Imaging of delayed-type hypersensitivity reaction by PET and 18F-galacto-RGD.

Abstract:
Radiolabeled cyclic peptides containing the amino acid sequence arginine-glycine-aspartate (RGD peptides) have successfully been used to image the expression of the alpha(v)beta(3) integrin in malignant tumors. However, the alpha(v)beta(3) integrin also plays an important role in angiogenesis induced by chronic inflammatory processes. Therefore, the aim of this study was to evaluate whether radiolabeled RGD peptides may also be used to assess alpha(v)beta(3) expression in inflammatory diseases. We studied a hapten-induced delayed-type hypersensitivity reaction (DTHR) as a model for inflammatory processes, since DTHRs are involved in many human autoimmune disorders.

METHODS: The abdominal skin of mice was sensitized by application of 2,4,6-trinitrochlorobenzene (TNCB). One week later, a DTHR was elicited by challenging the right ear with TNCB. Application of TNCB was then repeated every 48 h to induce chronic skin inflammation. Small-animal PET and autoradiography with the alpha(v)beta(3) ligands (18)F-galacto-RGD and (125)I-gluco-RGD were performed at various times after TNCB application. The time course of tracer uptake by the treated ears was compared with histologic skin changes. RESULTS: The first challenge with TNCB caused, within 12 h, an acute inflammatory response with dense dermal infiltrates of polymorphonuclear leukocytes and...
lymphocytes. However, autoradiography revealed no significant increase in (125)I-gluco-RGD uptake at that time (mean uptake ratio for treated ear to untreated ear, 1.02 +/- 0.1 [SD]). Further challenges with TNCB resulted in chronic skin inflammation with markedly increased small-vessel density in the ear tissue. This was paralleled by a continuous increase in uptake of (125)I-gluco-RGD. After 13 challenges, the uptake ratio had increased to 2.30 +/- 0.27 (P< 0.005 compared with baseline). Enhanced uptake of radiolabeled RGD peptides in chronic inflammation was also demonstrated noninvasively by PET with (18)F-galacto-RGD. Pretreatment of the mice with nonradiolabeled cyclic peptide c(RGDfV) almost completely blocked uptake of (18)F-galacto-RGD by the challenged ear, thus confirming the specificity of tracer uptake. CONCLUSION: Radiolabeled RGD peptides allow a noninvasive assessment of alpha(v)beta(3) expression in inflammatory processes. PET with (18)F-galacto-RGD might become a powerful tool to distinguish between the acute and chronic phases of T cell-mediated immune responses and may represent a new biomarker for disease activity in autoimmune disorders.