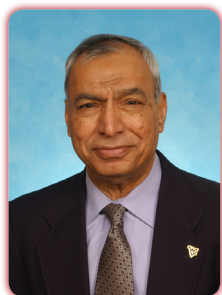


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S Jamal Mustafa

West Virginia University, USA

Coronary flow regulation and its signaling by adenosine

Adenosine acts through its receptors (A_1 , A_{2A} , A_{2B} and A_3) 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 Knock Outs (KO), we investigated the role for each AR in the regulation of CF. Using the isolated heart from A_3 KO mice; we reported an increase in A_{2A} -mediated CF. Similarly, we found an increase in CF in A_1 KO mice with A_{2A} agonist (CGS-21680; CGS). In addition, in A_{2A} KO mice response to CGS was abolished, thus confirming the KO. On the other hand, A_{2A} KO mice showed a decrease in CF to NECA (non-selective agonist). BAY60-6583 (A_{2B} selective agonist; BAY) 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. In addition, exogenous adenosine-induced increase in CF in wild type, 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 A_1 and A_3 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 H_2O_2 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 its 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.

sjmustafa@hsc.wvu.edu