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Involvement of NADPH oxidase in coronary flow regulation by adenosine receptors

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Adenosine increases Coronary Flow (CF) through the activation of A_{2A} and A_{2B} Adenosine Receptors (ARs). However, these mechanisms are not fully understood. We previously showed that adenosine-induced increase in CF is in part through NADPH oxidase (Nox), which is independent of A_1 or A_3 ARs. In this study, we hypothesize that adenosine-mediated increase in CF is through Nox activation and depends on A_{2A} but not on A_{2B} ARs. Functional studies were conducted using Langendorff mouse hearts. Hydrogen peroxide (H_2O_2) production was measured in isolated coronary arteries from WT, A_{2A} and A_{2B}AR KO mice using immunofluorescence. Adenosine-induced concentration-dependent increase in CF was attenuated by the specific Nox2 inhibitor gp91 ds-tat or reactive oxygen species (ROS) scavenger EUK134 in both WT and A_{2B} but not A_{2A} AR KO hearts. Similarly, the A_{2A} AR selective agonist CGS-21680-induced increase in CF was significantly blunted by Nox2 inhibition in both WT and A_{2B} AR KO, while the A_{2B} AR selective agonist BAY 60-6583-induced increase in CF was not affected by Nox2 inhibition in WT. In intact isolated coronary arteries, adenosine-induced (10μM) increase in H_2O_2 formation in both WTand A_{2B}AR KO mice was attenuated byNox2 inhibition, whereas adenosine failed to increase H_2O_2 production in A_{2A} AR KO mice. In conclusion, adenosine-induced increase in CF is partially mediated by Nox2-derived H_2O_2, which critically depends upon the presence of A_{2A} AR. 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 a Professor of Physiology and Pharmacology at West Virginia University (WVU). He received Dean's Award for Excellence in Research from SOM in 2008 and became a Robert C Byrd Professor in 2010 and received Chancellor's Award for Outstanding Achievement in Research and Scholarly Activities from HSC in 2013. He has published over 200 manuscripts. Our past work has led to the approval of an A_{2A} selective AR agonist (Lexican®) for myocardial perfusion imaging. Currently, we are using AR and β adrenergic receptor KOs to better understand the relationship between these receptors in coronary flow regulation.

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