# Protective mechanisms of inosine in platelet activation and cerebral ischemic damage.

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## Abstract

Inosine is a naturally occurring nucleoside degraded from adenosine. Recent studies have demonstrated that inosine has potent immunomodulatory and neuroprotective effects. In the present study, we further investigated the inhibitory effects of inosine on platelet activation in vitro and in vivo, as well as in attenuating middle cerebral artery occlusion (MCAO)-induced focal cerebral ischemia in rats. METHODS AND RESULTS: Inosine concentration-dependently (0.5 to 6.0 mmol/L) inhibited platelet aggregation stimulated by agonists. Inosine (1.5 and 3.0 mmol/L) inhibited phosphoinositide breakdown, [Ca+2]i, and TxA2 formation in human platelets stimulated by collagen (1 microg/mL). In addition, inosine (1.5 and 3.0 mmol/L) markedly increased levels of cyclic guanylate monophosphate (GMP) and cyclic GMP-induced vasodilator-stimulated phosphoprotein Ser157 phosphorylation. Rapid phosphorylation of a platelet protein of molecular weight 47,000 (P47), a marker of protein kinase C activation, was triggered by collagen (1 microg/mL). This phosphorylation was markedly inhibited by inosine (3.0 mmol/L). Inosine (1.5 and 3.0 mmol/L) markedly reduced hydroxyl radical in collagen (1 microg/mL)-activated platelets. In in vivo studies, inosine (400 mg/kg) significantly prolonged the latency period of inducing platelet plug formation in mesenteric venules of mice, and administration of 2 doses (100 mg/kg) or a single dose (150 mg/kg) of inosine significantly attenuated MCAO-induced focal cerebral ischemia in rats. CONCLUSIONS: Platelet aggregation contributes significantly to MCAO-induced focal cerebral ischemia. The most important findings of this study suggest that inosine markedly inhibited platelet activation in vitro and in vivo, as well as cerebral ischemia. Thus, inosine treatment may represent a novel approach to lowering the risk of or improving function in thromboembolic-related disorders and ischemia-reperfusion brain injury.