T5-2

PRECLINICAL ANALYSIS OF MELANOMA WITH GA-68 LABELED PROCAINAMIDE DERIVATIVES

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Introduction: Malignant melanoma is the most aggressive form of skin cancers. Although, only 3–5 percent of the skin cancer is melanoma, it possesses the worst prognosis. Nowadays one of the most efficient methods in tumor diagnostics is PET imaging; several recent studies focus on the development of melanoma specific tracer. Previous researches have shown that benzamide derivatives were proven to be specific markers for detection of melanoma. The aim of this study was to radiolabel the NODAGA and HBED-CC chelator conjugated PCA derivative with Ga-68, and in order to PET imaging, to apply the labeled compounds on animal models of melanoma. Moreover, we aimed an extensive testing of the compounds under in vitro and in vivo conditions.
Methods: The procainamide was conjugated with NODAGA and HBED-CC chelators. The complete ligands were purified with RP-HPLC and then were lyophilized. The product was characterized by ESI-MS and ^{1}H-NMR. The ^{68}Ge/^{68}Ga generator (Eckert-Ziegler, Obninsk) was eluted by using 0.1 M with 5 mL HCl. The labeling was accomplished on pH = 4.5–4.6 in NaOAc buffer at room temperature and at 95 °C for five minutes. The melanin specificity of ^{68}Ga-HBED-CC-PCA and ^{68}Ga-NODAGA-PCA was investigated in vitro and in vivo using amelanotic (MELUR and A375) and melanin containing (B16-F10) melanoma cell lines. Tumour-bearing animals were prepared by subcutaneous injection of B16-F10, MELUR and A375 melanoma cells into C57BL/6 ($n = 10$) and SCID ($n = 9$) mice.
Results: Procainamide derivatives conjugated with two different chelators were prepared successfully. The compounds possessed excellent radiochemical purity (≥ 98%). The octanol-PBS partition coefficients (LogP) of the two radiolabeled compounds were determined. Based on the results of the in vitro measurements the ^{68}Ga-NODAGA-PCA showed significantly ($p \leq 0.01$) higher accumulation than the ^{68}Ga-HBED-CC-PCA on the B16-F10 cell line.
Conclusion: Two ^{68}Ga labelled PCA derivatives were developed, which could selectively accumulate in melanin producing melanoma cells. The uptake values of the compounds are diverse and the in vivo preclinical measurements have confirmed, that the ^{68}Ga-NODAGA-PCA possessed higher uptake on tumour models. Therefore, it was proven that the heterobifunctional chelators also served as pharmacokinetic modifiers, and by their selection the distribution profile of the radioligands within the organism can be considerably modifiable.

T5-3

PET/MR IMAGING OF APN/CD13 EXPRESSION OF EXPERIMENTAL TUMORS USING 68GA-LABELLED NGR DERIVATIVES

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INTRODUCTION: Aminopeptidase N (APN/CD13) plays an important role in neo-angiogenic process and metastatic tumor cell invasion. Our previous studies have already shown that ^{68}Ga-labelled NGR peptides specifically bind to APN/CD13 expressing tumor cells. The ^{68}Ga labelled NGR peptides were enabled to investigate the neo-angiogenic process with Positron Emission Tomography (PET). The aim of this study was to investigate and compare the ^{68}Ga-NOTA-c(NGR), ^{68}Ga-NODAGA-NGR (tioether) and ^{68}Ga-NODAGA-NGR (sarcosine) specificity of APN/CD13 in hepatocellular carcinoma (He/De) and mesoblastic nephroma (Ne/De) tumor models using PET/MRI.
Methods: He/De (hepatocellular carcinoma) and Ne/De (mesoblastic nephroma) cells were used for the induction of heterotopic transplanted [subcutaneously ($n = 4$) and under the left kidney capsule ($n = 4$)] tumor models in Fischer-344 rats. Whole body PET/MRI (nanoScan PET/MRI, Mediso Ltd, Hungary) scans and ex vivo biodistribution studies were performed using tumor-bearing and control ($n = 3$) animals 90 min after intravenous injection of 6.9 ± 0.2 MBq ^{68}Ga-NOTA-c(NGR) or ^{68}Ga-NODAGA-NGR (tioether) or ^{68}Ga-NODAGA-NGR (sarcosine) and two weeks after tumor cell implantation. The imaging of neoangiogenetic process with ^{68}Ga-NOTA-c(NGR) was compared with ^{68}Ga-NODAGA-NGR (tio) and ^{68}Ga-NODAGA-NGR (sar) tracer. Aminopeptidase N receptor expression of He/De and Ne/De tumors was verified by western blot analysis.
Results: In control animals using ^{68}Ga-NOTA-NGR high SUVmean values were observed in abdominal organs, however, in the case of ^{68}Ga-NODAGA-NGR (tio) and ^{68}Ga-NODAGA-NGR (sar) it was much higher. SUVmean and Tumor/Muscle(SUVmean) ratios were found higher after injection of ^{68}Ga-NOTA-NGR, than the administration of ^{68}Ga-NODAGA-NGR (tio) or ^{68}Ga-NODAGA-NGR (sar) in Ne/De tumor bearing animals. In the case of He/De tumor bearing animals comperable SUVmean and Tumor/Muscle(SUVmean) values were detected. Higher SUVmean and Tumor/Muscle(SUVmean) ratios were measured after the injection of ^{68}Ga-NOTA-NGR, than after that of the ^{68}Ga-NODAGA-NGR (tio) or ^{68}Ga-NODAGA-NGR (sar). The APN/CD13 receptors attendance was demonstrated with Western blot analysis.
Conclusions: Among the investigated radiopharmacons the ^{68}Ga-NOTA-c(NGR) showed the highest binding affinity to APN/CD13 positive tumors by PET/MRI imaging. Therefore, ^{68}Ga-NODAGA-NGR (tio) showed sufficient and ^{68}Ga-NODAGA-NGR (sar) showed the worst properties for the detection of APN/CD13 expression.
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T5-4

INVESTIGATION OF MSH RECEPTOR EXPRESSION USING GA-68- AND SC-44-LABELED MOLECULES

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INTRODUCTION: Alpha melanocyte stimulating hormone (alpha-MSH) enhances melanogenesis in melanoma malignum by binding to melanocortin 1 receptor (MC1R). Earlier studies demonstrated that MSH analogues (e.g. NAPamide) specifically binds to MC1R receptor. Radiolabeled NAPamide is a promising radiotracer for the detection of melanoma tumors by Positron Emission Tomography (PET). In this present study the MCR1 selectivity of the newly developed Sc-44-labeled DOTA-NAPamide was investigated using melanoma tumors.
METHODS: MC1R positive (B16-F10) and negative (A375) melanoma cell lines were used. Cells (1×10^6/ml tube) were incubated for 30 or 60 min in the presence of 0.74 MBq of Sc-44- or Ga-68-labeled DOTA-NAPamide. After the incubation time samples were washed and the radioactivity was measured with calibrated gamma counter. For the induction of tumor models 1×10^5 A375 or B16-F10 tumor cells were injected subcutaneously into the left shoulder area of CB17 SCID or C57BL/6J mice, respectively. For imaging studies mice were injected intravenously with 13 ± 1.2 MBq of Sc-44/Ga-68-labeled DOTA-NAPamide 15 ± 1 days after tumor cell inoculation. 20-min static whole body PET scans were acquired 60 min after radiotracer injection using preclinical PET/MRI. Radiotracer uptake was expressed in terms of standardized uptake values (SUVs).
RESULTS: In vitro and in vivo imaging experiments showed that Ga-68- and Sc-44-labeled DOTA-NAPamide specifically bind to MC1 receptors of B16-F10 cell and tumors. B16-F10 cells showed significantly ($p \leq 0.01$) higher in vitro radiotracer accumulation than that of A375 cells. In animal experiments, significantly ($p \leq 0.01$) higher Ga-68-DOTA-NAPamide (SUVmean: 0.38 ± 0.02), and Sc-44-DOTA-NAPamide (SUVmean: 0.52 ± 0.13) uptake was observed in subcutaneously growing B16-F10 tumors, than in A375 tumors, where the SUVmean values of Ga-68-DOTA-NAPamide and Sc-44-DOTA-NAPamide were 0.04 ± 0.01 and 0.07 ± 0.01, respectively. We found that the tumor-to-muscle (T/M SUVmean) ratios were approximately 15-fold higher than the T/M ratios of A375 tumors, and this difference was also significant ($p \leq 0.01$) using both radiotracers. No difference was observed between Ga-68- and Sc-44-labeled DOTA-NAPamide uptakes.
CONCLUSION: The investigated Sc-44-labeled DOTA-NAPamide, as a newly developed PET radiopharmaceutical specifically binds to MC1 receptors of melanoma cells. Due to its high specificity Sc-44-DOTA-NAPamide is a promising PET radiotracer for the detection of melanocortin 1 receptor positive melanoma tumors in the clinical routine.

T6. CLINICAL NUCLEAR MEDICINE

T6-1

CARDIAC 18F-FDG PET/CT IN CONNECTIVE TISSUE DISEASES

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INTRODUCTION: Cardiac involvement is a common complication in connective tissue diseases particularly in systemic sclerosis (SSc). In SSc the immuno-inflamatory damage leads to myocardial fibrosis and consequent myocardial dysfunction. The development of overt myocardial manifestation is recognized as powerful adverse prognostic factor. 18F-FDG PET/CT has increasing role in inflammatory diseases with myocardial manifestation. The aim of this study was to assess the diagnostic utility of cardiac 18F-FDG PET/CT in patients with SSc, and to evaluate simultaneously results of 2Dimensional Speckle Tracking Echocardiography (STE).
METHODS: 17 patients with connective tissue diseases (13 patients with SSc and 4 patients with suspected arteritis, age: 57.3 ± 10, 13 female, 4 male) where enrolled in the prospective study. After low carbonhidrate-diet (previous 24 hours) and extended fasting (6 hours) cardiac ^{18}F-FDG-PET/CT acquisition was performed in 2D mode and short-whole-body in 3D mode. Within 24 hours all patients underwent comprehensive echocardiography focusing on left ventricular myocardial mechanics applying STE. The recommended 17 segment model was used to assess the 18F-FDG activity and for the calculation of myocardial strain as well. On -FDG PET/CT the segmental myocardial 18-FDG uptake in kBq/cc by PMOD software was calculated. The strain values were measured offline by speckle tracking EchoPAC software.
RESULTS: Among 17 patients 5 patients (29%) showed significantly increased 18F-FDG uptake (18.6 ± 6.8 kBq/cc vs. 7.77 ± 3.4 kBq/cc, $p < 0.01$) in the myocardium. In patients where the 18F-FDG uptake was increased, measured global left ventricular longitudinal strain values (19.4 ± 2.7% vs. 13.4 ± 8%, $p < 0.01$) was decresed. There was a negative correlation between myocardial strain and 18F-FDG uptake ($p < 0.05$, $r = -0.54$) In 4 patients with arteritis, the 18-FDG uptake was not increased (4 ± 0.2 kBq/cc), and left ventricular strain values were also in physiological range (21.5 ± 2%).
CONCLUSION: 18F-FDG PET/CT is a promising imaging tool to detect myocardial manifestation of SSc. In the active condition of the myocardial involvement STE provides a simple, non-invasive modality to detect subtle mechanical changes in myocardium.