Gd-complex of Macrocyclic DTPA Conjugate of 2,2′-Diaminobiphenyl: A New MR Contrast Agent for Both Angiography and Brain-Tumor Imaging

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Introduction

Contrast-enhanced magnetic resonance angiography (CE-MRA) is well established for the diagnosis and management of vascular disease. CE-MRA offers a safe alternative to computed tomography, because it requires neither ionizing radiation nor iodinated contrast media. CE-MRA can be supplemented with time-resolved angiography, flow measurement, vessel wall imaging, and plaque characterization for a more comprehensive assessment of vascular disease. Standard extracellular contrast media are currently used for almost all CE-MRA applications. Angiography during the first pass provides strong and selective enhancement of the vessel of interest. During the steady state, however, angiography is not useful because of rapid extravasation of such extracellular contrast media resulting in decreasing vascular and increasing background signal. In this regard it is strongly required for an advent of new-generation MRI contrast agents with special functions such as the blood-pool effect. Herein, we report the synthesis of Gd-complex of macrocyclic DTPA conjugate of 2,2'-diaminobiphenyl for use as a new class of MR contrast agent for both angiography and brain-tumor imaging.

Material and Methods

All reagents were purchased from commercial sources and used as received. DTPA-bis(anhydride), 2,2'-diaminobiphenyl, were synthesized in our lab according to literature method. FAB-mass spectra were obtained by using a JMS-700 model (Jeol, Japan) mass spectrophotometer. T_1 measurements were carried out using an inversion recovery method with variable inversion time (TI) at 1.5 T (64 MHz). T_1 relaxation times were obtained from the non-linear least square fit of the signal intensity measured at each TI value. For *in vivo* MRI, the mice were anesthetized by 1.5% isoflurane in oxygen. MR images of anaesthetized mice (n=4) for MRA and rats (n=3) for MRI were obtained pre- and post- GdL (0.1 mmol Gd/kg) injection by tail vein with a 3 Tesla (T) MR unit (GE Healthcare, Milwaukee, WI, USA) with home-made small animal RF coil. The imaging parameters for SE(Spin Echo) are as follows: repetition time (TR) = 550 ms; echo time (TE) = 11 ms; 4 mm field of view (FOV); 128×128 matrix size; 0.8 mm slice thickness; number of acquisition (NEX) = 4. CE-MRA was carried out with a 3.0 Tesla (T) MR unit (Magnetom Tim Trio, Siemens Medical Solution, Erlangen, Germany) equipped with 8HR wrist coil. The imaging parameters for CE-MRA vibe are as follows: repetition time (TR) = 3.3 ms; echo time (TE) = 1.3 ms; 17 mm field of view (FOV); 0.9 mm slice thickness; 192×65 matrix size; number of acquisition (NEX) = 1

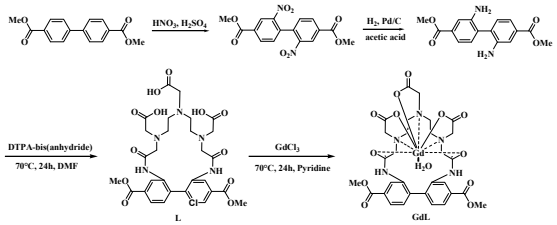
Results and Discussion

The target complex, GdL was synthesized as illustrated in Scheme 1, and its formation confirmed by microanalysis and spectroscopic techniques. GdL reveals very high R_1 relaxivity of 12.15mM^{-1}sec^{-1}, the value of which is nearly 3 times as high as that of analogous macrocyclic system, Dotarem® (R_1=3.7 mM^{-1}sec^{-1}). Kinetic inertness of GdL, as expressed as $R_1^P(t)/R_1^P(0)$, is compared even better than most of commercially available acyclic DTPA-bis(amides) analogues such as Multihance® and Omniscan® (Figuer 1). Yet, the same plot of GdL is located approximately midway between that of Dotarem®, a Gd-macrocyclic system and those of Gd-acyclic DTPA analogues such as Multihace® and Omniscan®. These observations clearly demonstrate the macrocyclic effect. The most remarkable feature of GdL in connection with its blood pool effect can be characterized by the prolonged high signal enhancement of not only the abdominal aorta and heart but also carotid artery with its long-circulating time as long as 120 min (Figure 2). Such a long-circulating time might have caused the brain-tumor imaging as well that can be seen in Figure 3. All-in-all, the present system may put a new entry into a novel and practical MR contrast agent for both angiography and brain-tumor imaging.

Conclusion

GdL exhibits a very strong high blood-pool effect as well as pretty high R_1 relaxivity, demonstrating at the same time brain-tumor imaging capability.

Scheme 1.



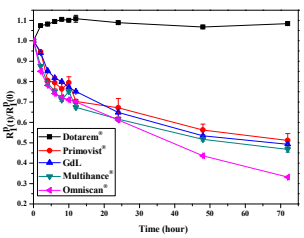
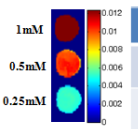


Figure 1. Evolution of $R_1^P(t)/R_1^P(0)$ as a function of time time for various MRI CAs

Table 1. T_1, R_1, T_2, R_2 values for [Gd(**L**)(H_2O)]•$n$$H_2O$ and Dotarem®



sample	T_1 [msec]	R_1 [mM^{-1} s^{-1}]	T_2 [msec]	R_2 [mM^{-1} s^{-1}]
GdL	82.87±1.04	12.15±0.33	76.72±1.69	12.65±0.34
Dotarem®	270.30±2.92	3.7±0.04	244.54±12.5	4.1±0.21

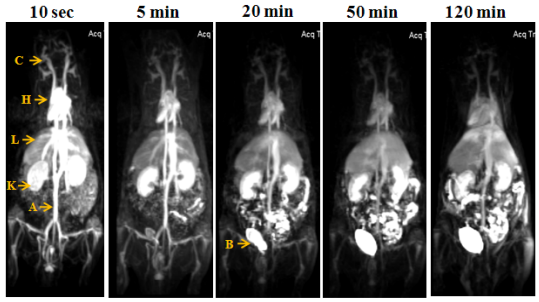


Figure 2. *In vivo* MR coronal maximum intensity projection images of rat obtained with GdL : C, Carotid artery; H, Heart; L, Liver; K, Kidney; A, Abdominal aorta; B, Bladder.

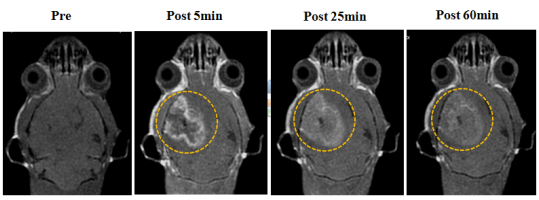


Figure 3. *In vivo* MR coronal images of brain tumor (C6-glyoma cell) obtained with GdL.