

Channels of Preconditioning

Potassium Drain that Protects the Brain

PERIOPERATIVE stroke and/or neurologic dysfunction, accompanied with significant mortality or incapacitating sequelae, not infrequently complicates cardiac, vascular, or neurologic surgery. Indeed, a recent study in ANESTHESIOLOGY showed a remarkably high incidence of perioperative stroke, greater than 1 per 200 such patients,[1] even after noncardiac or nonvascular surgery. Therefore, clinical strategies aimed at either protecting the brain or enhancing its tolerance to ischemic or anoxic insults are worthwhile from the clinical point of view. In an article published in this issue of the Journal, Bantel *et al.*[2] provide a fascinating preclinical series of studies examining the mechanisms of brain protection by anesthetics.

A particular mechanism of tolerance, by which cells become resistant to subsequent lethal events, is mediated by *preconditioning*, and within this context *ischemic preconditioning* develops when brief, sublethal episodes of ischemia activate endogenous protective mechanisms rendering organs resistant to subsequent, more severe ischemic events.[3] Mimicking ischemic preconditioning, *anesthetic preconditioning* is a similar protective mechanism whereby exposure to an inhaled anesthetic also renders a tissue tolerant to a subsequent ischemic insult. Anesthetic preconditioning for myocardial protection has been studied extensively and shown to be relevant in clinical situations as well.[4] Likewise, any benefits conferred by preconditioning strategies, including anesthetics, may be of value for protecting the brain or any neurologic tissue, even though such strategies have not been investigated in the brain as extensively as in the heart. However, several questions have been raised regarding feasibility of neuronal preconditioning, practical aspects, and its possible impact on perioperative outcome, especially after procedures with high incidence of perioperative stroke and adverse neuropsychiatric sequelae.[5–7]

Is neuronal preconditioning feasible? Several preclinical and clinical studies positively indicate that neurons can also be preconditioned against ischemia. Mechanisms of neuronal preconditioning have been recently reviewed by Gidday[8] and Obrenovitch.[9] It is evident that even without preconditioning, neurons naturally recruit endogenous countermeasures against ischemic injury; however, adaptive responses mobilized as a response to preconditioning are of a significantly different nature. The preconditioning cascade includes stimuli that, *via* sensors and transducers, activate downstream transcription factors, ultimately modulating gene expression. Then, novel proteins may act as effectors enhancing the resistance of neurons to ischemia, and/or preexisting proteins may be modulated by posttranslational modification acting as effectors, as well. By these cascades, a latent neuroprotective phenotype is established before ischemia, which, together with other specific cellular responses, eventually results in a reprogrammed brain or other neuronal tissue, capable of tolerating ischemia better.

The classic preconditioning stimuli are brief, sublethal episodes of ischemia, but other agents can trigger the preconditioning cascade in neurons, as well. These include molecules (such as glutamate, reactive oxygen species, inflammatory cytokines, and caspases) that in high concentrations are deleterious, but at lower concentrations initiate adaptive cascades. Of clinical interest is also the fact that drugs, such as anesthetics[6,10,11] or the adenosine triphosphate–sensitive potassium (K_{ATP}) channel openers,[12] may act on and be recognized by molecular sensors in a fashion that initiates the preconditioning signaling cascade. Molecular sensors include a variety of neurotransmitters, neuromodulators, cytokine receptors, ion channels, and redox-sensitive enzymes.[8] Of particular clinical and pharmacologic interest are the K_{ATP} channels, which, in addition to their role as sensors, may also have a parallel role as effectors of the phenotype that provides resistance to ischemia.[12]

Can anesthetics precondition the brain against ischemia? In the heart, preconditioning with volatile anesthetics mimics ischemic preconditioning in a fashion that involves K_{ATP} channel activation. The same is true in the brain: Preconditioning with inhaled anesthetics protects neurons from ischemia-induced death as well.[10,13,14] However, it is not really clear what preconditioning of the central nervous system is and how beneficial it really is. Could it simply be a period of hibernation? This would be beneficial in promoting survival of critical patients, but would not be beneficial for the quality of life. Although inhaled anesthetics may not be practically applicable in all clinical settings wherein neuroprotection is desirable, they nevertheless may be suitably used to optimize perioperative outcome after

This Editorial View accompanies the following article: Bantel C, Maze M, Trapp S: Neuronal preconditioning by inhalational anesthetics: Evidence for the role of plasmalemmal adenosine triphosphate–sensitive potassium channels. ANESTHESIOLOGY 2009; 110:986–95.

Accepted for publication December 22, 2008. Supported in part by National Institutes of Health grant Nos. GM066730 and HL034708 (to Dr. Bosnjak) and National Institute for Neurological Disorders and Stroke S049420A (to Dr. Sarantopoulos), Bethesda, Maryland. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

surgical procedures associated with high-risk adverse neurologic sequelae. Studies of pertinent mechanisms may also lead to identification of novel and clinically more feasible means of neuronal preconditioning in clinical settings.[10]

Isoflurane, the most studied inhaled anesthetic, confers ischemic preconditioning in brain neurons of various species[10,13,14] in an age-specific and sex-specific fashion.[15] Preconditioning effects have also been shown for halothane[10,13,14] and sevoflurane.[16] In this issue of ANESTHESIOLOGY, Bantel *et al.*[2] provide further evidence supporting the role of plasmalemmal K_{ATP} channels as mediators and possibly effectors of neuronal preconditioning induced by the novel anesthetic gas xenon. Their study is also indicative of the multiple, diverse mechanisms by which neuronal preconditioning is attained. They show that xenon and sevoflurane at clinical concentrations precondition neurons, but *via* different pathways. Only xenon induced preconditioning *via* opening of plasmalemmal K_{ATP} channels; sevoflurane did not. Because K_{ATP} channels are proven "metabolic sensors," the agents activating these channels might initiate the preconditioning response in a way that most closely resembles that of the "physiologic" ischemic preconditioning. The next task is to elucidate which signal it is that the K_{ATP} channels generate to bring about longer-lasting cellular changes.

Many studies do not distinguish between mitochondrial K_{ATP} channels, neuronal K_{ATP} channels, and cardiac or vascular muscle K_{ATP} channels. These are clearly separate molecular entities with their own specific, but overlapping, pharmacologic profile. Bantel *et al.*[2] attempted to unambiguously distinguish between these, and one would hope that this will become a recurrent theme in future studies of neuronal preconditioning. K_{ATP} channels are octamers, consisting of four pore-forming (Kir6.x) coupled to four regulatory sulfonylurea receptor subunits (SURx). Three tissue-specific subtypes have been identified: Kir6.2/SUR1 (β-cell/neuroendocrine/neuronal), Kir6.2/SUR2A (cardiac and skeletal muscle type), and Kir6.2 (or 6.1)/SUR2B in smooth muscles.[17,18] In contrast to other types, neuronal K_{ATP} channels remain relatively underinvestigated, and their roles remain less well understood. Plasmalemmal Kir6.2/SUR1 channels are present in the brain, in areas such as hypothalamus, forebrain, and striatum.[12] These channels are activated by adenosine diphosphate, in the presence of Mg^{2+}, and are inhibited by high or physiologic intracellular adenosine triphosphate concentrations.[12,19] Oxygen depletion leads to anoxic depolarization, whereby opening of voltage-gated channels results in Ca^{2+} overload activating lethal cascades and promoting cell death.[12] However, parallel activation of K_{ATP} channels (from reduction of intracellular adenosine triphosphate) produces outward K^+ flux, membrane hyperpolarization, and reduced excitability. Concomitant limitation of transmembrane ionic fluxes results in energy conservation mainly by decreased activity of ion pumps that consume approximately half of the total energy used by the brain.[12] Activation of K_{ATP} channels also reduces excitatory neurotransmission, including glutamate release, thus limiting the extent of excitotoxic injury. The protective effects of K_{ATP} channels against neuronal death from ischemic insults have been confirmed by a number of studies,[18,20] including observations in mutant mice lacking Kir6.2.[19]

Mitochondrial K_{ATP} channels are also inhibited by adenosine triphosphate and mediate cytoprotective actions and preconditioning against cerebral and cardiac ischemia.[12] Both types of channels may act in a coordinated fashion,[12] but Bantel *et al.*[2] showed that this was not the case with xenon. Nevertheless, xenon, in contrast to halogenated anesthetics, at clinical concentrations independently enhanced plasmalemmal K_{ATP} channel activity by 50%, which is sufficient to trigger preconditioning. These findings should be verified in more complex systems: *e.g.*, is xenon preconditioning, but not sevoflurane preconditioning, lost in K_{ATP} knockout animals? The authors also implied that effective preconditioning may involve more than one diverse pathway in which K_{ATP} channels may or may not participate. These pathways may produce neuroprotection by converging to the same downstream effectors,[8] which will require further investigation. Further investigations are also needed to examine the role of K_{ATP} channels as mediators of preconditioning and protection against ischemic or anoxic injury in the spinal cord,[21] retina,[22] and peripheral nerves.[23]

Although there is no doubt that xenon may limit ischemic neuronal injury *via* a preconditioning effect,[24,25] controversy arises from the notion that it may exacerbate ischemic damage to brain neurons and aggravate neurologic sequelae by combined cardiopulmonary bypass and cerebral air emboli.[26] Therefore, further work is needed to ultimately document its efficacy and safety before indisputable, widespread acceptance for clinical use as a preconditioning and neuroprotective agent. The findings by Bantel *et al.*[2] are important and might stimulate the future investigations to combine systems-, cellular-, and molecular-level approaches. Clearly, in this challenging task, there is a need for more cross-talk between the different approaches taken by the large number of independent findings to make lasting contributions.

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