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Preconditioning the Brain Moving on to the Next Frontier of Neurotherapeutics

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In December 2011, the 2nd Translational Preconditioning Meeting was held at the University of Miami Miller School of Medicine. The motivation for this meeting arose from the success of the first meeting organized by Dr Guohua Xi and Dr Richard Keep at the University of Michigan, which took place in Ann Arbor in 2009. The main goal of the Miami meeting was to discuss and identify effective strategies to promote the basic science research of ischemic preconditioning for neurological diseases, with the ultimate objective of advancing ischemic preconditioning therapies to clinical use. With this goal in mind, the meeting was divided into clinical and basic science sessions. The discussions were organized in a question-and-answer format. More than 40 national leaders in the field attended the meeting to exchange ideas and brainstorm on ways to translate the basic science of preconditioning to clinical neurology (for a list of attendees and meeting agenda, please see online-only Supplemental Materials). The meeting took place over only 1 day and, given the early stages of development of this workshop, it was felt prudent to limit attendance to United States nationals. The organizers acknowledged this as a shortcoming of the conference that will, hopefully, be remedied in the future as the scope of the meeting expands. The purpose of this editorial is to summarize the key elements that arose out of these discussions in response to several questions posed to the attendants.

The preconditioning phenomenon rests on the basic premise that organisms have developed complex and active defenses to counter adversarial conditions such as starvation and oxygen deprivation.[1,2] From an evolutionary point of view, successful adaptation to environmental stress ensured survival. Triggering these innate defense systems to maintain cellular homeostasis, in the face of noxious injury, is at the root of the preconditioning response, which rests on the central principle that mild forms of stress induce tolerance to an otherwise lethal injury. Thus, it has been shown that preconditioning the brain with brief occlusions of

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a cerebral artery leads to a reduction in infarct size in laboratory models of stroke or cardiac arrest.[3–6]

Many stimuli, such as ischemia, pharmacological agents, hypoxia, hypothermia, and essentially anything that causes cellular stress, induce a preconditioning response.[7] In laboratory models of ischemia, consistent protection from noxious durations of ischemia has been demonstrated in many different organs. Whereas preconditioning is one of the most powerful laboratory anti-ischemic strategies known, its clinical potential has remained unexplored in neurological disorders. Several clinical studies have been completed in cardiac medicine and, for the most part, have shown a diminution of surrogate markers of myocardial ischemia.[8] Only few such studies have been reported concerning neurological conditions, and many questions remain regarding the most favorable clinical setting to test the preconditioning phenomenon, the optimal preconditioning stimulus, and whether a cerebral preconditioning response can even be induced in humans who, in contrast to laboratory animals, are elderly and have multiple comorbidities.[9–11]

A recent PubMed search lists >1160 entries for ischemic preconditioning and brain alone, showing a trend of logarithmic increase in publications in this field over the past few years (1986–2012). Such an abundance of largely preclinical data naturally begets the question of whether the concept of preconditioning is ready to be incorporated into clinical trials. The general sentiment of the attendees was to proceed with clinical studies, prudently. A few preliminary trials already have been completed in neurological disorders and others were in progress. Many preconditioning trials have been performed in cardiac medicine, even though the optimal preconditioning stimulus for myocardial protection also remains poorly characterized. Although all agreed that the past failures of translating neuroprotection to clinical medicine needed to be avoided, applying STAIR-like criteria[12] to preconditioning agents or techniques was controversial and not fully endorsed. It was clear from the discussion that STAIR-like criteria should be tailored specifically to preconditioning and should be different from those developed for neuroprotection, because this phenomenon is clearly distinct from poststroke treatment.

There was a general understanding that such trials needed to be conducted cautiously and needed to be exploratory, with an emphasis on finding suitable biomarkers to measure whether a preconditioning response is even able to be elicited in humans. There was concern that the stress of concomitant disease, advanced age, and widespread medication use in human subjects might modify and even prevent preconditioning. The search for a suitable biomarker also could be the objective of additional laboratory investigations of preconditioning and may be valuable in separating responders to a preconditioning stimulus from nonresponders. An additional focus of preliminary trials would include safety. Although this is readily apparent with pharmaceutical preconditioning and requires drug safety testing and compliance with Food and Drug Administration regulations, it also may apply to the safety of other preconditioning stimuli such as remote preconditioning in which transient ischemia is induced in a limb.

Remote preconditioning, which has been tested in animal models by means of limb ischemia,[13–15] was generally felt to be easily instituted and readily available; however, it

remained uncertain if this is the most effective preconditioning stimulus, with other considerations including volatile anesthetics or pharmacological agents already tested in the clinic for other ailments. Most preconditioning studies in cardiology and some conducted in neurological disorders were performed with remote preconditioning using limb ischemia as a stimulus. Some attendees cautioned against this presently preferred preconditioning technique, just because of its ease of use and ready availability.

In several clinical settings, preconditioning was not felt to be readily achievable. This included stroke and cardiac arrest, in which the unpredictable nature of the event precluded previous treatment. In these types of clinical scenarios, basic science animal models should attempt to determine predictive factors for as yet unpredictable but associated diseases (eg, diabetes, hypertension, smoking, transient ischemic attacks for stroke). In addition, in stroke and cardiac arrest, the evolving strategy of postconditioning might be of greater practical value. Nevertheless, it is not clear yet if preconditioning and postconditioning, although both cytoprotective, are based on the same phenomenon. More appropriate settings include preconditioning before interventions, such as cardiac or coronary artery bypass graft surgery, or after subarachnoid hemorrhage, with the risk of eliciting delayed cerebral ischemia. Similar clinical settings have been proposed in reviews of preconditioning and, interestingly, in the past, for studies of prophylactic neuroprotection.[16–19]

Based on these fruitful and insightful discussions, the afternoon session was dedicated to the basic science of preconditioning, seen from the perspective of the clinical scenarios reviewed in the morning session. The discussion led to the suggestion that new STAIR-like criteria should be developed and tailored to the preconditioning or postconditioning paradigms. Although these criteria may require further development, several suggestions emerged, such as proper animal models, which closely simulate the clinical condition to be studied. For example, if subarachnoid hemorrhage is the clinical target and remote preconditioning is used for neuroprotection, then appropriate animal models should be used for preclinical design and its mechanisms should be defined before clinical trial design. Another proposal suggested that both basic science and clinical grant applications require the participation of both basic scientists and clinicians to better-translate basic science research on preconditioning into the clinic.

There was a discussion on whether investigators in the field should design clinical trials immediately if a drug (eg, pharmacological preconditioning) is found to be protective against stroke rather than study its mechanisms of action. This was controversial because there are many examples in which the prompt bypass of a rigorous definition of mechanisms of action of a given drug has failed to promote neuroprotection for stroke and other neurological diseases.

Another point that came across in the afternoon session was that on careful review of the literature, it was clear that almost anything that caused some degree of stress induces ischemic tolerance. This fact is puzzling. Why would volatile anesthetics have such similar effects as pharmacological or remote preconditioning? It is highly unlikely that the mechanisms are the same. This issue raised an active discussion that clearly suggests the need for additional investigations on the topic.

In conclusion, the success of the meeting was in the exchange of ideas and interest to continue to investigate the therapeutic potential of the preconditioning phenomenon. Great enthusiasm with the format of the meeting was expressed by most participants. It was generally felt that more time was needed to discuss key issues. By expanding the duration of the workshop in the future, it would be more feasible to attract leaders in the field from around the world. Passing on the torch, Dr John Zhang from Loma Linda University will lead the effort to organize the 3rd Translational Preconditioning Meeting in 2013, which will be co-organized by Dr Gabriel Haddad from University of California San Diego and Dr Nestor Gonzalez from University of California Los Angeles. In addition, it was also felt that these discussions should continue. It was suggested to establish a blog in which investigators in the field can maintain an active participation in these issues. Although this is not yet established, Dr John Zhang suggested continuing the discussion in a blog at NeuroNetwork (http://www.theneuronetwork.com).

Finally, the authors of this editorial acknowledge that not everything discussed in the meeting is presented here. Only the most salient ideas are summarized. We also recognize that the points discussed here do not necessarily reflect the opinion of all the participants. Many of the issues addressed will be peer-reviewed in articles submitted to a special issue of the journal *Translational Stroke Research* that is dedicated to proceedings of this meeting.

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