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Commentary

Cellular Adaptation to Ischemia; Ischemic Conditioning to Confer Neuroprotective Benefits in Mild Cognitive Impairment and Alzheimer's disease

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Abstract

Small, controlled doses of ischemia induced in a healthy limb has been demonstrated to strengthen the body's tolerance to larger more toxic doses. Ischemic conditioning utilising protocols of remote ischemic conditioning (RIC) and physiological ischemic training (PIT) trigger mechanisms of cellular adaptation to ischemia. These protocols may represent practical and translatable therapies for neurological diseases, such as mild cognitive impairment and Alzheimer's disease, that have an ischemic or inflammatory basis. Whilst the current literature supports the neuroprotective and anti-hypertensive effects of RIC and PIT, to date there has been no investigation into the effects of PIT utilising isometric exercise training (IET) on cognitive performance outcomes in an elderly neuropathological cohort. However, it seems feasible that the anti-hypertensive effects elicited through IET might be a stimulus for improvements in systemic and neurovascular circulation and as a result, enhanced cognitive performance.

Keywords: *Alzheimer's Disease, Blood Pressure, Hypertension, Ischemic Conditioning, Isometric Exercise Training, Mild Cognitive Impairment, Reactive Hyperaemia, Remote Ischemic Conditioning, Vascular Risk Factors*

Ischemia is thought to play a pivotal role in the aetiology and progression of Alzheimer's disease [1–3] with reduced cerebral blood flow (CBF) the manifestation of this [4]. Ischemia arises as a consequence of restricted blood flow and compromises the efficient circulation of oxygen, nutrients, other important blood borne factors, and the removal of toxic metabolic waste. Cellular dysfunction arising from ischemia will often result in cell death. Ischemia may be partial as in the case of hypoperfusion which occurs in conditions such as mild cognitive impairment (MCI) and AD or total as in the case of heart attack and stroke. Ischemia is associated with serious physiological implications. However, through a process of ischemic conditioning, small controlled doses of ischemia delivered to a healthy limb is able to strengthen the body's tolerance to larger more toxic doses [5]. This type of treatment is currently administered to patients to improve the outcomes of heart attack [6] and ischemic stroke [7, 8]. Two methods of inducing remote limb ischemia are remote ischemic conditioning (RIC) and physiological ischemic training (PIT). RIC involves inflating a blood pressure cuff to above systolic blood pressure (SBP) to induce total ischemia via full occlusion of the brachial artery, followed by reperfusion after cuff deflation [9]. PIT involves subjecting skeletal muscle to intense contraction via the application of isometric contraction using handgrip dynamometer or tourniquet to induce partial occlusion of the brachial artery followed by reperfusion [10].

Ischemic Conditioning

The practice of ischemic conditioning to elicit cellular adaptation in the myocardium has been utilised for approximately 30 years [6]. Research investigating the neuroprotective potential of RIC began approximately10 years later with initial findings reporting RIC as an effective method of limiting neural tissue damage after stroke [11]. Since then there has only been a small amount of research in this area, with exciting results, Mouse models of vascular cognitive impairment have shown increased CBF, reduction in inflammation, reduced amyloid-beta deposition and improved cognition [12]. Human trials have shown increased CBF [9], the enhancement of neuroplasticity [13], and motor and cognitive learning enhancements in healthy adults [14].

As with RIC, PIT has been shown to stimulate collateral formation in the myocardium [15], upregulate vascular endothelial growth factor (VEGF) production, and promote angiogenesis [16]. More recent research reported that the application of PIT using isometric exercise training (IET), at 50% Maximal Voluntary Contraction (MVC), to patients with acute cerebral infarction promoted brain collateral formation via the increased expression of VEGF and recruitment of endothelial progenitor cells [17]. The same researchers also reported a positive correlation between increased CBF and improved motor function. More recently, improvement in cognitive performance and reduction in systemic arterial stiffness was demonstrated in a cohort of non-elderly, non-neuropathological adults after 8 weeks of IET at 30% MVC [18]. Traditionally, IET using handgrip dynamometer has been successfully demonstrated as an anti-hypertensive therapy [19]. IET can elicit blood pressure (BP) reductions greater than those achieved through aerobic exercise and equivalent to those achieved

through monotherapy with beta-blocker [20]. Furthermore, there is a considerable amount of research that links hypertension to conditions of cognitive decline such MCI and AD [21].

The Role of Hypertension

Hypertension, a hallmark of aging, has been linked with cerebrovascular pathology, hypoperfusion [22], and cognitive decline [23]. Imaging studies have demonstrated an association between brain atrophy and untreated hypertension [24] and positive correlations have been demonstrated among SBP, diastolic blood pressure, and burden of neural AD pathology [21, 25]. Hypertension is associated with structural and functional changes in cerebrovascular pathways. These deleterious alterations are potentially reversible [26]. Subsequently, improving CBF may also lead to improvements in cognitive performance. The treatment and management of hypertension has been observed to slow cognitive decline in individuals with AD [27] and to reduce the risk of progression from MCI to AD Li et al. [17].

Change Mechanisms of Ischemic Training

Whilst the signalling mechanisms involved in ischemic conditioning are not fully understood, evidence obtained through animal models and clinical trials suggest that **signalling initiation** occurs via autacoids such as adenosine, bradykinin, and calcitonin gene-related peptide. To varying extents each of these autacoids are involved in neuromodulation, inflammatory mediation, and vasodilation [28]. **Signal transmission** to the brain is believed to occur through an interaction between humoral and neural pathways such as peripheral and autonomic nervous systems, blood borne factors (IL-10, and nitrite), immune and anti-inflammatory factors (IL-6, IL-10, IL-1ra), and endogenous carbon monoxide [9]. Abnormalities in the metabolism of endogenous carbon monoxide have been linked to a variety of diseases including neurodegenerations, hypertension, heart failure, and inflammation [29]. Mitochondria play a prominent role in **signal transduction** with most pathways that are triggered by ischemic conditioning converging on the mitochondria [5].. Mitochondrion are the energy packages of the cell and are responsible for regulating cell metabolism. Nitrite protects mitochondria from oxidative stress and is upregulated after the application of RIC, as is CBF [9]. Inadequate CBF is a contributor to oxidative stress in brain cells and has significant implications in neurological diseases such as AD where the mitochondria are ravaged by oxidative stress [30, 4].

Considerations for Future Investigation

Dementia is Australia's second leading cause of death in adults over 65 years [31] and is the greatest cause of disability among the elderly. Both RIC and PIT/IET represent practical and translatable therapies for neurological diseases that have an ischemic or inflammatory basis. Whilst the current literature supports the neuroprotective and anti-hypertensive effects of PIT/IET, to date there has been no investigation into the effects of this protocol on cognitive performance outcomes in an elderly neuropathological cohort. However, it seems feasible that the anti-hypertensive effects elicited through IET might be a stimulus for improvements in systemic and neurovascular circulation and as a result, enhanced cognitive performance.

The potential for limb ischemia to trigger neuroprotective physiological responses to support and repair the brain has been demonstrated via RIC and PIT/IET protocols and introduces exciting therapeutic potential for individuals with MCI and AD. The application of RIC and PIT/IET may create an ischemic event that is adequate to confer neuroprotective benefits and anti-hypertensive effects in elderly adults with cognitive impairment or AD. Further investigations within this domain have the potential to yield life-changing results for many individuals.

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