Short communication

Inhibitors of phosphatidylinositol 3-kinase: effects on reactive oxygen species and platelet aggregation

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Abstract:
Phosphoinositide 3-kinase (PI 3-kinase) exists in cells as a family of isoforms. The enzymes are important regulators of fundamental metabolic processes, such as energy utilization, growth, cell proliferation and survival. They are activated by cell surface receptors for hormones, and by G-protein coupled receptors. Enzyme p110 gamma, in particular, catalyzes production of second messengers from inositol phospholipids, including phosphoinositide (3,4,5) triphosphate or PtdIns (3,4,5) P3, PtdIns (3,4) P2 and PtdIns (3) P. The objective of this study was to combine the role of PI 3-kinase in ROS generation and in platelet aggregation through the use of four chemically unrelated inhibitors of PI 3-kinase: wortmannin, LY-294002, resveratrol and quercetin. In this study, we describe the effects of four PI 3-kinase inhibitors on the production of reactive oxygen species (ROS) and platelet aggregation induced by a diversity of agonists. Neutrophils and platelets were obtained from human blood and macrophages from mouse peritoneal cavity. ROS production was measured by a luminol-enhanced chemiluminescence assay; aggregation was measured in platelet-rich plasma (PRP) with a Chronolog Dual Channel Lumi-Aggregometer. Effects of graded concentrations of four enzyme inhibitors (wortmannin, LY-294002, resveratrol and quercetin) were evaluated. All inhibitors caused concentration-dependent depression of ROS generation and human platelet aggregation. They differed only in their potencies as revealed by concentration-response data. Moreover, inhibitors blocked activity of three chemically unrelated stimulants of aggregation: ADP, collagen and epinephrine. We conclude that inhibition of PI 3-kinase would appear to be a useful therapeutic goal in those conditions where the activities of platelets and/or phagocytes become aberrant.

Key words:
phosphatidylinositol 3-kinase, platelet aggregation, wortmannin, LY 294002, resveratrol, quercetin, luminol-enhanced chemiluminescence assay