Dokumenttyp: journal article

Autor(en) des Beitrags:
Notni, Johannes; Steiger, Katja; Hoffmann, Frauke; Reich, Dominik; Kapp, Tobias G; Rechenmacher, Florian; Neubauer, Stefanie; Kessler, Horst; Wester, Hans-Jürgen

Titel des Beitrags:
Complementary, Selective PET Imaging of Integrin Subtypes \(\alpha_5\beta_1\) and \(\alpha_v\beta_3\) Using \(^{68}\text{Ga}\)-Aquibeprin and \(^{68}\text{Ga}\)-Avebetrin.

Abstract:
Despite in vivo mapping of integrin \(\alpha_v\beta_3\) expression being thoroughly investigated in recent years, its clinical value is still not well defined. For imaging of angiogenesis, the integrin subtype \(\alpha_5\beta_1\) appears to be a promising target, for which purpose we designed the PET radiopharmaceutical \(^{68}\text{Ga}\)-aquibeprin. \(^{68}\text{Ga}\)-aquibeprin was obtained by click-chemistry (CuAAC) trimerization of a \(\alpha_5\beta_1\) integrin-binding pseudopeptide on the triazacyclononane-triphosphinate (TRAP) chelator, followed by automated \(^{68}\text{Ga}\) labeling. Integrin \(\alpha_5\beta_1\) and \(\alpha_v\beta_3\) affinities were determined in enzyme linked immune sorbent assay on immobilized integrins, using fibronectin and vitronectin, respectively, as competitors. M21 (human melanoma)-bearing severe combined immunodeficient mice were used for biodistribution, PET imaging, and determination of in vivo metabolization. The expression of \(\alpha_5\) and \(\beta_3\) subunits was determined by immunohistochemistry on paraffin sections of M21 tumors. \(^{68}\text{Ga}\)-aquibeprin shows high selectivity for integrin \(\alpha_5\beta_1\) (50% inhibition concentration \([\text{IC}_{50}] = 0.088\) nM) over \(\alpha_v\beta_3\) \([\text{IC}_{50} = 620\) nM\) and a pronounced hydrophilicity (log \(D \approx -4.2\)). Severe combined immunodeficient mice xenografted
with M21 human melanoma were found suitable for in vivo evaluation, as M21 immunohistochemistry showed not only an endothelial and strong cytoplasmatic expression of the \( \beta_3 \) integrin subunit but also an intense expression of the \( \beta_5 \) integrin subunit particularly in the endothelial cells of intratumoral small vessels. Ex vivo biodistribution (90 min after injection) showed high uptake in M21 tumor (2.42 ± 0.21 percentage injected dose per gram), fast renal excretion, and low background; tumor-to-blood and tumor-to-muscle ratios were 10.6 ± 2.5 and 20.9 ± 2.4, respectively. (\( 68 \)Ga-aquibeprin is stable in vivo; no metabolites were detected in mouse urine, blood serum, kidney, and liver homogenates 30 min after injection. PET imaging was performed for (\( 68 \)Ga-aquibeprin and the previously described, structurally related c(RGDfK) trimer (\( 68 \)Ga-avebetrin, which shows an inverse selectivity for integrin \( \beta_v\beta_3 \) (IC50 = 0.22 nM) over \( \beta_5\beta_1 \) (IC50 = 39 nM). In vivo target specificity was proven by cross-competition studies; tumor uptake of either tracer was not affected by the coadministration of 40 nmol (~5 mg/kg) of the respective other compound. (\( 68 \)Ga-aquibeprin and (\( 68 \)Ga-avebetrin are recommendable for complementary mapping of integrins \( \beta_5\beta_1 \) and \( \beta_v\beta_3 \) by PET, allowing for future studies on the role of these integrins in angiogenesis, tumor progression, metastasis, and myocardial infarct healing.