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In vitro and ex vivo characterization of GdEOBDTPA by multinuclear Magnetic Resonance

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1-Introduction. GdEOBDTPA is an open chain contrast agent showing higher relaxivity than GdDTPA and targeting the hepatobiliary system. The aim of this work was: i-to determine the parameters defining its relaxivity in aqueous solution using H-1, H-2 (1) and O-17 NMR (2,3), ii-to test its stability in phosphorylated metabolites solutions by P-31 NMR (4), iii-to analyse its possible interactions with blood proteins by H-1 and H-2 NMR, and finally-to study its metabolic and relaxation effects on ATP, phosphodiesters (PDE), phosphomonooesters (PME) and inorganic phosphate (Pi) of the excised and perfused rat liver by P-31 NMR.

2-Subjects and methods. GdEOBDTPA and EOBDTPA were generous gifts of Schering A.G.-Berlin. EOBDTPA was deuterated in α of the carboxylic groups. The other compounds were purchased from Sigma (human serum albumin-HSA, ATP, phosphocreatine) or Behring (serum kontrollegen). Proton Nuclear Resonance Dispersion profiles were recorded on an IBM Research relaxometer and additional points at 200 and 300 MHz were obtained on Bruker MSL-200 and AMX-300 spectrometers. H-2, O-17 and P-31 NMR spectra were obtained on a Bruker MSL-200 spectrometer. Rat livers were perfused in a recirculating mode as described elsewhere (5) and submitted to 20 min of perfusion with a Krebs Henseleit solution containing 1 mM of GdEOBDTPA but free of EDTA. P-31 spectra of perfused rat livers were recorded at 121 MHz on the Bruker AMX-300 spectrometer.

3-Results.

Aqueous solution: The solvent H-1 NMRD profiles, the rotational correlation times (calculated from H-2 relaxation rates), the exchange time τM and the number of coordinated water molecules (both obtained by O-17 NMR) show that the higher relaxivity of GdEOBDTPA as compared to GdDTPA results from a shorter distance between coordinated water molecule and Gd3+ and to a slower tumbling of the complex. The values of the number of coordinated water molecules and of the exchange time are however similar to those of GdDTPA.

Protein solutions: H-1 NMRD profiles of GdEOBDTPA dissolved in serum or in human serum albumin solution show a hump at high field which is characteristic of an interaction between the complex and the macromolecules. The dissociation constant between GdEOBDTPA and HSA calculated from H-2 and H-1 relaxation rates is in the range of 4 to 1.1 mM.

Stability test: The variations of R1 of P-31 of ATP, Pcr and Pi after addition of GdEOBDTPA show that the competition of ATP with GdEOBDTPA to form gadolinium-ATP complex is much slower that with GdDTPA. The thermodynamic stabilities of these compounds are however identical.

Perfused livers: P-31 relaxed spectra (TR=3s) show only little change during GdEOBDTPA perfusion or during the washout with Krebs Henseleit buffer: ATP and Pi levels are unchanged indicating that GdEOBDTPA does not impair the metabolism of hepatocytes. The linewidths of the ATP peaks are temporarily increased showing the internalization of the contrast agent. The increase of P-31 peak heights of PME, PDE and Pi in saturated spectra (TR=80ms) results from the relaxation effects induced by GdEOBDTPA and further confirms that GdEOBDTPA enters the hepatocytes.

4-Conclusion. The presence of an aromatic ring on the ligand induces a decrease of the distance between water and Gd3+, an increase of τR, interactions with albumin, and internalization of the complex into hepatocytes, a trend which seems therefore general for this kind of benzene derivatives of GdDTPA (6).

In vitro and ex vivo characterization of GdEOBDTPA by multinuclear magnetic resonance

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Introduction: GdEOBDTPA is an open chain contrast agent showing higher relaxivity than GdDTPA and a targeted distribution due to intramolecular shielding. The aim of this study was: i) to determine the parameters defining its relaxivity in aqueous solution using 1H, 2H [1] and 17O NMR [2,3]. ii) to test its stability in phosphorylated metabolites solutions by 1P NMR [4], iii) to analyse its possible interactions with blood proteins by 1H and 13C NMR, and finally to study its metabolic and relaxation effects on ATP, phosphodyastases (PDE), phosphomonoesters (PME) and inorganic phosphate (Pi) of the excised and perfused rat liver by 31P NMR.

Subjects and methods: GdEOBDTPA and EOBDTPA were generous gifts of Schering A.G.-Berlin. EOBDTPA was deuterated in α of the carboxylic groups. The other compounds were purchased from Sigma (human serum albumin-HSA, ATP, phosphocreatine) or Behring (serum control). Proton Nuclear Resonance Dispersion profiles were recorded on an IBM Research relaxometer and additional points at 200 and 300 MHz were obtained on Bruker MSL-200 and AMX-300 spectrometers. 2H, 17O and 31P NMR spectra were obtained on a Bruker MSL-200 spectrometer. Rat livers were perfused in a recirculating mode as described elsewhere [5] and submitted to 20 min of perfusion with a Krebs Henseleit solution containing 1 mM of GdEOBDTPA but free of EDTA. 31P spectra of perfused rat livers were recorded at 121 MHz on the Bruker AMX-300 spectrometer.

Results: Aqueous solution: The solvent 1H NMRD profiles, the rotational correlation times calculated from 1H relaxation rates, the exchange time t_M and the number of coordinated water molecules (both obtained by 17O NMR) show that the higher relaxivity of GdEOBDTPA as compared to GdDTPA results from a shorter distance between coordinated water molecule and Gd3+ and to a slower tumbling of the complex. The values of the number of coordinated water molecules and of the exchange time are however similar to those of GdDTPA.

Protein solutions: 17O NMRD profiles of GdEOBDTPA dissolved in serum or in a protein solution at high concentration is characteristic of an interaction between the complex and the macro-molecules. The dissociation constant between GdEOBDTPA and HSA calculated from 2H and 17O relaxation rates is in the range of 4 to 1.1 mM.

Stability test: The variations of R2 of 17P of ATP, PCR and Pi after addition of GdEOBDTPA to a mixture of ATP with GdEOBDTPA to form gadolinium-ATP complex is much slower than with an IBM Research relaxometer. The thermodynamic stabilities of these compounds are however identical.

Perfused livers: 17P relaxed spectra (TR = 3 s) show little change during GdEOBDTPA perfusion or during the washout with Krebs Henseleit buffer: ATP and Pi levels are unchanged indicating that GdEOBDTPA does not interact with rat hepatocytes. The linewidths of the ATP peaks are temporarily increased showing the internalization of the contrast agent.

The increase of 31P peak heights of PME, PDE and Pi in saturated spectra (TR = 80 ms) results from the relaxation effects induced by GdEOBDTPA and further confirms that GdEOBDTPA enters the hepatocytes.

Conclusion: The presence of an aromatic ring on the ligand induces a decrease of the distance between water and Gd3+, an increase of T2, interactions with albumin, and internalization of the complex into hepatocytes, a trend which seems therefore general for this kind of benzene derivatives of Gd-DTPA [6].

References

Interventional MRI

280 Interventional MR Imaging
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To reduce patient morbidity and mortality and thus health care costs, minimally invasive procedures are increasingly employed. Imaging is an integral part of many of these procedures. It is needed for (1) pre-procedure planning, (2) guidance and control during the procedure itself and (3) assessment of the efficacy of the procedure. MR Imaging provides excellent soft tissue contrast, multiplanar imaging capabilities and good spatial resolution. Data can be acquired in a three-dimensional format, permitting reformating in any plane, using a number of different vantage points. The flow sensitivity of the MRI experiments allow for the non-invasive imaging of the arterial as well as venous vasculature. New three-dimensional techniques provide tremendous vascular detail and have been shown to be useful in the evaluation of a number of applications throughout the body. In addition MR is capable of providing functional information, including quantitation of both flow velocities and absolute flow volumes using the phase contrast technique.

One of the unique features of MR imaging pertains to the temperature sensitivity of the MR experiment. In fact there are three different physical properties that are measurable with MR and are temperature dependent. All three will be discussed.

Current MRI technology, employing high resolution 3D imaging with data segmentation is already employed for detailed procedure planning and the assessment of therapeutic effectiveness. Despite its very favorable imaging properties making MRI a potentially ideal modality for monitoring and controlling invasive therapeutic procedures, MRI has played a very limited role in this respect, largely owing to the lack of patient accessibility. The availability of open MRI configurations now permits to take advantage of the unique imaging features inherent to MRI for the purpose of guidance and control while the procedure is actually performed by an interventionalist. Various scanner designs will be introduced. Advantages and disadvantages will be outlined.

281 MRI guided therapy
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The non-diagnostic use of cross-sectional imaging modalities is limited. This condition is primarily related to the difficulty to integrate these systems with therapeutic procedures and devices which potentially call for image guidance. Image-guided therapy is a new emerging field which has a close relationship to interventional radiology, minimally invasive surgery, and computer assisted visualization. Image guidance for minimally invasive surgical and interventional therapeutic procedures is necessitated by the spatial restriction of direct visual control. The goal of interventional MRI is to provide real time image guidance for surgical and interventional procedures. The first superconductive open magnet system specifically designed for interventional use is being tested. The open configuration system allows the physician full access to the patient and provides interactive control of image planes. We describe our experience with this system in localizing, targeting and directing therapeutic interventions.