Verdict in the Smooth Muscle $K_{ATP}$ Channel Case
Guilty of Blood Pressure Control But Innocent of Sudden Death Phenotype

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A TP-sensitive potassium ($K_{ATP}$) channels are expressed throughout the body. Their ability to open in the face of cellular energy depletion, thus increasing membrane K+ permeability and dampening excitability, makes them the go-to channel for tissues at times of metabolic crisis. They thus contribute to glucose sensing and neuroprotection within the brain, glucose-dependent insulin secretion, ischemic cardioprotection, and the control of arterial diameter and blood flow.1,2 This ubiquity has, however, made assigning roles to channel populations in specific cellular compartments problematic. $K_{ATP}$ channels form as octamers of 4 pore-forming subunits (either Kir6.1 or Kir6.2) surrounded by 4 regulatory sulphonylurea receptor subunits (SUR1, SUR2A, or SUR2B). These can come together in various combinations to form functional channels, and although tissues tend to favor one dominant form, they undoubtedly express subpopulations with different subunit profiles.2 Several strains of transgenic mice have been developed in which the genes encoding different subunits have been disrupted. These display distinct phenotypes2 but experience channel loss in several different tissues. In the current issue, Aziz et al3 have substantially clarified the role of $K_{ATP}$ channels in smooth muscle by generating novel knockout mice that selectively lack these channels in smooth muscle but retain them in all other cellular compartments. Their study shows that smooth muscle $K_{ATP}$ channels help regulate blood pressure and the response of arteries to vasoconstrictors but are not responsible for the hypercontractile, sudden death phenotype seen in some global $K_{ATP}$ knockouts. This complements a significant body of work that indicates a central role for smooth muscle $K_{ATP}$ channels in the regulation of arterial tone but also highlights the potential importance of endothelial, cardiac, and neuronal $K_{ATP}$ channels in the regulation of vascular contractility.

Previous transgenic models designed to investigate the role of vascular $K_{ATP}$ channels have targeted either Kir6.1 or SUR2 proteins, which form the dominant smooth muscle channel.2 Both SUR2 and Kir6.1 global knockout mice have phenotypes consistent with in vivo studies and extensive in vitro electrophysiological data showing that smooth muscle $K_{ATP}$ channels provide a background K+ conductance important in the regulation of membrane potential and smooth muscle contractility under both basal conditions and in response to vasoactive transmitters.1,2 Mechanistically, this is driven by the steep relationship between membrane potential and Ca2+ influx in smooth muscle, whereby relatively small hyperpolarizations induced by the opening of $K_{ATP}$ channels by vasodilators cause a significant reduction in Ca2+ influx via voltage-sensitive Ca2+ channels. Removal of functional smooth muscle $K_{ATP}$ channels would, therefore, be expected to rid cells of an important relaxant pathway, making them more contractile. Consistent with this, studies with SUR2 null mice, which lack sulphonylurea-sensitive $K_{ATP}$ channels in cardiac, skeletal, and smooth muscle, show that they are hypertensive and experience sudden death caused by spontaneous coronary artery vasospasm.4 Similarly, in Kir6.1 null mice, coronary vasospasm leads to >90% mortality within 6 weeks from birth, and, unlike wild-type, these mice also die in response to application of the vasoconstrictor methylergometrine,5 suggesting a tendency for severe coronary hypercontractility. Sudden death in both SUR2 and Kir6.1 null mice is preceded by electric disturbances in the heart muscle in the form of ST elevation, a change in the shape of the ECG indicative of acute myocardial ischemia, and prolonged conduction block that eventually stops the heart. This resembles Prinzmetal angina in humans, a form of unstable angina that involves hypercontractility of the coronary arteries. Surprisingly, however, when SUR2B is selectively returned to smooth muscle in SUR null mice, to restore smooth muscle $K_{ATP}$ channels, spontaneous coronary vasospasm persists.6 The phenotype is only rescued when cardiac $K_{ATP}$ channels are restored,7 suggesting that $K_{ATP}$ channels outside of smooth muscle exert considerable influence over vascular contractility and undermining the central role of smooth muscle $K_{ATP}$ channels in the regulation of vascular tone in the whole animal.

Recently, however, smooth muscle $K_{ATP}$ channels are back in the frame. Mice expressing smooth muscle–specific Kir6.1 gain-of-function mutants have low blood pressure, consistent with the influence of overactive $K_{ATP}$ channels,4 and now in the current issue, Aziz et al3 have used the Cre-Lox system to produce mice that lack functional $K_{ATP}$ channels in smooth muscle while retaining these channels in heart and brain. These mice are hypertensive but, unlike global Kir6.1 knockouts, show no obvious ECG abnormalities and no sudden death, even in the presence of the vasoconstrictor ergonovine. Thus, smooth muscle $K_{ATP}$ channels contribute to blood pressure regulation, but Kir6.1-containing $K_{ATP}$ channels in other cells have a significant input into vascular control.
There are plenty of candidates for the location of these ex-smooth muscle Kir6.1-containing K\(_{ATP}\) channels (Figure). The endothelium is perhaps the prime candidate, given the control this cellular compartment has over the release of vasoactive signals. The vasodilator adenosine has been shown to dilate the coronary microcirculation through the activation of endothelial K\(_{ATP}\) channels and the release of nitric oxide.\(^6\) A likely mechanism is that the opening of cell surface K\(_{ATP}\) channels elevates cytosolic Ca\(^{2+}\) and activates nitric oxide synthase by increasing the driving force for Ca\(^{2+}\) entry via voltage-insensitive Ca\(^{2+}\) channels. K\(_{ATP}\) channels may also be inside endothelial cells and associated with secretory granules. Expression of dominant-negative Kir6.1 in endothelial cells leads to enhanced endothelin-1 secretion and increased basal coronary perfusion pressure, suggesting a role for these channels in the mediated exocytosis of this vasoconstrictor.\(^9\) The loss of functional K\(_{ATP}\) channels that gives rise to the exaggerated smooth muscle contraction seen in coronary vasospasm may also originate from an imbalance of paracrine signals coming from the heart or a change in autonomic control. Here, it is interesting to note that autonomic hyperactivity has long been suggested as a potential trigger for Prinzmetal angina.\(^11\)

**Disclosures**

None.

**References**


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