Response to Letter Regarding Article, "Reactive Oxygen Species-Induced Stimulation of 5¢AMP-Activated Protein Kinase Mediates Sevoflurane-Induced Cardioprotection"


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Response to Letter Regarding Article, “Reactive Oxygen Species–Induced Stimulation of 5′AMP-Activated Protein Kinase Mediates Sevoflurane-Induced Cardioprotection”

We thank Dr Lotz and colleagues for their interest in our recently published article in Circulation demonstrating that sevoflurane-induced AMP kinase (AMPK) activation protects the heart against ischemia/reperfusion injury. We agree that the central question of whether AMPK activation is beneficial or detrimental is still unresolved. In our opinion, the ambivalent role of AMPK emerges because it controls the balance of energy substrates used by the heart, which is influenced by specific conditions under which the heart functions (ischemia/reperfusion, diabetes mellitus, hypertension).

Regarding their concerns about compound C, we emphasize that compound C is the only available AMPK antagonist that inhibits AMPK activation and that the indicated cardiotoxicity is based on unpublished observations. Our observations of reduced phosphorylation of AMPK and endothelial nitric oxide synthase supported the inhibitory effects of compound C on AMPK activation. In addition, the 2 concentrations of compound C used affected both AMPK phosphorylation and cardioprotection, whereas the low dose did not affect coronary flow.

To unravel all facets of the complex role of AMPK, in vivo studies are indeed required. However, in AMPKα2 knockouts, AMPK and endothelial nitric oxide synthase activity are only partly suppressed because the AMPKα1 isoform is still active. We deliberately chose isolated Langendorff-perfused hearts because they allowed well-controlled ex vivo conditions and excluded confounding systemic hemodynamic and humoral effects of sevoflurane and inhibitors. Under our conditions, the additional activation of AMPK by sevoflurane was beneficial against ischemia/reperfusion injury, whereas reactive oxygen system scavenging abolished the augmented AMPK phosphorylation and cardioprotection. The next step is to assess cardioprotection in vivo with a focus on the time course of AMPK signaling in healthy, diabetic, and conditional AMPK knockout animals.

Thus, our study provides valuable information on the cardioprotective and signaling effects of AMPK, highlights a beneficial role in anesthetic cardioprotection, and indicates the importance of assessing whether AMPK activation can overcome the loss of cardioprotection during type 2 diabetes mellitus.

Disclosures

None.

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