Inhibition of NAD(P)H oxidase attenuates aggregation of platelets from high-risk cardiac patients with aspirin resistance

Gyorgyi Stef1*, Anna Csiszar2*, Zhao Xiangmin2, Peter Ferdinandy3, Zoltan Ungvari2, Gabor Veress1

1 State Hospital for Cardiology, Balatonfüred 8230, Hungary
2 Department of Physiology, New York Medical College, Valhalla, New York 10595, USA
3 Cardiovascular Research Group, Department of Biochemistry, University of Szeged, Szeged, Hungary

*These authors contributed equally to this manuscript

Correspondence: Zoltan Ungvari, e-mail: zoltan_ungvari@nymc.edu

Abstract:
Up to one-third of serious vascular events in high-risk patients is attributable to a failure of aspirin (ASA) to suppress platelet aggregation. We hypothesized that inhibition of NAD(P)H oxidase may inhibit aggregation of platelets from ASA-resistant (ASA-R) patients. Thus, platelet-rich plasma was isolated from ASA-sensitive (ASA-S) and ASA-R patients (aspirin resistance was defined as higher than expected aggregation to collagen and epinephrine [≥ 40%] after chronic oral treatment with 100 mg/day ASA). Aggregation to adenosine diphosphate (ADP) (5 and 10 \( \mu \)mol/l), collagen (2 \( \mu \)g/ml) and epinephrine (10 \( \mu \)mol/l) was measured by optical aggregometry. Maximal aggregation of ASA-R platelets to collagen and epinephrine was significantly decreased by DPI and apocynin, whereas they had no effect in ASA-S platelets. Maximal aggregation to ADP was unaffected by NAD(P)H oxidase inhibition in either group. In ASA-R platelets both NADPH-driven \( \Omega^{2-} \) production (lucigenin chemiluminescence assay) and expression of gp91\( ^{phox} \) and p67\( ^{phox} \) subunits of the NADPH oxidase (Western blotting) tended to increase. Collectively, inhibition of NAD(P)H oxidase effectively suppressed collagen and epinephrine-induced aggregation of platelets from ASA-R patients, which may represent a novel pharmacological target for cardioprotection in high-risk cardiac patients.

Key words: oxidative stress, thrombocyte, NADPH oxidase, thrombosis, coronary artery disease, myocardial infarction