BMC Pharmacology

Poster presentation

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BAY 58-2667, an NO-independent guanylyl cyclase activator, pharmacologically post-conditions rabbit and rat hearts

Thomas Krieg*[1], Yanping Liu[2], Thomas Rütz[1], Carmen Methner[1], Xi-Ming Yang[2], Stephan B Felix[1] and James M Downey[2]

Address: [1]Department of Cardiology, Ernst-Moritz-Arndt University, Greifswald, Germany and [2]Department of Physiology, University of South Alabama, Mobile, AL, USA

Email: Thomas Krieg* - krieg@uni-greifswald.de

* Corresponding author

from 4th International Conference of cGMP Generators, Effectors and Therapeutic Implications
Regensburg, Germany. 19–21 June 2009

Published: 11 August 2009

BMC Pharmacology 2009, **9**(Suppl 1):P36 doi:10.1186/1471-2210-9-S1-P36

This abstract is available from: http://www.biomedcentral.com/1471-2210/9/S1/P36

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Background

BAY 58-2667 (cinaciguat) directly activates soluble guanylyl cyclase without tolerance in a NO-independent manner, and its hemodynamic effect is similar to that of nitroglycerin. We tested whether BAY 58-2667 could make both rabbit and rat hearts resistant to infarction when given at the end of an ischemic insult.

Methods and results

All hearts were exposed to 30-min regional ischemia followed by 120-(isolated hearts) or 180-(*in situ* hearts) min reperfusion. BAY 58-2667 (1–50 nM) infused for 60-min starting 5-min before reperfusion significantly reduced infarction from 33.0 ± 3.2% in control isolated rabbit hearts to 9.5–12.7% ($p < 0.05$). In a more clinically relevant *in situ* rabbit model infarct size was similarly reduced with a loading dose of 53.6 μg/kg followed by a 60-min infusion of 1.25 μg/kg/min (41.1 ± 3.1% infarction in control hearts to 16.0(±)4.4% in treated hearts, $p < 0.05$). BAY 58-2667 similarly decreased infarction in the isolated rat heart, and protection was abolished by co-treatment with a protein kinase G (PKG) antagonist, or a mitochondrial K_{ATP} channel antagonist. Conversely, N^{ω}-nitro-L-arginine-methyl-ester-hydrochloride, a NO-synthase inhibitor, failed to block BAY 58-2667's ability to decrease infarction, consistent with the latter's putative NO-independent activation of PKG. Finally, BAY 58-2667 increased myocardial cGMP content in reperfused hearts while cAMP was unchanged.

Conclusion

When applied at reperfusion BAY 58-2667 is an effective cardioprotective agent with a mechanism similar to that of ischemic preconditioning and, hence, should be a candidate for treatment of acute myocardial infarction in man.