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

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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 μmol/l), collagen (2 μg/ml) and epinephrine (10 μmol/l) in the absence and presence of the NAD(P)H oxidase inhibitors: diphenylene iodonium (DPI) (1 μmol/l) and apocynin (3×10^{-4} 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 $O_2^{\bullet -}$ 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