Effect of P-selectin inhibition on leukocyte-endothelium interaction and survival after global cerebral ischemia.

Abstract:
Cerebral ischemia induces activation of leukocyte-endothelium interactions requiring upregulation of specific adhesion molecules including the selectins. The aim of the current study was to elucidate the therapeutic potency of P-selectin blockade on microcirculatory disturbances and secondary brain damage after global cerebral ischemia. Global cerebral ischemia for 15 minutes was induced in Mongolian gerbils. Functional blockade of P-selectin was achieved by pretreatment with the antibody RB 40.34 (2 mg/kg, n = 7). In vivo observation of brain microcirculation was performed by epifluorescence microscopy of a cranial window. Survival was assessed daily up to 4 days after ischemia. In the control group leukocyte rolling increased during reperfusion with a maximum at 3 h (28 +/- 14 x 100 microm(-1) x min(-1)) and was significantly reduced by the P-selectin antibody (13 +/- 9 x 100 microm(-1) x min(-1), p< 0.05). No effect on firm leukocyte adhesion was observed (4 +/- 3 vs. 2 +/- 1 x 100 microm(-1) x min(-1)). The survival of animals that received the P-selectin antibody (28 %) was significantly reduced compared with controls (71 %). Anti-P-selectin antibody reduces leukocyte rolling but has no positive effect on survival. Our data question the role of the inflammatory response in the development of secondary brain damage and do not support this kind of therapeutical approach in global cerebral ischemia.