Gd-BOPTA transport in rat hepatocytes: uptake and biliary excretion are highly temperature dependent

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Purpose

Gd-BOPTA is a hepatobiliary contrast agent (CA) for MRI whose uptake into hepatocytes is not fully understood. Evidence exists that Gd-BOPTA enters into rat hepatocytes through a transporter belonging to the Oatps [1-3]. After its intracellular transport, Gd-BOPTA is eliminated into the bile through the ATP-dependent Mrp2[4,5]. Information is lacking on the regulation of Gd-BOPTA transport. Although a temperature dependence of transport through Oatps and Mrps has been previously reported [6-8], its influence on the MR SI is unknown. Consequently, the aim of our study is to determine the temperature dependence of Gd-BOPTA transport after having set up a method to quantify Gd-BOPTA uptake using radiotracers (^{153}Gd, ^{153}Sm, and ^{67}Ga) and radioactivity measurements. All the experiments were performed in the isolated perfused rat liver using radiolabeled CAs and MRI.

Materials and Methods

To determine the best radiotracer to label Gd-DTPA, an extracellular CA, and Gd-BOPTA, livers were perfused with KHB solution containing either ^{153}Gd-labeled Gd-DTPA, ^{153}Gd-labeled Gd-BOPTA, ^{153}Sm-labeled Gd-DTPA, ^{153}Sm-labeled Gd-BOPTA, ^{67}Ga-labeled Gd-DTPA, or ^{67}Ga-labeled Gd-BOPTA (200 µM, 38°C, 30 min, 30 mL/min). To determine the effect of temperature on Gd-BOPTA transport, livers were perfused with ^{153}Gd-labeled Gd-BOPTA at 12, 25, 30, 36 and 38°C (200 µM, 30 min, 30 mL/min). Additionally, a single liver in each group was perfused with ^{153}Gd-labeled Gd-DTPA. For bile collection, the common bile duct was cannulated with a PE 10 catheter. After the 30-min perfusion period, 5 biopsies and the total bile volume were collected and the radioactivity was measured. The remaining liver was weighted and used for MR imaging. T1-weighted imaging of tubes containing at least 4 ml of liver tissue was performed on an Intera 1.5 T MR system (Philips Medical Systems, Cleveland, Ohio) using a fast field echo sequence with the following imaging parameters: saturation prepulse, TR/TE 4.3/1.3 msec, FA 80°, FOV 20 cm, matrix size 96 X 128, slice thickness 20 mm. A coil used for human knee imaging was used.

Results and discussion

When livers were perfused with ^{153}Gd-labeled Gd-DTPA (200 µM, 38°C), the concentration of Gd-DTPA in the liver was 23.3 µM (Fig. 1). The liver uptake was much higher when livers were perfused with 200 µM ^{153}Gd-labeled BOPTA (441.6 µM). When CAs were labeled with ^{153}Sm, similar results were obtained (22.6 µM for Gd-DTPA and 421.8 µM for Gd-BOPTA). In contrast, when CAs were labeled with ^{67}Ga, the radioactivity was similar for Gd-DTPA and Gd-BOPTA, (37.7 µM and 46.8 µM respectively). Interestingly, the MRI signal intensity (SI) was two times higher in tubes containing biopsies collected from livers perfused with Gd-BOPTA than in those perfused with Gd-DTPA, independently of the radiotracer.

At 38°C, 5.3 µmol/12 g liver x 30 min of ^{153}Gd-labeled Gd-BOPTA accumulated in the liver and 7.1 µmol/12 g liver x 30 min in the bile (Fig. 2). In contrast, only 0.3 µmol/12 g liver x 30 min was measured in the liver and no CA was detected in the bile when livers were perfused with ^{153}Gd-labeled Gd-DTPA. Gd-BOPTA uptake and excretion were highly temperature-dependent and the lower the temperature, the lower the transport. Only 0.5 µmol/12 g liver x 30 min was measured in the liver and no CA was detected in the bile at 12°C. The decreased transport of Gd-BOPTA into hepatocytes was also observed on MR images (Fig. 3), the SI in tubes containing liver tissue declined with the temperature.

Conclusion

Radiolabeling of CAs is accurate and useful to quantify CAs and thus to better interpret the SI observed in MRI. Labeling with ^{153}Gd and ^{153}Sm is appropriate in contrast to ^{67}Ga-BOPTA. Regulation mechanisms are important for Gd-BOPTA transport because uptake into hepatocytes and biliary excretion are highly temperature-dependent. Interestingly, small variation in temperature (from 36°C to 38°C) importantly modifies the MR images.

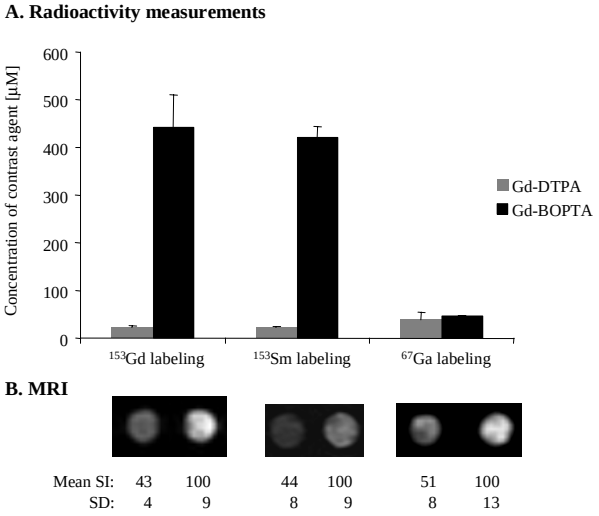

Fig. 1: CA concentration in livers and MRI of tubes containing biopsies collected from livers perfused 30 min with Gd-DTPA and Gd-BOPTA solution (200 µM, 38°C) labeled with ^{67}Ga, ^{153}Sm, and ^{153}Gd. SI of Gd-DTPA tubes were expressed as percentage of Gd-BOPTA tubes set to 100% (n=3).

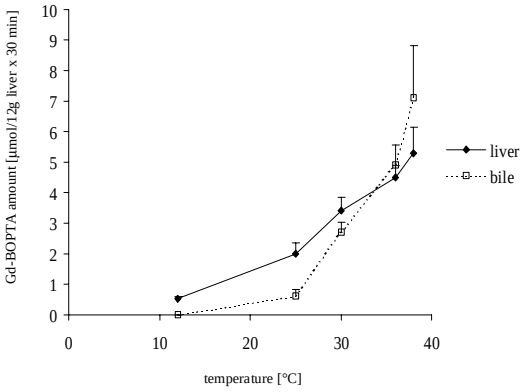

Fig. 2: Amount of Gd-BOPTA in the liver and in the bile after 30 min perfusion (200 µM, ^{153}Gd-labeling) as a function of the perfusion temperature (12, 25, 30, 36 and 38°C) (n=3).

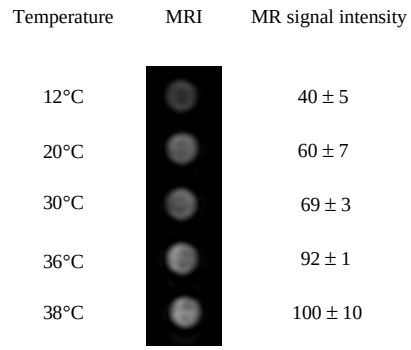

Fig. 3: MRI of and MR SI of tubes containing biopsies collected from livers perfused 30 min with Gd-BOPTA (200 µM) at 12, 25, 30, 36 and 38°C. SI were expressed as percentage of tubes containing tissue of livers perfused at 38°C set to 100 % (mean ± SD, n=3).

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