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Nonsteroidal anti-inflammatory agents inhibit stimulated neutrophil adhesion to endothelium: adenosine dependent and independent mechanisms.

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Abstract

All nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit neutrophil aggregation (homotypic cell-cell adhesion) and do so without affecting expression of CD11b/CD18. Since the first step in acute inflammation is a critical interaction between neutrophils and the vascular endothelium (heterotypic cell-cell adhesion), we determined whether NSAIDs diminish the adherence of neutrophils to the endothelium.

At anti-inflammatory concentrations (0.5-5 mM) sodium salicylate, an NSAID that does not inhibit prostaglandin synthesis, inhibited stimulated but not unstimulated neutrophil adherence to endothelial cells (IC50 < 1 mM, P < 0.00001). Salicylates have previously been shown to inhibit oxidative phosphorylation and, predictably, sodium salicylate inhibited oxidative phosphorylation, as evidenced by depletion of ATP stores (875 +/- 75 pmol/10(6) PMN, [2.92 +/- 0.25 mM]) in stimulated (FMLP, 0.1 microM) but not resting neutrophils treated with anti-inflammatory doses of sodium salicylate (EC50 = 1 mM, P < 0.00001).

Indomethacin and piroxicam (10 and 30 microM) only minimally decreased ATP concentrations in stimulated and resting neutrophils. ATP is metabolized to adenosine, and we have previously demonstrated that both endogenously released (180-200 nM) and exogenous adenosine (IC50 = 250 nM) inhibit stimulated neutrophil adherence to endothelial cells.

To determine whether the increased metabolism of ATP and the resultant increase in adenosine release were responsible for inhibition of neutrophil adhesion to endothelium, we determined whether addition of adenosine deaminase (ADA, 0.125 IU/ml), an enzyme that converts extracellular adenosine to its inactive metabolite, inosine, affected inhibition of neutrophil adhesion to endothelium by stimulated neutrophils. ADA significantly reversed inhibition of neutrophil adherence to endothelium by sodium salicylate (0.5-5 mM, P < 0.00001).

This suggests that sodium salicylate inhibits neutrophil adherence by increasing adenosine release. Whereas indomethacin and piroxicam (10-50 microM) also inhibited stimulated neutrophil adherence to endothelial cells, ADA did not affect their inhibition of adherence. These studies demonstrate a heretofore unexpected antiinflammatory mechanism for salicylates: salicylates increase ATP hydrolysis and thereby enhance release of adenosine. Moreover, these data are consistent with the hypothesis that NSAIDs differ from one another with respect to their mechanisms of action.