Coronary flow regulation and its signaling by adenosine

Adenosine acts through its receptors (A₁, A₂ₐ, A₂₈, and A₃) via G-proteins and causes an increase in Coronary Flow (CF) mostly through A₂ₐ AR. However, the role of other ARs in the modulation of CF is not well understood. Using Knock Outs (KO), we investigated the role for each AR in the regulation of CF. Using the isolated heart from A₁ KO mice; we reported an increase in A₂ₐ-mediated CF. Similarly, we found an increase in CF in A₂₈ KO mice with agonist (CGS-21680; CGS). In addition, in A₂ₐ KO mice response to CGS was abolished, thus confirming the KO. On the other hand, A₂ₐ KO mice showed a decrease in CF to NECA (non-selective agonist). BAY60-6583 (A₂₈ selective agonist; BAY) was without an effect on CF in A₂₈ KO mice; however, it increased CF significantly in A₁ KO. CGS also caused a significant increase in CF in A₂₈ KO mice. In addition, exogenous adenosine-induced increase in CF in wild type, A₁ KO and A₂₈ 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 A₂ₐ and A₂₈ 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 A₂ₐ/B may release H₂O₂ which then activates KATP channels, leading to vasodilation. These studies may lead to the better understanding of the role of ARs in coronary disease and better therapeutic approaches.

Biography

S Jamal Mustafa is a Professor of Pharmacology at West Virginia University School of Medicine and a Senior Advisor to the Pilot Core of the West Virginia Clinical Science and Translational Institute. He has served as an Assistant Dean for Research at the Health Sciences Center from 2005-15. He has received Dean’s Award for Excellence in Research from School of Medicine in 2008 and became a Robert C Byrd Professor in 2010. In addition, he received Chancellor’s Award for Outstanding Achievement in Research and Scholarly Activities from Health Sciences Center in 2013. He had published over 200 manuscripts. For almost 40 years, he had been studying the role of adenosine receptors in coronary flow regulation and it is signaling in coronary smooth muscle and endothelial cells from various species including human. He and his teams past work has led to the approval of a selective A2A adenosine receptor agonist (Lexican®) for myocardial perfusion imaging. Currently he and his team are using adenosine receptor and beta-adrenergic receptor knockout mice to understand the relationship between these receptors in coronary flow regulation leading to treatment of coronary artery disease.

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