

## The surprising role of vascular $K_{ATP}$ channels in vasospastic angina

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### Commentary

The golden age of single-channel electrophysiology was punctuated by the discovery of a curious class of potassium-selective channels in the surface membranes of heart cells (1, 2). These channels, silent under normal metabolic conditions, become robustly active when submembrane ATP is depleted. The opening of such  $K_{ATP}$  channels was soon recognized to underlie the loss of cellular excitability during metabolic stress (3, 4) and (later, in an in vivo correlate) to mediate the so-called ST segment elevation, an electrocardiographic change diagnostic of transmural injury during prolonged coronary ischemia (5). While these channels were discovered in heart cells, they are broadly-distributed throughout the body; their most obvious physiological role is in the pancreas, where they transduce changes in glucose concentration into alterations of  $\beta$  cell excitation and insulin secretion (6). Ironically, the role of  $K_{ATP}$  channels in the heart, where they were first discovered, remains mysterious. In the present issue and in recent work published elsewhere, new surprises emerge regarding the identities and the roles of  $K_{ATP}$  channels in the vasculature. The general molecular structure of  $K_{ATP}$  channels was clarified by the pioneering work of the Bryan, Aguilar-Bryan (7) and Seino laboratories (8).  $K_{ATP}$  channels turn out to be complex hetero-octamers of four subunits encoded by sulfonylurea receptor (Sur) genes, surrounding a central pore made up of four Kir6-encoded K channel [...]

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The golden age of single-channel electrophysiology was punctuated by the discovery of a curious class of potassium-selective channels in the surface membranes of heart cells (1, 2). These channels, silent under normal metabolic conditions, become robustly active when submembrane ATP is depleted. The opening of such  $K_{ATP}$  channels was soon recognized to underlie the loss of cellular excitability during metabolic stress (3, 4) and (later, in an in vivo correlate) to mediate the so-called ST segment elevation, an electrocardiographic change diagnostic of transmural injury during prolonged coronary ischemia (5). While these channels were discovered in heart cells, they are broadly-distributed throughout the body; their most obvious physiological role is in the pancreas, where they transduce changes in glucose concentration into alterations of  $\beta$  cell excitation and insulin secretion (6). Ironically, the role of  $K_{ATP}$  channels in the heart, where they were first discovered, remains mysterious. In the present issue and in recent work published elsewhere, new surprises emerge regarding the identities and the roles of  $K_{ATP}$  channels in the vasculature.

The general molecular structure of  $K_{ATP}$  channels was clarified by the pioneering work of the Bryan, Aguilar-Bryan (7) and Seino laboratories (8).  $K_{ATP}$  channels turn out to be complex hetero-octamers of four subunits encoded by sulfonyleurea receptor (*Sur*) genes, surrounding a central pore made up of four *Kir6*-encoded K channel subunits (9). Different tissues express different permutations of the three possible Surs (*Sur1*, and the *Sur2* splice variants, *Sur2A* and *Sur2B*) and two pore-forming subunits (*Kir6.1* and *Kir6.2*). The conventional surface  $K_{ATP}$  channels in the heart are formed by *Sur2* and *Kir6.2*, whereas those in pancreatic  $\beta$  cells

consist of *Sur1* and *Kir6.2*.  $K_{ATP}$  channels have a rich pharmacology (10), including a number of venerable vasodilators (e.g., the  $K_{ATP}$  channel agonists diazoxide and minoxidil) and anti-diabetic agents (notably the  $K_{ATP}$  channel blocker glybenclamide), which were in clinical use long before their targets were recognized.

### Physiological roles for cardiac $K_{ATP}$ channels

$K_{ATP}$  channels have received much attention recently due to two related puzzles. First, a spirited controversy rages regarding the role of  $K_{ATP}$  channels in cardioprotection against ischemia. Drugs that open  $K_{ATP}$  channels clearly confer resistance to ischemia, while blockers prevent the development of ischemic preconditioning (11). The controversy lies in the mechanism of the cardioprotection and in the precise identity of the channels responsible. Much evidence points to mitochondria as the site of action (11), but the mitochondrial site of action came into question when *Kir6.2* knockout mice were found to lack surface, but not mitochondrial  $K_{ATP}$  channels, and to be resistant to ischemic preconditioning (12).

The second puzzle surrounded the physiological role of the *Kir6.1* subunit, which is found in many tissues at the mRNA and protein levels. Little was known about *Kir6.1* until it was recently knocked-out by Miki and coworkers (13). The loss of *Kir6.1* produced a dramatic, discrete phenotype: The mice developed spontaneous bouts of coronary vasospasm and ST elevation, which often proved fatal due to conduction block. These mice reproduced key features of vasospastic or Prinzmetal angina, a syndrome of sudden coronary vasoconstriction without underlying atherosclerosis. Vascular smooth muscle cells from *Kir6.1* knockout mice were found to

have no detectable  $K_{ATP}$  currents and to lack all vasodilatory responses to  $K_{ATP}$  channel agonists.

In the present issue, Chutkow et al. (14) further clarify the identity of vascular smooth muscle  $K_{ATP}$  channels by showing that *Sur2* knockout mice also develop a Prinzmetal phenotype and loss of  $K_{ATP}$  channels in vascular muscle, while manifesting the expected lack of  $K_{ATP}$  currents in cardiac cells. The inescapable conclusion of these two studies (13, 14) is that the  $K_{ATP}$  channels of vascular smooth muscle consist of one or another splice variant of *Sur2* along with *Kir6.1*. That particular combination of subunits thus represents a promising target for the development of novel anti-anginal compounds. The new results give reason to wonder whether nicorandil, a remarkably effective anti-anginal drug commonly used in Japan and Europe (but sadly absent from the US pharmacopeia), might preferentially activate *Sur2* and *Kir6.1* channels.

### Open questions

The concordant findings between these two recent papers raise a number of critical questions and leave others unanswered. Some of these relate to the relationships among known  $K^+$  channels. For instance, are the vascular  $K_{ATP}$  channels that disappear with knockout of *Sur2* or *Kir6.1* truly conventional  $K_{ATP}$  channels, or might they be identical to the previously described nucleotide diphosphate-sensitive ( $K_{NDP}$ ) channels (15)? More extensive characterization of the pharmacological and single-channel properties of the wild-type channels will be required to sort out this question. Likewise, the identity of the mitochondrial  $K_{ATP}$  channels that have been implicated in cardiac preconditioning remains in doubt. Miki et al. argue that mitochondrial  $K_{ATP}$  channels are not encoded by *Kir6.1*, as evidenced by a preserved mitochondrial flavoprotein

response to the cardioprotective  $K_{ATP}$  channel agonist diazoxide (13). Since flavoprotein responses also remain intact in *Kir6.2* knockout mice (12), it may be that neither of these subunits contributes to the channel activity found in mitochondria. Indeed, a role for Sur2, the known partner for Kir6.2 in cardiac tissue, seems unlikely, based on the distinctive pharmacological profile of mitochondrial  $K_{ATP}$  channels (10), but direct tests in the present knockouts would provide additional welcome information.

It is also unclear, given the wide distribution of  $K_{ATP}$  channels throughout the vasculature, why *Kir6.1* and *Sur2* knockout mice exhibit a primary coronary phenotype. Coronary vessels may be unusually prone to episodic vasoconstriction, but it remains to be seen if a similar pattern of events might occur in other organs — although perhaps with relatively benign effects. However, perhaps the most urgent clinical question to arise from this work concerns how faithfully the two models reproduce human Prinzmetal angina. The

sex distribution of affected mice in the present report (14) does not mirror the female preponderance in humans. Moreover, conduction disturbances and sudden death are not typical features of the clinical syndrome. Do these terminal events arise simply from the severity of ischemia, or does the knockout of  $K_{ATP}$  channels per se confer susceptibility to unstable cardiac impulse transmission? Additional studies with pharmacological vasoconstrictors in wild-type mice, along the lines of those reported by Miki et al. (13), would presumably help in sorting out this important question.

1. Noma, A. 1983. ATP-regulated  $K^+$  channels in cardiac muscle. *Nature*. **305**:147–148.
2. Trube, G., and Hescheler, H. 1984. Inward-rectifying channels in isolated patches of the heart cell membrane: ATP-dependence and comparison with cell-attached patches. *Pflugers Arch*. **401**:178–184.
3. Nichols, C.G., and Lopatin, A.N. 1997. Inward rectifier potassium channels. *Annu. Rev. Physiol*. **59**:171–191.
4. O'Rourke, B., Ramza, B.M., and Marban, E. 1994. Oscillations of membrane current and excitability driven by metabolic oscillations in heart cells. *Science*. **265**:962–966.
5. Li, R.A., Leppo, M., Miki, T., Seino, S., and Marbán, E. 2000. Molecular basis of electrocardiographic

- ST-segment elevation. *Circ. Res*. **87**:837–839.
6. Ashcroft, F.M., and Gribble, F.M. 1999. ATP-sensitive  $K^+$  channels and insulin secretion: their role in health and disease. *Diabetologia*. **42**:903–919.
7. Aguilar-Bryan, L., et al. 1995. Cloning of the beta cell high-affinity sulfonylurea receptor: a regulator of insulin secretion. *Science*. **268**:423–426.
8. Inagaki, N., et al. 1995. Reconstitution of IKATP: an inward rectifier subunit plus the sulfonylurea receptor. *Science*. **270**:1166–1170.
9. Clement, J.P., IV, et al. 1997. Association and stoichiometry of  $K(ATP)$  channel subunits. *Neuron*. **18**:827–838.
10. Liu, Y., Ren, G., O'Rourke, B., Marbán, E., and Seharaseyon, J. 2001. Pharmacological comparison of native mitochondrial  $K(ATP)$  channels with molecularly defined surface  $K(ATP)$  channels. *Mol. Pharmacol*. **59**:225–230.
11. Liu, E., et al. 1999. Mitochondrial ATP-dependent potassium channels. Viable candidate effectors of ischemic preconditioning. *Ann. NY Acad. Sci*. **874**:27–37.
12. Suzuki, M., et al. 2002. Role of sarcolemmal  $K(ATP)$  channels in cardioprotection against ischemia/reperfusion injury in mice. *J. Clin. Invest*. **109**:509–516. doi:10.1172/JCI200214270.
13. Miki, T., et al. 2002. Mouse model of Prinzmetal angina by disruption of the inward rectifier Kir6.1. *Nat. Med*. **8**:466–472.
14. Chutkow, W.A., et al. 2002. Episodic coronary artery vasospasm and hypertension develop in the absence of Sur2  $K_{ATP}$  channels. *J. Clin. Invest*. **110**:203–208. doi:10.1172/JCI200215672.
15. Fujita, A., and Kurachi, Y. 2000. Molecular aspects of ATP-sensitive  $K^+$  channels in the cardiovascular system and  $K^+$  channel openers. *Pharmacol. Ther*. **85**:39–53.