Chapter 1

Ischemic Postconditioning after Stroke: Another Concept for the Trigeminocardiac Reflex?

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Abstract

Ischemic postconditioning is a concept for preventing ischemia/reperfusion injury in cerebral infarction. It has been evolved into experimental research by a broad range of stimuli/triggers and has not yet found its place in translational research. This review, therefore, first examines a potential clinical application of this concept and also provides insight into the phenomenon of trigeminocardiac reflex (TCR) and its oxygen-conserving component as a pillar of the ischemic postconditioning concept in humans. This concept serves as an example that only innovative therapeutic approach will substantially improve the current stroke research.

Keywords: ischemic tolerance, stroke, treatment

1. Introduction

Extensive experimental studies have shown that the mechanisms of cerebral ischemia include glutamate excitotoxicity, calcium toxicity, free radicals, nitric oxide, and inflammatory reactions, as well as dysfunctions of endoplasmic reticulum and mitochondrion, and it is an evolving topic from basic research to clinical applications during the past two to three decades [1–5]. These injury cascades are interconnected in complex ways, suggesting that only a few neuroprotective substances can offer therapeutic effects [6–10]. Thus, it is necessary to compare the novel and innovative therapeutic approaches in ischemia models. All these tremendous works have led to some substantial research in cellular and molecular pathways that have spurred the studies in potential neuroprotection, mainly in pharmacological fields, such as anti-excitotoxic treatment, calcium channel antagonist, approaches for inhibition of oxidation, inflammation, and apoptosis. However, several decades of research have not led to a new

breakthrough concept of stroke treatment [11–21]. Nevertheless, there are still the same topics that we are dealing with our work. This chapter, therefore, shows the wide range of today's stroke research and also opens the door to the need for some innovative areas of studies in this topic, such as ischemic postconditioning, a strategy that has emerged during the past years.

Here, we present an innovative therapeutic approach covering several of the already known concepts of ischemic stroke treatment, leading to an easy clinical application.

2. Trigeminocardiac reflex

The trigeminocardiac reflex (TCR) is defined as the sudden onset of parasympathetic dysrhythmia, sympathetic hypotension, apnea, and/or gastric hypermotility during mechanical/thermic stimulation of any of the sensory branches of the trigeminal nerve [22–65]. The sensory nerve endings of the trigeminal nerve send neuronal signals through the Gasserian ganglion to the sensory nucleus of the trigeminal nerve, forming the afferent pathway of the reflex arc (see **Figure 1**) [45, 48, 49]. This afferent reflex pathway continues along the short internuncial nerve fibers in the reticular formation to connect with the efferent reflex pathway to the motor nucleus of the vagus nerve [45, 49, 65]. Clinically, the TCR has been reported to occur during nearly all skull base surgeries [22, 28, 53, 61]. Apart from these clinical reports, the physiological function of this brainstem reflex has not yet been fully explored, but different connections to the oxygen-conserving reflex are found [34–38, 55, 56, 63, 64].

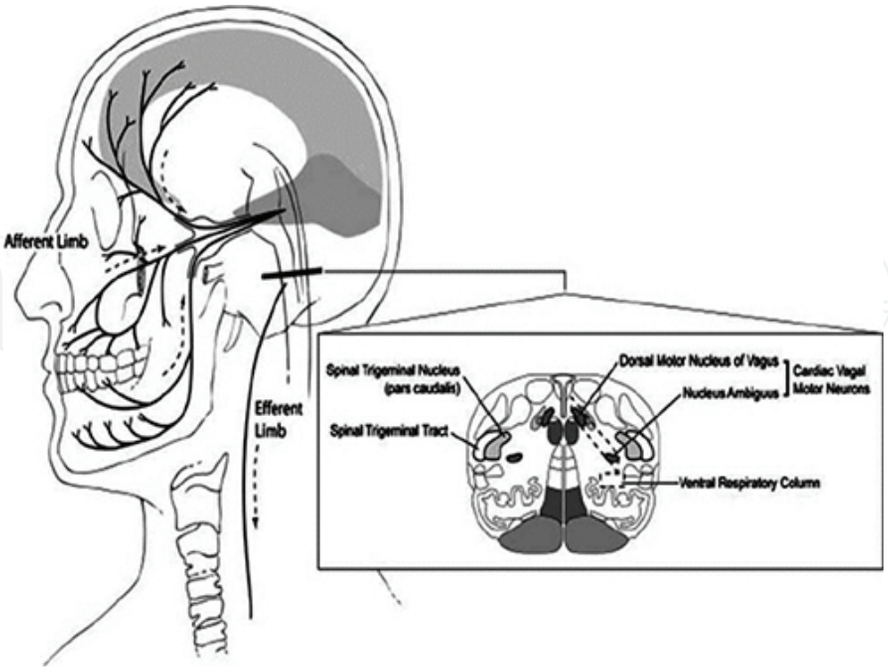

Figure 1. Summary of the trigeminocardiac reflex.

3. Oxygen-conserving reflex

From experimental findings, it may be suggested that the TCR represents an expression of a central neurogenic reflex, leading to rapid cerebrovascular vasodilatation generated from excitation of oxygen-sensitive neurons in the rostral ventrolateral medulla oblongata [39, 55, 56]. By this physiological response, the adjustments of the systemic and cerebral circulations are initiated to divert blood to the brain or to increase blood flow to it (see **Figure 2**) [25, 39]. As it is accepted that the diving reflex and ischemic tolerance appear to involve at least partially similar physiological mechanisms, the existence of such endogenous neuroprotective strategies may extend the known clinical appearance of the TCR and include the prevention of other potential brain injury states as well [25]. This existence of an oxygen-conserving reflex may be in line with the suggestion that the TCR is physiological, but not a pathophysiological entity.

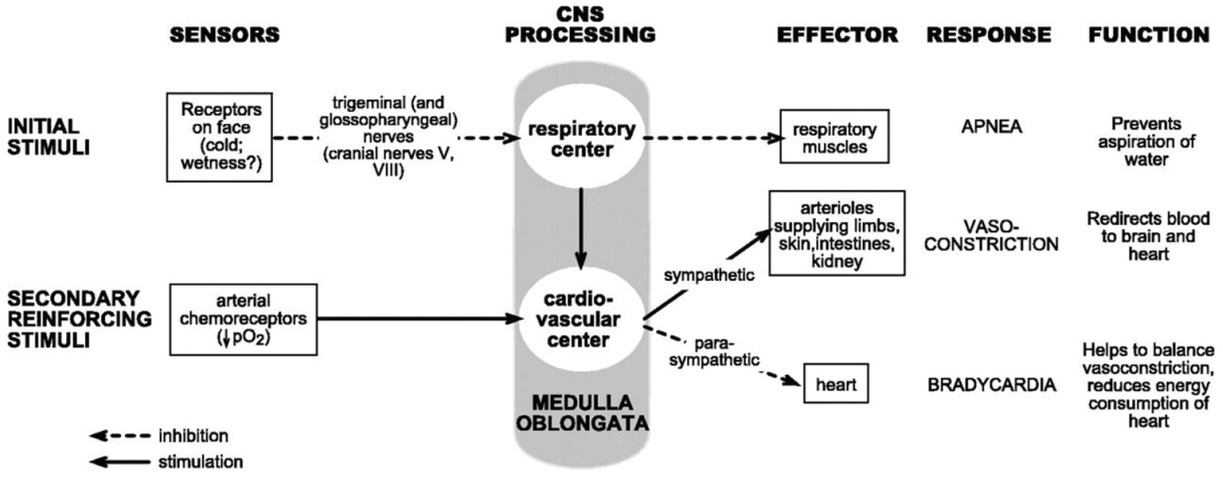

Figure 2. Oxygen-conserving reflex (adapted with permission from Hiebert and Burch [66]).

4. Postconditioning

Brief interruption (10–60 s, depending on the model) of the blood flow, applied immediately after the onset of reperfusion following an ischemic event, is observed to provide protection [19–21]. In the initial study in an anesthetized canine model of coronary artery occlusion-reperfusion, three cycles of coronary artery reperfusion alternating with 30 s of reocclusion were associated with a significant reduction in both the infarct size and the endothelial dysfunction [14–18]. Similar findings are now also demonstrated in the rat's brain. This "postconditioning" is so named because the stimulus is applied after the ischemia and is now also conferred by other species.

The protective effect of postconditioning can be achieved by occluding the ipsilateral common carotid artery (CCA), which is clinically relevant, for the ipsilateral CCA is accessible. Also,

postconditioning can also be induced through volatile anesthetics. Isoflurane, for example, reduces the infarct size by 50%, if administered early during reperfusion. Likely, this effect is mediated through the PI3K pathway. Other pharmacological agents administered at the start of reperfusion have been shown to be cardioprotective (see **Figure 3**). This includes the following:

1. Adenosine
2. Nitric oxide
3. Cytokines
4. Complement inhibitors

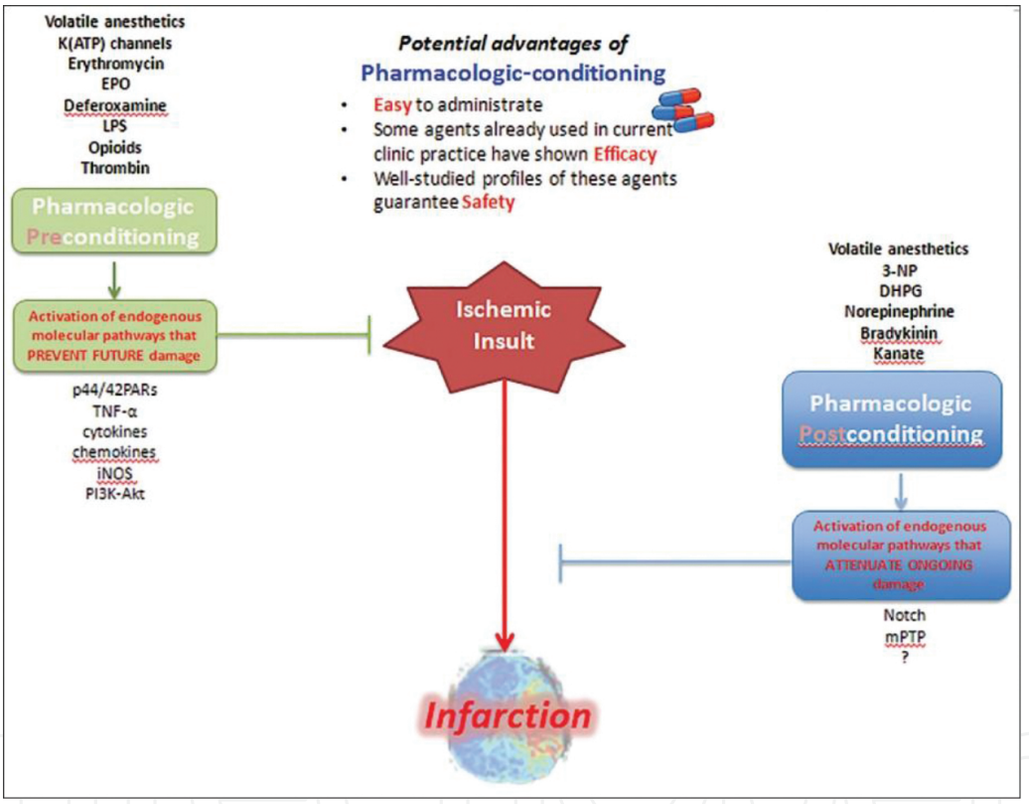

Figure 3. Postconditioning (adapted with permission from Esposito et al. [67]).

However, whether this approach should be described as "pharmacological postconditioning" or as a "postreperfusion treatment" has been debated [20]. Since the mechanisms of postconditioning have not been fully elucidated and the importance of the alternating cycles of ischemia-reperfusion has not been appreciated nor determined to be critical to protection, direct association to 'postconditioning' (whatever 'conditioning' means at reperfusion) should be debated.

Experimental studies support the neuroprotective potency of postconditioning to reduce the infarct size, endothelial dysfunction, and neutrophil accumulation in the jeopardized area [21].

These experimental results suggest that within the first minutes of reperfusion, endogenous processes are initiated, which help to reduce reperfusion injury after a limited duration of ischemia. The multiplicity of cell types that are affected by postconditioning (i.e., vascular endothelial cells and inflammatory cells) reflects the complexity of reperfusion injury and suggests a broad network of effects within this complex interactive web of responses. Also, delayed postconditioning, which is clinically more relevant, also improved glucose uptake, inhibited edema, and mitigated blood-brain barrier leakage in the penumbra, and finally, attenuated the exacerbating effect of tissue plasminogen activator (t-PA).

5. Trigeminocardiac reflex and postconditioning in stroke

Some studies have shown that postconditioning reduces infarction in the period immediate after a stroke [20]. However, more studies are needed to better understand this phenomenon and to translate it into the clinic. Postconditioning seems to reduce the cerebral ischemic injury by blocking the overproduction of ROS and lipid peroxidation, and by inhibiting apoptosis. The initial inhibiting effect on ROS may lead to an improved activity of the Akt and K_{ATP} channels, which contributes to the protection of postconditioning. Also, the changes in the MAPK pathways and the δPKC and εPKC activities are also associated with the protection of postconditioning.

However, what is the connection with the TCR? The TCR is, in our opinion, a specific example of a group of related responses generically defined by Wolf as oxygen-conserving reflexes. Within seconds after this TCR initiation, there is a vast and differentiated activation of sympathetic nerves. The suggested effect of the TCR in the brain is a constant elevation in cerebral blood flow (CBF) that is not associated with changes in the cerebral metabolic rate of oxygen (CMRO2) or cerebral glucose metabolic rate (CMRglc) and hence represents a primary cerebrovascular vasodilatation. The brain can protect itself from ischemia by distinct (endogenous) physiological mechanisms, which probably involve two separate systems of neurons in the CNS. The one who mediates a reflexive neurogenic neuroprotection emanates from oxygen-sensitive sympathoexcitatory reticulospinal neurons of the rostral ventrolateral medulla (RVLM). These cells, excited within seconds by a reduction in CBF or CMRO2, initiate the systemic vascular components of the oxygen-conserving diving reflex. They profoundly increase CBF without changing CMRO2 and CMRglc and, hence, rapidly and efficiently provide the brain with oxygen [39]. Upon cessation of the stimulus, the systemic and cerebrovascular adjustments return to normal. The system mediating reflex protection projects through as-yet-undefined projections from the RVLM to the upper brainstem and/or thalamus to engage a small population of neurons in the cortex, which appear to be dedicated to transducing a neuronal signal into vasodilation [39]. Two lines of evidence indicate that the RVLM neurons are essential for the expression of the cerebrovascular vasodilation elicited by hypoxia [55]. First, electrical stimulation of RVLM in intact or spinalized rats site-specifically and dose-dependently elevates rCBF, but not CMRO2 or CMRglc [39]. In this manner, these data replicate hypoxic vasodilatation. The response can only be attributed to stimulation of the reticulospinal sympathoexcitatory neurons since these are the only neurons in the region

excited by over 50% elevation of CBF produced by hypoxemia [39]. The fact that such lesions do not affect the vasodilatation elicited by hypercarbia indicates that the response is stimulus selective. Thus, much of the cerebrovascular vasodilatation elicited in the cerebral cortex by hypoxemia is a reflex that results from excitation of oxygen-sensitive brainstem neurons, and not by a direct effect of hypoxia on blood vessels nor by stimulation of arterial chemoreceptors whose activity, while regulating blood flow to most vascular beds, is without force in the cerebral circulation [55, 56]. It also appears to relay the central neurogenic vasodilatation elicited from other brain regions, including excitation of axons innervating the fastigial nucleus. This mode of protection would be initiated under conditions of global ischemia and/or hypoxemia because the signal is detected by medullary neurons. The concept that the brain may have neuronal systems dedicated to protecting itself from (ischemic) damage, at first appearing to be a novel concept, is, upon reflection, not surprising since the brain is not injured in naturalistic behaviors characterized by very low levels of rCBF, such as diving or hibernation.

Such neuroprotective adaptations may also underlie preconditioning strategies. The diving reflex, hibernation, and ischemic tolerance appear to involve at least partially similar physiological mechanisms because most of the signals, transducers, and effectors that are well established in ischemic tolerance have also been demonstrated in hypoxia-tolerant or hibernating animals. A better and more detailed understanding of the pathways, transmitters, and molecules engaged in such protection may provide new insights into novel therapies for a range of disorders characterized by neuronal death. Recent clinical studies suggest such an endogenous neuroprotective effect in the human brain.

6. Conclusions and take-home message

The TCR is certainly the most influential and most innovative concept in skull base surgery of the past 20 years. In addition, the TCR steps out of this shadow and opens the door to significant therapeutical options in neurological disorders.

The here presented concept is also exemplary for this book: to think out of the box is needed to make further substantial improvements in today's stroke research and its clinical application. The time that simple systematic reviews with its not negligible bias lead to improved therapeutic approaches is over. Now the time of concepts integrating knowledge from different sources has begun: the ischemic preconditioning by the TCR is one such approach, the use of 3-D-printing in neuroradiology aneurysm treatment another. However, this book also shows that we have to prove these concepts in different ways.

"Tempora mutantur, et nos mutamur in illis" shows that stroke research has to make the next step to overcome the standstill of the last years. This book is—if any—a subtle step in this direction, but it shows that we need newer models to cover and explain all important aspect of stroke and its treatment.

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