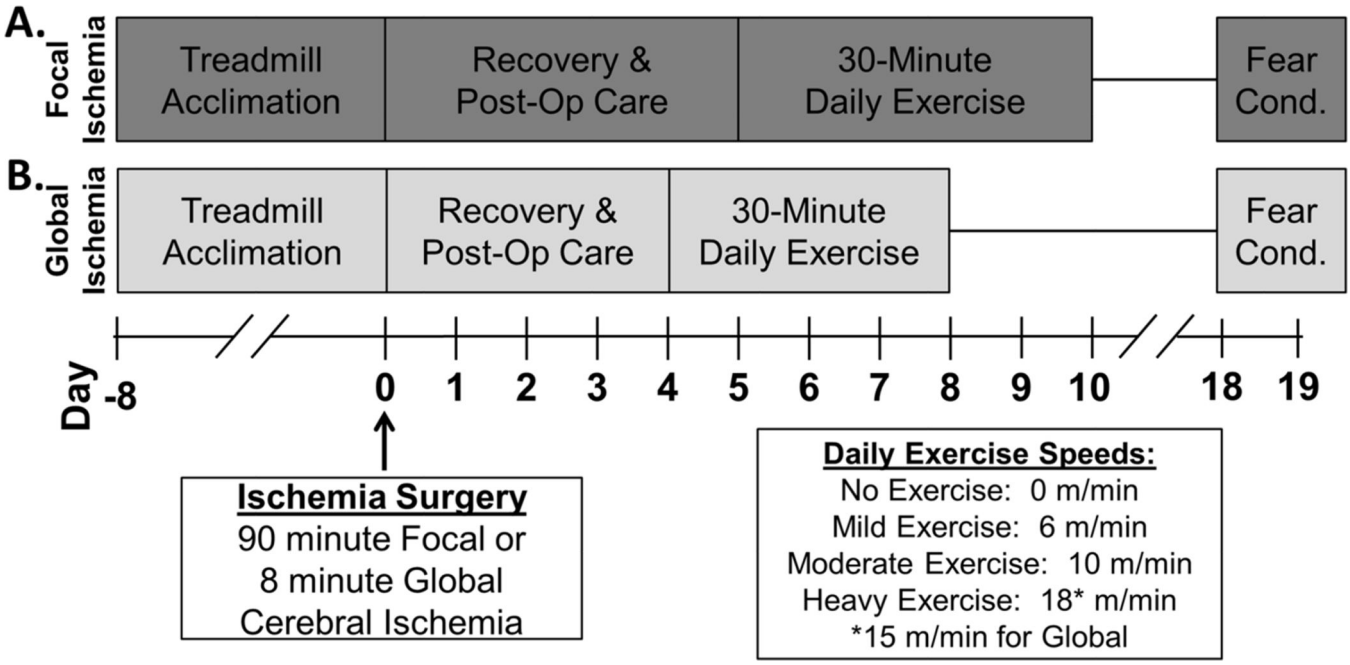

Figure 1. Experimental timeline

Adult, male Sprague-Dawley rats were acclimated to treadmill walking (5 m/min for 5 minutes) over 8 days prior to surgery. (A) Rats were subject to focal ischemia, recovered for four full days, then randomized to exercise speed. Daily exercise consisted of a 2-minute warm-up at 5 m/min followed by 30 minutes at randomized speed. Completing 6 days of exercise, rats were undisturbed until contextual fear conditioning. (B) Rats subject to global cerebral ischemia received a similar training paradigm but began exercise after 3 full days of recovery and exercised for 5 days. Unable to maintain the higher speed, rats randomized to heavy exercise after global ischemia ran at 15 m/min.

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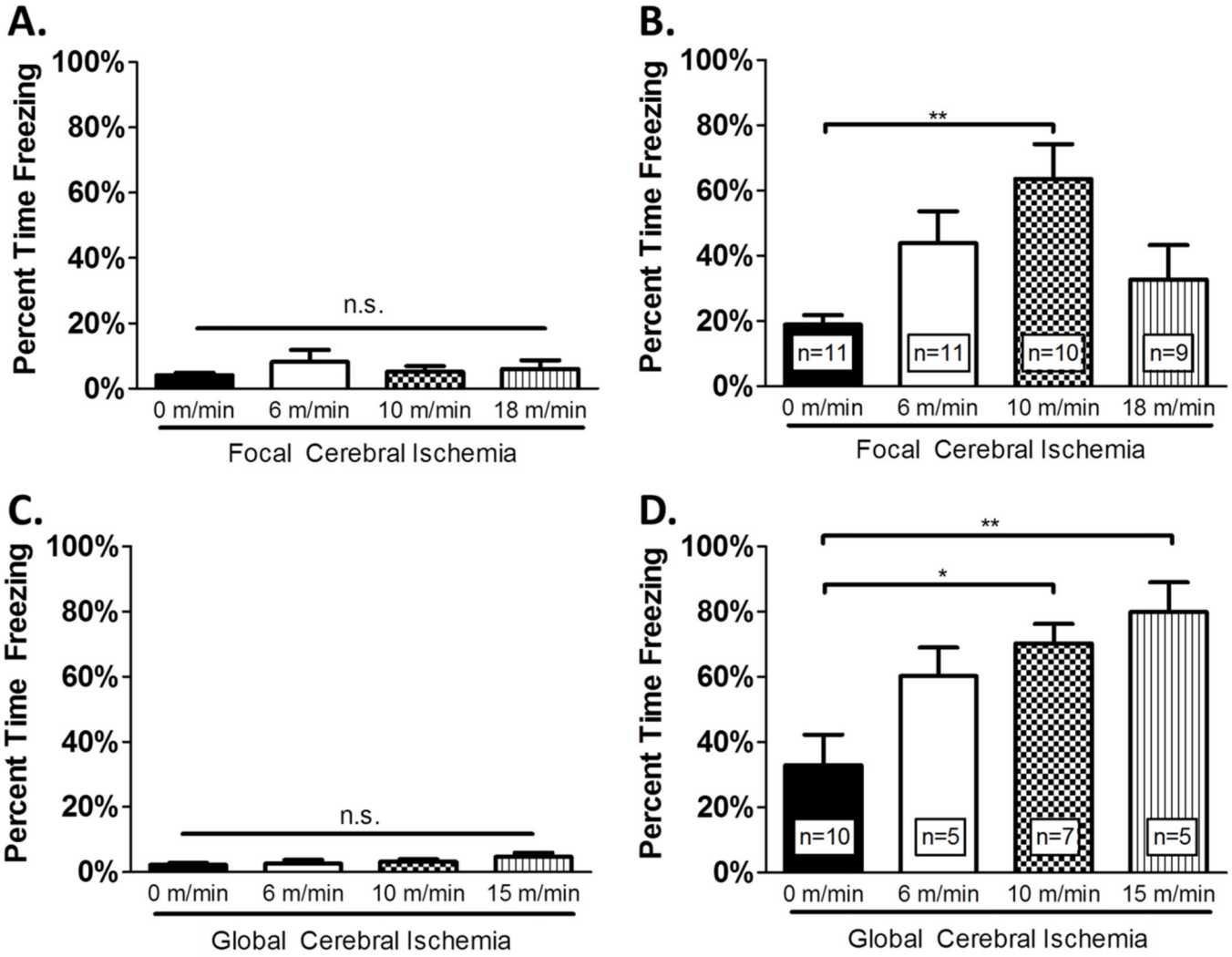

Figure 2. Short period of moderate exercise enhances contextual fear memory

(A, C) There were no significant differences at baseline between groups. (B, D) As compared to non-exercised animals (0 m/min), rats subject to moderate (10 m/min) exercise had enhanced fear memory after focal and global cerebral ischemia. Heavy exercise (15 m/min) after global cerebral ischemia also significantly improved hippocampal-dependent contextual fear memory. *$p<0.05$, **$p< 0.01$ Bonferroni Post-hoc.