

Aspirin inhibits ox-LDL-mediated LOX-1 expression and metalloproteinase-1 in human coronary endothelial cells

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Received 8 April 2004; received in revised form 29 June 2004; accepted 2 July 2004

Available online 12 August 2004

Time for primary review 11 days

Abstract

Background: Aspirin is thought to exert salutary effects in vascular disease states by inhibiting platelet aggregation. Endothelial activation, accumulation of oxidized low-density lipoprotein (ox-LDL) and intense inflammation also characterize atherosclerotic plaque in acute myocardial ischemia. Ox-LDL induces expression of lectin-like receptors (LOX-1) on endothelial cells and leads to the expression of matrix metalloproteinases (MMPs), which destabilize the atherosclerotic plaque. We hypothesized that aspirin may interfere with LOX-1 expression and subsequent MMP activation.

Methods and results: Cultured human coronary artery endothelial cells (HCAECs) were incubated with aspirin (1–5 mM), sodium salicylate (5 mM) or the cyclo-oxygenase inhibitor indomethacin (0.25 mM) before treatment with ox-LDL. Aspirin, in a dose- and time-dependent fashion, reduced ox-LDL-mediated LOX-1 expression ($P<0.01$). Ox-LDL also increased MMP-1 expression and activity, and treatment of HCAECs with aspirin decreased this effect ($P<0.01$). Ox-LDL also enhanced the activity of p38MAPK in HCAECs, and aspirin blocked this effect of ox-LDL ($P<0.01$). Treatment of HCAECs with salicylate, but not indomethacin, resulted in a suppression of LOX-1 expression, an effect similar to that of aspirin. Importantly, both aspirin and salicylate, but not indomethacin, decreased superoxide anion generation in ox-LDL-treated HCAECs ($P<0.05$).

Conclusion: These observations suggest that aspirin inhibits ox-LDL-mediated LOX-1 expression and interferes with the effects of ox-LDL in intracellular signaling (p38MAPK activation) and subsequent MMP-1 activity. These novel effects of aspirin may complement its platelet inhibitory effect in acute myocardial ischemia.

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Keywords: Aspirin; Endothelial cells; Lectin-like ox-LDL receptor (LOX-1); MAP kinase; Metalloproteinases; Oxidation

This article is referred to in the Editorial by G. Kojda (pages 192–194) in this issue.

1. Introduction

Acetylsalicylic acid (aspirin) has been used in the primary and secondary prevention of cardiovascular disease for the

past two decades. Aspirin decreases the evolution of vascular events by 20–25% in patients with a variety of vascular diseases [1]. This drug is now a cornerstone of therapy in patients with acute coronary syndromes. The American Heart Association/American College of Cardiology Task Force recommends immediate administration in patients with suspected acute myocardial infarction or unstable angina [2].

The pathogenesis of acute coronary syndrome is generally believed to involve rupture and/or hemorrhage into a vulnerable atherosclerotic plaque [3,4]. Following the disruption of endothelial lining, platelets adhere to subendothelial surface, and intense platelet aggregation

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