

## 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,<sup>1</sup> 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.*<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5-7</sup>

Is neuronal preconditioning feasible? Several preclinical and clinical studies positively indicate that neurons can also be preconditioned against ischemia. Mecha-

nisms of neuronal preconditioning have been recently reviewed by Gidday<sup>8</sup> and Obrenovitch.<sup>9</sup> 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<sup>6,10,11</sup> or the adenosine triphosphate-sensitive potassium ( $K_{ATP}$ ) channel openers,<sup>12</sup> 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.<sup>8</sup> 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.<sup>12</sup>

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.<sup>10,13,14</sup> 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

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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.<sup>10</sup>

Isoflurane, the most studied inhaled anesthetic, confers ischemic preconditioning in brain neurons of various species<sup>10,13,14</sup> in an age-specific and sex-specific fashion.<sup>15</sup> Preconditioning effects have also been shown for halothane<sup>10,13,14</sup> and sevoflurane.<sup>16</sup> In this issue of *ANESTHESIOLOGY*, Bantel *et al.*<sup>2</sup> 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.*<sup>2</sup> 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 ( $\beta$ -cell/neuroendocrine/neuronal), Kir6.2/SUR2A (cardiac and skeletal muscle type), and Kir6.2 (or 6.1)/SUR2B in smooth muscles.<sup>17,18</sup> 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.<sup>12</sup> These channels are activated by adenosine diphosphate, in the presence of  $Mg^{2+}$ , and are inhibited by high or physiologic intracellular adenosine triphosphate concentrations.<sup>12,19</sup> Oxygen depletion leads to anoxic depolarization, whereby opening of voltage-gated channels results in  $Ca^{2+}$  overload activating lethal cascades and promoting cell death.<sup>12</sup> 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.<sup>12</sup> 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,<sup>18,20</sup> including observations in mutant mice lacking Kir6.2.<sup>19</sup>

Mitochondrial  $K_{ATP}$  channels are also inhibited by adenosine triphosphate and mediate cytoprotective actions and preconditioning against cerebral and cardiac ischemia.<sup>12</sup> Both types of channels may act in a coordinated fashion,<sup>12</sup> but Bantel *et al.*<sup>2</sup> 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,<sup>8</sup> 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,<sup>21</sup> retina,<sup>22</sup> and peripheral nerves.<sup>23</sup>

Although there is no doubt that xenon may limit ischemic neuronal injury *via* a preconditioning effect,<sup>24,25</sup> 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.<sup>26</sup> 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.*<sup>2</sup> 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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## References

1. Bateman BT, Schumacher HC, Wang S, Shaefi S, Berman MF: Perioperative acute ischemic stroke in noncardiac and nonvascular surgery: Incidence, risk factors, and outcomes. *ANESTHESIOLOGY* 2009; 110:231-8

2. 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
3. Murry CE, Jennings RB, Reimer KA: Preconditioning with ischemia: A delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; 74:1124-36
4. Julier K, da Silva R, Garcia C, Bestmann L, Frascarolo P, Zollinger A, Chassot PG, Schmid ER, Turina MI, von Segesser LK, Pasch T, Spahn DR, Zaugg M: Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: A double-blinded, placebo-controlled, multicenter study. *ANESTHESIOLOGY* 2003; 98:1315-27
5. Hans P, Bonhomme V: The rationale for perioperative brain protection. *Eur J Anaesth* 2004; 21:1-5
6. Warltier DC, Kersten JR, Pagel PS, Gross GJ, Todd MM: Anesthetic preconditioning: Serendipity and science. *ANESTHESIOLOGY* 2002; 97:1-3
7. Warner DS: Perioperative neuroprotection: Are we asking the right questions? *Anesth Analg* 2004; 98:563-5
8. Gidday JM: Cerebral preconditioning and ischaemic tolerance. *Nat Rev Neurosci* 2006; 7:437-48
9. Obrenovitch TP: Molecular physiology of preconditioning-induced brain tolerance to ischemia. *Physiol Rev* 2008; 88:211-47
10. Kitano H, Kirsch JR, Hurn PD, Murphy SJ: Inhalational anesthetics as neuroprotectants or chemical preconditioning agents in ischemic brain. *J Cereb Blood Flow Metab* 2007; 27:1108-28
11. Stadnicka A, Marinovic J, Ljubkovic M, Bienengraeber MW, Bosnjak ZJ: Volatile anesthetic-induced cardiac preconditioning. *J Anesth* 2007; 21:212-9
12. Soundarapandian MM, Zhong X, Peng L, Wu D, Lu Y: Role of  $K_{ATP}$  channels in protection against neuronal excitatory insults. *J Neurochem* 2007; 103:1721-9
13. Kapinya KJ, Lowl D, Futterer C, Maurer M, Waschke KF, Isaev NK, Dirnagl U: Tolerance against ischemic neuronal injury can be induced by volatile anesthetics and is inducible NO synthase dependent. *Stroke* 2002; 33:1889-98
14. Wang L, Traystman RJ, Murphy SJ: Inhalational anesthetics as preconditioning agents in ischemic brain. *Curr Opin Pharmacol* 2008; 8:104-10
15. Kitano H, Young JM, Cheng J, Wang L, Hurn PD, Murphy SJ: Gender-specific response to isoflurane preconditioning in focal cerebral ischemia. *J Cereb Blood Flow Metab* 2007; 27:1377-86
16. Payne RS, Akca O, Roewer N, Schurr A, Kehl F: Sevoflurane-induced preconditioning protects against cerebral ischemic neuronal damage in rats. *Brain Res* 2005; 1034:147-52
17. Aguilar-Bryan L, Bryan J: Molecular biology of adenosine triphosphate-sensitive potassium channels. *Endocr Rev* 1999; 20:101-35
18. Liss B, Roeper J: Molecular physiology of neuronal  $K_{ATP}$  channels. *Mol Membr Biol* 2001; 18:117-27
19. Sun HS, Feng ZP, Miki T, Seino S, French RJ: Enhanced neuronal damage after ischemic insults in mice lacking Kir6.2-containing ATP-sensitive  $K^+$  channels. *J Neurophysiol* 2006; 95:2590-601
20. Ballanyi K: Protective role of neuronal  $K_{ATP}$  channels in brain hypoxia. *J Exp Biol* 2004; 207:3201-12
21. Caparrelli DJ, Cattaneo SM II, Bethea BT, Shake JG, Eberhart C, Blue ME, Marban E, Johnston MV, Baumgartner WA, Gott VL: Pharmacological preconditioning ameliorates neurological injury in a model of spinal cord ischemia. *Ann Thorac Surg* 2002; 74:838-44
22. Ettaiche M, Heurteaux C, Blondeau N, Borsotto M, Tinel N, Lazdunski M: ATP-sensitive potassium channels ( $K_{ATP}$ ) in retina: A key role for delayed ischemic tolerance. *Brain Res* 2001; 890:118-29
23. Hoke A: Neuroprotection in the peripheral nervous system: Rationale for more effective therapies. *Arch Neurol* 2006; 63:1681-5
24. Ma D, Hossain M, Pettek GK, Luo Y, Lim T, Akimov S, Sanders RD, Franks NP, Maze M: Xenon preconditioning reduces brain damage from neonatal asphyxia in rats. *J Cereb Blood Flow Metab* 2006; 26:199-208
25. Wilhelm S, Ma D, Maze M, Franks NP: Effects of xenon on *in vitro* and *in vivo* models of neuronal injury. *ANESTHESIOLOGY* 2002; 96:1485-91
26. Jungwirth B, Gordan L, Blobner M, Schmehl W, Kochs EF, Mackensen GB: Xenon impairs neurocognitive and histologic outcome after cardiopulmonary bypass combined with cerebral air embolism in rats. *ANESTHESIOLOGY* 2006; 104:770-6