Laropiprant attenuates EP\textsubscript{3} and TP prostanoid receptor-mediated thrombus formation

Sonia Philipose\textsuperscript{1}, Viktória Kónya\textsuperscript{1}, Mirjana Lazarevi\textsuperscript{ć}\textsuperscript{1}, Lisa M Pasterk\textsuperscript{1}, Gunther Marsche\textsuperscript{1}, Sasa Frank\textsuperscript{2}, Bernhard A Peskar\textsuperscript{1}, Ákos Heinemann\textsuperscript{1*}, Rufina Schuligoi\textsuperscript{1}

From 18th Scientific Symposium of the Austrian Pharmacological Society (APHAR). Joint meeting with the Croatian, Serbian and Slovenian Pharmacological Societies. Graz, Austria. 20-21 September 2012

Background
The use of the lipid-lowering agent niacin is hampered by a frequent flush response which is largely mediated by prostaglandin (PG) D\textsubscript{2}. Therefore, concomitant administration of the D-type prostanoid (DP) receptor antagonist laropiprant has been proposed to be a useful approach in preventing niacin-induced flush. However, antagonizing PGD\textsubscript{2}, which is a potent inhibitor of platelet aggregation, might pose the risk of atherothrombotic events in cardiovascular disease. Therefore, we investigated the effects of laropiprant on platelet function.

Methods
Platelet aggregation assays were performed \textit{ex vivo} using a platelet aggregation analyser (Aggregometer II). Blood from healthy human donors was used to obtain platelet-rich plasma. The expression of P-selectin and activation of glycoprotein IIb/IIIa was examined using CD62P and PAC1 antibodies, respectively, by direct flow cytometry. \textit{In vitro} thrombus formation was assessed by flowing whole blood on collagen-coated Cellix biochips at \textasciitilde30 dyn/cm\textsuperscript{2} using the Mirus nanopump.

Results
\textit{In vitro} treatment of platelets with laropiprant prevented the inhibitory effects of PGD\textsubscript{2} on platelet function, \textit{i.e.} platelet aggregation, P-selectin expression, activation of glycoprotein IIb/IIIa and thrombus formation. In contrast, laropiprant did not prevent the inhibitory effects of acetylsalicylic acid or niacin on thrombus formation. At higher concentrations, laropiprant by itself attenuated platelet activation induced by thromboxane (TP) and E-type prostanoid (EP)-3 receptor stimulation, as demonstrated in assays of platelet aggregation, P-selectin expression, and activation of glycoprotein IIb/IIIa. Inhibition of platelet function exerted by EP\textsubscript{4} or I-type prostanoid (IP) receptors was not affected by laropiprant.

Conclusions
These \textit{in vitro} data suggest that niacin/laropiprant for the treatment of dyslipidemias might have a beneficial profile with respect to platelet function and thrombotic events in vascular disease.

Acknowledgements
S.P. was funded by the PhD Program Molecular Medicine of the Medical University of Graz. This study was supported by the Jubiläumsfonds of the Austrian National Bank (OeNB, grants 13487 and 14263) and the Austrian Science Fund (FWF, grants P22521-B18, P19473-B05, P21004-B02 and P22976-B18).

Author details
\textsuperscript{1}Institute of Experimental and Clinical Pharmacology, Medical University of Graz, 8010 Graz Austria. \textsuperscript{2}Institute of Molecular Biology and Biochemistry, Medical University of Graz, 8010 Graz, Austria.

Published: 17 September 2012

doi:10.1186/2050-6511-13-S1-A14
Cite this article as: Philipose et al. Laropiprant attenuates EP\textsubscript{3} and TP prostanoid receptor-mediated thrombus formation. BMC Pharmacology and Toxicology 2012 13(Suppl 1):A14.