Therapeutic potential of prophylactic exercise for intracerebral hemorrhage

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Exercise and brain health: Physical activity helps promote and maintain our brain health, including memory and cognitive performance. Research has shown that exercise is a safe behavioral intervention that reduces the risk of hypokinetic diseases, such as hypertension, diabetes, and lipid metabolic disorders. In addition, accumulating evidence now suggests that increased physical activity has positive effects in both preventing and ameliorating multiple brain diseases, including stroke. Although stroke is often accompanied by severe long-term disability and dementia, exercise is considered effective in enhancing neurological functions, even in stroke patients. Recent systematic reviews and meta-analyses indicate that aerobic physical activity promotes multiple health outcomes, including neurological behaviors and cognitive performance in stroke patients (Luo et al., 2020). Pre-clinical studies using rodent models of stroke have also demonstrated that exercise has therapeutic potential by influencing neuroinflammation, neuroprotection, remyelination, and astrogliosis (Svensson et al., 2015). Because aging is a major risk factor for stroke, and because polypharmacy among older adult patients has become a serious social issue around the world, it is worthwhile pursuing the potential of exercise as a non-pharmacological therapy for stroke.

Exercise and intracerebral hemorrhage (ICH): In most cases, stroke is divided into the ischemic and hemorrhagic stroke. Between these, ICH, representing 10–20% of all stroke patients, is characterized by rupture of blood vessels and formation of hematoma within the brain parenchyma, leading to inflammation, neuronal death, and edema in the brain. The brain tissue damage caused by ICH results in high mortality and severe motor and sensorimotor dysfunction. Although therapeutic strategies intended for neuroprotection in ICH patients are still unavailable, the relationship between physical exercise and recovery from ICH has been confirmed by research. From the viewpoint of rehabilitation, physical activity after ICH is considered essential to promote motor functional recovery in patients with hemorrhagic stroke. Also, in pre-clinical studies using a rodent model of ICH, exercise after ICH induction enhanced motor functional recovery. However, ICH patients may be unwilling to exercise or may even be unable to exercise, since ICH patients may suffer from neurological deficits. Therefore, exercise "after" ICH is sometimes difficult as a therapeutic treatment for ICH.

To overcome the limitations of the therapeutic potential for exercise-related treatment for central nervous system diseases, preconditioning accompanied by exercise may be a practical non-pharmacological preventive therapy for stroke. Preconditioning is defined as the procedure in which brief episodes of a noxious stimulus below the threshold of damage are applied to the target organ to protect it against subsequent damaging injuries. For stroke insults, preconditioning stimuli may include hypoxia, ischemia, oxidative stress, and anoxia; however, these stimuli may sometimes be harmful to patients, and we may need to be cautious when using them as therapeutic interventions. In this regard, preconditioning with exercise is plausible because exercise can be considered a mild stressor, and more importantly, is safe.

Exercise preconditioning has been implied to be effective for both ischemic and hemorrhagic stroke. A retrospective study showed that patients with ischemic stroke who reported moderate (1 to 3 times/week) or high (over 4 times/week) levels of regular physical activity before onset have better functional outcomes (Stroud et al., 2009). Another study also reported that light physical activity pre-stroke, such as 2 to 4 hours/week, results in less severe cases in ischemic stroke patients (Reinholdsson et al., 2018). In addition, a case-control study indicated that regular dynamic exercise even reduces the likelihood of ICH among men, presumably through suppressing increases in blood pressure (Thrift et al., 2002). Moreover, in pre-clinical studies, preconditioning with exercise has been confirmed to improve the pathologies of ischemic stroke (Sakakima, 2019), and interestingly, just a short exercise session before stroke could improve functional outcomes in a rat model of ischemic stroke via enhancing regenerative angiogenic responses (Pianta et al., 2019). Although it is still not clear whether preconditioning with exercise would have beneficial effects on ICH pathology, we recently reported that preconditioning with treadmill exercise showed better recovery from the devastating pathologies of ICH in mature adult mice (Kinoshita et al., 2021).

Exercise preconditioning and ICH pathology in mice: In our recent study published in Stroke (Kinoshita et al., 2021), male C57BL/6J (25-week-old) mice were subjected to 6 weeks of treadmill exercise total. One week was spent on habituation exercise, where running speed began at 2 m/min and was increased by 2 m/min every 2 minutes until a maximum speed of 10 m/min was reached; the duration of the daily exercise was initially set at 20 minutes and was increased daily by 10 minutes up to 60 minutes. In the following 5 weeks, mice were then subjected to running exercise at a speed of 10 m/min for 60 minutes/day. Thereafter, the mice received a collagenase injection (0.025 U collagenase type VII) into the right striatum to induce ICH. We conducted various neurological function tests up to 8 days after ICH, after which brain and plasma samples were prepared to assess hematoma volume, phagocytotic microglial numbers in the peri-lesion area, and plasma soluble factors. After ICH induction, mice suffered from body weight loss regardless of exercise preconditioning, but mice with exercise preconditioning showed faster recovery from ICH-induced body weight loss. Mice with exercise preconditioning also showed a better outcome in neurological function after ICH in multiple neurological tests. In addition, at 8 days after ICH induction, the lesion volume in the exercise preconditioning group was significantly smaller than that of the mice in the sedentary group.

After determining that exercise preconditioning had beneficial effects on ICH recovery as evaluated by histological and behavioral assays, we investigated whether there are parallel changes in the biological responses in circulating blood and glial cells. At 8 days after ICH induction, mice with exercise preconditioning had larger circulating amounts of multiple pro-survival factors, including osteopontin, compared to levels of pro-survival factors in ICH mice without exercise preconditioning. This finding is consistent with the idea that

circulating blood factors in animals with exercise preconditioning would show beneficial effects on neuronal function (Horowitz et al., 2020). Although we have not examined which cell type(s) contribute to the increase in levels of circulating osteopontin and other pro-survival factors in ICH mice with exercise preconditioning, a recent study has demonstrated that Treg cell-derived osteopontin promotes tissue-reparative microglial reaction and behavioral recovery after ischemic stroke in mice (Shi et al., 2021). Interestingly, we confirmed that the number of CD36/Iba1-double-positive cells (e.g., phagocytic microglia/macrophage) in the exercise group was significantly larger at day 8 after ICH induction. Microglial phagocytosis is an important mechanism of hematoma resorption after ICH, and our findings may provide a novel insight into the protective mechanisms by which exercise preconditioning exerts brain protection against hemorrhagic stroke.

Conclusion and future remarks: Our recent study highlighted above furthered our understanding of the therapeutic potential of exercise for ICH. Nonetheless, there are still many questions that we need to consider. For example, we still do not yet know what conditions of exercise would be ideal for stroke patients. It seems that exercise preconditioning may have some advantages as a therapeutic option over post-stroke exercise. As discussed, stroke patients may not be willing/may be unable to exercise after stroke onset due to neurological deficits. In addition, although physical activity is in general supportive for brain health, some preclinical studies indicate that under some conditions, performing exercise early in the post-stroke period could cause serious damage to brain tissue (Tamakoshi et al., 2021). On the other hand, some disadvantages in exercise preconditioning may also exist. Because we cannot predict when stroke patients will experience stroke onset, it is difficult to determine when we should start prophylactic exercise to prepare for future stroke onsets. In addition, even for healthy people, it is sometimes painful and challenging to engage in regular physical activity, so shorter exercise periods may be more acceptable as a therapeutic intervention. On top of these concerns, to optimize the conditions of exercise preconditioning for stroke, further pre-clinical mechanistic studies are required. Notably, the mechanistic studies are critical for not only optimizing the exercise treatment protocols, but also for developing a new therapy for stroke. The concept of therapeutic exercise mimetics is now attracting our attention as a novel class of therapeutics that copy the beneficial effects of physical exercise (Gubert and Hannan, 2021). Therefore, we may also need to try developing a therapy that is equivalent to "exercise in a pill" or "exercise in a device" for an aged population at higher risk of stroke who is, in general, less willing or less able to exercise (Hess et al., 2015).

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