Novel Myristoylated Polyarginine Peptides for Molecular Neuroimaging: Initial In Vivo Studies

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Introduction

Recently we have demonstrated that a myristoylated polyarginine peptide (MPAP) could cross the blood brain barrier (BBB) non-invasively. Furthermore, the delivery module could carry a fluorescent cargo across the BBB and its distribution was conveniently detected by in vivo optical imaging. From this study we suggested that MPAP has the potential to be a molecular imaging agent in various applications for carrying targeting molecules/therapeutic drugs across the BBB. However, to increase the detection limit that is relevant for a clinical study, we modified MPAP to incorporate an MR imaging moiety (gadolinium). The accompanying poster from our laboratory describes the design and synthesis of MPAP-Gd. In this pilot study, we assessed whether a gadolinium-modified delivery module could be detected in the brain tissue in vivo using high resolution MRI.

Materials and Methods

$MPA_{11}P$-Gadolinium ($MPA_{11}P$-Gd) was synthesized using solution and solid phase chemistry. The resultant compound consisted of a myristoylated peptide containing 11 arginines and conjugated to DOTA, which served as gadolinium chelate.

For our preliminary imaging studies we administered $MPA_{11}P$-Gd in athymic nude mice (n=3, 20 nmol) intraperitoneally and subjected them for vivo MR imaging before injection and 24 and 48 hours post-injection. MR imaging was performed using a 9.4 T Bruker horizontal bore scanner (Billerica, MA) equipped with ParaVision 3.0 software. For the quantitative comparison, T1 maps of the head were acquired using a T1 inversion recovery sequence with the following parameters: TE = 8.257 ms; TR = 10000 ms; TI = 0.001-200.000-400.000-800.000-1600.000- 3200.000-6400.000 ms; FOV = 19.2 x 19.2 mm; image matrix = 128 x 64; slice thickness = 0.5 mm.

The images were processed using Marevisi 3.5 software (Institute for Biodiagnostics, National Research Council, Canada). In each slice the brain was manually segmented and a T1 map image was created for qualitative analyzes. For quantitative analysis, 6 slices were segmented. The data from these slices were compiled together, normalized for total volume and plotted in histograms using MatLab 7.0 software.

Results

On visual inspection, no differences could be detected between the T1 maps before and after $MPA_{11}P$-Gd administration at the dose injected. Calculating the mean T1 for the segmented brain did not result in a significant change. However, analysis of the T1 histogram peak heights and locations showed a difference in T1 pre- and post-injection as seen in Figure 1. Twenty-four hours after administration of MPAP-Gd there was a shift towards a lower T1 time returning back to pre-injection values 48 hours later. All three animals demonstrated the same pattern in T1 shifting 24 hours after administration.

Conclusions

The preliminary results of this pilot study demonstrated that $MPA_{11}P$-Gd could be detected in vivo using high resolution MRI. As such, this molecular agent has a potential for in vivo molecular neuroimaging. Further studies are required to improve the ability to visualize the difference between pre- and post-contrast images. In our future work we are planning to investigate the dose regiment and different routes of administration.

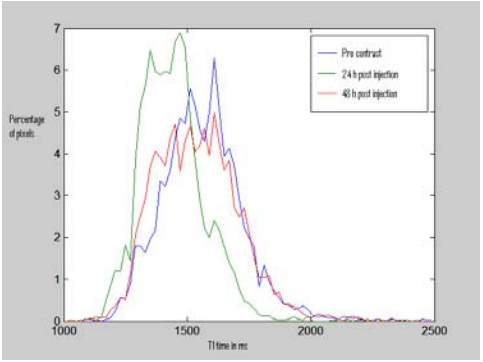

Figure 1. Representative T1 map histogram.