Reduced Severity of Outcome of Recurrent Ipsilateral Transient Cerebral Ischemia Compared with Contralateral Transient Cerebral Ischemia in Rats

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Background: To investigate whether prior transient ischemic attack (TIA) had a preconditioning effect on subsequent cerebral infarction in a rat model using middle cerebral artery occlusion (MCAO). *Methods:* Thirty-six adult male Sprague–Dawley rats were divided into 3 groups: those with transient (5 minutes) left MCAO (left TIA) (n = 15), those with transient right MCAO (right TIA) (n = 15), and a sham operation group (n = 6). Seven days after the initial transient MCAO, rats in all groups underwent permanent left MCAO. After 24 hours, all rats underwent motor function measurement (the Garcia score and tilting plane test), magnetic resonance imaging, postmortem brain examination, and biomarkers of stroke. *Results:* Following permanent MCAO, the Garcia score, the brain edema area of T2-weighted images, brain infarction volume, and the level of tumor necrosis factor α mRNA of the ipsilateral and contralateral TIA groups showed no significant difference. The angle of sliding off in the tilting plane test, the mean intensity of the brain edema area of T2-weighted images, levels of matrix metalloproteinase 9, interleukin-1β, inducible nitric oxide synthase mRNA, and apoptosis-related proteins, BAX, and phosphorylated-p38, were lower in the ipsilateral TIA group compared with the contralateral TIA group. *Conclusion:* The main finding of this study was that a transient, mild, unilateral focus of cerebral ischemia (or TIA) in either the left or right hemisphere, which is then followed by a second unilateral severe and focal ischemic event, results in brain injury. The severity of the brain injury following this second ischemic event will be alleviated when the second insult is ipsilateral to the first TIA. **Key Words:** Stroke—neuroprotection—cerebral ischemia—animal model.
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Received May 16, 2017; revision received July 10, 2017; accepted July 15, 2017.

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Sources of Funding: This work was supported by the National Natural Science Foundation of China with Grant Numbers 81672252, 81272169, 81171855 to J.J.; Grant Number 81472151 to L.Z; Grant Number 81702229 to Z.H.; Shanghai Municipal Commission of Health and Family Planning, Key developing disciplines with Grant Number 2015ZB0401.

Author contributions: C.F., L.Z., and J.J. designed the study; C.F., L.Z., Z.H., P.S., L.D., G.W., and W.N. designed and performed the experimental procedures; C.F. and L.Z. analyzed the data; C.F., L.Z., and J.J. wrote the manuscript. All authors reviewed the manuscript.

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1052-3057/$ - see front matter

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http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2017.07.035

Introduction

Clinically, a transient ischemic attack (TIA) is a risk factor for subsequent cerebral infarction or stroke, with stroke being preceded by a TIA in 23% of stroke patients.[1] Following a TIA, the incidence of stroke is high, particularly in the immediate days and weeks following the TIA.[2] Moreover, it has been reported that a 1-day interval between the TIA and stroke results in more severe damage to the brain than a 3-day interval.[3] Despite negative findings of infarction by cerebral magnetic resonance imaging (MRI), accumulating underlying cell damage following TIA may also lead to neurological deficits.[4-6]

Paradoxically, some epidemiological and clinical studies have reported that stroke patients who have had a previous TIA had better functional and vital clinical outcomes, suggesting that although TIA is a risk factor for stroke, the occurrence of prior cerebral ischemia may have a protective or preconditioning effect on subsequent more severe cerebral ischemia.[7-11] Ischemic preconditioning (IP) was first described in the heart for myocardial ischemia and induces tolerance to ischemia following a short-duration, noninfarction ischemic event, which protects against further severe ischemic episodes.[12] The TIA that precedes cerebral infarction, or stroke, also appears to be a clinically relevant IP stimulus in the brain that induces ischemic tolerance and triggers neuroprotective mechanisms.[7,9,11]

Although the positive effect of IP is well established in animal models of cerebral ischemia and has also been described in some clinical studies, there is still some conflict in clinical studies in stroke patients.[13] It remains unclear how a prestroke TIA affects the diverse cellular and molecular mechanisms that may protect against tissue damage from cerebral infarction or stroke. There are many factors involved in the pathogenesis and outcome of the TIA and stroke, including frequency, duration, interval, and location.

The aim of this study was to determine whether the role of the TIA in preconditioning the cerebrum for subsequent stroke is dependent on both events affecting the same location in the brain. To test this hypothesis, a rat model of unilateral transient cerebral ischemia included 5 minutes of middle cerebral artery occlusion (MCAO), followed by ipsilateral or contralateral cerebral infarction induced by a permanent MCAO (pMCAO).

Methods

Animals

Adult male Sprague–Dawley rats weighing 250-300 g were purchased from the Sino-British Sippr/BK Lab Animal Ltd (Shanghai, China). The rats were housed under a 12:12-hour light/dark cycle with food and water available ad libitum. All animal experiments were approved by the Animal Experimental Committee of Fudan University, Shanghai, China (Permit Number: ETCA2013BN0002) and were in strict accordance with the National Institutes of Health (NIH) Guidelines for Care and Use of Laboratory Animals. All efforts were made to minimize distress to the experimental animals and to limit the number of animals used.

An Optimal Animal Model for TIA

The experiment protocol is shown in Figure 1, A. A total of 24 rats (n = 6/group, in the 5- and 10-minute groups; n = 4/group, in the 15-minute, 20-minute, and sham groups) were used to develop an optimized animal model for a TIA using MCAO. There were 3 criteria of

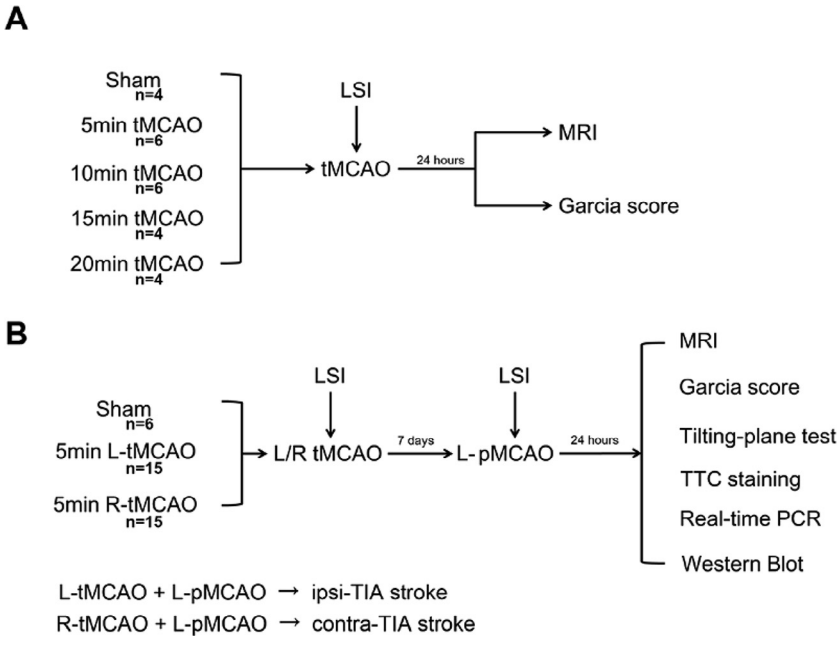

Figure 1. *Experimental protocol. (A) Establishment of prior TIA stroke model and determination of the appropriate ischemia time for the rat TIA model. (B) Stroke outcome comparison between ipsi-TIA stroke and contra-TIA stroke. At 24 hours after L-pMCAO, all the rats underwent neurological deficit evaluation (the Garcia score and tilting plane test) and MRI scan. Then, all the rats in each group were randomized to TTC staining and molecular detection (real-time PCR and Western blot). Abbreviations: L-pMCAO, left permanent middle cerebral artery occlusion; LSI, laser speckle imaging; L-tMCAO, left tMCAO; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; R-tMCAO, right tMCAO; TIA, transient ischemic attack; tMCAO, transient middle cerebral artery occlusion; TTC staining, 2,3,5-triphenyl tetrazolium chloride staining.*

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