Characterization of A Type 1 Collagen Targeted PET Tracer

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Renal fibrosis occurs in many diseases of the kidney, including chronic kidney disease (CKD). Renal fibrosis is characterized by an excessive accumulation and deposition of extracellular matrix components, mainly type I collagen. Determination of the presence and extent of renal fibrosis may aid in the prediction of the long-term outcome of renal function in CKD. Biopsy is considered the gold standard in the diagnosis of renal fibrosis; however biopsy is inherently invasive and does not easily lend itself to following the disease thru time. A noninvasive technique such as PET would both allow the detection and monitoring of renal fibrosis progression. A type I collagen-specific cyclic peptide, EP-3533, has been identified and used as a contrast agent in MRI after conjugation with three Gd-DOTA chelates (Caravan et al 2007). To explore the potential for imaging with PET, which can provide a quantitative assessment of regional peptide localization, we have prepared an EP-3533 conjugate incorporating the NODAGA chelating agent at its amine terminus, and radiolabeled that conjugate with generator-produced positron-emitting ^{68}Ga (68-minute half-life). In vitro association kinetics binding of the labeled peptide was performed in collagen type 1 coated plates, where ^{68}GaDOTA-EP-3533 exhibited a K_d of 0.2 μM for type I collagen. To better characterize the tracer in an animal model, renal fibrosis was induced in male Wistar rats by clamping the renal artery and vein of the left kidney for 50 minutes. Thus providing both a diseased and control kidney in each animal. Approximately 10 weeks after surgery both left (fibrotic) and right (normal) kidneys were resected and frozen and mounted in OTC for cryotomy. Longitudinal sections obtained from each kidney were used for autoradiography. ROI analysis found an approximate two- to four-fold region-dependent increase in binding in fibrotic tissue compared to normal. Collagen and non-collagen protein levels were determined in the same kidney sections that had been used for autoradiography using a commercially available staining assay. This assay yielded a 1.7-fold difference in collagen levels between normal and fibrotic tissue. Additionally, representative slices were stained with Sirius Red for histological evaluation. Preliminary data indicates that 68Ga-NODAGA-EP-3533 binds to collagen-rich tissue, consistent with the literature for Gd-DOTA-EP-3533. In vivo studies in an animal model of fibrosis are needed to further characterize this tracer and its potential for PET tracer detection and monitoring of Renal Fibrosis.