Monocyte cAMP Content Is Decreased in Patients With Stable Angina

Marie Anne Punchard, Aranzazu Ortega Pozzi, Teresa Perez de Prada, Monica Torres Coronado, Pablo Gonzalez, Panayotis Fantidis

A crucial event in atherosclerosis is the formation of foam cells. Vascular cell adhesion molecule-1 (VCAM-1), intercellular cell adhesion molecule-1 (ICAM-1), macrophage chemoattractant protein-1 (MCP-1), and macrophage colony stimulating factor (M-CSF) are important molecules that contribute to foam cell formation.

Removal of excess free cholesterol from macrophages, neutralization of monocyte migration inhibitory factor (MIF), and reduction of proinflammatory cytokine concentrations are important goals for the prevention of foam cell formation and the development of atherosclerosis.

Increases in intracellular cAMP concentration inhibit the expression of ICAM-1 and VCAM-1, decrease the production of MCP-1 and M-CSF, increase the expression of antiinflammatory cytokines, and decrease the expression of MIF and proinflammatory interleukins. In addition, cAMP analogs induce the ABCA1 secretory pathway, by which apolipoproteins (apoA-I) actively remove free cholesterol from cells; treatment of macrophages with cAMP analogs causes parallel increases in apo-I–mediated cholesterol efflux.

On the basis of the role of cAMP in the expression of proatherogenic and antiatherogenic molecules, we postulated that the intracellular cAMP concentrations of peripheral monocytes may be low in patients with coronary artery disease.

We studied 80 patients with chronic stable angina (SA) who were consecutively admitted to our hospital, and 67 healthy age-matched healthy volunteers with no known coronary artery disease or risk factors. Coronary angiography was carried out with all patients.

Total plasma cholesterol (mg/dL), LDL-cholesterol (mg/dL), and HDL-cholesterol (mg/dL) were measured by colorimetric methods (Sigma Diagnostics Inc). Serum interleukin (IL)-6 (pg/mL) was measured by enzyme immunoassay (EIA; Diagnostic Products Corporation).

Peripheral blood mononuclear cells were separated from whole blood by density-gradient centrifugation on Ficoll-Paque columns, and monocytes were isolated by magnetic separation technology (MACS, Miltenyi Biotec GmbH). Monocytes were resuspended in RPMI-1640 (Gibco) containing 10% fetal bovine serum and 10% pooled normal human serum, and were then counted in a Neubauer chamber and stored at −80°C. The monocyte pellet was lysed ultrasonically for 180 seconds, and the intracellular levels of cAMP (pmol/10^6 cells) were measured by ELISA (Cayman Chemical R&D Systems Europe; the intra-and interassay coefficients of variation have been determined at multiple points of the curve. The coefficient variation is less than 5% in the 0.2 to 10 pmol/mL range). The kit instructions were followed.

Intracellular cAMP values (mean±SD) were analyzed by the 2-tailed test for unpaired observations. The null hypothesis was rejected when P≤0.05.

The clinical characteristics of the patients at the time of admission are presented in the Table. Intracellular cAMP concentrations were significantly higher (P=0.001) in controls compared with SA patients (controls, 0.28±0.15 pmol/10^6 cells; and SA patients, 0.13±0.02 pmol/10^6 cells).
Previous studies reported that cellular cAMP content may have an important protective role, impeding the formation of atherosclerotic lesions,4–8 and that high cellular cAMP may promote reendothelialization, maintain endothelial cell function, and prevent the induction of procoagulant activity in response to certain cytokines.9,10 Indeed, cAMP enhancer drugs relieve the symptoms of patients with intermittent claudication, significantly increasing walking distances compared with placebo,11 improve serum lipid profile,12 reduce the incidence of atherosclerosis in mice,13 and suppress apoptosis.14 Furthermore, C-reactive protein reduced the antiinflammatory IL-10 production in human macrophages via inhibition of cAMP production.15

Intracellular cAMP concentration is determined by stimulation of adenylyl cyclase and by intracellular breakdown of this nucleotide by phosphodiesterases. The present work is a small preliminary study, and it was beyond the scope of the study to assess whether adenylyl cyclase is inhibited, or the phosphodiesterases are activated in subjects that develop coronary artery disease. However, our results provide the first demonstration that monocyte cAMP content is decreased in patients with SA, suggesting new ways to evaluate the role of cellular cAMP content in the development of atherosclerosis.

Sources of Funding
This study was supported by grants from Comunidad Autónoma de Madrid (No. 8.4/001) and Sociedad Española de Cardiología.

Disclosures
None.

References
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Arterioscler Thromb Vasc Biol. 2007;27:436-437
doi: 10.1161/01.ATV.0000252709.13329.7c
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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