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Update on preconditioning investigation for traumatic brain injury

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Traumatic brain injury (TBI) is one of the leading causes of morbidity and mortality worldwide. Though much progress has been made in the field of medicine and technology, there is no effective pharmacological therapy for TBI in the clinic. Preconditioning scenarios can serve as a potential neuroprotective strategy as well as induce tolerance against harmful cascades of cellular events following primary injury. An effective preconditioning strategy against TBI could be groundbreaking for scientists in this field as well as in the clinical setting. This review focuses on the current status of preconditioning methods in TBI studies and elucidating the mechanisms underlying the beneficial effects of various preconditioning scenarios. Further preconditioning studies are needed to aid in understanding the molecular pathological mechanisms of brain damage and recovery as well as developing novel and effective intervention strategies for TBI.

Keywords: Preconditioning, Traumatic brain injury, Methods, Mechanisms

Introduction

Traumatic brain injury (TBI) is a significant cause of death and disability worldwide (Capizzi et al., 2020), but there is currently no effective pharmacological therapy. It is well known that primary mechanical injury leads to focal brain structural damage and diffuse axonal injury, followed by secondary brain injuries, including neuroinflammation, blood brain barrier (BBB) disruption, and neuronal cell death (Monsour et al., 2022). Although many injurious pathways are well defined, it has been a major challenge to identify ways to mitigate these pathways to reduce secondary brain damage after TBI. Preconditioning has been investigated at a basic-science level to determine the endogenous and pluripotent neuroprotective effects, and has shown potential as a new therapy for TBI (Yokobori et al., 2013).

The term "preconditioning" was first introduced by Janoff in 1964 (Janoff, 1964) to describe a phenomenon in which brief episodes of a noxious stimulus with sublethal insult or stress induce certain advantageous intrinsic mechanisms for protection and repair, creating a tolerance in the organ to the insult and, thus, protecting it from subsequent lethal injuries (Janoff, 1964; Dirnagl et al., 2009). Since then, various research on preconditioning has been aimed at understanding endogenous neuroprotective mechanisms and identifying innovative therapeutic strategies that prevent or reduce neuronal damage (Dirnagl and Meisel, 2008; Stetler et al., 2014). The results from preconditioning studies in stroke have been very promising and are now being applied in the clinic (Dirnagl et al., 2009; Hess et al., 2021), but preconditioning investigations in TBI have been limited. The main reason is the majority of TBI that occur are accidental, so previous investigations have focused more on post-TBI intervention and treatment. However, sport and military-related mild TBI or high-risk elective neurosurgical patients, such as aneurysm reconstructions, which occur in a more predictable and orchestrated timeframe (Stetler et al., 2014), make preconditioning interventions and treatment of mild TBI feasible. Importantly, the concept of preconditioning is highly attractive for investigators to study the endogenous molecular mechanisms underlying neuroprotection after TBI elicited by preconditioning, which may help in developing new therapy (Stetler et al., 2014). Effective preconditioning stimuli in TBI are numerous and diverse, ranging from heat

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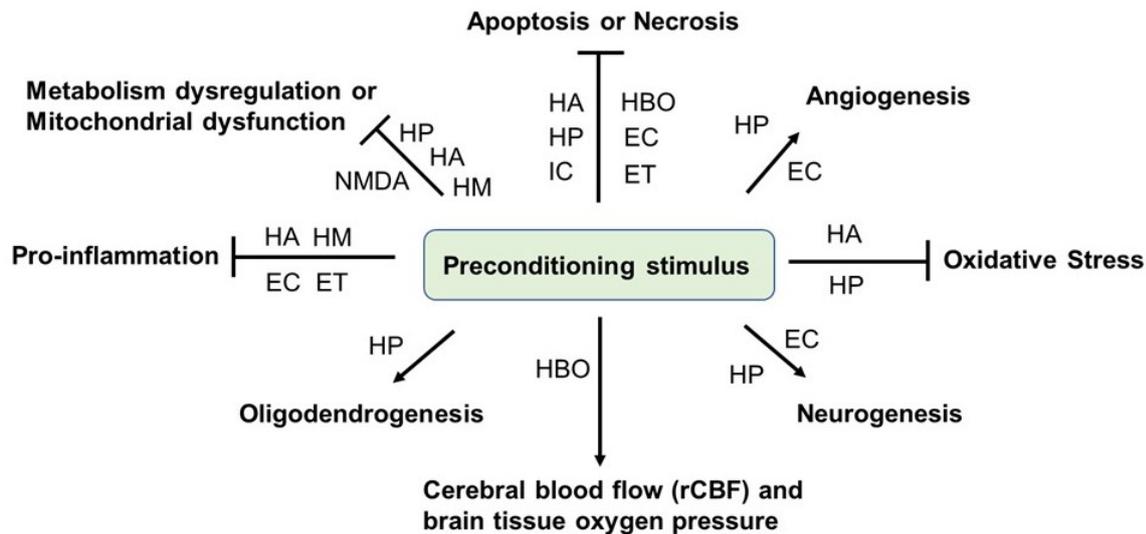
Figure 1. Preconditioning-mediated beneficial effects in TBI studies. Animal studies on TBI have demonstrated that various preconditioning stimuli or stresses trigger numerous beneficial effects in TBI animal models, including inhibition of metabolism dysregulation, mitochondrial dysfunction, pro-inflammation, oxidative stress, and neuronal cell death, while promoting neurogenesis, oligodendrogenesis, angiogenesis, cerebral blood flow, and brain tissue oxygen pression. HA: heat acclimatiion; HM: hypothermia; HP: hypoxia; IC: ischemic; HBO: hyperbaric oxygen; EC: exercise; ET: endotoxin; NMDA: N-methyl-D-aspartate

acclimation, hypoxia, ischemic, physical exercise, hyperbaric oxygen, and exposure to neurotoxins and pharmacological agents. These preconditioning stimuli are vastly different, but the sublethal exposure of these stimuli can confer protection against TBI through multiple mechanisms, such as activation of extra- and intracellular defense mechanisms, inhibition of neuronal cell death and oxidative stress, reduction in neuroinflammation, and induction of neurogenesis, etc. (Stetler et al., 2014). An improved understanding of preconditioning in TBI would help us identify innovative therapeutic strategies that prevent or at least reduce neuronal damage (Dirnagl and Meisel, 2008).

Previous studies have already summarized TBI pathophysiology and discussed existing animal studies demonstrating the efficacy of preconditioning in TBI (Yokobori et al., 2013; Stetler et al., 2014). In this review, we focused on the current progress in the experimental methods of preconditioning in TBI, and then elucidating the mechanisms underlying preconditioning that triggers endogenous neuroprotection.

Preconditioning methods and mechanisms for TBI
Many deleterious stimuli including heat acclimation, hypoxia, ischemia, hyperbaric oxygen, endotoxin, drugs, and stimuli that essentially induces cellular stress, such as anesthetics, and physical exercise have been reported as preconditioning methods for TBI. Below we summarized these methods and elucidated the associated underlying mechanisms of each stimulus (Figure 1 and Table 1).

Temperature preconditioning –Heat acclimation (HA) and hypothermia (HM)
Heat acclimation (HA) (34°C 30 d) is a well-established preconditioning model that confers neuroprotection against experimental closed head injury (CHI) (Beit-Yannai et al., 1997; Umschweif et al., 2013b). Heat acclimation is unique from other preconditioning methods since this global physiological adaptation has been shown to induce cross-tolerance against other stressors, including TBI (Shein et al., 2007a; Horowitz et al., 2015).

The precise mechanisms underlying HA preconditioning-induced neuroprotection against TBI have been thoroughly studied, including reduced basal metabolic rate and improved heat tolerance (Horowitz, 2002), inhibited apoptotic neuronal cell death (Umschweif et al., 2015), activated heat shock response (HSP)(Su et al., 2009), anti-oxidative stress, and anti-inflammation (Shein et al., 2007c; Shein et al., 2007a; Shein et al., 2008), which are mediated by several molecular effectors and signaling cascades. Accumulating evidence suggested that Akt is a key cellular pro-survival signaling pathway that mediates HA-induced neuroprotection. Preconditioning via HA induces neuroprotection by increasing Akt phosphorylation at thr308 (Shein et al., 2007b). Further study suggested that HA mediates neuroprotection by inhibiting Akt downstream at the GSK3β/β-catenin pathway after TBI (Umschweif et al., 2013b). Another key mediator of HA preconditioning-induced neuroprotection in TBI is heat inducible factor-1 alpha (HIF1α). Studies suggested that HA confers neuroprotection against CHI by increasing HIF1α (Shein et al., 2007b; Umschweif et al., 2013a) and its downstream erythropoietin receptor (Shein et al., 2005). Angiotensin II receptor type 2 (AT2) has also been found to be an upstream regulator of neuroprotection and neurorepair in injured HA mice (Umschweif et al., 2014). In addition, microglia-derived brain-derived neurotrophic factor (BDNF) has shown to be capable of mediating HA-conferred neuroprotection following experimental TBI (Shein et al., 2008).

In addition, temperatures below homeostatic temperatures (hypothermia) can induce a tolerant state. Hypothermia has now been applied after TBI in the clinic and in experimental research (Lewis et al., 2017; Hui et al., 2021). However, research on the effect of hypothermia preconditioning on TBI-induced brain damage is scarce. Only one study has reported that hypothermic preconditioning (mice were placed at room temperature for approximately 60 min until the core temperature was lowered to 25 °C Then, mice were transferred to a freezer (5 °C) and the core body temperature of mice decreased to 16–18 °C for 45 min) improves cognitive impairment by enhancing synaptic plasticity, inhibiting microglial activation, and improving hypometabolism in the brains of TBI mice (Liu et al., 2017).

Hypoxic preconditioning
Hypoxic preconditioning is a well-established preconditioning model that increases the inherent tolerance of brain tissue

Table 1. Summary of preconditioning investigation for TBI

Preconditioning	TBI animal models	Targeting mechanisms	References
Heat acclimation preconditioning	Closed head injury (CHI)	Inhibits GSK3β and c-Jun-N-terminal kinase, and Induces β-catenin Phosphorylation	(Umschweif et al., 2013b)
	CHI	Augments concentration of Low molecular weight antioxidants	Beit-Yannai et al., 1997
	CHI	Inhibits apoptotic neuronal cell death by increasing Bcl-x, and reducing Bad and cytochrome c release,	(Umschweif et al., 2015)
	Diffuse axonal injury (DAI)	Increases HSP70 in neurons.	(Su et al., 2009)
	CHI	Enhances pre-injury expression of anti-inflammatory IL-10, IL-4 and reduces post-injury TNFα expression	Shein et al., 2007c
	CHI	increases Akt phosphorylation at thr[308]	(Shein et al., 2007b)
	CHI	Enhances HIF-1 prosurvival pathway	(Umschweif et al., 2013a)
	CHI	Activates HIF-1/EpoR signaling	(Shein et al., 2005)
	CHI	Activates AT2, BDNF/TrkA and HIF-1 signaling	(Umschweif et al., 2014)
Hypothermia preconditioning	Repetitive mild brain injury	Increases the expression of PSD93, PSD95 and NR2B	(Liu et al., 2017)
Hypoxic preconditioning	CCI	Activates HIF-1α/GLUTs signaling	(Wu et al., 2021)
	CCI	Up-regulates Nrf2/HO-1 signaling	(Shu et al., 2016)
Ischemic preconditioning	Fluid percussion brain injury (FPI)	NA	(Perez-Pinzon et al., 1999)
Hyperbaric oxygen (HBO) preconditioning	CCI	Inhibits the expression of MMP-9	(Hu et al., 2008)
	Weight drop model	NA	(Hu et al., 2010)
Exercise preconditioning:	CCI	increases VEGF-A, EPO, and HO-1	(Taylor et al., 2015)
	FPI	Inhibits IL-1β, TNFα expression, MPO activity; increases IL-10 expression and Na⁺,K⁺-ATPase activity.	(Mota et al., 2012)
	FPI	Induces HSP70/NF-κB/IL-6/synapsin I axis	(Chio et al., 2017)
	CCI	Enhances BDNF pathway, amplify HSP70 expression, reduces Bid, Puma, decreases mitochondrial cytochrome c and AIF release, inhibits AIF translocation to the nucleus, attenuates caspase activation.	(Zhao et al., 2015)
	FPI	Increases the number of CD34+ stem cells	(Zhou et al., 2017)
Endotoxin preconditioning	CCI	Prevents the up-regulation of caspase 3 and caspase 7 in CA1 and CA3	(Eslami et al., 2020)
	CCI	Increases CD11b, interferon β in uninjured mice, while reduces CD68 and IL-6 in injured mice	(Longhi et al., 2011)
	Impact-acceleration injury	Downregulates the oncostatin M receptor	(Turner et al., 2017)
	CCI	Decreases IL-1β and TNF-α over-expression	(Eslami et al., 2015)
N-methyl-D-aspartate (NMDA) preconditioning	CHI	augments activities of mitochondrial complexes II and IV, and creatine kinase	(Boeck et al., 2013)
	CHI	NA	(Costa et al., 2010)
	CHI	NA	(Moojen et al., 2012)
Other preconditioning:			
Behavioral preconditioning	Acceleration impact model of diffuse brain injury	Increases VEGFR2	(Kreipke et al., 2007)
Anesthetic preconditioning	High-impact trauma in fly	NA	(Johnson-Schlitz et al., 2022)
Blast Preconditioning	Blast Injury	Inhibition of kyneurinine-3-monoxygenase	(Harper et al., 2019)
L-lactate preconditioning	CCI	Potentiates GPR81 signaling	(Zhai et al., 2020)
Glycolytic preconditioning	CHI	Reduces cytochrome C oxidase activity	(Solano Fonseca et al., 2021)

suffering from severe hypoxia or ischemic insult (Stetler et al., 2014; Liu et al., 2021a). Accumulating evidence suggested that hypoxic preconditioning also protects the brain against TBI (Chang et al., 2013; Shu et al., 2016; Wu et al., 2021). For example, hypoxic preconditioning has been reported to protect neuronal cells against CCI in rats through upregulation of HIF-1α/glucose transporters (GLUTs) signaling pathway and stimulation of glucose transport (Wu et al., 2021). Another study suggested that the neuroprotection of hypoxic preconditioning

on rat brain against TBI can be ascribed to up-regulation of the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) and hemo ocygenase 1 (HO-1) expression, thereby alleviating oxidative stress damage (Shu et al., 2016). In addition, hypoxic conditioning of stem cells has also shown therapeutic potential against TBI. Previous study suggested that TBI rats treated with hypoxic-preconditioned mesenchymal stem cells (MSC) secretome, which included hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF),

performed significantly better in both motor and cognitive tasks, showed an increased in neurogenesis, and had significantly less brain damage than the TBI rats treated with the normoxic-preconditioned MSC secretome (Chang et al., 2013). In addition, it has been reported that intracranial transplantation of hypoxic-preconditioned induced pluripotent stem cells (iPSC)-derived neural progenitor cells alleviate neuropsychiatric defects after TBI in juvenile rats (Wei et al., 2016). More recently, hypoxic preconditioning has been reported to enhance the differentiation of bone marrow stromal cells into mature oligodendrocytes to promote remyelination via modulation of the pro-survival mammalian target of rapamycin (mTOR)/HIF-1α/VEGF pathway in controlled cortical impact (CCI) mice models (Yuan et al., 2020).

Ischemic preconditioning

Ischemic preconditioning now has proven efficacy against stroke in numerous animal and clinical studies (Gao et al., 2021; Hess et al., 2021). Moreover, remote ischemic conditioning in trauma patients with severe TBI can significantly decrease secondary brain injury (Joseph et al., 2015). However, only one study employed ischemic preconditioning for TBI, but this approach has shown beneficial effects. Research has demonstrated that ischemic preconditioning 48 h prior to fluid-impact brain injury had fewer necrotic cell counts and less contusion volume than the control group (Perez-Pinzon et al., 1999). Therefore, the protective fortification established by ischemic preconditioning may be able to extend to acute brain injury.

Hyperbaric oxygen (HBO) preconditioning

Compared with other preconditioning stimuli, hyperbaric oxygen (HBO) is benign and has clinically translational potential (Hu et al., 2016). Accumulated evidence shows that HBO preconditioning not only reduces ischemic brain injury (Stetler et al., 2014; Liska et al., 2018), but also induces tolerance to TBI (Hu et al., 2008; Hu et al., 2010; Eve et al., 2016). Moreover, it has been suggested that hyperbaric oxygen preconditioning treatment (HBOT) is a potential treatment for post-traumatic stress disorder for individuals that have sustained TBI (Eve et al., 2016). The mechanism of HBO preconditioning-induced neuroprotection, including the inhibitory effect on the expression of matrix metallopeptidase 9 (MMP-9) (Hu et al., 2008), which plays a key role in promoting neuronal cell death (Zhao et al., 2006), and the amelioration of regional cerebral blood flow (rCBF) and brain tissue oxygen pressure (PbtO2) (Hu et al., 2010).

Exercise preconditioning

A considerable set of evidence suggest that exercise preconditioning attenuates neuronal loss, reduces neuroinflammation, and improves neurological outcomes after TBI (Mota et al., 2012; Taylor et al., 2015; Zhao et al., 2015; Chio et al., 2017). Multiple factors have been reported to mediate neuroprotection evoked by exercise preconditioning. It has been reported that exercise preconditioning increases the expression of specific neuroprotective genes and proteins (VEGF-A and erythropoietin [EPO], but not HO-1) in the brain (Taylor et al., 2015). In addition, exercise preconditioning reduces initial damage and limits long-term secondary degeneration after fluid percussion brain injury (FPI) by improving the cerebral inflammatory status profile, including reducing pro-inflammatory cytokines tumour necrosis factor alphas (TNFα) and interleukin (IL)-1 beta, and increasing anti-inflammatory IL-10 in rats (Mota et al., 2012). Moreover, exercise preconditioning has been shown to attenuate neurological deficits by stimulating a critical HSP70/nuclear factor kappa-light-chair-enhancer of activated B cells (NF-κB)/IL-6/synapsin I axis in TBI rats (Chio et

al., 2017). Additionally, exercise preconditioning activated multiple antiapoptotic mechanisms, including BDNF and HSP70, reduced,the proapoptotic Bcl-2 family molecules (Bid, Puma), decreased mitochondria permeabilization with the attenuated release of cytochrome c and apoptosis-inducing factor (AIF), reduced AIF translocation to the nucleus, and attenuated caspase activation (Zhao et al., 2015). Recently, cold water swimming (3 minutes at 4°C) preconditioning has been reported to promote the proliferation of endothelial progenitor cells and angiogenesis in peripheral blood and hippocampus, concurrent with amelioration of cognitive deficits caused by the experimental rat model of TBI (Zhou et al., 2017).

Endotoxin preconditioning

Excessive inflammation after TBI can cause secondary neuronal injury and long-term neurological deficits (Liu et al., 2021b). Despite endotoxin lipopolysaccharide (LPS) (Hang et al., 2004) and its toll-like receptors (TLRs) (Jiang et al., 2018) playing detrimental roles in neuroinflammation in TBI, accumulating evidence suggest that endotoxin preconditioning with a low/sublethal dose of LPS prior to TBI provides robust neuroprotection. It has been reported that LPS preconditioning inhibits neural damage and apoptosis induced by trauma in the hippocampus (Eslami et al., 2020). Moreover, the beneficial effects of LPS preconditioning with low doses can last for up to one month after injury, the mechanisms involved might be associated with modulating microglial/macrophage activity and facilitating M2 microglia activation (Longhi et al., 2011). Another study showed that single low-dose LPS preconditioning was neuroprotective in a close-head model of diffuse axonal injury and significantly reduced the post-injury gliosis response near the corpus callosum, possibly by activating TLR4 signaling cascades and downregulating the oncostatin M receptor to suppress innate immunity and astrocyte activation (Turner et al., 2017). Low-dose LPS preconditioning has also been reported to prevent the acceleration of kindling epileptogenesis by decreasing IL-1β and TNF-α over-expression, and the number of damaged neurons in the hippocampus of TBI rats (Eslami et al., 2015).

N-methyl-D-aspartate (NMDA) preconditioning

It is well established that glutamatergic excitotoxicity-induced cellular damage after TBI is mediated by the excitatory neurotransmitters, glutamate and aspartate, through the excessive activation of N-methyl-D-aspartate (NMDA) receptors (Costa et al., 2010; Boeck et al., 2013). Preconditioning with a low dose of NMDA was also used as a strategy for protection against TBI. It has been reported that NMDA preconditioning improves short-term motor deficits after mild TBI in mice (Costa et al., 2010). Subsequently, NMDA preconditioning has been reported to prevent object recognition memory impairment and increase brain viability, inducing impairment of long-term memory in TBI mice (Moojen et al., 2012). Mechanistically, after 24 h, TBI mice preconditioned with NMDA demonstrated augmented activities of complexes II and IV in the cerebral cortex and/or cerebellum, and creatine kinase in the cerebral cortex (Boeck et al., 2013).

Other preconditioning

In addition to the aforementioned preconditioning methods, which had been extensively studied, other preconditioning techniques have also been reported to protect against TBI. These preconditioning methods needs to be further studied and precise mechanisms have yet to be elucidated. For example, behavioral preconditioning consisting of daily exposure of animals to the radial arm maze enhances cognitive outcome after brain trauma. In this study, increased angiogenesis was proposed to underlie the cognitive sparing seen in pre-conditioned animals (Kreipke et al., 2007). Anesthetic preconditioning has been found to

confer neuroprotection against TBI. Pre-exposure to isoflurane or sevoflurane preconditioned fed control flies to TBI, reducing the risk of death but had no preconditioning effect in obese flies, suggesting that obesity thwarts the brain-protective effect of anesthetic preconditioning (Johnson-Schlitz et al., 2022). Moreover, a study has found that low-intensity blast preconditioning protects retinal ganglion cells following blast-mediated TBI (Harper et al., 2019). Recent studies suggested that metabolism-associated pathways or molecules can also confer preconditioning against TBI. It has been found that L-lactate preconditioning promotes plasticity-related protein expression and reduces neurological deficits by potentiating G protein-coupled (GPR)-81 signaling in rat TBI models (Zhai et al., 2020). Furthermore, glycolytic preconditioning in astrocytes has also been demonstrated to mitigate neurodegeneration after closed-head TBI in mice (Solano Fonseca et al., 2021). Interestingly, miRNA-21 preconditioning has been proposed to induce tolerance to TBI (Lopez et al., 2017).

Perspective

In this review, we introduced multiple preconditioning experimental methods in the animal TBI model and the mechanisms underlying preconditioning that triggers endogenous protection against TBI. Despite the promising pre-clinical studies outlined above, the translation of evidentiary experimental preconditioning into clinical implementation remains a big challenge.

Based on the preconditioning studies in TBI, multiple TBI animal models, including CCI, CHI, etc. have been employed in the preconditioning studies. The preconditioning effects and underlying neuroprotective mechanisms may be similar but may also be distinct between different TBI models. Notably, the most common pathological mechanisms shared by multiple preconditioning strategies is anti-apoptosis or necrosis, followed by inhibition of metabolic dysregulation or mitochondrial dysfunction, and anti-pro-inflammatory responses (Figure 1). Whether other mechanisms also underlie the beneficial effect of various preconditioning need to be further investigated. It has been discovered that some preconditioning strategies have a relatively short-term effect, as the preconditioning response fades within a week or two (Stetler et al., 2014). Future directions should investigate how to make the preconditioning provide continuous neuroprotection for a long period of time after TBI. Compared to other preconditioning methods, the physical means of preconditioning such as temperature preconditioning, HBO, and exercise may potentially be employed for TBI therapy. This is because they are non-invasive, relatively safe, and especially relevant for the possible clinical implication in specific populations at risk of TBI, such as soldiers, sport combatants, or individuals involved in any high-risk physical activities (Yokobori et al., 2013). However, the results obtained from animal experiments may not be directly applicable to humans, and further comprehensive studies are still required. In addition, the mechanistic studies suggested that multiple pathways, including HIF1, HSP, and TLRs/NF-κB pathways have been found to be the common molecular mechanisms underlying the beneficial effects of multiple preconditioning strategies against different TBI models (Table 1). Importantly, HIF1 and HSP signaling pathways play central roles in cross-tolerance among heat acclimation, hypoxia, and exercise preconditioning approaches (Ely et al., 2014). Therefore, targeting these pathways may be promising to the treatment of TBI in the future. Considering that metabolism dysregulation plays a central pathological role in initiating secondary brain injury after TBI (Brooks and Martin, 2014), and metabolic preconditioning have shown promising effects in TBI animal studies (Zhai et al., 2020; Solano Fonseca et al., 2021), future preconditioning studies

by employing metabolic stress may help in investigating metabolism dysregulation-associated endogenous anti-inflammatory and/or neuroprotective mechanisms. Another promising field in the use of preconditioning methods for TBI is to combine the approach with stem cells. It has been well-established that preconditioning strategies can enhance neural stem cell-based therapy for ischemic stroke (Othman and Tan, 2020). Emerging evidence suggest that hypoxic-preconditioned stem cells, including MSC (Chang et al., 2013), hypoxia-preconditioned iPSC-derived neural progenitor cells (Wei et al., 2016), and bone marrow stromal cells (Yuan et al., 2020) have shown promising and beneficial effects in TBI animal studies. Therefore, stress preconditioning of stem cells may lead to innovative and promising new therapy in TBI, however, these preconditioning strategies remain to be further explored.

In summary, this review provided updates on various methods of TBI preconditioning based on current findings on this topic, as well as introduced the underlying mechanisms of some preconditioning methods in TBI. Understanding the means and mechanisms of stimuli that induce these endogenous mechanisms in the brain will aid in the translation of interventions to prevent and/or limit TBI. Substantial work is still required to decipher preconditioning methods and determine the mechanisms involved.

Conflict of interest statement

The authors declare no competing financial interests.

References

Beit-Yannai E, Kohen R, Horowitz M, Trembovler V, Shohami E (1997) Changes of biological reducing activity in rat brain following closed head injury: a cyclic voltammetry study in normal and heat-acclimated rats. J Cereb Blood Flow Metab 17:273-279.

Boeck CR, Carbonera LS, Milioli ME, Constantino LC, Garcez ML, Rezin GT, Scaini G, Streck EL (2013) Mitochondrial respiratory chain and creatine kinase activities following trauma brain injury in brain of mice preconditioned with N-methyl-D-aspartate. Mol Cell Biochem 384:129-137.

Brooks GA, Martin NA (2014) Cerebral metabolism following traumatic brain injury: new discoveries with implications for treatment. Front Neurosci 8:408.

Capizzi A, Woo J, Verduzco-Gutierrez M (2020) Traumatic Brain Injury: An Overview of Epidemiology, Pathophysiology, and Medical Management. Med Clin North Am 104:213-238.

Chang CP, Chio CC, Cheong CU, Chao CM, Cheng BC, Lin MT (2013) Hypoxic preconditioning enhances the therapeutic potential of the secretome from cultured human mesenchymal stem cells in experimental traumatic brain injury. Clin Sci (Lond) 124:165-176.

Chio CC, Lin HJ, Tian YF, Chen YC, Lin MT, Lin CH, Chang CP, Hsu CC (2017) Exercise attenuates neurological deficits by stimulating a critical HSP70/NF-kappaB/IL-6/synapsin I axis in traumatic brain injury rats. J Neuroinflammation 14:90.

Costa T, Constantino LC, Mendonca BP, Pereira JG, Herculano B, Tasca CI, Boeck CR (2010) N-methyl-D-aspartate preconditioning improves short-term motor deficits outcome after mild traumatic brain injury in mice. J Neurosci Res 88:1329-1337.

Dirnagl U, Meisel A (2008) Endogenous neuroprotection: mitochondria as gateways to cerebral preconditioning? Neuropharmacology 55:334-344.

Dirnagl U, Becker K, Meisel A (2009) Preconditioning and

tolerance against cerebral ischaemia: from experimental strategies to clinical use. Lancet Neurol 8:398-412.

Ely BR, Lovering AT, Horowitz M, Minson CT (2014) Heat acclimation and cross tolerance to hypoxia: Bridging the gap between cellular and systemic responses. Temperature (Austin) 1:107-114.

Eslami M, Alizadeh L, Morteza-Zadeh P, Sayyah M (2020) The effect of Lipopolysaccharide (LPS) pretreatment on hippocampal apoptosis in traumatic rats. Neurol Res 42:91-98.

Eslami M, Sayyah M, Soleimani M, Alizadeh L, Hadjighassem M (2015) Lipopolysaccharide preconditioning prevents acceleration of kindling epileptogenesis induced by traumatic brain injury. J Neuroimmunol 289:143-151.

Eve DJ, Steele MR, Sanberg PR, Borlongan CV (2016) Hyperbaric oxygen therapy as a potential treatment for post-traumatic stress disorder associated with traumatic brain injury. Neuropsychiatr Dis Treat 12:2689-2705.

Gao P, Tang S, Chen H, Zhou X, Ou Y, Shen R, He Y (2021) Preconditioning increases brain resistance against acute brain injury via neuroinflammation modulation. Exp Neurol 341:113712.

Hang CH, Shi JX, Tian J, Li JS, Wu W, Yin HX (2004) Effect of systemic LPS injection on cortical NF-kappaB activity and inflammatory response following traumatic brain injury in rats. Brain Res 1026:23-32.

Harper MM, Woll AW, Evans LP, Delcau M, Akurathi A, Hedberg-Buenz A, Soukup DA, Boehme N, Hefti MM, Dutca LM, Anderson MG, Bassuk AG (2019) Blast Preconditioning Protects Retinal Ganglion Cells and Reveals Targets for Prevention of Neurodegeneration Following Blast-Mediated Traumatic Brian Injury. Invest Ophthalmol Vis Sci 60:4159-4170.

Hess DC, Khan MB, Kamat P, Vaibhav K, Dhandapani KM, Baban B, Waller JL, Hoda MN, Blauenfeldt RA, Andersen G (2021) Conditioning medicine for ischemic and hemorrhagic stroke. Cond Med 4:124-129.

Horowitz M (2002) From molecular and cellular to integrative heat defense during exposure to chronic heat. Comp Biochem Physiol A Mol Integr Physiol 131:475-483.

Horowitz M, Umschweif G, Yacobi A, Shohami E (2015) Molecular programs induced by heat acclimation confer neuroprotection against TBI and hypoxic insults via cross-tolerance mechanisms. Front Neurosci 9:256.

Hu Q, Manaenko A, Matei N, Guo Z, Xu T, Tang J, Zhang JH (2016) Hyperbaric oxygen preconditioning: a reliable option for neuroprotection. Med Gas Res 6:20-32.

Hu S, Li F, Luo H, Xia Y, Zhang J, Hu R, Cui G, Meng H, Feng H (2010) Amelioration of rCBF and PbtO2 following TBI at high altitude by hyperbaric oxygen pre-conditioning. Neurol Res 32:173-178.

Hu SL, Hu R, Li F, Liu Z, Xia YZ, Cui GY, Feng H (2008) Hyperbaric oxygen preconditioning protects against traumatic brain injury at high altitude. Acta Neurochir Suppl 105:191-196.

Hui J et al. (2021) Safety and efficacy of long-term mild hypothermia for severe traumatic brain injury with refractory intracranial hypertension (LTH-1): A multicenter randomized controlled trial. EClinicalMedicine 32:100732.

Janoff A (1964) Alterations in Lysosomes (Intracellular Enzymes) during Shock; Effects of Preconditioning (Tolerance) and Protective Drugs. Int Anesthesiol Clin 2:251-269.

Jiang H, Wang Y, Liang X, Xing X, Xu X, Zhou C (2018) Toll-Like Receptor 4 Knockdown Attenuates Brain Damage and Neuroinflammation After Traumatic Brain Injury via Inhibiting Neuronal Autophagy and Astrocyte Activation.

Cell Mol Neurobiol 38:1009-1019.

Johnson-Schlitz D, Fischer JA, Schiffman HJ, Scharenbrock AR, Olufs ZPG, Wassarman DA, Perouansky M (2022) Anesthetic Preconditioning of Traumatic Brain Injury Is Ineffective in a Drosophila Model of Obesity. J Pharmacol Exp Ther 381:229-235.

Joseph B, Pandit V, Zangbar B, Kulvatunyou N, Khalil M, Tang A, O'Keeffe T, Gries L, Vercruysse G, Friese RS, Rhee P (2015) Secondary brain injury in trauma patients: the effects of remote ischemic conditioning. J Trauma Acute Care Surg 78:698-703; discussion 703-695.

Kreipke CW, Morgan R, Kallakuri S, Rafols JA (2007) Behavioral pre-conditioning enhances angiogenesis and cognitive outcome after brain trauma. Neurol Res 29:388-394.

Lewis SR, Evans DJ, Butler AR, Schofield-Robinson OJ, Alderson P (2017) Hypothermia for traumatic brain injury. Cochrane Database Syst Rev 9:CD001048.

Liska GM, Lippert T, Russo E, Nieves N, Borlongan CV (2018) A Dual Role for Hyperbaric Oxygen in Stroke Neuroprotection: Preconditioning of the Brain and Stem Cells. Cond Med 1:151-166.

Liu B, Wang L, Cao Y, Xu W, Shi F, Tian Q, Zhou X (2017) Hypothermia pretreatment improves cognitive impairment via enhancing synaptic plasticity in a traumatic brain injury model. Brain Res 1672:18-28.

Liu J, Gu Y, Guo M, Ji X (2021a) Neuroprotective effects and mechanisms of ischemic/hypoxic preconditioning on neurological diseases. CNS Neurosci Ther 27:869-882.

Liu N, Han J, Li Y, Jiang Y, Shi SX, Lok J, Whalen M, Dumont AS, Wang X (2021b) Recombinant annexin A2 inhibits peripheral leukocyte activation and brain infiltration after traumatic brain injury. J Neuroinflammation 18:173.

Longhi L, Gesuete R, Perego C, Ortolano F, Sacchi N, Villa P, Stocchetti N, De Simoni MG (2011) Long-lasting protection in brain trauma by endotoxin preconditioning. J Cereb Blood Flow Metab 31:1919-1929.

Lopez MS, Dempsey RJ, Vemuganti R (2017) The microRNA miR-21 conditions the brain to protect against ischemic and traumatic injuries. Cond Med 1:35-46.

Monsour M, Ebedes D, Borlongan CV (2022) A review of the pathology and treatment of TBI and PTSD. Exp Neurol 351:114009.

Moojen VK, Damiani-Neves M, Bavaresco DV, Pescador BB, Comim CM, Quevedo J, Boeck CR (2012) NMDA preconditioning prevents object recognition memory impairment and increases brain viability in mice exposed to traumatic brain injury. Brain Res 1466:82-90.

Mota BC, Pereira L, Souza MA, Silva LF, Magni DV, Ferreira AP, Oliveira MS, Furian AF, Mazzardo-Martins L, Silva MD, Santos AR, Ferreira J, Fighera MR, Royes LF (2012) Exercise pre-conditioning reduces brain inflammation and protects against toxicity induced by traumatic brain injury: behavioral and neurochemical approach. Neurotox Res 21:175-184.

Othman FA, Tan SC (2020) Preconditioning Strategies to Enhance Neural Stem Cell-Based Therapy for Ischemic Stroke. Brain Sci 10.

Perez-Pinzon MA, Alonso O, Kraydieh S, Dietrich WD (1999) Induction of tolerance against traumatic brain injury by ischemic preconditioning. Neuroreport 10:2951-2954.

Shein NA, Horowitz M, Shohami E (2007a) Heat acclimation: a unique model of physiologically mediated global preconditioning against traumatic brain injury. Prog Brain Res 161:353-363.

Shein NA, Horowitz M, Alexandrovich AG, Tsenter J, Shohami E (2005) Heat acclimation increases hypoxia-inducible factor 1alpha and erythropoietin receptor expression:

implication for neuroprotection after closed head injury in mice. J Cereb Blood Flow Metab 25:1456-1465.

Shein NA, Tsenter J, Alexandrovich AG, Horowitz M, Shohami E (2007b) Akt phosphorylation is required for heat acclimation-induced neuroprotection. J Neurochem 103:1523-1529.

Shein NA, Doron H, Horowitz M, Trembovler V, Alexandrovich AG, Shohami E (2007c) Altered cytokine expression and sustained hypothermia following traumatic brain injury in heat acclimated mice. Brain Res 1185:313-320.

Shein NA, Grigoriadis N, Horowitz M, Umschwief G, Alexandrovich AG, Simeonidou C, Grigoriadis S, Touloumi O, Shohami E (2008) Microglial involvement in neuroprotection following experimental traumatic brain injury in heat-acclimated mice. Brain Res 1244:132-141.

Shu L, Wang C, Wang J, Zhang Y, Zhang X, Yang Y, Zhuo J, Liu J (2016) The neuroprotection of hypoxic preconditioning on rat brain against traumatic brain injury by up-regulated transcription factor Nrf2 and HO-1 expression. Neurosci Lett 611:74-80.

Solano Fonseca R, Metang P, Egge N, Liu Y, Zuurbier KR, Sivaprakasam K, Shirazi S, Chuah A, Arneaud SL, Konopka G, Qian D, Douglas PM (2021) Glycolytic preconditioning in astrocytes mitigates trauma-induced neurodegeneration. Elife 10.

Stetler RA, Leak RK, Gan Y, Li P, Zhang F, Hu X, Jing Z, Chen J, Zigmond MJ, Gao Y (2014) Preconditioning provides neuroprotection in models of CNS disease: paradigms and clinical significance. Prog Neurobiol 114:58-83.

Su Z, Han D, Sun B, Qiu J, Li Y, Li M, Zhang T, Yang Z (2009) Heat stress preconditioning improves cognitive outcome after diffuse axonal injury in rats. J Neurotrauma 26:1695-1706.

Taylor JM, Montgomery MH, Gregory EJ, Berman NE (2015) Exercise preconditioning improves traumatic brain injury outcomes. Brain Res 1622:414-429.

Turner RC, Naser ZJ, Lucke-Wold BP, Logsdon AF, Vangilder RL, Matsumoto RR, Huber JD, Rosen CL (2017) Single low-dose lipopolysaccharide preconditioning: neuroprotective against axonal injury and modulates glial cells. Neuroimmunol Neuroinflamm 4:6-15.

Umschweif G, Alexandrovich AG, Trembovler V, Horowitz M, Shohami E (2013a) Hypoxia-inducible factor 1 is essential for spontaneous recovery from traumatic brain injury and is a key mediator of heat acclimation induced neuroprotection. J Cereb Blood Flow Metab 33:524-531.

Umschweif G, Alexandrovich AG, Trembovler V, Horowitz M, Shohami E (2013b) The role and dynamics of beta-catenin in precondition induced neuroprotection after traumatic brain injury. PLoS One 8:e76129.

Umschweif G, Shabashov D, Alexandrovich AG, Trembovler V, Horowitz M, Shohami E (2014) Neuroprotection after traumatic brain injury in heat-acclimated mice involves induced neurogenesis and activation of angiotensin receptor type 2 signaling. J Cereb Blood Flow Metab 34:1381-1390.

Umschweif G, Shein NA, Alexandrovich AG, Trembovler V, Horowitz M, Shohami E (2015) Heat acclimation provides sustained improvement in functional recovery and attenuates apoptosis after traumatic brain injury. J Cereb Blood Flow Metab 35:1901.

Wei ZZ, Lee JH, Zhang Y, Zhu YB, Deveau TC, Gu X, Winter MM, Li J, Wei L, Yu SP (2016) Intracranial Transplantation of Hypoxia-Preconditioned iPSC-Derived Neural Progenitor Cells Alleviates Neuropsychiatric Defects After Traumatic Brain Injury in Juvenile Rats. Cell Transplant 25:797-809.

Wu X, Wang C, Wang J, Zhu M, Yao Y, Liu J (2021) Hypoxia

preconditioning protects neuronal cells against traumatic brain injury through stimulation of glucose transport mediated by HIF-1alpha/GLUTs signaling pathway in rat. Neurosurg Rev 44:411-422.

Yokobori S, Mazzeo AT, Hosein K, Gajavelli S, Dietrich WD, Bullock MR (2013) Preconditioning for traumatic brain injury. Transl Stroke Res 4:25-39.

Yuan X, Luo Q, Shen L, Chen J, Gan D, Sun Y, Ding L, Wang G (2020) Hypoxic preconditioning enhances the differentiation of bone marrow stromal cells into mature oligodendrocytes via the mTOR/HIF-1alpha/VEGF pathway in traumatic brain injury. Brain Behav 10:e01675.

Zhai X, Li J, Li L, Sun Y, Zhang X, Xue Y, Lv J, Gao Y, Li S, Yan W, Yin S, Xiao Z (2020) L-lactate preconditioning promotes plasticity-related proteins expression and reduces neurological deficits by potentiating GPR81 signaling in rat traumatic brain injury model. Brain Res 1746:146945.

Zhao BQ, Wang S, Kim HY, Storrie H, Rosen BR, Mooney DJ, Wang X, Lo EH (2006) Role of matrix metalloproteinases in delayed cortical responses after stroke. Nat Med 12:441-445.

Zhao Z, Sabirzhanov B, Wu J, Faden AI, Stoica BA (2015) Voluntary Exercise Preconditioning Activates Multiple Antiapoptotic Mechanisms and Improves Neurological Recovery after Experimental Traumatic Brain Injury. J Neurotrauma 32:1347-1360.

Zhou ZW, Li YD, Gao WW, Chen JL, Yue SY, Zhang JN (2017) Cold water swimming pretreatment reduces cognitive deficits in a rat model of traumatic brain injury. Neural Regen Res 12:1322-1328.