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Molecular mechanisms of coronary flow regulation by adenosine

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Adenosine acts through its receptors (A₁, A_{2A}, A_{2B}, and A₃) via G-proteins and causes an increase in coronary flow (CF) mostly through A_{2A} AR. However, the role of other ARs in the modulation of CF is not well understood. Using KOs, we investigated the role for each AR in the regulation of CF. Using the isolated heart from A₃ KO mice; we reported an increase in A_{2A}-mediated CF. Similarly, we found an increase in CF in A₁ KO mice with A_{2A} agonist (CGS-21680). Also, in A_{2A} KO mice, response to CGS was abolished. On the other hand, A_{2A} KO mice showed a decrease in CF to NECA (non-selective agonist). BAY60-6583 (A_{2B} selective agonist) was without an effect on CF in A_{2B} KO mice; however, it increased CF significantly in A_{2A} KO. CGS also caused a significant increase in CF in A_{2B} KO mice. Also, exogenous adenosine-induced increase in CF in WT, A_{2A} KO, and A_{2B} KO mice were significantly reduced with catalase. BAY-induced increase in CF in WT was significantly inhibited with glibenclamide. Overall, our data support stimulatory roles for A_{2A} and A_{2B} and inhibitory roles for A₁ and A₃ in the regulation of CF. These observations provide new evidence for the presence of all four ARs in CF regulation. We propose, that activation of A_{2A/B} may release H₂O₂ which then activates KATP channels, leading to vasodilation. These studies may lead to better understanding of the role of ARs in coronary disease and may lead to better therapeutic approaches.

Biography

S. Jamal Mustafa is an Assistant VP for Research at HSC at West Virginia University (WVU). He received Dean's Award for Excellence in Research from SOM and became a Robert C. Byrd Professor in 2010 received Chancellor's Award for Outstanding Achievement in Research and Scholarly Activities from HSC, in 2013. He has published over 190 manuscripts. His past work has led to the approval of an A_{2A} selective AR agonist (Lexican®) for myocardial perfusion imaging. Currently, he is using AR and β adrenergic receptor KOs to better understand the relationship between these receptors in coronary flow regulation.

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