meta-Iodobenzylguanidine, an inhibitor of arginine-dependent mono(ADP-ribosyl)ation, prevents neointimal hyperplasia.

Authors: Yau L., Molnar P., Moon M.C., Buhay S., Werner J.P., Molnar K., Saward L., Del Rizzo D., Zahradka P.

Publication Date: 2008

Abstract:

The association of ADP-ribosylation with cell proliferation and ischemia-reperfusion injury suggests that it may be a suitable target for therapeutic control of revascularization-induced injury. The purpose of this study was to investigate the inhibitory actions of ADP-ribosylation inhibitors on restenosis. In organ culture, the poly(ADP-ribose) polymerase (PARP) inhibitor 3,4-dihydro-5-methylisoquinolinone (PD128763) was unable to prevent neointimal hyperplasia, whereas the arginine-dependent mono(ADP-ribosyl) transferase (ART) inhibitor meta-iodobenzylguanidine (MIBG) was highly effective (EC<inf>50</inf> 21 muM). Treatment with 3-aminobenzamide (3AB), a less potent ART inhibitor, also produced a significant reduction in neointimal hyperplasia. Single doses (25 mM) of MIBG and 3AB were also applied within a fibrin coagulum directly to the adventitial surface of the porcine femoral artery after balloon catheter injury in vivo. MIBG reduced the neointimal index, measured 14 days after angioplasty, by 82%, whereas 3AB was ineffective. However, when extended to 45 days, the neointimal index was not significantly decreased by MIBG treatment relative to control. Assessment of MIBG release from the fibrin glue showed that the bulk of the compound was eluted within 3 days, suggesting that the vehicle was not suitable for long-term delivery. On the other hand, direct infusion of MIBG into vessels was able to reduce neointimal hyperplasia over 14 days in organ culture. These data support the conclusion that the cellular retention characteristics of MIBG contribute significantly to the efficacy of this compound. Based on these results, ART, but not PARP, may be a credible target for therapeutic treatment of