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Tackling issues in the path toward clinical translation in brain conditioning: Potential offered by nutraceuticals

Joseph S Tauskela, Miled Bourourou[1], Nicolas Blondeau[1]

Abstract:

Brief periods of ischemia have been shown in many experimental setups to provide tolerance against ischemia in multiple organs including the brain, when administered before (preconditioning) or even after (postconditioning) the normally lethal ischemia. In addition to these so-called ischemic conditionings, many pharmacological and natural agents (e.g., chemicals and nutraceuticals) can also act as potent pre- and post-conditioners. Deriving from the original concept of ischemic preconditioning, these various conditioning paradigms may be promising as clinical-stage therapies for prevention of ischemic-related injury, especially stroke. As no proven experimentally identified strategy has translated into clinical success, the experimental induction of neuroprotection using these various conditioning paradigms has raised several questions, even before considering translation to clinical studies in humans. The first aim of the review is to consider key questions on preclinical studies of pre- or post-conditioning modalities including those induced by chemical or nutraceuticals. Second, we make the argument that several key issues can be addressed by a novel concept, nutraceutical preconditioning. Specifically, α-linolenic acid (alpha-linolenic acid [ALA] an omega-3 polyunsaturated fatty acid), contained in plant-derived edible products, is essential in the daily diet, and a body of work has identified ALA as a pre- and post-conditioner of the brain. Nutritional intervention and functional food development are an emerging direction for preventing stroke damage, offering the potential to improving clinical outcomes through activation of the endogenous protective mechanisms known collectively as conditioning.

Keywords:

Brain ischemia, ischemic conditioning, neuroprotection, nutraceutical, stroke

Department of Translational Bioscience, Human Health Therapeutics, National Research Council Canada, Ottawa, Ontario, Canada K1A 0R6, [1]University of Côte d'Azur, Centre National de la Recherche Scientifique, IPMC, UMR7275 Sophia Antipolis, F-06560, France

Address for correspondence:
Dr. Nicolas Blondeau, Institut de Pharmacologie Moléculaire et Cellulaire, UMR7275, Centre National de la Recherche Scienti ique, F-06560, Valbonne, France. E-mail: Blondeau@ipmc.cnrs.fr

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Introduction

Stroke represents a leading cause of death in developed and developing countries. Stroke can be considered as a "brain attack" because of its rapid onset and often devastating consequences. The core lesion is irreversible, leading to functional impairments, paralysis, speech, motor, and cognitive deficits, all of which are associated with long-term disability and frequent psychiatric complications such as dementia, anxiety disorders, and poststroke depression.[1] Stroke has an incidence of approximately 250–400 in 100 000 cases and a mortality rate of around 30%, so stroke remains as a major challenge in modern medicine.[2,3] So far, the most accepted treatment in the clinic to counteract ischemic stroke is tissue type plasminogen activator, but its therapeutic window is restricted to 4.5 h after stroke onset.[4,5] While achieving recanalization using mechanical clot disruption, locally injected thrombolytic agents, or both intra-arterial thrombolysis and mechanical clot removal in cerebral ischemia is also the focus of intense investigations,[6] the lack of

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pharmacological treatment for ischemic stroke resulting from the poor translation of neuroprotective approaches from experimental models to clinical trials accentuates the necessity of considering alternative methods for protecting the brain.

Some scientists see great potential in "brain conditioning," a concept that was first associated with the discovery of preconditioning. The term preconditioning was introduced as early as in the 1960s,[7,8] despite the fact that most attribute the origins of this concept to Murry *et al*. in 1986 in the field of myocardial infarction.[9] Since the original description of this phenomenon, preconditioning has been demonstrated in almost all mammals including humans and has been established in many other tissues including the brain. Preconditioning of the brain by imposing a stressful but nondamaging stimulus is an established experimental modality that triggers a transient adaptive response able to substantially reduce neuronal injury resulting from subsequent exposure to an otherwise harmful stimulus (for review see[10]). A plethora of preclinical evidence has not only established that ischemic "conditioning" is neuroprotective but also that brain preconditioning may be achieved by drugs, environmental stimuli, and natural agents such as nutraceuticals, in numbers that approach previously discovered, acute neuroprotectant candidates. Indeed, the experimental demonstration that certain nutrients can act as "natural preconditioners" to increase brain resistance against stroke provides a basis for the use of dietary supplementation as a natural product "nutraceutical" capable of reducing the incidence of stroke and its deleterious consequences (for review see[11-13]). Being mindful that diet and physical and mental activity may be also viewed as an innate form of preconditioning, the "conditioning" phenomenon appears to be a promising and potent approach to consider translational prospects.

The overarching theme of a wide range of acute neuroprotective treatments in clinical translation has been one of failure. Lessons–learned from these experiences must be utilized in the preclinical evaluation of emergent neuroprotective modalities, and this includes brain conditioning. It is crucial to evaluate preconditioning as any other drug therapy and in particular, to determine its strengths but, perhaps more importantly, to determine weaknesses. In this regard, it can be quite useful to evaluate preconditioning at the level of *in vitro* models of stroke. Such preclinical studies on brain conditioning are not typically incorporated into approaches for clinical translation, due to their reductionist nature, even though proof of concepts, discovery of the pleiotropic nature of numerous preconditioning modalities, and weaknesses is usually first demonstrated at this level.[14] At the *in vivo* stroke model level, as long ago as 1999, a series of criteria from the Stroke Therapy Academic Industry Round Table (STAIR) were recommended to identify neuroprotective agents with the best chance of success in clinical trials. The initial six recommendations were outlined in defining the drug dose–response curve and its time window of efficiency in well-characterized models of both permanent and transient occlusions, spanning rodents to gyrencephalic species, based on blinded and physiologically controlled reproducible studies evaluating histological and functional outcomes assessed acutely and long term.[15] Since then, substantial advances have occurred, and the STAIR preclinical recommendations have been regularly updated.[16] To improve the quality of preclinical studies of purported conditioning therapies toward clinical application, STAIR recommendations should be closely followed in studies to identify robust conditioning modalities to assist in averting continued failures in neuroprotective clinical trials in stroke.

What Exactly is Preconditioning and what Discerns Preconditioning from Drug Pretreatment?

Cerebral ischemic preconditioning exposes the brain to a nonlethal disruptive event, from which follows a temporal window of tolerance so that a subsequent major ischemic insult does not create as much (or no) damage. Transient ischemic attacks are thus able to provoke ischemic tolerance in the brain. Clinical application of preconditioning has usually been viewed as an impracticality since neurons had to be stimulated to a point close to death in order for ischemic preconditioning to induce this state of tolerance; the state of tolerance is limited in duration, requiring a more accurate assessment of when an ischemic attack will occur, which is a very difficult task indeed for the vast majority of strokes. However, it has been now shown that mild preconditioning by certain drugs (chemical preconditioning as opposed to ischemic preconditioning induced by transient ischemic attack) and postconditioning exposures can yield equivalent neuroprotective effects. The rationale is that neurons would not need to be taken to the "brink of death" with some drug inducers. As one example at the mechanistic level, our investigations into preconditioning based on chronic elevations in excitatory synaptic neurotransmission to induce downregulated synaptic scaling is a modality based closer to normal neuronal homeostasis.[14] On a potentially more practical level, we introduce nutraceutical preconditioning in sections below.

Confusion between terminologies and methods used in the conditioning field may also have impeded interest and research efforts. While very nice attempts

to provide conceptual integration and clear definitions of this field were made,[10,17] in view of an increasing publication rate of studies of brain ischemic conditioning, caution is warranted in retaining clear definitions of the several related, but different concepts in the conditioning field will certainly prove to be useful. Drug-induced preconditioning should not be confused with pretreatment. The difference between drug therapy and chemical preconditioning is that in chemical preconditioning, the drug used as preconditioner would reprogram the cell activating broad protective responses (genetic and molecular)[18] whereas an acutely applied drug acts on specific cellular signaling activated by ischemia. In essence, no matter the stimulus, the preconditioner does not simply activate competing protective mechanisms or inhibit injury pathways to counteract the injury cascades triggered by ischemia but actually profoundly improves the resistance of the cell, its perception, and response to ischemia.[10,17,19] In some respects, preconditioning is a sort of "hormesis." This term hormesis is used to describe a dose–response relationship phenomenon characterized by low-dose stimulation and high-dose inhibition, being independent of chemical/physical agents and biological models.[20,21] Nevertheless, the "overall" preconditioning phenomenon extends beyond hormesis: a low level of stress triggers pathways that protect the organs/cells against a subsequent higher level of stress. Hence, preconditioning is an adaptive response, in which the first stimulus influences the effect of a second stressor. Therefore, the terminology of preconditioning/preconditioner should apply to all stressors, drugs, and natural compounds that are able to induce tolerance within a certain time frame; the temporal aspect is important as a delay is required for the transition to a tolerant state, and in fact, the necessity for a delay after preconditioning onset is an essential hallmark of the preconditioning phenomenon. The duration of the delay required may vary depending on the type of preconditioning model employed, particularly in the case of the induction of preconditioning by a molecule (chemical or nutraceutical preconditioning).

The preconditioning effect requires time for genomic changes and protein synthesis, in contrast to the vast majority of drugs intended to exert an acute effect. Thus, chemical preconditioning provokes the creation of protective pathways, which a conventional drug treatment is not designed for. Moreover, preconditioning is pleiotropic by nature, targeting several pathways of ischemic injury, and acting at multiple time points, whereas drug therapy is not designed for this flexibility and must act directly on specific cellular targets to avoid side effects.[22] Preconditioning possesses a "built-in redundancy" in generating a protective effect, which could lead to the identification of a drug therapy able to induce preconditioning. Summarizing, preconditioning genetically reprograms the response of the brain to ischemia and favors cell survival by inducing new protective pathways as opposed to drug therapies, which suppress deleterious effectors produced by ischemia.

In the literature, the terms preconditioning and "exposure" have often been confused while they do not refer to the same idea: preconditioning is the fact of activating the tissue by exposure to a stimulus known as a preconditioner, whereas tolerance is the result of the preconditioning. Tolerance exists when the tissue is protected as if it was "trained" to respond to an otherwise disruptive event such as ischemia.

In the field of "cell conditioning," another experimental protective modality targeting ischemia was also established first in the myocardium in 2003: postexposure to a low intensity ischemic stimulus after a massive (normally lethal) exposure to the same type of stimulus has been shown to be as effective as ischemic preconditioning in reducing infarct size.[23] Postconditioning is different from preconditioning in the way that the conditioning refers to the action of inducing a low degree of stress after exposure to a high level of stress of the same sort. In the field of cerebral protection, ischemic postconditioning, induced by repetitions of transient interruption in blood flow during early reperfusion, also reduces ischemic injury to levels similar to that achieved with preconditioning.[24-26] In addition, both preconditioning and postconditioning seem to activate a common subset of cellular signaling, consistent with findings that protection is not additive when combined, as opposed to being used separately.

The field of brain postconditioning is relatively immature, but given an increasing number of publications, the term postconditioning risks being confused with posttreatment, particularly for the evaluation of nonischemic-based chemical or nutraceutical postconditioners. As for preconditioning, postconditioning differs considerably from posttreatment. The time frame is an important consideration, as "rapid" postconditioning may not face the same translational issues associated with posttreatment. Indeed postconditioning-induced activation of pleiotropic protective pathways could be rapid enough to protect the brain from cell death due to an ability to potentially target temporal and regional complexities of stroke-induced pathologic signaling pathways. In contrast, most posttreatment-based pharmacology is designed to block one step of the neurotoxic ischemic cascade. Moreover, "delayed" postconditioning is of high interest as it could be efficiently applied several days after the ischemia.

Such a treatment can result in blocking not only the deleterious pathways driven by glutamate excitotoxicity (peri-infarct depolarizations) but also more delayed neurotoxicity mechanisms such as inflammation and programmed cell death. As well, postconditioning can enhance restorative mechanisms such as neurotrophic factor production and also favors the preservation of the vasculature to improve the perfusion of brain regions experiencing low rates of perfusion (penumbra), thereby preventing the expansion of the damage.[27,28] Consequently, ischemic postconditioning and remote postconditioning may possess higher translational value than preconditioning counterparts[29] and postconditioning agents hold significant promise as clinical-stage therapies for reducing ischemic damage.

How can Preconditioning Concepts aid in Clinical Translation to the Brain?

The issues and frustration of failures of human clinical trials in ischemia are a common theme in protection of the heart and the brain. Cardioprotection from ischemia still needs improvement, and myocardium conditioning remains a viable option to continue to pursue. Preconditioning and postconditioning applied to myocardial infarction predate these concepts in the brain. Postconditioning may represent an eventual influence for the future management of acute myocardial infarction, based on several clinical studies showing that postconditioning the human myocardium of patients undergoing percutaneous coronary intervention by repetitively inflating and deflating an angioplasty balloon displayed a reduced infarct size.[30,31] Nevertheless, the heterogeneity in procedures in the management of acute myocardial infarction makes the systematic implementation of postconditioning still challenging in real-world scenarios. While such studies assist in anticipating issues likely to arise in translating ischemic cerebral pre- and post-conditioning into therapy, they also strengthen the clinical value of understanding the molecular mechanisms associated with conditioning that will be crucial in the search of agents for pharmacological/chemical/nutraceutical pre- and post-conditioning.

While similar issues may arise when considering cardiac or cerebral preconditioning (or postconditioning) for clinical trials, it is clearly established at the preclinical level that preconditioning is not limited to a cell type, tissue or organ, or to various ischemic pathologies. Epileptic preconditioning offering tolerance to epilepsy follows a similar process: a milder seizure protects the brain from a subsequent more serious seizure.[32,33] Moreover, "cross-tolerance" has also been described in numerous findings, in which preconditioning can trigger resistance to different kinds of subsequent insults.[32] One explanation of this "cross-tolerance phenomenon" is that several insults have some protein degradation-based commonality in the mechanism of neurotoxicity including excitotoxicity, oxidative stress, and apoptosis. Hence, any preconditioner inducing tolerance to either of these components may be broadly effective: various sublethal insults such as epilepsy, endotoxins, anoxia, hyperthermia, and spreading depression were also described to promote tolerance to ischemia and reciprocally.[10,22,32] The benefit of this phenomenon known as "cross-tolerance" against ischemia, epilepsy insults dominated by glutamatergic excitotoxicity was also observed in chemical (by drugs such as adenosine or K_{ATP} channel agonists) and nutraceutical (alpha-linolenic acid [ALA] and certain lysophospholipids) preconditioning.[34-37]

Cerebral preconditioning may thus protect the brain from diverse neurodegenerative challenges. While it is still unclear whether all cellular signaling activated by preconditioning is required for inducing efficient tolerance, any activator of one of the major pathways may suffice to trigger preconditioning. This has opened up research in chemical preconditioning, seeking a molecule that could stimulate the mechanisms of preconditioning triggering cerebral tolerance.

How to Identify a Preconditioner Maximizing the Therapeutic Index and Still Meeting Clinical Trial Requirements?

The identification and development of neuroprotective preconditioners may address issues accounting for why acute neuroprotectants have been a dismal failure in clinical stroke trials. A landmark study concluded that translation of the acute neuroprotectants to clinical trials may have been largely unjustified since drugs given to acute stroke patients performed no better than those drugs for which only animal testing was done, especially based on the long-term and clinically relevant outcomes.[38,39] Thus, historically, experimental studies focused on demonstrating efficacy, but the decision to proceed to clinical trials was not based on demonstrable superiority relative to other candidates. While considerable uncertainty can exist in defining criteria for comparing "best-between-class" neuroprotectants, particularly in view of the uncertainty surrounding the relative importance of various neurotoxic signaling pathways activated by ischemia, it is more difficult to understand why pursuing "best-in-class" agents has not been more aggressively pursued. Using a "lessons-learned" approach and adopting to the field of conditioning, a conceptual consensus and improved experimental

methodologies are required to narrow down the choice of preconditioning agents to be pursued. Indeed, different types of preconditioners, while sometimes producing somewhat dissimilar protection, all prove somewhat efficient, as the neuronal death is lower with any preconditioner used against moderately lethal transient ischemia. This is a consistent finding both *in vivo* and *in vitro*.

We have performed a large body of *in vivo* testing of different forms of preconditioning – ischemic, epileptic, chemical, and nutraceutical – against the ischemic insult (*in vivo* model of 6 min of global ischemia) and concluded that the best-in-class may not be identified in such a model, at least as far as determining which one offers the greatest degree of neuroprotection. Indeed, 6 min global ischemia – considered a lethal but not harsh ischemia - conducted on rats kills ~75% of hippocampal neurons, while preconditioning by sublethal 3 min ischemia preserved almost the entire hippocampus. Similarly, cross-tolerance obtained by epileptic preconditioning also conferred more than 90% of cell survival.[32] Chemical preconditioning by cromakalim induced approximately 70% of protection and by phenylisopropyladenosine resulted in 85% of neuronal survival.[34] Nutraceutical preconditioning with intravenous injection of particular lysophospholipids (lysophosphatidylcholine or lysophosphatidylinositol[37]) or by ALA (the long chain omega-3 fatty acids precursor contained in plant-derived edible products[35,36]) 3 days before the 6 min ischemia offered better protection than chemical preconditioning, similar to the levels observed with ischemic and epileptic preconditioning. Thus, the "brink-of-death" requirement for preconditioners appears to have been circumvented with nutraceuticals, while not causing any loss in tolerance. It will be important to pursue these promising results by further head-to-head comparisons against harsher ischemia.

The necessity of raising awareness of the importance evaluating efficiency of preconditioners is even more striking *in vitro*. Indeed, in rat neuronal cultures subjected to oxygen and glucose deprivation (OGD) capable of killing 50%–75% of neurons, this neurotoxicity was completely ablated by preconditioning by the putative mitochondrial K_{ATP} opener, diazoxide or the antianginal drug, bepridil, but only partially prevented by 3-NPA preconditioning but not by other nonselective K_{ATP} openers, nicorandil or cromakalim, while preconditioning by transient glucose and amino acid deprivation reduced OGD-induced death from about 65% to about 20%.[40-42] In other studies, OGD induced more than 50% death of cultured cortical neurons, with preconditioning by cycloheximide, erythropoietin or hypoxia providing near-complete protection; preconditioning by OGD and heat stress provided intermediate protection.[43-46]

While there is a clear value in comparing preconditioners against the same test insult, to isolate the "best-in-class" preconditioners, it is crucial to test these preconditioners against more realistic lethal OGD insult capable of killing most of the neurons and even harsher conditions.[22] As far as we are aware, no studies had considered this approach, so we devoted considerable attention to comparing preconditioners selected from the literature reported to provide protection against a test OGD insult capable of causing less than total neuronal death (i.e., lethal), except we increased the harshness of this insult in our study [Figure 1]. Among the 43 putative preconditioners we screened, neuroprotection against an OGD insult sufficiently long to kill neurons many times over, achieved by extending the insult duration well past the threshold required to kill all neurons, was observed in 12 cases.[14] This establishes that a "ceiling" of neuroprotection is encountered in many preconditioners facing an extending exposure to OGD (increasing duration from 60 min to 90 min OGD) and confirms the value of comparing preconditioners against the "harsher" test to resolve the most potent preconditioner.

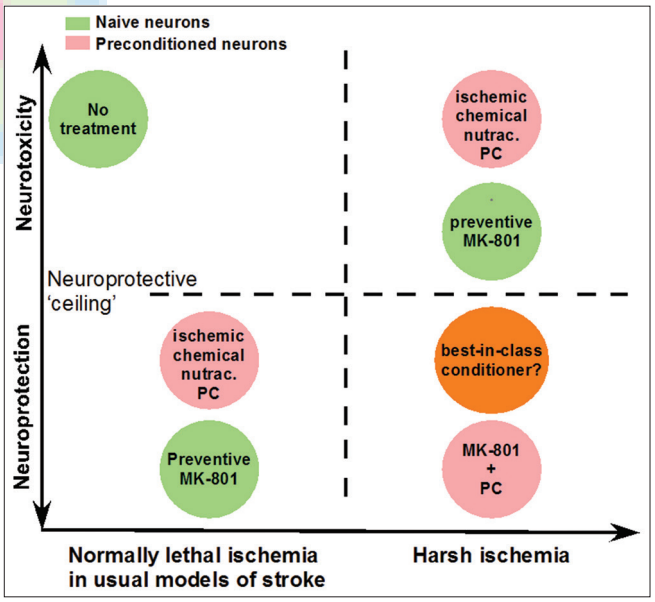

Figure 1: Preconditioning (PC, ischemic, chemical, and nutraceutical) as well as the NMDA receptor antagonist, MK-801, used as an experimental gold-standard neuroprotectant, abolish neurotoxicity usually induced by "normally" lethal conditions (sufficient to kill neurons in most of the experimental paradigms). Preconditioning failed under harsher supralethal ischemic conditions (sufficient to kill neurons many times over), thereby identifying a "ceiling" to such neuroprotective approaches. To circumvent this ceiling, the combination of MK-801 with preconditioning extends the potency of neuroprotection – to various degrees depending on the nature of preconditioning – against supralethal ischemic conditions.[14] This indicates the existence of a neuroprotective "reserve" that should be the focus of our attention and the necessity to explore the future therapy in harsher model of ischemia to identify the best-in-class opportunity

Does Conditioning Adequately Overcome Major Problems Identified in Clinical Stroke Trials, which are Primarily Issues of Efficacy, Side Effects, and Timing of Administration? Are Chemical or Nutraceutical Preconditioning Appropriate to be Used as a Preemptive Protective Approach in Patients at High Risk of Stroke or as Postconditioning Therapy?

In the traditional view of preconditioning, such as by ischemia, cells have to be stressed and taken to the brink of death, so the implementation of preconditioning stimuli is risky. Conceptually, this risk may also exist with chemical preconditioners since many of the compounds used have the capability to be neurotoxic. This is not to mitigate the inherent value of conditioning but to caution that the dose and toxicity of the chemical - and even nutraceutical preconditioners - may be one of the major limitations of the systematic application in human. In the traditional view of preconditioning, another issue of importance is the timing of administration. Medication-induced preconditioning was viewed as limited to patients who already suffered or at elevated risk of ischemic brain injury because of the significant risk of undergoing a more serious stroke. The tolerant state is not permanent, but recent studies are encouraging, showing that preconditioning can be continually performed within a regular time frame to ensure a constant state of tolerance to an impending stroke.[47,48] Therefore, the significance and applicability will be better for a preconditioner which is easy to administer, well tolerated, accessible, inexpensive, and able to induce a prolonged state of tolerance to ischemia. The same criteria apply for postconditioning procedures or postconditioners. Based on these criteria, it is tempting to believe that a new future in brain conditioning may be based on nutraceutical preconditioning.[11]

Nutraceutical is a term coined from nutrition and pharmaceutical fields without any regulatory definition and is commonly used in marketing. It refers to foods or one of its constituents that provides medical or health benefits including the prevention and/or treatment of a disease. We and others have made an attempt to redefine and limit its definition to agents isolated from foods, with efficacy evaluated as medicinal forms, at least at the preclinical level.[11,13,49,50] Such a definition should allow nutraceutical research to being pursued according to (for instance) the STAIR guidelines for stroke investigation.

The concept of nutraceutical preconditioning is supported by our recent discovery that an essential nutrient, ALA which is an essential omega-3 polyunsaturated fatty acid required as part of our daily diet, is an efficient brain pre- and post-conditioner against stroke.[12,13,51] ALA-induced preconditioning is pleiotropic in nature through the activation of multiple endogenous protective transduction pathways, in a similar broad fashion as with ischemic, epileptic, and other well-established chemical preconditioners. As an example, ALA preconditioning induced the expression of the neuroprotective HSP70 heat shock protein, and the expression and activation of the transcription factor nuclear factor-kB, within a similar time frame and neuronal localization shared by ischemic, epileptic, and adenosine and K_{ATP} channel opener preconditioning.[35,36] ALA preconditioning also reprograms the brain, improving its capacity of neuronal plasticity by the induction of transcription and transduction of several genes involved in neurogenesis and synaptogenesis.[52] ALA preconditioning is also multicellular in nature with a capability of targeting not only neurons but also the entire neurovascular unit, by also triggering brain artery vasodilatation.[53] Moreover, the value of nutraceutical preconditioning is increased in considering the timing and administration routes. Taken prophylactically in the diet as is being increasingly recommended to reduce the risk of having a stroke,[54,55] ALA preconditioning reduces stroke-induced brain damage in an experimental murine model of ischemia induced by 60 min of middle carotid artery occlusion (MCAo).[56] Since successful translation of conditioning modalities, as with any other therapeutic opportunities, will depend on the demonstration of efficacy provided at the time of reperfusion and on functional deficits resulting from stroke, we evaluated the effect of ALA postconditioning in the 30 min MCAo model, which is recommended for studying long-term functional outcomes.[57] ALA postconditioning given intravenously during the reperfusion period, as for any given drug that may mimic ischemic postconditioning, minimizes long-term impairment of the spatial learning and memory, evaluated using the Morris water maze test at 2 weeks after surgery, and long-term neuronal damage in the hippocampus, a brain region supporting memory function.[58] Therefore, compared to ischemic or chemical postconditioning approaches, ALA postconditioning appears promising in circumventing apparent major issues in the field - safety, timing, and administration routes.

This novel concept of nutraceutical preconditioning is not restricted to ALA but may, in fact, be extend to other existing or nutraceuticals to be identified. Other compounds extracted from food or plants conforming to the definition of nutraceuticals contain molecules that have already been demonstrated to act as pre- or post-conditioners in *in vivo* or *in vitro* models of ischemic stroke: these include epigallocatechin 3-gallate (green tea), resveratrol (red grapes), quercetin (apples), the organosulfur compounds allicin (garlic), L-sulforaphane (broccoli), phenolic acids such as rosmarinic and carnosic acid (rosemary), and

ginseng.[59,60] While the list is not exhaustive, a clear proof of the capacity of such compounds – whether in functioning as pre- or post-conditioners – may support the concept for nutraceuticals being considered as conditioners of the brain against ischemia. In addition, based on the demonstration that pre- and post-conditionings induce cross-tolerance to trauma, epilepsy, SCI, and neurodegenerative insults, the underlying pleiotropic benefits of nutraceutical preconditioning may also prove beneficial in other neurologic pathologies.

Conclusion

Despite uncertainties in the field of brain preconditioning against cerebral ischemia, nutraceutical pre- and post-conditioning holds significant promise and represents promising fields of investigation. Both pre- and post-conditioning will afford early or delayed protection of individuals against strokes, which would be a major achievement given the severity of brain damage and numerous deaths. Moreover, the concept of nutraceutical preconditioning appears more "natural" than other drug therapies, by creating an overall protective effect with minimization of side effects associated with drug therapies. Furthermore, the concept of using a natural compound to produce a sort of "natural" protection by activating prosurvival signaling is appealing (e.g., stimulating endogenous mechanisms in a way that reprograms the brain to cause protection against ischemia). Nutraceutical preconditioning also acts on several levels as it has multiple targets, contrary to therapeutic drugs, which have a single specific target. This is positive in itself as ischemia induces a complex process of cellular destruction and needs to be addressed on multiple levels. Altogether, such studies foster the interest of this novel concept of brain pre- and post-conditioning by nutraceuticals because such an approach would circumvent most of the issues such as the administration routes and timing issues, which thus far have plagued the preconditioning and neuroprotectant translation to a stroke patient. Overall, the field of nutraceutical conditioning against cerebral ischemia appears promising, justifying more research to be able to fully grasp all its implications, and to potentially lead to human clinical trials if deemed safe and efficient.

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Conflicts of interest

There are no conflicts of interest.

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