Dual MRI-SPECT agent for pH-mapping

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Introduction

Alterations in extracellular tissue pH accompany many disease processes, such as cancer, inflammation and infection. In tumours, extracellular pH is often lower than in normal tissue and it can be correlated with prognosis.[1] Therefore, the capability to image tissue pH in the clinic would offer a generic method for detecting disease and response to treatment. There are currently no such methods that could be used in the clinic, even if advances have been made for the in vivo measurement of tumor pH.[2]

Despite the good pH responsiveness of several reported Gd(III) containing systems, their practical use has been hampered by the need of knowing their local concentration in order to unambigously assign the observed variations to changes in relaxivity and not to changes in the local concentration of the paramagnetic agent.

Herein we report our results aimed at developing a dual MRI/SPECT pH-responsive agent where the SPECT-active moiety acts as a reporter of the concentration of the MRI responsive one thus allowing the transformation of the observed ^{1}H-relaxation rates into relaxivities to recover the information relative to the pH determination.

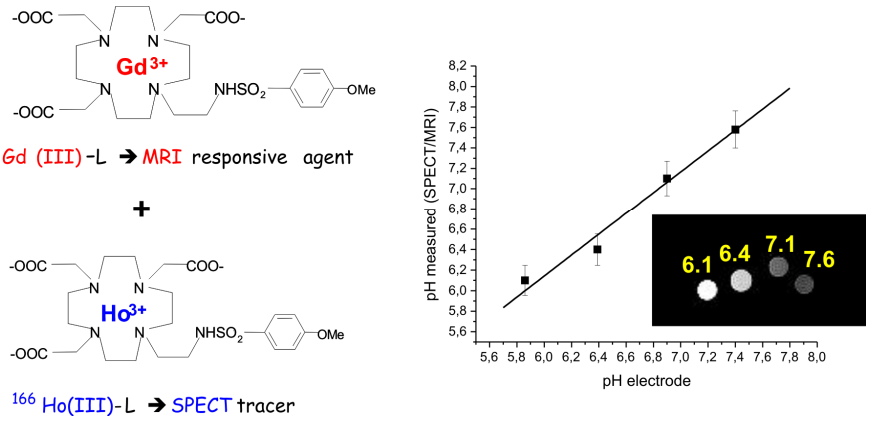
Methods

The relaxivity pH dependence of the Gd-containing complex was measured on a a Bruker Avance300 spectrometer operating at 7.1T equipped with a microimaging probe by using a Saturation Recovery Spin Echo sequence (TE = 2.6 ms, 16 variable TR ranging from 40 to 5000 ms, NEX = 1, FOV = 1.1x1.1 cm^2, 3 slices, slice thickness = 1 mm). The exact concentration of Gd-complexes solutions was measured through a relaxometric method. Ho(III)-L was prepared using a commercial $HoCl_3$ salt which natural abundance is 100% ^{165}Ho (SPECT inactive). ^{165}Ho, when exposed to a neutron flux, transforms into ^{166}Ho that is unstable ($t_{½}$ 26.6 h) and emits γ-radiation (6.6% at 80.6 KeV and 0.9% at 1.38 MeV) which may be exploited for the determination of the probes concentration via gamma camera. For neutron irradiation (36 MeV protons, 18 μA, 2 h), a cyclotron-driven neutron activator, realized on a modification of the ARC method, has been installed on a beam line of the Scanditronix MC40 Cyclotron (*K*=40) of the Joint Research Centre (JRC, Ispra, Italy). Then the samples underwent to γ-counting to yield the quantitative information by the use of two different calibration lines previously obtained by measuring γ-rays emission at 80.6 Kev and 1.38 MeV as a function of the Ho-complex concentration. The exact concentration of Ho(III)-L complex for each experimental point has been independently determined through the Evans's method.

The final MR-image of a phantom consisting of four tubes containing different concentrations of Ho(III)-L/Gd(III)-L (20:1) complexes and pH ranging from 5.9 to 7.4 was registered on a Bruker 300 spectrometer equipped with a micro-imaging probe operating at 7.1T using a standard T_1 weighted multislice multiecho sequence (TR = 250 ms, TE = 3.3 ms, NEX = 6, FOV = 1.15x1.15 cm^2, 3 slices, slice thickness = 1 mm).

Results

Herein we report our results aimed at developing a dual MRI/SPECT pH-responsive system where the MRI moiety and the SPECT moiety are represented by two chelates differing only for the coordinated lanthanide(III) ion being Gd(III) for the former and Ho(III) for the latter. Ho(III)-L and Gd(III)-L are expected to share the same biodistribution when administered *in vivo* . The relaxivity of Gd-L is strongly pH-dependent as as a consequence of a change in the hydration state (q). In fact this macrocyclic Gd(III) complex shows high relaxivity at acidic pH (q=2) and low relaxivity at basic pH (q=0)[3]. Ho(III)-L displays very low relaxivity enhancement at any pH values. The SPECT inactive ^{165}Ho, when exposed to a neutron flux, transforms into ^{166}Ho that is unstable ($t_{½}$ 26.6 h) and emits γ-radiation (6.6% at 80.6 KeV and 0.9% at 1.38 MeV) which may be exploited for the determination of the probes concentration via gamma counting. By the use of previously determined calibration lines at the two energy values, it was possible to extract the Ho(III) concentrations of the samples, and from these the corresponding Gd(III) concentrations as for all four specimens the same Ho/Gd ratio was used (20.6:1). Next, through the use of the relationship between the relaxivity and pH, which may be considered quite linear in the pH range 6-7.5, the MR imaging data may be analyzed to estimate pH of the samples. A good correspondence between the pH measured by a pH electrode and the values determined by the SPECT/MRI probe (error ca. 3%) was obtained.



Conclusions

In summary, the herein reported proof of concept has shown that a novel method for mapping pH by using a dual MRI/SPECT agent based on two "chemically equivalent" lanthanide(III) complexes is now available. By properly designing the structure of the L ligand, one may pursue different applications for this kind of MRI/SPECT dual probes, for instance as responsive of enzymatic activity or metabolites concentration.

References

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