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Letter

An Overview on the Cross- Generational Effect of Remote Ischemic Preconditioning Stimuli

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Remote ischemic preconditioning is an endogenous phenomenon in which the application of one or more brief cycles of non-lethal ischemia and reperfusion to an organ or tissue protects a remote organ or tissue from a sustained episode of lethal ischemia [1]. So far, the neuroprotective drug therapy has been a dismal failure in clinical stroke trials. In addition, numerous reviews have suggested major limitations of neuroprotective stroke clinical trials at both the research preclinical and clinical levels [2]. Based on the fact that early exposure to a non-injurious preconditioning stimulus confers an ischaemic tolerance to a subsequent ischemic challenge in the brain [3]. Therefore, targeting mechanisms of innate cytoprotection present an alternative strategy for drug development based on the reproducibility of neuroprotection against ischaemia achieved in many varied models of preconditioning.

In general, the mechanisms underlying the phenomenon of remote ischemic conditioning (RIC) can be considered inter-related events start with initial events occurring in the remote organ or tissue in response to the RIC stimulus, the protective signal which is conveyed from the remote organ or tissue to the target organ or tissue and the events occurring in the target organ or tissue which confer the protective effect [1]. The initial events of preconditioning stimuli occur at the cellular levels in the remote tissues or organs. It possible to be a quick response in the cellular defence function to the stress factors for health maintenance inside the cell. The cellular response involves changes in ion channels permeability, protein phosphorylation and post-translational modification *via* a signal transduction system. These events represent a transient protective phenotype that can be induced within minutes of exposure to preconditioning stimuli [4]. The signals generated from preconditioning stimulus may include blood-borne factor (s), neuronal mechanisms, and/or systemic responses. Intriguingly, plasma from human volunteers subjected to remote ischemic preconditioning protected human endothelial cells from hypoxia-induced cell damage indicating to compromising blood- born elements [5]. Such elements has been reported to involve nitric oxide, stromal derived factor-1 alpha, microRNA-144, microRNA-1, but also other, not yet identified factors [6,7]. Major advances in myocardial RIC came with the use of skeletal muscle as the ischemic stimulus can be transferred, even across species, with plasma-derived dialysate [7]. Another study showed that RIC applied on the hind limb activated lymphocyte cell kinase (Lck) mediating neuroprotection through PKC_{ε}-Lck-Fyn pathway [8]. The activated lymphocyte may involve in transmitting pro conditioning stimuli from remote organs like hind limb to the brain, that needs further investigation. The events in the target organs involve long term response that may extend to weeks or perhaps months. The long term response after RIC in the target organs compromise orchestrated reprogramming mechanisms that confer neuroprotection [9]. For instant, Intracardiac signal transduction events involve: adenosine, bradykinin, cytokines, and chemokines, which activate specific receptors; intracellular kinases; and mitochondrial function [7].

It has been reported that long term response to preconditioning stimulation may lead to induce genomic reprogramming and regulate cellular homeostasis process such as autophagy. For example, cytosine-phosphate-guanine (CpG) evokes preconditioning stimulus though Toll- like receptors activation. Based on that, brain miRNA expression in response to CpG preconditioning showed that miRNAs regulate endogenous responses to stroke and that manipulation of these miRNAs may have the potential to acutely activate novel neuroprotective processes that reduce damage [10]. Moreover, gene expression of the unfolded protein response (UPR) is affected by preischemic treatment by increasing the expression of Ca^{2+} binding protein: GRP 78 and transcriptional factor ATF6 in reperfusion times. Thus, ischemic preconditioning exerts a role in the attenuation of endoplasmic reticular stress response, which might be involved in the neuroprotective phenomenon of ischemic tolerance. Another aspect to be consider is that preconditioning regulates cellular autophagy, an intracellular catabolic process in which the cytoplasmic constituents, such as aggregated proteins and dysfunctional organelles, are surrounded by a double membrane, termed the autophagosome, and are transported to lysosomes for degradation and recycling [11]. The endoplasmic reticulum (ER) of neural cells responds to the interruption of blood flow by the unfolded protein response (UPR), which can be highly variable, depending on dosage and duration of ischemic treatment, and intensity of UPR signals [12]. Consequently, factors which have an effect on autophagy in human brain like normal aging, reactive oxygen species (ROS), methylation silencing of autophagy genes may attribute in ischemia tolerance [13,14]. Therefore, there is a growing body of evidence shows that certain level of autophagy activation is associated with neuroprotection due to ischemic preconditioning stimuli [15,16]. However, the contribution of autophagy to ischemia preconditioning-associated neuroprotection remains incompletely investigated.

From an evolutionary point of view, it is well known that successful adaptation to environmental stress ensure survival. In this context, we hypothesize that genomic and cytophysiological alterations due to IRC stimuli can be magnified for long- lasting neuroprotective phenotype that may promote gross- generation adaptation. Interestingly, cross-generational adaptation to cerebral ischemia seen in the stroke-prone spontaneously hypertensive rat (SHRSP)

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is retained in the first filial generation of rats. The first filial males that received Y chromosome from SHRSP parents showed decreased sensitivity to the ischemia than those with Y chromosome inherited from reference strain [17]. Another significant aspect is an epigenetic response that may result in cell adaptation to environmental stimuli. One of suggested mechanisms is the ability of environmental factors to trigger epigenetic changes in eukaryotic cells, thus contributing to transient or stable, and potentially heritable, changes in gene expression program in the absence of alteration in DNA sequence [18]. As mentioned above, one of the cytophysiological process mediated preconditioning stimuli is autophagy. This process has been shown to be inhibited due to methylation silencing of ULK2 gene in astrocyte [14]. In addition, whole genome screening showed an association between DNA methylation at the promoter or gene body level and microvascular density and to a lesser extent with blood flow recovery and revascularization of ischemic limbs [19]. Based on the literature, the cross- generation effects of ischemic preconditioning and its related mechanisms remain entirely elusive. Therefore, further studies are required to investigate the cross- generation adaptation to lethal- ischemia. Genomic- wide DNA methylation and global gene expression analysis will be useful to explore cross- generational effects of ischemic preconditioning and its related signalling pathways.

References

1. Lim SY, Hauselony DJ. Remote ischemic conditioning: from bench to bed side. Front Physiol. 2012; 3: 27.
2. Tauskela S, Blondeau N. Prescription for stroke: Should preconditioning be investigated as a drug? Ischemic Tolerance of the Brain. 2009: 85-139.
3. Gidday JM. Cerebral preconditioning and ischaemic tolerance. Nat Rev Neurosci. 2006; 7:437-448.
4. Perez-Pinzon MA, Xu GP, Dietrich WD, Rosenthal M, Sick TJ. Rapid preconditioning protects rats against ischemic neuronal damage after 3 but not 7 days of reperfusion following global cerebral ischemia. J Cereb Blood Flow Metab. 1997; 17: 175-182.
5. Weber NC, Riedemann I, Smit KF, Zitta K, van de Vondervoort D, Zuurbier CJ, et al. Plasma from human volunteers subjected to remote ischemic preconditioning protects human endothelial cells from hypoxia-induced cell damage. Basic Res Cardiol. 2015; 110: 17.
6. Gill R, Kuriakose R, Gertz ZM, Salloum FN, Xi L, Kukreja RC. Remote ischemic preconditioning for myocardial protection: update on mechanisms and clinical relevance. Mol Cell Biochem. 2015; 402: 41-49.
7. Heusch G, Botker HE, Przyklenk K, Redington A, Yellon D. Remote ischemic conditioning. J Am Coll Cardiol. 2015; 75: 177-195.
8. Bae ON, Rajanikant K, Min J, Smith J, Baek SH, Serfozo K, et al. Lymphocyte cell kinase activation mediates neuroprotection during ischemic preconditioning. J Neurosci. 2012, 23; 32: 7278-7286.
9. Stenzel-Poore MP, Stevens SL, King JS, Simon RP. Preconditioning Reprograms the Response to Ischemic Injury and Primes the Emergence of Unique Endogenous Neuroprotective Phenotypes Stroke. 2007; 38: 680-685.
10. Vartanian KB, Mitchell HD, Stevens SL, Conrad VK, McDermott JE, Stenzel-Poore MP. CpG preconditioning regulates miRNA expression that modulates genomic reprogramming associated with neuroprotection against ischemic injury. J Cereb Blood Flow Metab. 2015; 35: 257-266.
11. Yan WJ, Dong HL, Xiong LZ. The protective roles of autophagy in ischemic preconditioning. Acta Pharmacol Sin. 2013; 34: 636-643.
12. Lehotsky J, Račay P, Pavlikova M, Tatarkova Z, Urban P, Chomova M, et al. Cross-talk of intracellular calcium stores in the response to neuronal ischemia and ischemic tolerance. Gen Physiol Biophys. 2009; 28: F104-F114.
13. Lipinski MM, Zheng B, Lu T, Yan Z, Py BF, Ng A, et al. Genome-wide analysis reveals mechanisms modulating autophagy in normal brain aging and in Alzheimer's disease. Proc Natl Acad Sci U S A. 2010; 107: 14164-14169.
14. Shukla S, Patric IR, Patil V, Shwetha SD, Hegde AS, Chandramouli BA, et al. Methylation silencing of ULK2, an autophagy gene, is essential for astrocyte transformation and tumor growth. J Biol Chem. 2014; 289: 22306-22318.
15. Fan J, Zhang Z, Chao X, Gu J, Cai W, Zhou W, et al. Ischemic preconditioning enhances autophagy but suppresses autophagic cell death in rat spinal neurons following ischemia-reperfusion. Brain Res. 2014; 1562: 76-86.
16. Jiang T, Yu JT, Zhu XC, Zhang QQ, Tan MS, Cao L. Ischemic Preconditioning Provides Neuroprotection by Induction of AMP-Activated Protein Kinase-Dependent Autophagy in a Rat Model of Ischemic Stroke. Mol Neurobiol. 2015; 51: 220-229.
17. Carswell HV, Anderson NH, Clark JS, Graham D, Jeffs B, Dominiczak AF, et al. Genetic and gender influences on sensitivity to focal cerebral ischemia in the stroke-prone spontaneously hypertensive rat. Hypertension. 1999, 33: 681-865.
18. Chiariotti L, Angrisano T, Keller S, Florio E, Affinito O, Pallante P, et al. Epigenetic modifications induced by Helicobacter pylori infection through a direct microbe-gastric epithelial cells cross-talk. Med Microbiol Immunol. 2013; 202: 327-337.
19. Gubernator M, Slater SC, Spencer HL, Spiteri I, Sottoriva A, Riu F. Epigenetic profile of human adventitial progenitor cells correlates with therapeutic outcomes in a mouse model of limb ischemia. Arterioscler Thromb Vasc Biol. 2015; 35: 675-688.

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