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Preconditioning Provides Neuroprotection in Models of CNS Disease: Paradigms and Clinical Significance

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Abstract

Preconditioning is a phenomenon in which brief episodes of a sublethal insult induce robust protection against subsequent lethal injuries. Preconditioning has been observed in multiple organisms and can occur in the brain as well as other tissues. Extensive animal studies suggest that the brain can be preconditioned to resist acute injuries, such as ischemic stroke, neonatal hypoxia/ischemia, trauma, and agents that are used in models of neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease. Effective preconditioning stimuli are numerous and diverse, ranging from transient ischemia, hypoxia, hyperbaric oxygen, hypothermia and hyperthermia, to exposure to neurotoxins and pharmacological agents. The phenomenon of "cross-tolerance," in which a sublethal stress protects against a different type of injury, suggests that different preconditioning stimuli may confer protection against a wide range of injuries. Research conducted over the past few decades indicates that brain preconditioning is complex, involving multiple effectors such as metabolic inhibition, activation of extra- and intracellular defense mechanisms, a shift in the neuronal excitatory/inhibitory balance, and reduction in inflammatory sequelae. An improved understanding of brain preconditioning should help us identify innovative therapeutic strategies that prevent or at least reduce neuronal damage in susceptible patients. In this review, we focus on the experimental evidence of preconditioning in the brain and systematically survey the models used to develop paradigms for neuroprotection, and then discuss the clinical potential of brain preconditioning. In a subsequent components of this two-part series, we will discuss the cellular and molecular events that are likely to underlie these phenomena.

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1.0 Introduction

Until now, few pharmacological agents have been successfully translated to human acute brain injury (*e.g.*, stroke or traumatic brain injury (TBI)) and other neurodegenerative diseases, even though many molecules have initially appeared promising in animal models. Although the reason for these failures is unclear, we believe that understanding the means and mechanisms of stimuli that trigger an endogenous and pluripotent neuroprotective response in the brain will aid in the translation of interventions to prevent and/or limit many human disorders. As long ago as the 16th century, the toxicologist Paracelsus observed, "The dose makes the poison." A corollary is that subtoxic doses of cellular stress can lead to the generation of a protective state, termed "preconditioning." Preconditioning has been most commonly employed in studies of ischemia. In stroke models, sublethal ischemic episodes reduce the size of an infarct in response to a subsequent longer duration ischemic challenge (Kirino *et al.*, 1991; Kitagawa *et al.*, 1990; Liu *et al.*, 1992). Consistently, evidence suggests that transient ischemic attacks may precondition humans against stroke (Moncayo *et al.*, 2000; Weih *et al.*, 1999). Such preconditioning can be elicited throughout the body, but it is of particular clinical interest in brain where the majority of neurons cannot regenerate and strokes can leave humans severely disabled.

The purpose of this two-part review is to demonstrate that preconditioning is actually a widely applicable phenomenon that can be applied to many disease states in addition to ischemia. Neurodegenerative diseases in particular involve a lengthy prodromal phase during which there may be subtoxic stress caused by a wide variety of events, some of which are similar to subtoxic insults prevalent in the brain of individuals suffering from ischemic stroke. In a widely cited review, it was argued that preconditioning is stereotypical in nature, that is, it follows a similar pattern in both cause and effect (Dirnagl *et al.*, 2003). If true, many findings from stroke models might be generalized to other disease models, including models of neurodegeneration. This is of obvious clinical importance because it would broaden the array of possible therapeutic targets for a multiplicity of diseases.

In order to review both the basic scientific literature as well as clinical applications, this review will explore the various preconditioning protocols currently used. In a second review we will focus on the underlying cellular mechanisms identified to date. In this first part of the two-part review, we will detail the preconditioning paradigms to induce brain tolerance against ischemic stroke and other acute brain injuries as well as neurodegenerative states that have been employed in animal models by categorizing the preconditioning stimuli. Part two of the review will deal with the mechanisms thus far understood to contribute to the preconditioned, or tolerant, state.

2.0 Relevant models of CNS diseases

In order to conceptualize the neural diseases that have appeared to be sensitive to preconditioning-induced protection, we will first describe the model systems of the major disease states within this section. The major models will be briefly described, not as a conclusive survey, but rather as a foundation upon which one can understand the disease context in which various preconditioning stimuli were found to be protective.

2.1 Global/focal ischemia

Ischemic brain injuries, resulting either from global or focal decreases in perfusion, are one of the most common causes of death and the leading cause of adult disability worldwide. Although many neuroprotective drugs have been shown to reduce infarction and improve neurological functioning in animal models of stroke, only tissue plasminogen activator (tPA) has been successfully translated into clinical application. The negative results of these

attempts have prompted research of endogenous modulators of neuroprotection as an alternative approach to therapy. Such endogenous modulators mediate the ischemic tolerance phenomenon, which was first identified in brain in the early 1990s and shown to have a neuroprotective role in cerebral ischemia (Kitagawa *et al.*, 1991; Kitagawa *et al.*, 1990).

The primary model of stroke used in basic research targets the region of the middle cerebral artery, an area highly sensitive to thrombotic occlusion in humans. The rodent model of middle cerebral artery occlusion (MCAO) can be performed by insertion of an intraluminal suture leading from the carotid artery to the juncture of the middle cerebral artery. In both preconditioning scenarios, as well as in severe ischemic insults, the suture is removed after a period of ischemia (transient focal ischemia), allowing reperfusion of cerebral blood flow. This MCAO model yields fairly reproducible injury in the ischemic core (typically within the striatum), as well as an extensive ipsilateral cortical penumbral region. Severe cerebral ischemic insult may also be achieved by permanent ligation or electrocoagulation of the middle cerebral artery.

Alternatively, brain ischemia can occur in the context of arrested blood circulation (often termed a “heart attack”). In order to model this scenario with the cerebral focus, models of global forebrain ischemia have been developed. In normotensive rats or mice, the vertebral arteries are permanently coagulated followed by transient ligation of the carotid arteries, typically lasting 8–10 min. This model leads to specific damage that is most noticeable in the CA1 region of the hippocampus. A similar model can be created through the transient ligation of the carotid arteries alone in either gerbils, which lack the circle of Willis formation for compensatory blood flow via the vertebral arteries, or spontaneously hypertensive rats.

Overall, global and focal ischemic models have been the most comprehensively examined, in terms of severe ischemic insults and sublethal ischemic preconditioning paradigms. However, several models of thrombotic stroke have been recently developed using either a photothrombotic technique or coagulation injury. While these thrombotic models better represent the natural formation of ischemic regions, they are more difficult to control and analyze. Although emerging data suggest that thrombotic models may be helpful in assessing therapeutic strategies in the preclinical settings, they have not yet been widely applied to preconditioning models.

Ischemia has also been widely modeled *in vitro*, and the effects of preconditioning stimuli have been studied in a variety of ischemic culture model systems. The most widely used system in preconditioning against ischemia is the use of the oxygen/glucose deprivation model, accomplished by replacing the culture medium with glucose-free medium and incubating the cultures in a hypoxia chamber (flushed with 95% argon and 5% CO_2). Enriched neuronal cultures are most sensitive to OGD, where 60–90 minutes of OGD yields significant cell death. Conversely, astrocytes are fairly resistant to OGD when cultured alone, requiring more than 6 hours of OGD to incur a significant amount of cell loss. Mixed neuron/astrocyte cultures have also been used, but again require significantly extended OGD parameters to induce cell toxicity.

2.2 Neonatal hypoxia/ischemia

Neonatal hypoxia/ischemia (HI) remains a clinical problem, as brain damage occurring in the perinatal period imposes a high risk of acute mortality and chronic disability (Vannucci and Vannucci, 1997). The immature brain paradoxically exhibits both sensitivity and resistance to HI injury, likely dependent on the stage of cerebral development and injury location (Vannucci and Hagberg, 2004). Cerebral blood flow in neonatal brain is particularly

sensitive to changes in systemic blood pressure, and it appears that cerebral blood flow is not autoregulated beyond a 10–20 mm Hg change in systemic pressure (Gill and Perez-Polo, 2008). This results in neonates being more susceptible to systemic hypoxia, as hypoxemia causes rapidly dysregulated systemic blood pressure and also disrupts the Circle of Willis. Once the systemic blood pressure drops, cerebral blood flow becomes acutely disrupted and ischemia ensues, leading the immature brain to be highly susceptible to hypoxic injury. When combined with unilateral ligation of the carotid artery, blood flow in the ipsilateral hemisphere drops by 40–60% of the contralateral side (Vannucci and Hagberg, 2004). Rat models of perinatal HI typically utilize neonatal pups at postnatal day 7 (P7), as the developmental state of the brain is estimated to be roughly equivalent to that of a human fetus or infant at 32–34 weeks of gestation (Vannucci and Vannucci, 1997). The neonatal HI model has several variations, but the most commonly used models combine unilateral carotid artery coagulation (compensated by collateral blood flow under normoxic conditions) and exposure to 8% O_2 (hypoxia) at normothermic temperature.

2.3 Surgical-related brain injury

Surgical brain injury (SBI) refers to the neurologic injuries caused by cardiopulmonary bypass surgery, with or without the use of hypothermic circulatory arrest, or neurosurgery itself. While each of these surgical scenarios are used to the benefit of the patient, they also carry risk of neurological injury. Minimizing such risks is of great interest as we attempt to improve surgical outcomes and overall quality of life for the patient.

Cardiopulmonary bypass is a technique widely used in cardiac surgeries to facilitate the surgical exposure of the heart by temporarily taking over the function of the heart and lungs during surgery. This technique thus maintains the circulation of blood and the oxygen content of the body. It is. However, cerebral injury is a significant risk for patients undergoing cardiopulmonary bypass surgeries. In order to reduce that risk, hypothermic circulatory arrest (HCA) has become a frequently used adjunct method to suspend blood flow during major vascular operations, such as repair of the aortic arch or neurosurgical excision of aneurysms of the vertebrobasilar circulation (McCullough *et al.*, 1999). The technique leads to both a relatively bloodless surgical area and a spontaneous decrease in brain metabolism due to the hypothermic component, leading to cerebral protection in the context of decreased blood flow. HCA, widely used clinically, has also been modeled in animals in order to determine additional strategies that further diminish potential for cerebral injury and lengthen the surgical time windows. Briefly, pigs are subjected to cooling of the brain core temperature to 18°C for 60 minutes or more (Hickey *et al.*, 2007; McCullough *et al.*, 1999; Yannopoulos *et al.*, 2010).

In addition to indirect cerebral injury from distal surgical procedures, most neurosurgeries are accompanied by unavoidable cortical and parenchymal incisions, intraoperative hemorrhage, brain lobe retraction, and thermal injuries from electrocautery, all of which are associated with brain damage (Jadhav and Zhang, 2008). These injuries have been modeled in mice and rats by excising a discreet region of the frontal lobe designed to model the general effects of brain tissue loss (Jadhav *et al.*, 2007).

2.4 Traumatic brain injury

Traumatic brain injury (TBI) is a major cause of death and disability worldwide, especially in young people (Prins and Giza, 2011). It can cause impairment of both sensory and motor functions that often persist for months and even years. As most TBI is accidental, investigators have tended to focus on therapies provided *after* the brain injury. However, with the emergence of sport- and military-related head injuries occurring in a more predictable and orchestrated timeframe, TBI now includes the potential to view the damage

as a manifestation of a chronic process, and thus it may benefit from preventative or preconditioning strategies. Examples of chronic TBI degeneration in humans include diffuse axonal injury, which is largely responsible for the persistent vegetative state after head trauma (Graham *et al.*, 2005), and chronic traumatic encephalopathy (CTE), which results from multiple concussive episodes of mild TBI (McKee *et al.*, 2013).

Recent studies in animal models of TBI have noted that several preconditioning scenarios can serve as a potential neuroprotective strategy (Costa *et al.*, 2010; Hu *et al.*, 2010b; Hu *et al.*, 2008). Although several TBI models have been developed in rats and mice, to date the most studied are the controlled cortical impact (CCI) model, fluid percussion injury (FPI), and the weight drop model (reviewed in Albert-Weissenberger and Siren, 2010; Cernak, 2005). Both CCI and FPI inflict impact or pressure directly on the intact dura following craniotomy. In contrast, the weight drop model can be delivered either to the closed skull or the directly to the intact dura. The particular models and forces applied generate different degrees of severity.

2.5 Chronic neurodegenerative diseases

Neurodegenerative diseases generally progress slowly and in most cases do not even emerge as clinical entities until relatively late in life. Recently, hypotheses regarding the underlying cause of neurodegenerative diseases have been extended to include two related concepts. First, the preconditioning or adaptive response to initial threats may be impaired (Texel and Mattson, 2011) or wane with age, impairing the cellular ability to adapt to a toxic insult. Second, the primary insult causing neurodegeneration may fail to elicit a preconditioning response. At this point, these scenarios remain largely hypothetical, but emerging preliminary evidence may lay the groundwork for bolstering preconditioning responses as possible targets for neuroprotection in chronic diseases.

Only a small number of studies have reproducibly established the preconditioning phenomenon in animal and cellular models of chronic neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD) (Figure 1). A large problem in determining the effects of preconditioning in such diseases lies in the limitations of the models themselves. Although several toxins can be used to selectively target and kill the affected neurons in humans, this does not typically mimic what we know (and, more likely, what we do not know) about the underlying pathology. PD studies have largely relied on rodent models in which 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 6-hydroxydopamine (6-OHDA) were used to destroy dopamine (DA) neurons, and more recently have included rotenone and known genetic mutations that lead to a small subset of familial PD (reviewed in Jackson-Lewis *et al.*, 2012). These models have some characteristics that reflect the clinical state, but, particularly with the former toxin models, the injury tends to be acute rather than chronic. Thus, developing preconditioning paradigms for a relatively acute toxicity model is likely to be inherently distinct from preconditioning stages in a chronic disease setting. As preconditioning stimuli typically elicit only transient protection and neurodegenerative diseases are chronic, long-term conditions, expansion of the limited studies in repetitive preconditioning stimuli is necessary. As will be discussed below, we propose that long-term preconditioning is also possible in neurodegenerative conditions and that adaptations against cellular stress can be long lasting provided the stimulus is applied continuously and is sublethal in intensity.

Despite the scarcity in preconditioning studies in neurodegenerative diseases, several *in vitro* models have established that preconditioning can protect against PD- and AD-related toxicity. In a variety of dopaminergic cultures, rotenone, 6-OHDA, and MPP^+ toxicity models have been developed to support PD animal models. AD *in vitro* models primarily focus on amyloid beta toxicity in organotypic hippocampal-entorhinal slice cultures and

neuronal cultures. The translation of these *in vitro* studies to chronic degenerative animal models will significantly aid in the understanding of sublethal stress and disease progression.

3.0 Preconditioning stimuli

The preconditioned state is typically defined by the response to a subtoxic stimulus that extends beyond its presence in the system, and that would become toxic if applied at higher doses and/or for longer durations. This review will focus primarily on the stimuli that are normally viewed as deleterious (*e.g.*, ischemia, inflammation and oxidative stress), but will also include stimuli such as anesthesia and exercise. The latter are commonplace, but induce cellular environments that fall under the definition of a preconditioned state. The underlying specific mechanisms of preconditioning stimuli will be detailed in the second component of our overall review. Here, we will describe known stimuli that induce preconditioning against specific injury models.

3.1 Ischemic preconditioning

3.1.1 Ischemic paradigms for studying preconditioning—Ischemic preconditioning has been extensively studied and reviewed over the past 20 years. Thus, we will briefly describe the most common paradigms. Two major models of cerebral ischemia are typically used, both as preconditioning stimuli and as brain injury models. Forebrain, or global, ischemic preconditioning has been effectively used to induce tolerance to severe focal or global ischemia (Liu *et al.*, 1992; Matsushima and Hakim, 1995; Zhou *et al.*, 2004). In such studies, brief occlusion of the bilateral common carotid arteries is combined with either vertebral artery coagulation (four-vessel occlusion, or 4VO) or systemic hypotension (two-vessel occlusion, or 2VO) (Figure 2). Severe global ischemic injury produced by extended occlusion (*e.g.*, 7–10 minutes) yields profound damage in the CA1 region of the hippocampus as well as in other regions. In contrast, no grossly observable damage occurs following the preconditioning stimulus (*e.g.*, 2–3 minutes occlusion) during the tolerant window (Perez-Pinzon *et al.*, 1997). Such “global/global” models of tolerance are well established to confer neuroprotection following the severe ischemic challenge. Bilateral common carotid artery occlusion (BCCAO) itself is also protective in mice (Speetzen *et al.*, 2013; Wu *et al.*, 2001). Either a single occlusion of 6 minutes or three 1 minute periods of BCCAO resulted in a transient reduction of cerebral blood flow, yet decreased neuronal damage following subsequent severe BCCAO (18 minutes) or MCAO (45 minute) (Speetzen *et al.*, 2013).

Focal ischemic preconditioning has been also been demonstrated to protect against either permanent or transient focal ischemia (Cardenas *et al.*, 2002; Stagliano *et al.*, 1999). The exact number of minutes of occlusion necessary to produce a tolerant state depends both on the animal species and strain and the downstream insult.

Subischemic paradigms, such as unilateral carotid arterial ligation or cortical spreading depression (CSD), may produce a tolerant state with only minor effects on blood flow. Unilateral carotid arterial ligation in and of itself is capable of producing a preconditioned state against subsequent forebrain global ischemia in rats (Bronner *et al.*, 1998). Moreover, with only moderate alterations in blood flow during the unilateral carotid arterial ligation (Coyle and Panzenbeck, 1990; De Ley *et al.*, 1985), an apparent vascular adaptive response was elicited and proposed to lead to better-maintained blood flow during a subsequent hypoxic/ischemic event (Bronner *et al.*, 1998). CSD has been used as a preconditioning stimulus against focal or global ischemia in rats (Matsushima *et al.*, 1996; Taga *et al.*, 1997), cardiac arrest cerebral ischemia (Kawahara *et al.*, 1995), or subsequent CSD or OGD in organotypic cultures (Gniel and Martin, 2013). CSD induces a significant decrease in

baseline cerebral blood flow over an extended period (Bronner *et al.*, 1998), and thus does to some extent mimic ischemic preconditioning. Infarct volume or hippocampal CA1 cell loss was reduced by CSD evoked *in vivo* by 2 hours of cortical application of potassium chloride occurring 3 days prior to focal ischemia (Matsushima *et al.*, 1996), 1, 3, or 7 days prior to forebrain ischemia (Taga *et al.*, 1997), or 3 days prior to cardiac arrest cerebral ischemia (Kawahara *et al.*, 1995). Organotypic cultures exposed to a 2-minute potassium chloride bath 7 minutes prior to OGD decreased intracellular calcium influx when compared to slices exposed to OGD alone (Gniel and Martin, 2013).

Although not commonly used to achieve preconditioning against neonatal hypoxia/ischemia (HI), ischemic preconditioning can be induced in neonates (P6–7) by 2 hours of ipsilateral reversible carotid artery occlusion followed by 6–22 hours of reperfusion before subsequent HI (Lin *et al.*, 2009b). Using this paradigm, protection was evident according to both histopathological and neurobehavioral outcomes. In addition to postnatal ischemic preconditioning, intrauterine sublethal ischemic preconditioning has also been reported to reduce brain injury following neonatal HI (Xiao *et al.*, 2000). In these studies uterine vasculature was clamped for 30 minutes at embryonic day 17 (E17), and HI was induced at P7 following normal delivery. Brain size in the ipsilateral hemisphere was closer to the contralateral hemisphere, and decreased cell injury was noted. These two models of ischemic preconditioning against neonatal HI target different brain developmental stages, and thus are likely to be mediated by different mechanisms. Analyses of different physiological, molecular, and cellular brain responses will provide important insights into the unique environment of the developing brain, and may provide clues for therapeutics in the adult scenario, as well.

An important point to consider in the effects of ischemic preconditioning is the precise definition of “protection.” Most studies have focused on increased cell survival, spine density, or infarct volume and have correlated that protection with an improvement in behavioral performance at a later time (Corbett *et al.*, 2006). However, an acute impairment in behavior has been observed following 15 minutes of sublethal preconditioning focal ischemia (Hua *et al.*, 2005), and structural changes have become evident several weeks after the preconditioning ischemic event (Sommer, 2008; Tanay *et al.*, 2006). The implication of subtle structural or acute behavioral changes due to the preconditioning stimulus – whether it represents a mechanism for protection or a potentially debilitating artifact is – still unknown.

3.1.2 Timeframe for ischemic preconditioning – rapid and delayed windows of tolerance—The actual paradigms of preconditioning stimuli used in experimental studies vary greatly in terms of time and duration. Nuances have emerged using ischemic preconditioning paradigms that indicate protection can be achieved in two distinct timeframes. “Delayed” ischemic preconditioning refers to the induction of the preconditioning stimulus hours to days prior to the severe insult (*e.g.*, 30-minute occlusion followed by 4 days of reperfusion prior to severe ischemia (Matsushima and Hakim, 1995). In comparison, “rapid” tolerance occurs when the window between the ischemic preconditioning stimulus and the severe insult is on the order of minutes. For example, in the model of global ischemic preconditioning followed by severe global ischemia, carotid arteries are clamped for several minutes and then allowed only a brief reperfusion (*e.g.*, 2 minutes of occlusion followed by a 30-minute reperfusion (Perez-Pinzon *et al.*, 1997)) prior to induction of the severe insult. If the severe ischemic insult occurs *between* these two windows (*i.e.*, from several hours to 24 hours following preconditioning), no protection is apparent. However, tolerance can be re-induced once the neuroprotective time window has passed (Chen *et al.*, 1994).

Delayed preconditioning is associated with longer-lasting molecular changes compared to the rapid preconditioning paradigm (Durukan and Tatlisumak, 2010). Rapid preconditioning, on the other hand, typically confers transient and less robust neuroprotection compared to delayed preconditioning, but does not appear to require *de novo* protein synthesis (Barone *et al.*, 1998; Dirnagl *et al.*, 2003). These two well-defined time windows of tolerance that open after a preconditioning event – one within minutes of the event that lasts 1–2 hour, and one 1–7 days following preconditioning (Figure 3) –are pivotal in understanding the cellular response to sublethal injury and the range of protection afforded against the subsequent severe insult that likely occur by the induction of differential and likely non-overlapping cellular mechanisms.

Improved outcomes following ischemic preconditioning against neonatal HI were observed in rapid, intermediate, and delayed preconditioned groups, and persisted for an extended time (to P42) (Lin *et al.*, 2009b). These findings draw a clear distinction with adult ischemic preconditioning models, where only limited and transient protection was observed in rapid preconditioned groups.

While the multiple windows of ischemic preconditioning have been fairly well established, it remains unknown if this phenomenon is unique to ischemic preconditioning or if it extends to other preconditioning stimuli. More comprehensive studies to determine time window and alternative timeframe responses in non-ischemic preconditioning stimuli may help to better understand generalized versus stimulus-specific responses to preconditioning.

3.1.3 Remote ischemic preconditioning—Remote ischemic preconditioning presents an interesting alternative to cerebral preconditioning because it is significantly less invasive and thus has a much higher potential for clinical translation. To date, the major paradigm establishing remote preconditioning uses subtoxic levels of ischemic preconditioning in extra-neural tissue. However, of particular interest, non-invasive, repeated acute constriction of a limb (upper arm in humans, hind- or forelimbs in rodents) also yielded a tolerant state in the brain. For example, transient (15–30 min) tourniquet application of the hind limb conferred neuroprotection following asphyxial cardiac arrest (Dave *et al.*, 2006) or transient focal ischemia (Hu *et al.*, 2012).

In addition to limb constriction, remote preconditioning against cerebral ischemic insults has also been achieved by occlusion of a major artery (*e.g.*, unilateral femoral artery (Ren *et al.*, 2008) or the infra-renal abdominal aorta (Malhotra *et al.*, 2011) (Figure 2), allowing for precisely controlled preconditioning protocols. In addition, transient occlusion of arteries supplying blood flow to major organs conferred a preconditioned state against stroke models. Silachev *et al.* demonstrated that remote renal ischemic preconditioning – attained by microvascular clamping of the unilateral renal arteries three times for 5 minutes each cycle – significantly decreased cerebral ischemic injury when MCAO was induced 24 hours following preconditioning (Silachev *et al.*, 2012). This protection was dependent on nephritic function, as pretreatment with the nephrotoxic drug gentamicin abrogated any renal preconditioning effect on cerebral ischemia.

Remote ischemic preconditioning was recently evaluated in SBI paradigms such as hypothermic circulatory arrest and following carotid endarterectomy. Hypothermic circulatory arrest, an increasingly used adjunct in vascular surgeries, incurs significant cerebral dysfunction (Jensen *et al.*, 2011). In a pig model of hypothermic circulatory arrest, remote preconditioning by limb ischemia was induced by applying a static pressure of 230 mm Hg with a blood pressure cuff wrapped around the right hind leg of pig, in 4 cycles of 5-minutes ischemia intermittent with 3 x 5-minutes reperfusion periods completed 1 hour before initiation of cardiopulmonary bypass. This protocol led to a faster recovery of cortical

neuronal activity as well as improved histological outcomes (Jensen *et al.*, 2011; Yannopoulos *et al.*, 2010).

When compared to brain ischemic preconditioning, remote ischemic preconditioning may have a wider therapeutic window (Ren *et al.*, 2008), although this observation is likely dependent on which remote preconditioning paradigm is used (Malhotra *et al.*, 2011). For example, remote preconditioning paradigms with limb tourniquets varied in the time between the preconditioning stimulus and the toxicity model from minutes to days (Dave *et al.*, 2006; Hu *et al.*, 2012; Ren *et al.*, 2008). Furthermore, remote ischemic *post*-conditioning via femoral artery occlusion for two to three cycles of 10–15 minutes has been observed to have neuroprotective effects in models of transient and permanent focal ischemia (Ren *et al.*, 2011; Ren *et al.*, 2008), as well as neonatal hypoxia/ischemia (Zhou *et al.*, 2011b).

The observation that remote preconditioning can lead to protection against subsequent ischemic insult in heart and brain broadens the pertinent systemic partners to include neural or humoral elements (Lim *et al.*, 2010). Remote preconditioning effects on neurological injury in theory would necessitate a breakdown in the blood-brain barrier (BBB) and/or the release of brain-permeable factors, or alternatively involve distal neurotransmission (Figure 4). Two major scenarios – humoral- and neurotransmission-based – have been proposed that could be translated into preconditioning models. First, humoral alterations were proposed as a logical extension of the sentinel system present in blood flow and the ready access to remote regions to which circulating factors have privilege. Evidence for this exists in models of remote preconditioning against myocardial infarction, where the cardioprotective effects of remote ischemic preconditioning were completely abolished by femoral vein occlusion (Lim *et al.*, 2010), indicating that humoral (*i.e.*, circulatory) pathways were critical. A role for humoral contributions in the establishment of the preconditioned state protective against subsequent cerebral ischemia has also emerged. Renal function was critical in the neuroprotective action of both remote renal ischemic preconditioning and the systemic injection of the mitochondrial-targeted cationic antioxidant SkQR1 (which accumulates in the kidneys), as nephrotoxicity or bilateral nephrectomy abolished the protective effects (Silachev *et al.*, 2012).

Neurotransmission may also be critical to remote preconditioning scenarios, either in conjunction with or independent of humoral components. Remote ischemic preconditioning against myocardial ischemia was partially abrogated by sciatic nerve resection, suggesting neural transmission plays a role in remote preconditioning (Lim *et al.*, 2010). Likewise, the sensory nerve inhibitors hexamethonium and capsaicin attenuated the neuroprotection afforded by remote limb ischemic preconditioning against subsequent transient cerebral ischemia (Malhotra *et al.*, 2011; Wei *et al.*, 2012a). Thus, the roles for neural and humoral elements – either separately or as a coordinated effort – in neuroprotection represent an exciting field of study for determining the mechanisms underlying the endogenous response to remote preconditioning.

Taken together, these studies suggest that remote ischemic preconditioning is emerging as a clinically feasible concept to deter brain injury, particularly in cases of surgical injury. Several preliminary studies have begun to evaluate the safety and efficacy in clinical settings; these are described below under the section “Clinical Potential of Preconditioning.”

3.2 Oxygen preconditioning – hypoxic and hyperbaric conditions

Altitude changes and/or atmospheric pressure represent conditions to which the human body can adapt. Consistent with the concept that “the dose makes the poison,” extreme changes in atmospheric oxygen are lethal. However, adaptation to controlled and limited changes can

be managed. The physical adaptations to alterations in atmospheric oxygen appear to extend not only to survival, but also to a preconditioned state.

3.2.1 Hypoxia—Hypoxic preconditioning has been modeled both *in vitro* and *in vivo*, and effectively preconditions against ischemic brain injury in both adults and neonates. Cultures or animals are placed in an airtight hypoxia chamber, where oxygen is replaced by nitrogen, typically to normobaric hypoxic conditions (8% oxygen). Initially described in neonatal ischemic tolerance models, neuroprotection via hypoxic preconditioning has been extended to multiple cultures and *ex vivo* conditions such as hippocampal organotypic cultures (Bickler and Fahlman, 2009; Bickler *et al.*, 2009; Gage and Stanton, 1996), primary neuronal cultures (Arthur *et al.*, 2004; Bruer *et al.*, 1997) or astrocytic cultures (Liu and Alkayed, 2005). These findings were later further extended to adult stroke tolerance models (Bernaudin *et al.*, 2002; Fan *et al.*, 2011; Lin *et al.*, 2003; Miller *et al.*, 2001; Tang *et al.*, 2006; Zhan *et al.*, 2010), with important distinctions from ischemic preconditioning. Specifically, the tolerant state induced by normobaric hypoxia appears to exist in a fairly rapid and limited timeframe, lasting only approximately 72 hours (Bernaudin *et al.*, 2002; Prass *et al.*, 2003; Zhan *et al.*, 2010). Conversely, sustained tolerance (7 d) was achieved in female rats by 4 weeks of daily exposure to hypoxic conditions in an altitude chamber (Lin *et al.*, 2003). The implications of preconditioning in female stroke models are as yet unknown, but likely to be distinct from male models. While incidence of stroke in women overall is lower than in men (age<85 years), the severity of outcome is higher (Appelros *et al.*, 2009; Persky *et al.*, 2010).

In addition to gender differences, a distinction in hypoxic preconditioning has emerged that indicates the phenomenon may also be age-dependent. In the neonatal HI brain, hypoxia also confers a preconditioned state (Gidday *et al.*, 1994; Ota *et al.*, 1998). Hypoxic preconditioning can be achieved by exposing neonatal rats (P6–7) to sustained hypoxia (*e.g.*, 3 hours at 8% O_2/92% N_2) in a humidified chamber held at 37°C. Disruption of systemic pH is avoided in neonatal hypoxia due to the increased respiration (hypocapnia). Preconditioning is then followed by normoxia for 24 hours, and then pathological HI. Neural and behavioral outcomes following this paradigm demonstrate substantial protection compared to non-preconditioned groups, and last for an extended period of time (*e.g.*, 7–8 weeks) (Gustavsson *et al.*, 2005). Indeed, the recovery following HI in the preconditioned groups can be near complete. However, in slices derived from *aged* animals (>2 years of age), hypoxic preconditioning did not confer protection against subsequent severe oxygen/glucose deprivation (OGD) (Bickler *et al.*, 2010). This discrepancy has also been observed in an ischemic preconditioning model against global ischemia (He *et al.*, 2005). These findings are in line with observations that neonates recover better from hypoxic/ischemic injury, and support the concept that aged brain either is more susceptible to oxidative injury (Xu *et al.*, 2007) or has diminished capacity to repair itself after sublethal or lethal injury (Mattson *et al.*, 2002). Further research is needed to determine the influence of age and gender on preconditioning in stroke models.

Hypoxic preconditioning was found to be protective against ischemic injury in cultured human brain endothelial cells (Zhang *et al.*, 2007), and drug inhibition of endothelial sphingosine kinase upregulation abrogated the neuroprotection afforded by hypoxic preconditioning against transient MCAO (Wacker *et al.*, 2009). Thus, hypoxic preconditioning could represent a relatively broad phenomenon that may extend to inclusion of preconditioning the cerebrovasculature. These observations have spurred major interest in identifying the multiple signaling pathways and physiological alterations conferring hypoxia-mediated protection against HI.

3.2.2 Hyperbaric oxygen preconditioning—Hyperbaric oxygen (HBO), a condition obtained by containment in a pressurized chamber infused with 100% O_2 flow, can protect against subsequent transient MCAO and global ischemia, as well as SBI and TBI. Similar to hypoxic and ischemic preconditioning, many different paradigms have been used to demonstrate that either rapid or delayed tolerance is affected by HBO. Preconditioning with pressures of 2 atmospheres absolute (ATA) every other day for 3 or 5 sessions was effective at inducing tolerance against global ischemia in the gerbil (Wada *et al.*, 1996; Wada *et al.*, 2001). Similarly, 2.5 ATA preconditioning 1 hour daily for 5 days protected against subsequent global ischemic injury in rat (Cheng *et al.*, 2011). When air (20% oxygen) rather than 100% O_2 was infused into the hyperbaric chamber the tolerance was negated, demonstrating a requirement for O_2 in the hyperbaric preconditioned state (Wada *et al.*, 2001).

As mentioned above, longer-term HBO preconditioning paradigms appear more effective at establishing tolerance than do acute paradigms. For example, preconditioning at 2.5 ATA for 1 hour per day for 5 days ending 24 hours prior to injury was effective at establishing tolerance in rats against global cerebral ischemia, transient focal ischemia with hemorrhagic transformation, and SBI (Jadhav *et al.*, 2010; Ostrowski *et al.*, 2008; Soejima *et al.*, 2012), whereas acute preconditioning (3 treatments of 1 hour at 2.5 ATA occurring 24, 12 and 6 hours prior to MCAO) was less effective, reaching significance only when assessed 24 hours following MCAO (Ostrowski *et al.*, 2008). Similarly, protection was observed following a regimen of 1-hour treatments at 2.5 ATA every 12 hours, beginning 2 days before ischemia (Li *et al.*, 2009). Under such conditions, improved outcomes were observed at 24 hours following ischemia.

In addition to conferring tolerance in adult models, HBO preconditioning has been found to be protective against neonatal HI (Freiberger *et al.*, 2006; Li *et al.*, 2008b). HBO conditioning was accomplished by exposure to 2.5 ATA for 2.5 hours, completed 24 hours prior to the HI injury. Less intense HBO (2 ATA for 1 hour) did not appear to confer a tolerant state, even with successive treatments or an extended timeframe (Freiberger *et al.*, 2006).

HBO preconditioning also leads to delayed neuroprotection against a weight drop model of TBI (Hu *et al.*, 2010b; Hu *et al.*, 2008), as well as improved neurological outcomes following SBI (cortical excision model) (Jadhav *et al.*, 2010; Jadhav *et al.*, 2009). In both models, HBO preconditioning was established by subjecting animals to 5 sessions of 2.5 ATA, 100% O_2 for 1 hour per day. Prior to TBI, the preconditioned animals were kept in a hyperbaric chamber (0.6 ATA) at a simulated pressure of 4000 m altitude for 3 days following HBO and then subjected to TBI 72 hours later (Hu *et al.*, 2008). HBO preconditioning improved regional cerebral blood flow and brain tissue O_2 pressure following TBI (Hu *et al.*, 2010b), and attenuated post-operative brain edema following SBI (Jadhav *et al.*, 2010; Jadhav *et al.*, 2009). Neurological outcomes following TBI or SBI were significantly improved when preceded by HBO preconditioning (Hu *et al.*, 2010b; Hu *et al.*, 2008; Jadhav *et al.*, 2010; Jadhav *et al.*, 2009). Further studies using more sensitive neurobehavioral or cognitive assays as well as improved histological assessments should further specify the protection conferred by HBO against TBI or SBI.

3.3 Temperature preconditioning – hypothermia and hyperthermia

Similar to oxygen modulations, temperatures above or below homeostatic temperatures can induce a tolerant state. Although the mechanisms are likely to be dissimilar, the concept remains that limited deviations from homeostasis appear to induce protective responses.

3.3.1 Hypothermia—Brain cooling (hypothermia) has been recommended in emergency medicine in the protection against neurological injury following cardiac arrest due to ventricular fibrillation (Azmoon *et al.*, 2011; Bernard, 2009). A brief period of hypothermia can also lead to preconditioning-like neuroprotection. Twenty minutes of hypothermic exposure (31–32°C) induced a delayed ischemic tolerance window that was initiated 6 hours after preconditioning and persisted for 2 days (Nishio *et al.*, 1999; Nishio *et al.*, 2000). Focal hypothermic preconditioning by selectively cooling the head was as effective as whole-body cooling for eliciting tolerance (Yunoki *et al.*, 2002). Similar mild hypothermic exposure was also reported to have a preconditioning effect at an acute phase of tolerance in *in vitro* models of ischemia. Hypothermic preconditioning (33°C for 20 minutes) applied 0 to 3 hours before OGD effectively prevented OGD-induced Purkinje cell death in rat cerebellar slices (Yuan *et al.*, 2004, 2006). This rapid neuroprotection induced by hypothermic preconditioning appeared dependent on the activation of signaling molecules and increased gene expression (Yuan *et al.*, 2004, 2006).

3.3.2 Hyperthermia—Brief *hyper*thermic exposure can also induce brain tolerance against ischemic injuries. In such studies, adult rats are placed in a water bath set at 42°C for 15 minutes or wrapped in a temperature-controlled heating pad until rectal temperature reaches 42°C. When examined 18 or 24 hours later, rats suffered a smaller infarct volume after MCAO (Xu *et al.*, 2002) and showed improved learning abilities and memory following diffuse axonal injury (Su *et al.*, 2009). The preconditioning effect against MCAO was not observed either at an earlier phase (6 hours after preconditioning) or at a later phase (48 hours after preconditioning) (Xu *et al.*, 2002). In addition, heat acclimation, a unique preconditioning paradigm established by chronic exposure to moderate heat, was also reported to induce endogenous protection against TBI (Shein *et al.*, 2007; Umschweif *et al.*, 2013; Umschwief *et al.*, 2010).

As will be discussed in detail in the second part of this series, heat stress is associated with the upregulation of heat shock proteins. Overexpression of heat shock proteins is protective in models of PD (Fan *et al.*, 2005; Fan *et al.*, 2006; Gorman *et al.*, 2005). Furthermore, heat shock preconditioning is protective against dopaminergic toxins (MPP+) in culture models (Fan *et al.*, 2005; Quigney *et al.*, 2003).

3.4 Pharmacological preconditioning

Pharmacological preconditioning is a clinically feasible paradigm that can be elicited by a wide variety of drugs. The classification of pharmacological preconditioning versus pharmacological pretreatment is somewhat nebulous, with the major distinction being that in the preconditioned state *protection is afforded in a timeframe beyond agent elimination*. Due to its ease of establishment compared to the more invasive or elaborate preconditioning protocols described above, pharmacological preconditioning has been accepted as a promising paradigm to combat cerebral ischemic injury in the clinic. However, many limitations still need to be overcome, such as understanding and thus titrating the indirect effects of the agent that elicits the preconditioned state. Potential mechanisms and downstream targets of pharmacological preconditioning will be discussed in the second component of this series.

3.4.1 Anesthetics/analgesics—Following the demonstration of anesthetic preconditioning in an animal model of myocardial infarction (Kersten *et al.*, 1997), accumulating evidence supports the protective capacity of anesthetic preconditioning against cerebral ischemic injury as well. Furthermore, a recent study suggests a preconditioning-like effect against an AD model. The dose, time window of tolerance and preconditioning

paradigms vary with agent and model. We will discuss here various aspects of these paradigms in the context of neurological injury.

3.4.1.1 Inhalational anesthetics: Currently used inhalational anesthetic agents include isoflurane, sevoflurane, and desflurane. Isoflurane is a potent anesthetic agent that has been used for decades in clinical anesthesia, but is currently being replaced by sevoflurane and desflurane due to the low blood:gas partition coefficient of the latter two drugs, resulting in both relatively rapid anesthesia induction and recovery from anesthesia. Both sevoflurane and isoflurane are accepted as having neuroprotective properties against adult and neonatal cerebral ischemic injury when used in preconditioning. Accumulating evidence indicates that isoflurane preconditioning (exposure to 1% to 2% isoflurane) provides a delayed protective effect (usually 24 hours after preconditioning) against ischemic neuronal injury both in *in vitro* models (Bickler and Fahlman, 2009; Bickler *et al.*, 2005; Li *et al.*, 2008a) and in adult and neonate *in vivo* models (Kitano *et al.*, 2007; Li and Zuo, 2009; McAuliffe *et al.*, 2007; Zhao *et al.*, 2007; Zhao and Zuo, 2004; Zheng and Zuo, 2004; Zhu *et al.*, 2010).

The timeframe used for isoflurane preconditioning varies between models. In ischemic neuronal culture model systems, 15 minutes to 2 hours of anesthetic preconditioning was used (Bickler *et al.*, 2005; Li *et al.*, 2008a), whereas 30 minutes to 4 hours were applied under different isoflurane concentrations in MCAO models (Kitano *et al.*, 2007; Li and Zuo, 2009; Zheng and Zuo, 2004; Zhu *et al.*, 2010). Repetitive exposure, which is achieved by isoflurane exposure for 1 hour per day for 5 days, induced ischemic tolerance in a time- and dose-dependent manner against MCAO (Xiong *et al.*, 2003), improved motor function and decreased the number of degenerating neurons following global ischemia (Zhang *et al.*, 2010). In addition to the delayed preconditioning observed in the adult, isoflurane preconditioning induced both rapid and delayed phases of ischemic tolerance in neonatal brains (McAuliffe *et al.*, 2007; Sasaoka *et al.*, 2009; Zhao *et al.*, 2007; Zhao and Zuo, 2004). P7 pups exposed to 1% or 2% isoflurane ending 15 minutes before the HI injury were protected against HI injury (Sasaoka *et al.*, 2009), as were pups exposed to isoflurane 24 hours before HI (McAuliffe *et al.*, 2007; Zhao *et al.*, 2007; Zhao and Zuo, 2004). The protection conferred by preconditioning 24 hours before HI was long-lasting, as improved functional outcomes were observed in adult mice that experienced preconditioning followed by neonatal HI injury (McAuliffe *et al.*, 2007; Zhao *et al.*, 2007).

Sevoflurane is also a volatile anesthetic that is now replacing isoflurane in modern anesthesiology due to the reduction in mucosal membrane irritation and the faster onset and offset. A large body of evidence indicates that sevoflurane is able to protect the brain against ischemic injury in various models (Warner *et al.*, 1993; Werner *et al.*, 1995). In preconditioning paradigms, sevoflurane elicited a rapid neuroprotection within 3 hours after preconditioning against OGD in neuronal or hippocampal slice cultures (Sigaut *et al.*, 2009; Velly *et al.*, 2009). This neuroprotective effect of sevoflurane preconditioning appeared at concentrations higher than 0.07 mM (Velly *et al.*, 2009) and only under modest OGD challenges (30 minutes or less for hippocampal slices) (Sigaut *et al.*, 2009). In animal models, sevoflurane preconditioning has been examined in both the adult global and focal cerebral ischemia models, as well as in neonatal models. Rapid preconditioning can be induced by sevoflurane exposure within 1 hour before ischemic injury in rats (Codaccioni *et al.*, 2009; Payne *et al.*, 2005; Wang *et al.*, 2007a), more clinically relevant for SBI., Sevoflurane exposure also conferred neuroprotection against either global (Payne *et al.*, 2005) or focal ischemia (Adamczyk *et al.*, 2010; Ye *et al.*, 2012a) during a late time window (from 1 to 3 days after preconditioning). In neonatal brain injury models, preconditioning with 1.5% sevoflurane alone or 0.75% sevoflurane in combination with 20% xenon significantly reduced infarct size in the model of neonatal asphyxia (Luo *et al.*, 2008). Likewise, delayed preconditioning with 8.4% desflurane or 3.1% sevoflurane improved

selective behavioral performance of adult mice previously subjected to neonatal HI injury (McAuliffe *et al.*, 2009).

In a transgenic model of AD (PS1/Swe/tau), female mice exposed to halothane in the presymptomatic stage performed better in a spatial memory test (Morris water maze) compared to un-exposed or isoflurane-exposed females (Tang *et al.*, 2011). The effect was short lived, but may suggest a preconditioning-like phenomenon possible in an AD model.

3.4.1.2 Opioid receptor agonists: Opioid receptors are associated with preconditioning-induced cardioprotection (Liang and Gross, 1999), and are widely expressed in the central nervous system. These receptors have been found to contribute to preconditioning models in brain, including hypoxia preconditioning (Gao *et al.*, 2012; Zhang *et al.*, 2006), and their agonists confer a preconditioned-like state. Morphine is a potent non-selective opioid receptor agonist and is frequently used as an analgesic conjunctive therapy in clinical anesthesiology. Morphine pretreatment provided both a rapid and delayed neuroprotection against OGD-induced neuronal injury in hippocampal slice cultures (Liu *et al.*, 2008a; Zhao *et al.*, 2006b). A delayed preconditioning effect was achieved in animals by a single injection of morphine (2 mg/kg or 8 mg/kg, i.p.) 24 hours before ischemic injury (Rehni *et al.*, 2008; Zhao *et al.*, 2006b). Morphine-induced pharmacological preconditioning not only reduced ischemic infarct size, but also reversed the impairment of memory and motor coordination induced by global and permanent focal ischemia (Rehni *et al.*, 2008; Zhao *et al.*, 2006b).

3.4.2 Ethanol—Light to moderate alcohol consumption has recently been associated with reduced risk of AD, stroke and cardiovascular disease (Belmadani *et al.*, 2004; Berger *et al.*, 1999; Krenz and Korthuis, 2012; Mehlig *et al.*, 2008; Mukamal *et al.*, 2003; Orgogozo *et al.*, 1997; Stampfer *et al.*, 1988). Heavy consumption of alcohol, on the contrary, is associated with increased stroke severity (Ducroquet *et al.*, 2013). Epidemiological data with alcohol consumption is difficult to interpret, as other components of alcoholic beverages (notably, resveratrol in red wine) have also been demonstrated to exert a preconditioning effect (Pinder and Sandler, 2004; Raval *et al.*, 2006; Singh *et al.*, 2013), and individual differences in alcohol metabolism may alter absorption and clearance rates. However, recent studies using animal models have demonstrated a role for ethanol in protecting against brain disease.

In animal models of cerebral ischemia, ethanol preconditioning protected against ischemic brain damage (Liao *et al.*, 2003; Wang *et al.*, 2010b; Wang *et al.*, 2007b). For example, it was shown that ethanol preconditioning, administered by gavage to gerbils with a moderate dose of ethanol as a single bolus (producing a peak plasma concentration of 42–46 mg/dl) 24 hours before ischemia, offered a number of beneficial effects against ischemic injuries, including behavioral deficit, delayed neuronal death, neuronal and dendritic degeneration, and oxidative DNA damage (Wang *et al.*, 2007b). Both pre- and post-treatment with intracerebroventricular infusion of ethanol (0.1%, 60 minutes prior or 30 minutes after ischemia) attenuated transient focal ischemic infarct (Liao *et al.*, 2003). Finally, alcohol can protect against NMDA receptor-mediated neurodegeneration in neuronal cultures *in vitro* (Cebere and Liljequist, 2003; Chandler *et al.*, 1993; Wegelius and Korpi, 1995).

Models of inflammatory neural diseases also benefit from pre-exposure to ethanol, which may allow some extrapolation to the inflammatory state in stroke or chronic neurodegeneration. Chronic ethanol intake (70 days) protected neurons from subsequent intraperitoneal LPS exposure (Singh *et al.*, 2007). In hippocampal-entorhinal cortical organotypic cultures, ethanol pre-exposure (20–30 mM, 6 days) significantly decreased neuronal degeneration due to exposure of the neuroinflammatory HIV-1 envelope

glycoprotein 120 (Belmadani *et al.*, 2001; Collins *et al.*, 2000). These studies demonstrate a possible role for ethanol in effecting a preconditioned state against neuroinflammatory processes.

Epidemiological studies focusing on AD risk factors have indicated that alcohol, if consumed in moderation, is inversely correlated with developing either cardiovascular disease or AD, two conditions that share many common risk factors (Collins *et al.*, 2009; Mehlig *et al.*, 2008; Mukamal *et al.*, 2003; Orgogozo *et al.*, 1997; Peters *et al.*, 2008). Specifically, 1–6 drinks per week were associated with reduced risk for developing dementia (Collins *et al.*, 2009; Mukamal *et al.*, 2003). Concurring with these observations, rat brain cerebellar cultures and hippocampal-entorhinal cortical organotypic cultures were protected against Aβ toxicity by moderate ethanol exposure prior to the insult (Belmadani *et al.*, 2004; Collins *et al.*, 2010; Mitchell *et al.*, 2009).

3.4.3 Stimulants—Several other drugs commonly used have had some association with a possible preconditioning effect. For example, although cigarette smoking is highly toxic and often leads to heart disease and cancer, smoking and ingestion of dietary nicotine is negatively correlated with PD (Baron, 1986; Nielsen *et al.*, 2013; Ross and Petrovitch, 2001). Nicotine has the ability to stimulate DA release (Giorguieff-Chesselet *et al.*, 1979; Grenhoff and Svensson, 1989), and thus may not be acting as a preconditioning stimulus but rather as a mask of the symptoms. Additionally, nicotine may also improve PD-related dyskinesias by acting on nicotinic, cholinergic receptors(Quik *et al.*, 2013; Quik *et al.*, 2009). Nicotine pretreatment (1.2 mg/kg, i.p. 2 hours prior to MCAO) reduced infarct volume when assessed a day after stroke (Chen *et al.*, 2013). However, smoking has long been associated with an *increased* risk in stroke, and consistent with this, several studies have conclusively demonstrated the deleterious effects of nicotine in a variety of ischemia models (Bradford *et al.*, 2011; Li *et al.*, 2012; Paulson *et al.*, 2010; Raval *et al.*, 2011).

On the other hand, in the context of this review, one might also consider a quite different hypothesis, namely that nicotine is neuroprotective at low doses by triggering a variety of cellular defenses, including those involving mitochondrial energy production and the inflammatory response. This proposal deserves future research, particularly in that it might suggest the development of other approaches to trigger similar cellular defenses without being either carcinogenic or a stress to the cardiovascular system.

Another neurotoxin that has been shown to have neuroprotective properties in low concentrations is methamphetamine. In a recent study using a dopaminergic cell line, we were able to show that although high concentrations of methamphetamine (2–3 mM) can be cytotoxic, exposure to lower concentrations (0.5–1.0 mM) for 24 hours prior to a 20-minute exposure to 6-OHDA (100 μM) was cytoprotective (El Ayadi and Zigmond, 2011). These findings with methamphetamine are consistent with many previous reports. For example, methamphetamine has also been shown to induce a tolerance to the neurotoxic effects of 3,4-methylenedioxymethamphetamine (Shankaran and Gudelsky, 1998), methamphetamine (Cadet *et al.*, 2009), other amphetamines (Abekawa *et al.*, 1997; Danaceau *et al.*, 2007; Graham *et al.*, 2008; Johnson-Davis *et al.*, 2003; Johnson-Davis *et al.*, 2004), and MPTP oxidation products (Kita *et al.*, 2003; Park *et al.*, 2002) as well as to 6-OHDA in an animal model of PD (Moroz *et al.*, 2004). Moreover, preconditioning and cross-tolerance using several different drugs have been shown by us and others in various *in vitro* models of the DA deficiency seen in PD (Leak *et al.*, 2006; Tai and Truong, 2002; Tang *et al.*, 2005).

3.5 Neurotoxic or neuroinflammatory agent preconditioning

Exposure to low doses of chemicals that are toxic at moderate concentrations may induce neuroprotection against ischemia, which reduces infarct size and improves functional

outcome in both cultured neuronal cells and animal stroke models (Marini and Novelli, 1991; Marini and Paul, 1992). The drugs included in the context of chemical preconditioning include primarily those whose known targets are typically detrimental in nature (*e.g.*, mitochondrial respiration inhibitors), that are excitotoxic or inflammatory in nature (*e.g.*, glutamate receptor agonists or toll-like receptor ligands) or that have been identified as critical elements of injurious states (*e.g.*, thrombin). In the context of this review, these chemicals have no therapeutic or social use, in contrast to the preconditioning stimuli described under pharmacological preconditioning.

3.5.1 Chemical preconditioning with drugs used for injury models

3.5.1.1 NMDA: Glutamate excitotoxicity contributes significantly to the cell death induced by ischemia and can be modeled with the use of high doses of glutamate receptor agonists, such as NMDA (Mandir *et al.*, 2000). However, subtoxic doses of NMDA-receptor agonists have been found to lead to the activation of intracellular pro-survival signaling in the absence of cell death (Lipsky *et al.*, 2001; Marini and Paul, 1992; Marini *et al.*, 1998; Ogita *et al.*, 2003; Zhu *et al.*, 2005). The neuroprotective effect of NMDA preconditioning has been examined in both *in vitro* and *in vivo* models of ischemia. Cultured neurons can be protected from an excitotoxic concentration of glutamate or exposure to lethal OGD by pretreatment with 50 μM NMDA (Grabb and Choi, 1999; Head *et al.*, 2008; Jiang *et al.*, 2005). In addition, preconditioning with a micro-injection of 10 μM NMDA into the prefrontal cortex induced a rapid protection against permanent occlusion of the middle cerebral artery in rats (Saleh *et al.*, 2009).

The excessive activation of NMDA receptor activity is also elemental in the cascade of events subsequent to TBI. Although NMDA receptor *antagonists* have been used as a possible neuroprotective agent in both animal TBI models and clinical trials (Muir, 2006; Rao *et al.*, 2001; Yurkewicz *et al.*, 2005), longterm therapy may reduce the capacity of the brain to recover, as glutamate exerts trophic effects contributing to neuronal reorganization after brain injury (Billard and Rouaud, 2007; Lo, 2008). Sublethal, transient NMDA preconditioning may therefore be a promising protective strategy in a mouse TBI model. Preconditioning by administration of a nonconvulsant dose of NMDA (75 mg/kg, i.p.) was induced 24 hours before mild TBI (Costa *et al.*, 2010), and selectively improved motor deficits (revealed by footprint tests) in a short timeframe after injury (Costa *et al.*, 2010).

3.5.1.2 Thrombin: Thrombin, a trypsin-like serine protease protein, converts soluble fibrinogen into insoluble strands of fibrin, as well as catalyzing many other coagulation-related reactions. Thrombin can be released from a ruptured cerebral aneurysm clot around a cerebral artery, and leading to the prolonged narrowing of blood vessels, and cerebral ischemia and infarction. In this manner, it has been used as a model for ischemic stroke (El Amki *et al.*, 2012; Sun *et al.*, 2011). In addition to vascular actions inducing cerebral ischemia, thrombin formation also contributes to brain edema after intracerebral hemorrhage (Lee *et al.*, 1995; Lee *et al.*, 1996a; Lee *et al.*, 1996b, Lee *et al.*, 1997), leading to worsened brain injury and poorer neurological outcomes. High concentrations of thrombin infused into the caudate nucleus causes inflammation, edema, reactive gliosis, and scar formation (Lee *et al.*, 1995; Lee *et al.*, 1996a; Lee *et al.*, 1996b; Nishino *et al.*, 1993). Despite these detrimental effects of thrombin, low concentrations of thrombin exert protective effects in neural cells against hypoglycemia and ischemia (Vaughan *et al.*, 1995). Following cerebrovascular injury, thrombin is produced immediately upon breakdown of the BBB and regulates gene expression and process outgrowth in neural cells. These effects were blocked by the brain thrombin inhibitor, protease nexin-1 (Vaughan *et al.*, 1995). Thus, the immediate presence of low levels of thrombin may aid in faster post-injury repair.

Prior studies indicated that a state of ischemic tolerance can be induced by thrombin both in organotypic hippocampal slice cultures and in MCAO mice. Low doses of thrombin (0.01 U/ml thrombin injected intracerebroventricularly) protected neurons against severe OGD and transient focal ischemia (Granziera *et al.*, 2007). Thrombin pretreatment also can significantly attenuate brain edema (Xi *et al.*, 1999).

Thrombin has also been investigated in a PD model. High doses of thrombin (20 U) cause degeneration of dopaminergic neurons and microglial activation in the substantia nigra (Carreno-Muller *et al.*, 2003; Choi *et al.*, 2003). However, stereotaxic infusions of low doses of thrombin (1 U) administered above the medial forebrain bundle though which DA neurons project from the ventral mesencephalon to the striatum and other telencephalic structures protect rats against subsequent infusions of 6-OHDA, a classic model of PD (Cannon *et al.*, 2005). Protection was evident in assessments of motor behavior, TH immunoreactive terminals in the striatum, and ventricular enlargement. Surprisingly, however, thrombin did not protect against DA depletion in this model of preconditioning, possibly suggesting that a defect in DA storage remained despite the sparing of DA terminals. The effects of thrombin, however, depended closely on the time of administration relative to 6-OHDA. If co-infused with 6-OHDA, thrombin at low doses actually increased behavioral deficits (Cannon *et al.*, 2007). In contrast, if thrombin was administered 7 days after 6-OHDA, it had protective behavioral and neurochemical effects (Cannon *et al.*, 2007). Further studies are warranted on whether the timing effects of thrombin fall within classical rapid or delayed preconditioning paradigms, and on elucidating the contrast between the thrombin-induced protection of TH-immunoreactive terminals without protection of DA stores.

3.5.1.3 6-OHDA: Most models of PD have focused on the use of toxins that target DA neurons. To use an analogy with the ischemic preconditioning literature, the simplest paradigm to establish preconditioning in PD models is to use a low dose of one of these toxins to protect against a subsequent challenge with a higher dose of the same toxin. Indeed, we have found that low concentrations of 6-OHDA protect dopaminergic MN9D cells against a high concentration of 6-OHDA applied 6 hours later (Leak *et al.*, 2006). Similarly, in a preliminary study *in vivo*, we have observed that a low dose of 6-OHDA (0.15 μg into the striatum) significantly reduced the loss of TH immunoreactive terminals in the striatum in response to a much higher dose of 6-OHDA (3 μg) administered 4 days later (R. Leak and M. Zigmond, unpublished observations).

3.5.2 Preconditioning with inflammation

3.5.2.1 Toll-like receptor ligands: Toll-like receptors (TLRs) are archetypal pattern recognition receptors that play essential roles in the innate immune response to foreign pathogens. TLRs are expressed in a variety of immunocytes such as B cells, dendritic cells, neutrophils, macrophages, and monocytes. TLRs are also present in the cerebral endothelium and in almost all types of brain parenchymal cells, including microglia (Olson and Miller, 2004), astrocytes (Bowman *et al.*, 2003), oligodendrocytes (Bsibsi *et al.*, 2002), and neurons (Tang *et al.*, 2007). At least 13 TLRs have been identified in mammals. Each TLR recognizes invaders through different exogenous pathogen-associated molecular patterns such as bacterial cell wall lipoprotein (TLR2) and lipopolysaccharide (LPS) (TLR4), bacterial DNA containing particular nonmethylated cytosine-guanine motifs (TLR9), viral double-strand RNA (TLR3), and single-strand RNA (TLR7) (Vance *et al.*, 2009). In addition to their role in recognition of pathogen-associated molecular patterns, TLRs can also sense cell damage through endogenous molecules that have been termed DAMPs (damage-associated molecular patterns) and initiate inflammatory responses to aseptic tissue injury (Kim *et al.*, 2009b; Yang *et al.*, 2010a; Yang *et al.*, 2010b).

Excessive inflammation after stroke can cause secondary neuronal injury and long-term neurological deficits (Barone and Feuerstein, 1999; Dirnagl *et al.*, 1999). Consistent with this, prolonged post-ischemic systemic administration of LPS, the most potent bacterial ligand of TLR4 receptor, is devastating to stroke outcome in the absence of a prolonged febrile response (Langdon *et al.*, 2010). Genetic ablation of either TLR2 or TLR4 conferred protection against brain damage following both transient and permanent focal cerebral ischemia (Caso *et al.*, 2007; Tang *et al.*, 2007; Ziegler *et al.*, 2007). Despite the detrimental role of TLRs in ischemia, stimulation of these receptors with a low/sublethal dose of their ligands prior to ischemia provides robust neuroprotection. For example, preconditioning with a low dose of LPS protected the brain against subsequent ischemic damage (Bordet *et al.*, 2000; Dawson *et al.*, 1999; Furuya *et al.*, 2005; Kunz *et al.*, 2007; Marsh *et al.*, 2009; Rosenzweig *et al.*, 2004; Yu *et al.*, 2010). Some other TLRs have also been suggested to be neuroprotective. For example, it has been shown that priming of TLR2 or TLR9 with their respective agonists can serve as a preconditioning stimulus and provide protection against brain ischemia (Hua *et al.*, 2008; Stevens *et al.*, 2008).

3.5.2.2 LPS: The hypothesis underlying the preconditioning effect of the potent TLR4 ligand LPS is that a small inflammatory stimulus dampens subsequent inflammatory responses associated with cerebral ischemia and mitigates against brain injury. The protective effect of LPS against cerebral ischemia is both dose- and time-dependent. The optimal preconditioning dose and duration of LPS depend on multiple factors, including the animal model, the route of LPS application, and the quantity of LPS. In mice, LPS is administered prior to ischemic challenge in experimental animals in a single systemic dose of 0.05 to 1 mg/kg, which would be a highly toxic dose in a human but is a low dose for mice. In a mouse transient MCAO model, the tolerance window is quite extended, appearing within 24 hours after LPS administration (0.2 mg/kg, i.p.) and extending through 7 days following LPS pretreatment (Rosenzweig *et al.*, 2007). Similarly, in a rat model, the neuroprotective effect can be observed with LPS treatment (0.9 mg/kg, i.v.) at least 2 days and up to 4 days prior to permanent MCAO (Tasaki *et al.*, 1997). Although the potential mechanisms will be discussed in in a second review, LPS preconditioning was also associated with decreased endothelium relaxation following transient MCAO (Bastide *et al.*, 2003), and with – improvement albeit delayed – in cerebral blood flow following permanent MCAO (Dawson *et al.*, 1999). These results suggest that LPS preconditioning may function on the cerebrovasculature as well as directly on neuronal tissue.

The protective effect of LPS preconditioning has also been demonstrated in *in vitro* models of ischemia. Low-dose LPS (1 μg/ml) pretreatment for 24 hours protected cortical neurons from OGD-induced cell death (Rosenzweig *et al.*, 2007). Application of LPS (1 μg/ml) or conditioned media from LPS-treated mixed glial cultures 24 hours before can also protect cerebellar granule neurons against the ischemic injury induced by mitochondrial toxin 3-NPA (Lastres-Becker *et al.*, 2006).

Preconditioning induced by LPS was observed not only in adult stroke models, as previously noted, but also in neonatal HI (Eklind *et al.*, 2005; Lin *et al.*, 2009a). However, uniquely to the neonates, the effect of LPS on immature brain varies depending on the interval between LPS application and HI and the intensity of HI (Eklind *et al.*, 2005). For example, a low dose of LPS (0.3 mg/kg, i.p.) administered 24 h before hypoxia-ischemia in P7 rats provided neuroprotection to the immature brain (Eklind *et al.*, 2005). Further study demonstrated that systemic LPS preconditioning (0.05 mg/kg, i.p.) in P7 rats 24 h prior to HI greatly reduced HI-induced cerebral inflammation and conferred long-term neuroprotection against brain damage and behavioral abnormalities (Lin *et al.*, 2009a). However, when administered 6 hours or 72 hours prior to HI, LPS exacerbated post-HI brain injury (Eklind *et al.*, 2005). It is possible that the brain development at the time of infection induction determines the

sensitizing or preconditioning effects of LPS; future studies geared at exploring this possibility may provide useful data on inflammatory responses in the different neonatal stages.

At higher doses, LPS is also highly toxic to dopaminergic cells. Prenatal or adult LPS exposure at higher doses consistently led to permanent DA neuronal loss in the substantia nigra (Carvey *et al.*, 2003; Ling *et al.*, 2004; Ling *et al.*, 2002) (Serotonin neurons, which are also affected in PD (Wang *et al.*, 2009), are also lost.) In wild-type adult male mice, intraperitoneal LPS by itself at a dose of 5 mg/kg can also cause delayed and progressive loss of DA neurons (Liu *et al.*, 2008b). Female mice are more resistant, reminiscent of the pattern in PD in which males have a somewhat higher likelihood of developing the disease than do females (Liu *et al.*, 2008b). LPS infusions directly into the striatum also caused progressive DA neuron degeneration and accumulation of α-synuclein and ubiquitin in remaining DA neurons (Choi *et al.*, 2009; Hunter *et al.*, 2009; Hunter *et al.*, 2007). Behavioral deficits were elicited in this model with loss of striatal DA and were alleviated with L-DOPA (Hunter *et al.*, 2009).

Despite the toxicity of LPS at higher doses on dopaminergic cells, LPS has also been used as a preconditioning stimulus at low concentrations in the context of dopaminergic loss. Pretreatment of organotypic slices of ventral midbrain with 1–10 ng/ml LPS protected against subsequent treatment with 100 ng/ml LPS (Ding and Li, 2008). This raises the interesting possibility that whereas a major inflammatory stress could be a risk factor for PD, a more minor inflammatory stimulus might actually be neuroprotective. Further studies of this hypothesis seem warranted.

Low-dose LPS preconditioning has also been reported to provide a delayed protection against brain injuries related to hypothermic circulatory arrest. In a piglet model of hypothermic circulatory arrest, preconditioning with 20 μg/kg LPS 3 days before surgery significantly reduced histological injury in the cortex, basal ganglia, and hippocampus, indicating that systemic LPS preconditioning induces global cerebral protection against brain injury from hypothermic circulatory arrest (Hickey *et al.*, 2007).

3.5.2.3 Other TLRs ligands: Preconditioning with other TLRs ligands uses similar paradigms. TLR9 preconditioning against transient focal ischemia could be achieved in experimental animals by systemic administration of its specific ligand, unmethylated CpG oligodeoxynucleotide (Stevens *et al.*, 2008). A concentration range from 20 μg to 40 μg for a single i.p. injection of CpG oligodeoxynucleotide 72 hours prior to transient MCAO conferred robust cerebral protection with a tolerance window beginning 1 day after injection and lasting at least 7 days (Stevens *et al.*, 2008). For *in vitro* studies, CpG oligodeoxynucleotide (0.5 to 5 μg/ml) pretreatment for 24 hours protected cortical neurons against OGD-induced cell death. A TLR2 agonist, Pam3Cys-Ser-Lys4, at 2 mg/kg has been shown to be protective to MCAO mice when applied i.p. 24 hours before insult (Hua *et al.*, 2008). Likewise, the TLR7 agonist Gardiquimod (40 μg) administered subcutaneously 72 hours prior to transient focal ischemia conferred neuroprotection (Leung *et al.*, 2012). As more is known about the effect of TLR ligand preconditioning, prophylactic TLRs stimulation may become a new paradigm for stroke management.

3.6 Systemic stress preconditioning

Most preconditioning studies deliver acute stressors to elicit neuroprotection. However, we have noted above that even chronic stress can be protective provided it is sublethal in concentration. Chronic organism stress, such as during physical exercise and caloric restriction or intermittent fasting appear to induce a preconditioned state.

3.6.1 Physical exercise—Exercise can be considered a form of mild stress (Arumugam *et al.*, 2006; Morton *et al.*, 2009), despite its popular view as being innocuous. Exercise raises levels of reactive oxygen species (ROS) and subsequent antioxidant defenses to deal with this subtoxic challenge (Morton *et al.*, 2009; Radak *et al.*, 2008; Radak *et al.*, 2001), just as would be expected of a prototypical preconditioning stimulus. Furthermore, exercise may function as a stressor simply by heating the organism (Lim *et al.*, 2008; Whitham and Fortes, 2008), and, thus, leading to mild heat stress, a preconditioning stimulus by itself, as described above. Animal studies demonstrate that physical exercise can reduce behavioral and neuropathological deficits after ischemic stroke (Ding *et al.*, 2005; Hu *et al.*, 2010c; Li *et al.*, 2004), and clinical studies are consistent with these findings. In the animal studies of this phenomenon, mice or rats experience either voluntary exercise such as running in a wheel (Hu *et al.*, 2010c) or forced exercise on a treadmill (Liebelt *et al.*, 2010) prior to ischemic insults. It was observed that a threshold of exercise must be reached to achieve benefits to the ischemic brain. For example, it has been shown that at least 2 or 3 weeks of pre-training on a treadmill is necessary to exert neuroprotection against ischemic stroke in rats (Jia *et al.*, 2009; Liebelt *et al.*, 2010). The nature of exercise-conferred neuroprotection seems to be multisystemic, including maintaining BBB and neurovascular integrity (Ding *et al.*, 2006), reducing cerebral inflammation (Ding *et al.*, 2005), inhibiting neuronal apoptosis (Liebelt *et al.*, 2010) and stimulating angiogenesis/neurogenesis (Brandt *et al.*, 2010).

There has been a great deal of interest in exercise as a protective factor against neurodegeneration. Significant evidence exists that exercise protects the nigrostriatal pathway against DA neuron toxins in animal studies (Petzinger *et al.*, 2010; Zigmond *et al.*, 2009; Zigmond *et al.*, 2012). Only a few of these studies will be highlighted below, with an emphasis on the more detailed studies.

Several studies have shown that exercise (and environmental enrichment) protects DA neurons in an MPTP mouse model. For example, 3 months of access to a running wheel reduced the loss of DA cells in the substantia nigra (Faherty *et al.*, 2005). Like other preconditioning interventions, the effect was dose-dependent, significant only after 2 months of exercise and maximal after 3 months of exercise (Gerecke *et al.*, 2010). Further support for the preconditioning effects of exercise comes from a recent study of chronic MPTP. In this case, 18 weeks of exercise for 1 hr 5 days a week on a treadmill improved balance and movement indicators, mitochondrial function, and effected protection against DA neuronal loss (Lau *et al.*, 2011). Furthermore, 4 weeks of running exercise prevented LPS-induced loss of DA neurons and motor dysfunction (Wu *et al.*, 2011). Not surprisingly, treadmill exercise also promoted angiogenesis in the striatum of MPTP-treated mice (Al-Jarrah *et al.*, 2010). It has been suggested that exercise may act to mitigate cortically-driven hyper-excitability in the basal ganglia (Gerecke *et al.*, 2010; Petzinger *et al.*, 2010). Our preliminary observations with 16–20-year-old female rhesus treated with MPTP indicate both a behavioral and neurobiological protective effect of 3 months of treadmill running (Zigmond *et al.*, 2009; Zigmond *et al.*, 2012). We have also used another model of exercise, casting a forelimb is associated with increased use (or exercise) of the contralateral forelimb, which would otherwise have been reduced by the unilateral toxin (*e.g.*, 6-OHDA) treatment (Tillerson *et al.*, 2001; Tillerson *et al.*, 2002). We found that forelimb casting for 7 days prior to infusion of 6-OHDA in the ipsilateral medial forebrain bundle dramatically reduced behavioral deficits and neurodegeneration (Tillerson *et al.*, 2001; Tillerson *et al.*, 2002).

3.6.2 Caloric restriction—Caloric intake – both excessive and restricted – exerts multiple effects on cellular systems and thus may affect neurological function and susceptibility to injury or degeneration. The role of caloric restriction (CR) in aging protection has now been fairly well established, and is associated with increased antioxidant capacity. The categorization of CR as a preconditioning stimulus is derived from two major concepts.

First, CR presents a spectrum of toxicity; severe CR (fasting, <50% caloric needs) has been found in increased oxidative stress in liver, whereas moderate CR (60–70% caloric needs) increased antioxidant capacity and effectively decreased oxidative stress. Secondly, moderate CR has been associated with increased mitochondrial respiration (Cerqueira *et al.*, 2012; Lin *et al.*, 2002), which increases ROS generation (Turrens, 2003). Whether moderate CR-mediated protection is due to the subsequent upregulation of antioxidant capacity and severe CR leads to overwhelming of such capacity has not yet been explored. A discussion of the mechanistic implications of CR are planned for a later review.

Moderate CR has recently been studied in the protection against global ischemia and neonatal HI. In the neonatal HI model, pregnant dams were subjected to normal diet or moderate or extreme CR, with no resulting differences in the CA1 of the pups or learning tasks in adulthood (Tu *et al.*, 2012). However, following HI, moderate CR significantly decreased brain volume loss and neurovascular damage (Tu *et al.*, 2012). Moderate CR also improved functional recovery following global ischemia in adult rats, despite not significantly improving CA1 cell death (Roberge *et al.*, 2008).

Epidemiological studies suggest that AD is more prevalent in countries with high-calorie diets, and that conditions promoting insulin-resistance and high levels of cholesterol raise the risk for the disease (Kalmijn *et al.*, 1997; Leibson *et al.*, 1997; Notkola *et al.*, 1998). Animals fed high-fat diets were also more vulnerable to some of the behavioral deficits that are observed in transgenic mouse models of AD (Schroeder *et al.*, 2010), and had disturbances in cerebrovascular integrity, synaptic density and reactive gliosis (Pepping *et al.*, 2013). On the other hand, caloric restriction or reducing meal frequency can extend lifespan and protect against various insults, including stroke, in diverse organisms ranging from worms and flies to mammals (Ingram *et al.*, 2007; Mattson *et al.*, 2004; Schroeder *et al.*, 2010; Yu and Mattson, 1999). Early studies extended the protective role of caloric restriction to neurodegenerative disease (Ingram *et al.*, 1987). Caloric restriction attenuated amyloid deposition, phospho-tau levels and neurological dysfunction in transgenic mouse models of AD (Halagappa *et al.*, 2007; Love, 2005; Mouton *et al.*, 2009; Wang *et al.*, 2005; Wu *et al.*, 2008; Zhu *et al.*, 1999), as well as amyloidosis in naturally aged squirrel monkeys (Qin *et al.*, 2006). An influence of caloric restriction on other neurodegenerative conditions, including PD, has also been reported (Duan and Ross, 2010). Intermittent fasting, a non-chronic form of caloric restriction, also demonstrated some benefit in transgenic AD mouse models (Halagappa *et al.*, 2007), as well was neuroprotective against seizures in hippocampal neurons (Duan *et al.*, 2001).

Caloric restriction has been reported to reduce behavioral and/or neurobiological abnormalities in *C. elegans*, rodent, and monkey models of PD (Duan and Mattson, 1999; Holmer *et al.*, 2005; Jadiya *et al.*, 2011; Maswood *et al.*, 2004) and to be efficacious in clinical PD, as well (Logroscino *et al.*, 1996).

It has been argued that restriction of caloric intake to 50–70% of normal is a form of mild stress that exerts preconditioning effects because it activates stress responses (Arumugam *et al.*, 2006; Kouda and Iki, 2010; Mattson *et al.*, 2002; Mattson *et al.*, 2004). Calorie-restricted animals also lower their metabolic rates, which could provide direct protection against damage to DNA and other insults (Duffy *et al.*, 1990; Duffy *et al.*, 1989). Another study found that caloric restriction altered the expression of mammalian genes associated with autophagy and lifespan (Hands *et al.*, 2009; Honjoh and Nishida, 2011; Jia *et al.*, 2004; Jung *et al.*, 2010; Kenyon, 2011; Paradis and Ruvkun, 1998; Tissenbaum and Ruvkun, 1998; Wu *et al.*, 2009), leading to the hypothesis that autophagy takes a “front seat in lifespan extension” (Petrovski and Das, 2010). Since the biggest risk factor for AD is aging, these studies on dietary-induced changes in lifespan may be highly relevant to this form of

neurodegeneration. Finally, it seems likely that the effects of caloric restriction are also related to the fact that calorie-restricted animals tend to exhibit more spontaneous locomotor activity (Duffy *et al.*, 1989; Poehlman *et al.*, 2001), which can be protective in its own right as noted above.

3.7 Subcellular stress – mitochondrial, proteotoxic and ER preconditioning

Subcellular stressors, including proteotoxic stress, ER stress, and mitochondrial stress, can be both endogenously and chemically induced and, under the latter situation, controlled in a dose-dependent manner. Proteotoxic stress arises from a long-term burden of misfolded proteins and proteasome inhibition such as occurs in PD (Braak and Del Tredici, 2009; McNaught *et al.*, 2003). We have shown that long-term proteasome inhibition with sublethal MG132 (2 weeks to 6 months duration of treatment) raised defensive proteins in dopaminergic cells (Leak *et al.*, 2008) and elicited long-term protection against oxidative toxicity from 6-OHDA (Leak et al., 2006). Likewise, induction of ER stress with thapsigargin protected against 6-OHDA in SH-SY5Y cells (Hara *et al.*, 2011). Thus, it appears possible that even chronic subcellular stress might elicit long-term adaptations in chronic neurodegenerative conditions.

Mitochondrial stress represents perhaps the best studied of subcellular stressors in the context of preconditioning. Neurons have particular sensitivity to mitochondrial function, as neuronal function is highly regulated by mitochondrial energetic stores and calcium buffering capacity. In addition, mitochondria are a major source of ROS as byproducts of oxidative phosphorylation. Several compounds that target mitochondrial function when used at subtoxic doses confer a preconditioned state in neurons.

3-NPA is an irreversible inhibitor of the mitochondrial protein succinate dehydrogenase (respiratory Complex II), an enzyme complex that participates in both the citric acid cycle and the electron transport chain, catalyzing the oxidation of succinate to fumarate with the reduction of ubiquinone to ubiquinol (Marini *et al.*, 2008). Inhibition of Complex II is associated with increased production of cellular ROS (Mandavilli *et al.*, 2005) and, in models of acute and chronic toxicity, 3-NPA can produce striatal neural damage similar to that observed in Huntington's disease (Brouillet *et al.*, 2005). However, subtoxic doses of 3-NPA (20 mg/kg) can also induce delayed (1–3 days) ischemic tolerance in rodent brains. 3-NPA significantly decreased neuronal apoptosis and reduced the subsequent neurological deficits and infarct volume within 24 to 72 hours after transient ischemia (Hoshi *et al.*, 2006; Kuroiwa *et al.*, 2000; Pera *et al.*, 2004; Zhu *et al.*, 2004), and also prevented delayed neurological deterioration at 7 days following ischemia (Kuroiwa *et al.*, 2000). The critical threshold in the dose needed to obtain preconditioning versus dosing that does not confer tolerance or causes toxicity is fairly narrow. In a model of 3-NPA preconditioning against permanent focal ischemia in rats, 10–15 mg/kg systemically administered 3 days prior to ischemia effectively afforded neuroprotection, but 5 or 20 mg/kg 3-NPA did not, and 25 mg/kg resulted in significant mortality (Hoshi *et al.*, 2005). The narrowness of the critical threshold for preconditioning and potential strain/ischemic model differences may explain why, in a gerbil model, 3–10 mg/kg 3-NPA did not confer tolerance against global ischemia, whereas another study found that low doses (3–4 mg/kg) were protective (Sugino *et al.*, 1999).

Several studies in both heart and neural settings have suggested that opening of the mitochondrial adenosine triphosphate-sensitive potassium (mtK^+_{ATP}) channel correlated with the preconditioned state (Oldenburg *et al.*, 2002; Ye *et al.*, 2012b), and may, in fact, underlie the tolerant state conferred by 3-NPA (Horiguchi *et al.*, 2003). Taken a step further, chemical preconditioning with compounds that directly open mtK^+_{ATP} have now been identified as providing tolerance to subsequent ischemic challenges.

Diazoxide is a prototypic mtK^+_{ATP} channel opener that causes local relaxation in smooth muscle and vasodilation in the treatment of malignant hypertension or acute hypertension (van Hamersvelt *et al.*, 1996). The preconditioning effects of diazoxide have been well documented in the heart and other organs, and have been further observed in ischemic neural injury (Kis *et al.*, 2003; Lenzser *et al.*, 2005; Rajapakse *et al.*, 2003; Wang *et al.*, 2011b) and glutamate-induced excitotoxicity (Nagy *et al.*, 2004). Administration of 20 or 40 mg/kg diazoxide, i.p., for 3 days prior to global cerebral ischemia conferred partial protection against brain edema in rats (Lenzser *et al.*, 2005). In addition, rapid preconditioning (15–30 minutes prior to injury) was achieved with diazoxide in a model of subdural hematoma (Nakagawa *et al.*, 2013), a model of photochemical thrombotic venous ischemia (Nakagawa *et al.*, 2005) and global cerebral ischemia in gerbils (Wang *et al.*, 2011b). An inhibitor of the mtK+ATP channel abolished the preconditioning effect in both of these models.

Several other small-molecule compounds that target the mtK^+_{ATP} channel have also been demonstrated to confer preconditioning against neural ischemic challenges. BMS-191095 is another mtK^+_{ATP} channel opener that has fewer known side effects compared to diazoxide (Kis *et al.*, 2004). In cultured cortical neurons, BMS-191095 effectively induced neuronal preconditioning against subsequent OGD (Kis *et al.*, 2004). Consistently, BMS-191095 also conferred neuroprotection against subsequent transient focal ischemia in rats (Mayanagi *et al.*, 2007). The non-selective K^+_{ATP} channel opener pinacidil was effective at establishing a preconditioned state against rotenone toxicity in the catecholaminergic PC12 cell line (Tai and Truong, 2002), a model that is somewhat related to PD. Together, these data suggest that mitochondrial K^+_{ATP} channel opening may be an avenue for establishing drug-mediated preconditioning.

4.0 Clinical potential of preconditioning

The extensive literature on preconditioning or tolerance suggests that exposure to a low level of cellular stress can reduce the vulnerability of cells to an otherwise toxic, or challenge, level of stress. As we have noted, the preconditioning stressor can be either the same as the challenge stress or different (termed “cross tolerance”). These phenomena have primarily been the subject of laboratory studies employing either *in vitro* or *in vivo* models. However, the reproducibility of the preconditioning phenomenon has led to studies on its application and significance in clinical settings.

4.1 Incidental preconditioning

Preconditioning may be induced quite naturally by a variety of sublethal insults that the patient experiences. For example, a patient might be exposed to a transient episode of hypoxia, which could result in cells responding to the mild stress by increasing their defenses and thereby raising the level of stress required for subsequent toxicity. This unplanned preconditioning can be termed “incidental,” and may help to explain the slow progression of neurodegenerative diseases such as PD and AD to which we have already alluded. Another example of incidental preconditioning might be the result from neuronal death. As neurons die they are likely to exert a stress on neighboring neurons by stimulating an inflammatory response that could affect healthy bystanders. Whereas that inflammatory response has been proposed as one of the causes of subsequent cell death in neurodegenerative diseases (Qian *et al.*, 2010), it is also possible that cell death can act to precondition the remaining neurons and in this way slow the progression of a disease, much as appears to occur in response to exogenous LPS (see above). There is already some precedence for the belief that preconditioning may occur naturally in humans with vascular disease. For example, humans suffering periods of angina within 7 days of myocardial infarction had lower mortality than those without previous angina (Kloner *et al.*, 1995; Muller *et al.*, 1990). Furthermore, transient ischemic attacks may help precondition the

human brain against subsequent ischemia (Moncayo *et al.*, 2000; Wegener *et al.*, 2004; Weih *et al.*, 1999). Notably, patients with preexisting steno-occlusive vascular disease have reduced subarachnoid hemorrhage-induced cerebral vasospasms (Kim *et al.*, 2012), a correlation that is suggestive of a preconditioned state. Thus, it also seems likely that mild stress can have positive clinical effects through preconditioning. Indeed, as previously discussed, perhaps preconditioning can also explain the seemingly paradoxical negative correlation between tobacco smoking and the incidence of PD (Allam *et al.*, 2004) or the apparently neuroprotective effects of alcohol (see above).

4.2 Purposeful preconditioning

Some forms of preconditioning might actually be purposefully introduced to prevent or retard disease. Epidemiological data suggest that individuals who engage in intense physical exercise are less likely to develop PD (Speelman *et al.*, 2011; Xu *et al.*, 2010), and an inverse correlation between activity levels and risk of developing PD and point to the benefits of exercise programs in improving postural control, balance and mobility (Allen *et al.*, 2010; Archer *et al.*, 2011; Chen *et al.*, 2005; Gobbi *et al.*, 2009; Nocera *et al.*, 2009; Xu *et al.*, 2010). Of course, one cannot rule out the potential confound that humans in the early prodromal phase of PD are less likely to stick to an exercise regime, thereby confounding the data. However, physical exercise is now widely recommended for patients with PD, although research is still required to differentiate between symptomatic effects and the true disease-modifying effects that are suggested by our animal studies, as well as to determine the optimal type and duration of exercise.

Since exercise stimulates mitochondrial respiration and oxidative stress (Di Meo and Venditti, 2001), it seems likely that these effects precondition neurons, reducing their vulnerability to subsequent stress. Caloric restriction or intermittent fasting is another example of preconditioning that might be applied to the clinic, particularly in individuals who are overweight (Mercken *et al.*, 2012). Other examples of stimuli that may help to precondition humans include dietary phytochemicals, anesthetics, and inflammatory mediators.

The concept of purposeful preconditioning with sublethal injury in the clinical setting has been explored primarily in the treatment of cardiac ischemic events (Hausenloy and Yellon, 2011) and may in turn be applicable to the brain during vascular neurosurgery or during surgical procedures with a high risk of cerebral ischemia. Indeed, cardiac surgery itself, such as coronary artery bypass graft surgery, can pose a risk to the brain. Alex and colleagues found some evidence of protection against neuropsychometric dysfunction following coronary artery bypass graft surgery with hyperbaric oxygen preconditioning (Alex *et al.*, 2005). Notably, repeated hyperbaric oxygen preconditioning before on-pump coronary artery bypass graft surgery reduced biochemical markers of neuronal injury (S100B protein and neuron-specific enolase release) and improved clinical outcomes in that it reduced intensive care stay and decreased use of inotropic drugs (Li *et al.*, 2011). Whereas the focus of preconditioning in the cardiac setting logically has rested on cardiac tissue, there is room to explore the effects on cognitive and cerebral functional outcomes.

In addition, surgical procedures on major vascular sites often carry significant risk of secondary cerebral ischemia or cognitive dysfunction. A small clinical study (12 patients) reported that ischemic preconditioning of the proximal artery (2 minutes followed by 30 minutes of reperfusion) prior to clipping of cerebral aneurysms attenuated tissue hypoxia (Chan *et al.*, 2005). Arterial stenoses represent a severe risk for ischemic stroke in humans, and remote limb preconditioning (RIPC) induced by bilateral upper limb ischemia (5 cycles, twice daily over 300 consecutive days) was recently found to significantly decrease the incidence of recurrent stroke in patients with intracranial arterial stenosis (Meng *et al.*,

2012). For carotid stenosis >70%, carotid endarterectomy (CEA) is the preferred treatment, but carries with it significant risk of neurocognitive deficits, which occur in approximately 20% of patients (Heyer *et al.*, 2002). Whether or not RIPC can reduce surgery-related neurocognitive deficits is still questionable (Meybohm *et al.*, 2013), but a pilot clinical trial has suggested that the procedure is safe in CEA patients (Walsh *et al.*, 2010). In addition, one study of patients undergoing cervical decompression surgery found that remote ischemic preconditioning reduced injury markers and improved recovery rates (Hu *et al.*, 2010a). Remote limb preconditioning in patients with subarachnoid hemorrhage was also found to be safe and tolerated in individuals with subarachnoid hemorrhage (Koch *et al.*, 2011), although no studies have yet indicated whether remote preconditioning confers neuroprotection in models of subarachnoid hemorrhage.

An important caveat is that ischemic preconditioning in humans may depend on the patient's tolerance of occlusion of a selected vessel and that the preconditioning ischemia may induce atrioventricular block (Apostolakis *et al.*, 2012). More evidence is thus required before a conclusion on preconditioning safety and efficacy in cardiovascular surgery can be drawn. Nonetheless, the studies so far seem promising and we hold out hope for a positive impact of purposeful preconditioning on the brain during neurosurgery.

4.3 Post-conditioning

Post-conditioning has become a major line of research in recent years and deserves a review in its own right. However, due to its highly relevant clinical applicability, we include mention of it within this section. The evidence for clinical efficacy of preconditioning is less compelling in the case of neurodegenerative disease as contrasted, for example, with timed neurosurgery. Keep and colleagues have discussed the difficulties associated with preconditioning against chronic brain diseases, in part due to a narrow therapeutic window when both stimulus dose and duration are considered (Keep *et al.*, 2010). However, combining the insights gained from preconditioning in surgical or controlled scenarios with emerging post-conditioning settings may help to identify situations advantageous for conditioning-induced neuroprotection.

Most cases of brain damage cannot be anticipated or are relatively rare. For example, PD affects only 1% of those at or above the age of 60, and TBI affects only about 1.5 million Americans each year, or less than 0.5% of the total population. For these reasons it would be extremely valuable if one could apply a conditioning stimulus *after* the initial toxic insult. Although post-conditioning will not protect against the initial damage produced by ischemia, TBI, or the onset of neurodegenerative diseases, a considerable amount of damage occurs in the period immediately after ischemia and TBI, and diseases such as PD and AD develop gradually over many years. Might post-conditioning protect against these sequelae?

Post-conditioning is an area of active investigation. In the case of post-conditioning of ischemia, the majority of the initial work was established in models of myocardial injury. However, recent advances have been made in establishing ischemic post-conditioning models against cerebral ischemia (Zhao, 2009; Zhao *et al.*, 2012). Thus far, the most robust ischemic post-conditioning paradigm involves repeated cycles of rapid reocclusion during the onset of reperfusion (Zhao *et al.*, 2006a). The exact parameters of the cycles appear to be highly sensitive. For example, 3 cycles, but not 10 cycles, of 10-second re-occlusion/30-second reperfusion effectively reduced infarct volume (Gao *et al.*, 2008), and 10 cycles, but not 3 cycles, of 10-second re-occlusion/10-second reperfusion reduced infarct (Gao *et al.*, 2008). In a global ischemic model, rapid preconditioning (administered at the onset of reperfusion) by six cycles of 10-second reperfusion/10-second re-occlusion significantly decreased TUNEL labeling and caspase-3 immunoreactivity 24–72 hours following ischemia (Zhang *et al.*, 2012). Surprisingly, post-conditioning induced 2 days following

moderate (10 minute) global ischemia conferred protection, as well (Burda *et al.*, 2006; Zhou *et al.*, 2011a), but not against slightly more severe ischemic insults (15 minutes global ischemia) (Burda *et al.*, 2006).The sensitivity of these paradigms correlates well with ischemic preconditioning, and with the concept that the "dose" of the preconditioning stimulus is critical to its beneficial effects.

As mentioned above, remote ischemic post-conditioning via femoral artery occlusion for two to three cycles of 10–15 minutes confers neuroprotective effects in models of transient and permanent focal ischemia (Ren *et al.*, 2011; Ren *et al.*, 2008), as well as neonatal HI (Zhou *et al.*, 2011b). The effect of remote ischemic post-conditioning in neonatal HI is interesting, as direct ischemic post-conditioning by common carotid artery did not appear to reduce infarct in neonates following HI (Leger *et al.*, 2012). Remote femoral ischemic preconditioning did not improve outcomes following ICH (Geng *et al.*, 2012).

Post-conditioning against myocardial injury can be elicited by non-ischemic stimuli that overlap with established *pre*conditioning stimuli, including inhalational anesthetics, G-protein coupled receptor ligands such as opioids, adenosine, bradykinin, insulin, erythropoietin, adipocytokines, and statins (Hausenloy and Yellon, 2009, 2011). Likewise, recent studies have included non-ischemic post-conditioning stimuli in neurological injury models. Anesthetics including isoflurane, sevoflurane and propofol have been found to be useful as post-conditioning stimuli. Isoflurane post-conditioning decreased infarct in rat corticostriatal slice cultures subjected to OGD and improved neurological outcomes following transient focal ischemia (Lee *et al.*, 2008). Administration of the anesthetic propofol for 4 hours at the onset of reperfusion led to long-term improvements in recovery following focal ischemia (Wang *et al.*, 2011a). Sevoflurane administered at the onset of reperfusion following focal ischemia reduced infarct and improved memory task performance (Adamczyk *et al.*, 2010; Wang *et al.*, 2010a), and improved neurological outcomes and CA1 cell survival in a model of BCCAO with hypotension (Jeon *et al.*, 2013). Again, the administration necessary for neuroprotection may be highly sensitive. When sevoflurane was administered at later time points following focal ischemia (5 minutes post-reperfusion) or following a model of incomplete ischemia (occlusion of right carotid artery combined with hypotension), protection was lost (Adamczyk *et al.*, 2010; Lee *et al.*, 2010).

Other common preconditioning stimuli are now demonstrating effects when administered in a post-conditioning paradigm. Hypothermia (33°C for 24 hours) following cardiopulmonary resuscitation decreased inflammation in the brain in pigs (Meybohm *et al.*, 2010). Normobaric hyperoxia (intermittent or continuous occurring during the ischemic period) reduced infarct volume and neurological deficits (Liu *et al.*, 2012). Intraventricular injection of LPS or lipooligosaccharide significantly *decreased* inflammation when administered 2 hours following instrastriatal injection of IL-1beta (Bingham *et al.*, 2013; Davis *et al.*, 2005). Hypoxic post-conditioning (three cycles of 15-minutes hypoxia/15-minutes reoxygenation) decreased cell death in cultured neurons exposed to toxic hypoxia (Yao *et al.*, 2011). Taken together, these results suggest that the post-conditioned state appears to be attained in a parallel fashion to the preconditioned state.

4.4 Preconditioning in therapeutic tool development

In addition to possibly promoting the tolerant state, preconditioning of cultured stem cells may provide a critical tool in the use of stem cells as therapeutics. To date, stem cell delivery into infarcted regions has been hampered by poor graft survival and/or differentiation. Although full differentiation and restoration of lost neurons appears unlikely, stem cells could be used as conduits for the release of trophic factors to minimize secondary or prolonged damage. Thus far, the application of preconditioning stem cells for therapeutic purposes in neuronal models *in vivo* has produced some positive results. Hypoxic

preconditioning of MSCs improved cell migration to the ischemic cortex when delivered intranasally 24 hours following transient focal ischemia (Wei *et al.*, 2013). The preconditioned MCSs also reduced ischemic infarct and improved behavioral outcomes better than non-preconditioned MCSs (Wei *et al.*, 2013), and intravenous injection 24 hours following transient focal ischemia led to decreased microglial activity and improved performance on the rotarod (Wei *et al.*, 2012b). Preconditioning of neural stem cells with minocycline or interleukin 6 *in vitro* led to improved graft survival and increased secretion of trophic factors when transplanted into ischemic brains following transient focal ischemia, as well as improved histological and behavioral outcomes (Sakata *et al.*, 2012a; Sakata *et al.*, 2012b). In models of TBI, tail vein injection of MSCs or the MSC culture medium (secretome) alone was found to be protective (Chuang *et al.*, 2012; Kim *et al.*, 2010). Hypoxic preconditioning of MSCs significantly improved the release of trophic factors from cultured MCSs, and improved the behavior and histological outcomes following secretome injection (Chang *et al.*, 2013). These studies have just begun to explore preconditioning in the development of a therapeutic tool, and will likely lead to further interesting applications of preconditioning.

5.0 Caveats: Have we been doing the right experiments?

Despite the promising animal studies outlined above, there remain significant hurdles before preconditioning can be more widely, safely, and effectively translated into the clinic. Limitations to clinical translation include the weaknesses inherent in most experimental studies. For example, although age and gender constitute major risk factors in stroke as in neurodegenerative diseases, studies in models of these conditions typically use young adult or even “teenage” rodents. In fact, aged animals may not precondition as well as do younger animals, which may suggest an important limitation to introducing preconditioning into some clinical situations (He *et al.*, 2005). A second concern relates to strain differences that have been observed in animal studies (Purcell *et al*., 2003), which may indicate that unique genetic characteristics of humans might reduce the generalizability of animal studies to patients, or that subpopulations of humans may respond differently to preconditioning stimuli.

Another consideration is that many clinical trials in human conditions have relied upon end-stage patient populations. However, clinical trials that focus upon milder cases are likely to have a far greater chance of success. Furthermore, common comorbidities such as hypertension, diabetes, and metabolic syndrome may well derail efforts to elicit endogenous neuroprotection because such conditions can reduce the effects of preconditioning, as has been shown in ischemia (Purcell *et al.*, 2003; Wang *et al.*, 2002). As suggested by Keep, Xi, and colleagues, the effects of gender, inflammation, smoking, atherosclerosis, aging, hypertension, and diabetes on human preconditioning all need to be factored into the final equation when assessing clinical outcomes (Keep *et al.*, 2010). Similar to pharmacogenomics, tailoring ischemic preconditioning to the patient population will be critical if preconditioning is ever to become widely used in the clinic. These considerations emphasize the importance of a bidirectional flow of information in translational studies, with clinical trials guiding animal studies as well as the reverse.

As mentioned above, in the case of ischemic preconditioning, questions have been raised because of a narrow therapeutic window (Keep *et al.*, 2010). Both the duration of the preconditioning stimulus and the time between the end of the preconditioning stimulus and the final stroke can have a significant impact on outcome. One of the inherent weaknesses of ischemic preconditioning is that the preconditioning response usually fades within a week or two. Thus, to maintain patients in a preconditioned state, one would have to re-apply the stimulus at set intervals. Whereas this may seem an insurmountable requirement, there is

some evidence that long-term preconditioning is feasible. For example, long-term hypo-perfusion protects against acute focal ischemia, improves motor function, and elicits structural changes in the brain, such as a rise in blood vessel density (Kim *et al.*, 2008). Moreover, dietary phytochemicals that can also precondition, such as resveratrol from grapes, can be ingested over the long term. Similarly, in principle, the preconditioning elicited by exercise can also be maintained chronically. In contrast, induction of direct ischemic preconditioning in humans is necessarily limited to those cases where we know the timing of the ischemic event, such as during interventions, including heart bypass, angioplasty, and neurosurgery. Also, it should be noted that the temporal kinetics of preconditioning efficacy are typically garnered from experimental models and may therefore need to be refined after gathering more clinical data. Because of the limited time window between preconditioning and a subsequent ischemic challenge, ischemic post-conditioning and remote preconditioning have also generated much research interest. Furthermore, remote preconditioning of a limb could perhaps occur at repeated intervals over the long term.

Of course, patients may already be preconditioned by spontaneously occurring transient ischemic attacks (Moncayo *et al.*, 2000; Wegener *et al.*, 2004; Weih *et al.*, 1999), perhaps even sleep apnea, dietary factors, physical activity, and the like. This would mean that purposeful induction of ischemia might push the brain towards a different location on the dose-response or duration-response curve than expected by the medical team. Indeed, this may explain failure in some clinical trials. This may detrimentally affect the safety profile of ischemic preconditioning, which is already of significant concern. Preconditioning stimuli by definition do not elicit cell death because they are sublethal in nature, but they can cause subtle behavioral deficits even in the absence of overt brain injury (Hua *et al.*, 2005). This finding underscores the importance of having patients in clinical trials for preconditioning also undergo cognitive testing. Finally, the lack of consensus in how to image and quantify human strokes is also likely to retard progress.

Despite all these limitations, the failure of many clinical trials of pharmacological interventions that were effective in animals has generated much interest in promoting *endogenous* protection in the human brain. Preconditioning (remote or direct) and post-conditioning still promise to be of clinical utility. Although two studies on transient ischemic attacks in humans did not gather evidence for preconditioning (Della Morte *et al.*, 2008; Johnston, 2004), a meta-analysis of preconditioning in patients undergoing cardiac surgery suggests that cardiac preconditioning reduced ventricular arrhythmias and inotrope requirements, as well as length of intensive care unit stay (Walsh *et al.*, 2008). A second meta-analysis of remote ischemic preconditioning in cardiac surgery patients also gathered evidence of protection (Takagi *et al.*, 2008). Further purposeful preconditioning studies for stroke as well as for other conditions in humans therefore seem warranted despite the limitations outlined here, particularly by changes in lifestyle (*e.g.*, increased exercise and dieting) that are likely to promote incidental conditioning.

In addition to direct or remote preconditioning, another potential use of preconditioning lies in the enhancement of stem cell survival in transplantation. Ischemic preconditioning of MSCs increased graft survival in infarcted heart (Kim *et al.*, 2009a), and oxytocin preconditioning appeared to improve functionality of MSCs related to ischemic protection of cultured rat cardiomyocytes (Noiseux *et al.*, 2012). Diazoxide – a common preconditioning stimulus described above – also improved the survival of MSCs (Suzuki *et al.*, 2010). Hypoxic preconditioning of the neonatal piglet brain led to increased proliferation of cultured SVZ-derived neural stem cells (Ara and De Montpellier, 2013), suggesting that the protective effects observed in tolerance models may be due at least in part to an improved

capacity for repair using preconditioned stem cells. These studies indicate that stem cells respond robustly to preconditioning stimuli, and thus may play a role in tolerance.

6.0 Summary

A central theme that emerges from synthesizing the preconditioning literature above is that preconditioning stimuli, though highly diverse, exert protective effects across a wide range of neurological injury. It is not likely that any one drug by itself will protect neurons from stroke as effectively as nature is able to accomplish through preconditioning. Instead, as has already been argued for many disease states, a “cocktail therapy” approach will likely be needed to mimic the manifold natural defenses that preconditioning elicits. In addition to a cocktail approach, the effect of the drugs will be influenced by lifestyle factors that affect preconditioning and stress, such as exercise, diet, smoking, sleep, social interactions, environmental complexity, and cognitive activity, to name only a few. Studying these factors in conjunction with preconditioning, to see if synergistic protective responses can perhaps be elicited by combining various protective regimens would be worthwhile for future investigations.

Preconditioning is defined as the same process that can be both protective and harmful to neurons. At this point it can be speculated that normal cellular processes that are protective in moderation can turn lethal when engaged in excess of normal homeostatic levels. It is important to note that this dose-dependency is not unlike preconditioning itself, where the dose of the initial stimulus tips the balance in favor of either adaptation or cell death in response to a second challenge. However, one must superimpose on this complexity the cell type, the duration and intensity of the stressful stimulus, the previous history of the cell (exposure to previous stressors), and genetic predispositions to weak or strong preconditioning responses. Given all of these complex variables, the dual nature of many cellular processes is perhaps not a paradox at all. However, much more needs to be understood about the context in which the conditioning stimulus is being applied. Particularly in the case of chronic neurodegenerative disease, it is possible that the application of a mild stress onto chronically stressed cells may exacerbate the disease state, rather than provide a therapy. This then requires advancement of knowledge not only into the mechanism of preconditioning stimuli and disease but also into the response of a diseased cell/tissue/organ to mild stress at different stages of the disease.

Finally, given the observation that the same sets of proteins are often involved in various types of neuroprotection and that the same sets of insults are present in both the ischemic and the chronically degenerating brain, it is likely that the specific mechanisms of ischemic preconditioning can be generalized to neurodegeneration. As argued above, the phenomenon of cross-tolerance – systemic, pharmacological, or remote preconditioning of a peripheral limb – may even protect the brain from neurodegenerative diseases. It is our hope that this review and its companion not only synthesize much of what is known about preconditioning but also generate fresh interest in exploring the brain’s powerful system of natural defenses.

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Abbreviations

MCAO	middle cerebral artery occlusion
2VO	two vessel occlusion
3-NPA	3-Nitropropionic acid
4VO	four vessel occlusion
BCCAO	bilateral common carotid artery occlusion
CSD	cortical spreading depression
6-OHDA	6-hydroxydopamine
Aβ	amyloid-beta
AD	Alzheimer's disease
ATA	atmospheres absolute
BBB	blood brain barrier
DA	dopamine
HBO	hyperbaric oxygen
HI	hypoxia/ischemia
HMGB1	high-mobility group protein box-1
HSP	heat shock proteins
LPS	lipopolysaccharide
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mtK$^{+}_{ATP}$ channel	mitochondrial adenosine triphosphate-sensitive potassium channel
NMDA	N-methyl-D-aspartate
NOS	nitric oxide synthase
OGD	oxygen/glucose deprivation
PD	Parkinson's disease
ROS	reactive oxygen species
SBI	surgical brain injury
TBI	traumatic brain injury
TH	tyrosine hydroxylase
TLR	toll-like receptor
MSCs	mesenchymal stem cells

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Highlights

1. Comprehensive overview of evidence related to neuroprotective effects of preconditioning paradigms in CNS disease models.
2. Thorough discussion of potential clinical significance derived from experimental preconditioning studies
3. Extension from preconditioning neuroprotection in stroke models to non-stroke models, including neurodegenerative diseases.

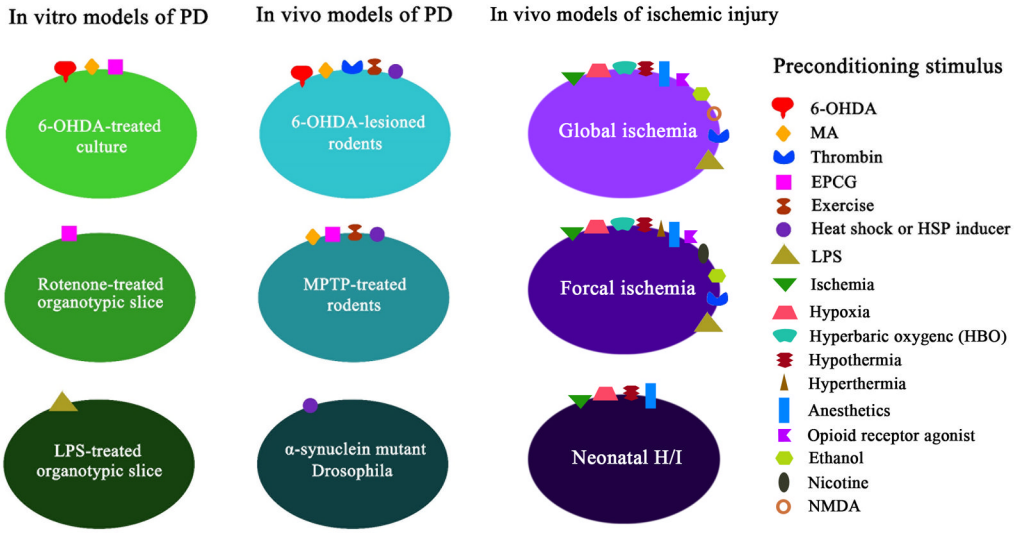

Figure 1. Preconditioning paradigms in different animal and cellular models of brain injury

Several kind of preconditioning stimuli, including neurotoxins, thrombin, EPCG, exercise and HSP inducers, have been reported to establish preconditioning against PD or stroke models. Commonly used PD models for preconditioning studies include 6-OHDA or MPTP-lesioned rodents and 6-OHDA-treated dopaminergic cells. Low-dose endotoxin LPS treatment was also applied to establish preconditioning in an *in vitro* PD model. The major animal models of stroke models used to study preconditioning include focal and global ischemia in adult rodents, and neonatal hypoxia/ischemia.

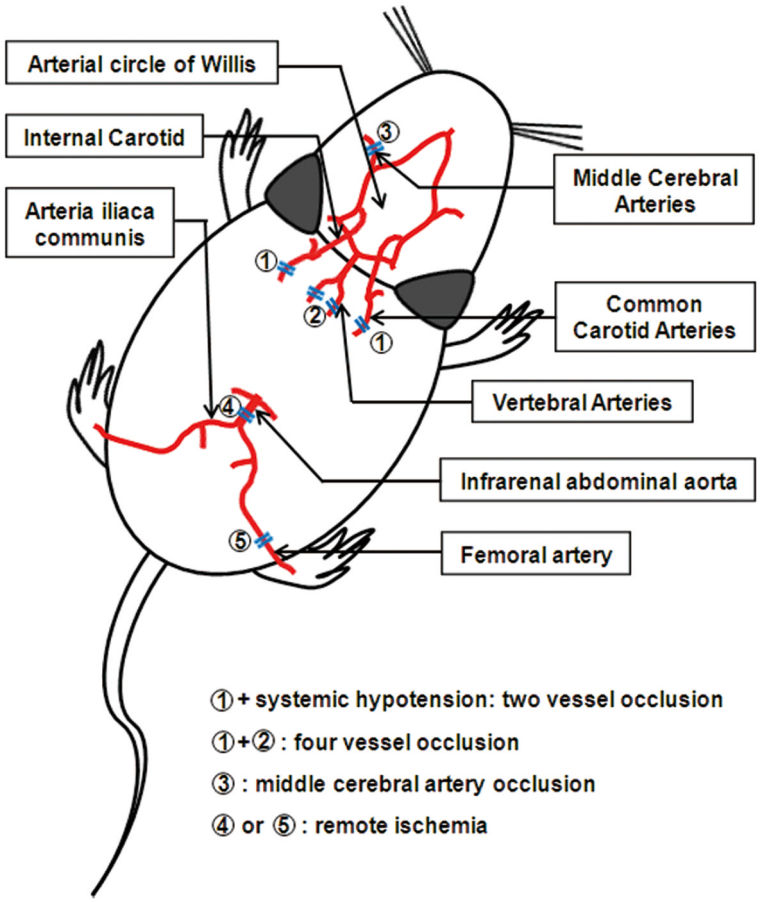

Figure 2. Ischemic paradigms to induce protection against cerebral ischemia in rodents

Ischemic preconditioning has been effectively used to induce protection against severe cerebral ischemia. Four paradigms have been tested in rodent models: 1. Brief occlusion of the bilateral common carotid arteries combined with either vertebral artery coagulation (4VO, ①+②); 2. Brief occlusion of the bilateral common carotid arteries with systemic hypotension (2VO, ①+systemic hypotension); 3. Brief occlusion of one middle cerebral artery (MCAO, ③); 4. Occlusion of unilateral femoral artery or the infrarenal abdominal aorta (remote ischemia, ④ or ⑤).

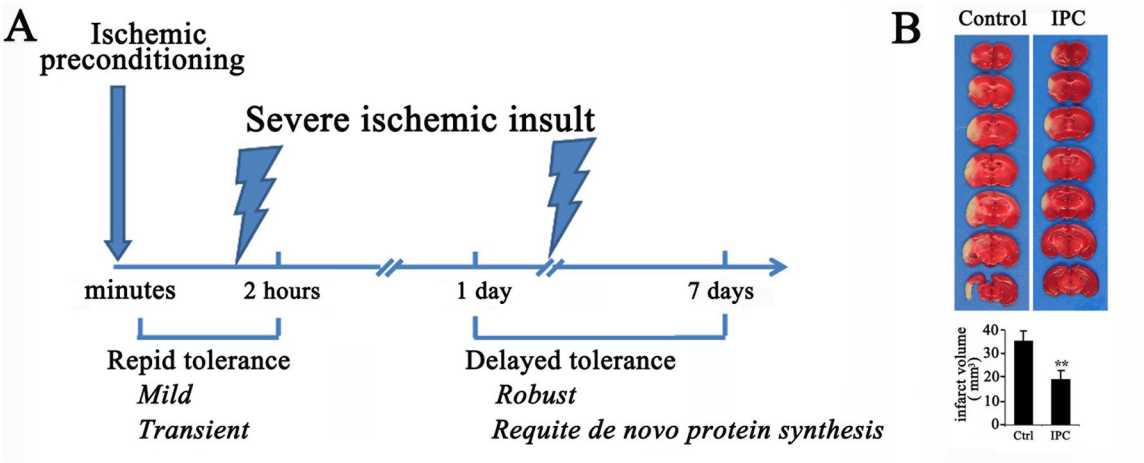

Figure 3. Timeframe for ischemic preconditioning in stroke models

A. There are two time windows of ischemic tolerance that open after a preconditioning stimulus. “Rapid” tolerance develops within minutes and lasts only 1–2 hours after preconditioning. Rapid tolerance typically confers transient and less robust neuroprotection compared to “delayed” tolerance, which develops 1–7 days following preconditioning and requires *de novo* protein synthesis. If the severe ischemic insult occurs between these two windows, no protection is typically elicited. **B.** Protection afforded by delayed ischemic preconditioning. Mice were subjected to ischemic preconditioning (IPC, 12 minutes of MCAO) or sham preconditioning (Control), allowed to recover for 48 h, and then subjected to 60 minutes of MCAO. Infarct size was determined by TTC staining. $P<0.01$.

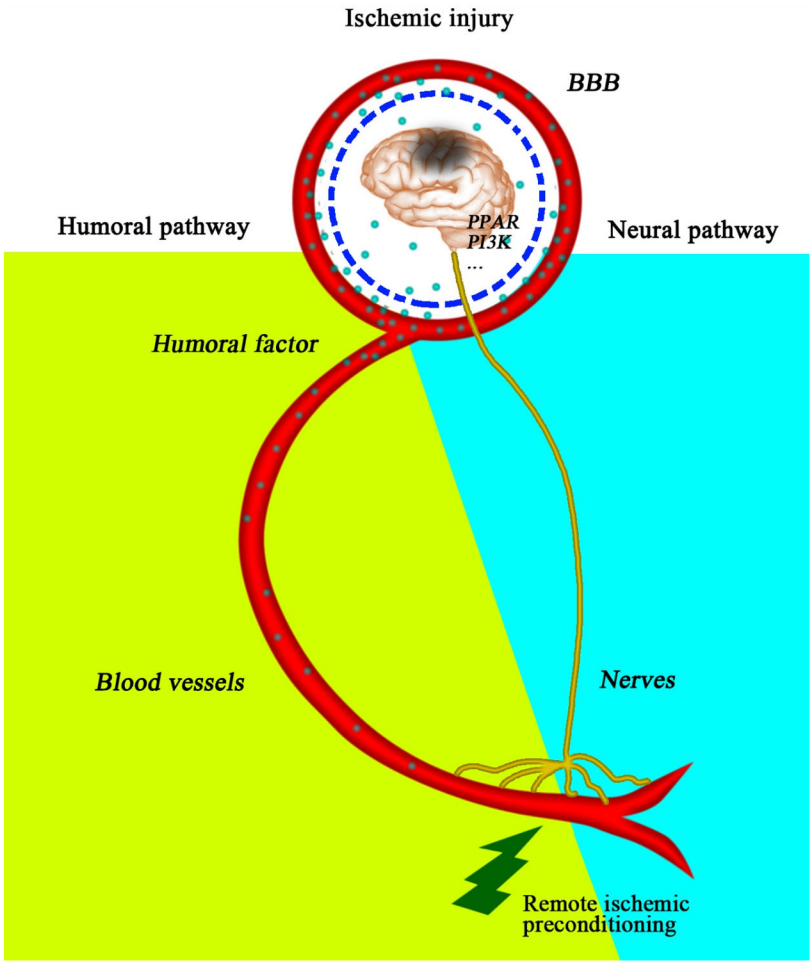

Figure 4. Predicted pathways underlying remote ischemia-induced protection against cerebral ischemic injury

Remote ischemic preconditioning may induce neuroprotection through neural as well as humoral pathways. Humoral effects would necessitate either a breach in the integrity of the BBB or involve brain permeable factors. Both humoral and neural elements may eventually trigger neuroprotective signaling, such as PPAR and PI3K pathways, in ischemic brain.

Table 1

Preconditioning paradigms which induce ischemic tolerance in adults

Preconditioning stimulus		Ischemic models	Time window of protection	References
Ischemia	Cerebral ischemia	Focal, global	1–2 hours, 1–7 days	Cardenas *et al.*, 2002; Liu *et al.*, 1992; Perez-Pinzon *et al.*, 1997; Stagliano *et al.*, 1999; Zhou *et al.*, 2004
	Remote ischemia	Focal	Immediately, 12–48 hours	Malhotra *et al.*, 2011; Ren *et al.*, 2008
Hypoxia	Normobaric hypoxia	Focal, global, OGD	1–3 days	Bickler *et al.*, 2009; Bruer *et al.*, 1997; Fan *et al.*, 2011; Miller *et al.*, 2001; Prass *et al.*, 2003; Zhan *et al.*, 2010
	Chronic low pressure	Focal	7 days	Lin *et al.*, 2003
Hyperbaric oxygen	Hyperbaric oxygen	Focal, global	1–2 days	Cheng *et al.*, 2011; Li *et al.*, 2009; Ostrowski *et al.*, 2008; Wada *et al.*, 1996; Wada *et al.*, 2001
Pharmacological	Inhalational anesthetics	Focal, global, OGD	1–3 hours, 1–3 days	Adamczyk *et al.*, 2010; Bickler and Fahlman, 2009, 2010; Codaccioni *et al.*, 2009; Kitano *et al.*, 2007; Li and Zuo, 2009; Payne *et al.*, 2005; Sigaut *et al.*, 2009; Velly *et al.*, 2009; Wang *et al.*, 2007b; Zheng and Zuo, 2004; Zhu *et al.*, 2010
	Morphine	Focal, global, OGD	30 minutes, 1 day	Liu *et al.*, 2008b; Rehni *et al.*, 2008; Zhao *et al.*, 2006
	Milrinone	Global	1 day	Saklani *et al.*, 2010
	Ethanol	Global	1 day	Wang *et al.*, 2010a; Wang *et al.*, 2007c
	Diazoxide	Global	3 days	Lenzser *et al.*, 2005
	Rosuvastatin	OGD, Spinal cord	3, 10 days	Die *et al.*, 2010; Domoki *et al.*, 2009
Neurotoxic agents	3-NPA	Focal	1–3 days	Hoshi *et al.*, 2006; Kuroiwa *et al.*, 2000; Pera *et al.*, 2004
	NMDA	Focal, OGD	30 minutes, 1 day	Grabb and Choi, 1999; Head *et al.*, 2008; Saleh *et al.*, 2009
	Thrombin	Focal, OGD	1 day	Granziera *et al.*, 2007a
TLR ligands	LPS	Focal, global, OGD	1–7 days	Bordet *et al.*, 2000; Dawson *et al.*, 1999; Furuya *et al.*, 2005; Kunz *et al.*, 2007; Marsh *et al.*, 2009; Rosenzweig *et al.*, 2004; Tasaki *et al.*, 1997; Yu *et al.*, 2010
	Others	Focal, OGD	1–3 days	Hua *et al.*, 2008; Stevens *et al.*, 2008
Temperature	Hypothermia	Focal, global, OGD	3 hours-2 days	Nishio *et al.*, 1999; Nishio *et al.*, 2000; Yuan *et al.*, 2004, 2006; Yunoki *et al.*, 2002
	Hyperthermia	Focal	6 hours-2 days	Xu *et al.*, 2002
Exercise	Exercise	Focal	Pre-exercise for 2–3 weeks	Ding *et al.*, 2005; Hu *et al.*, 2010c; Li *et al.*, 2004a; Liebelt *et al.*, 2010