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Boron-gadolinium binary system as a magnetic resonance imaging boron carrier*

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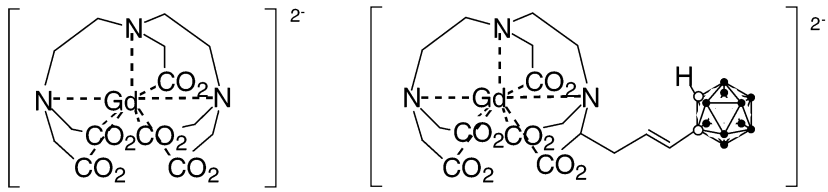
Abstract: The evaluation of the Gd-carborane DTPA complex as a magnetic resonance imaging (MRI) and boron carrier agent was carried out in vivo. The MRI revealed that the Gd-carborane DTPA was metabolized slower in the body in comparison with Gd-DTPA.

In order to improve and optimize efficient NCT treatment, it is necessary to follow the distribution of a carrier in the body in real time. For this purpose, positron emission tomography (PET) using fluorine-18-labeled fluoroboronophenylalanine (^{18}F-BPA) has recently been evaluated in humans. Magnetic resonance imaging (MRI) can also be used to follow the kinetics of the boron compounds. It is indeed a noninvasive tool, and contrast can be modified by the injection of extrinsic contrast agents. Although boron-11 MRI has been studied for this purpose, the actual nucleus for neutron capture reaction is boron-10, and, therefore, the administration of extra amounts of boron-11 compound (which does not undergo the nucleic reaction) is needed for MRI. The Gd-DTPA complex **1**, which is commercially available under the trade name of "Magnevist" and is used as an MRI contrast medium, is paramagnetic, therefore, its effect on the contrast of the images can be best seen on T_1-weighted images with short repetition times. The effect is caused by the gadolinium ion in the center, which induces an enhancement of T_1 relaxation. It has been observed that the blood–brain barrier of brain tumor is disrupted, and that the complex **1** can pass through this disrupted barrier and enter into the tumor tissue. Furthermore, gadolinium-157 has a higher thermal neutron capture cross-section (255 000 b) in comparison with that of boron-10 (3838 b). It occurred to us that a combination of gadolinium-157 and boron-10 might prove effective not only as an MRI but also as a neutron capture therapy. We have recently succeeded the synthesis of the Gd-DTPA complex **2** which contains a carborane unit attached via a palladium-catalyzed C–C bond formation reaction [1]. Herein, we report in vivo evaluation of the complex **2** using tumor-bearing rats by means of MRI, ICP, and α-autoradiographic methods.



Gd-DTPA 1 **Carborane Gd-DTPA 2**

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MRI OF RAT TUMOR WITH Gd-CARBORANE COMPLEX 2 [2]

Figure 1a shows the sagittal T_1-weighted MR image of a rat with a tumor implanted on its back before injection of any compounds, and Figs. 1b–d show the images at 4 min 23 s (b), 11 min 32 s (c), and 50 min 54 s (d) after injection of **2**. The signal intensity of kidney, liver, bladder, heart, and tumor on the images is calculated by the Philips software, and the intensity of the images vs. time is plotted in Figs. 2a and 2b. The signal intensity is plotted as the ordinate, and the time after injection is plotted on the horizontal axis. Although the dynamic change of the intensity in each tissue can be seen from these images, the comparison of the intensity among the tissues is not possible since the signal intensity strongly depends on the distance between the tissue and the surface coil. The contrast enhancement was observed in the center of tissue, which is indicated by the circle in Figs. 1c and 1d. The signal intensity of tumor tissues also increased rapidly after injection of **2** and decreased slowly (Fig. 2b). The signal intensity of kidney rapidly increased after injection of the compound and remained constant throughout the experiment period, whereas, that of liver, heart, and tumor rapidly increased after injection and decreased slowly (Fig. 2). Further, the contrast enhancement was also observed in the bladder at 50 min after injection, which is indicated by the arrow in Fig. 1d. The signal intensity of bladder increased at 45 min after injection (Fig. 2a). On the other hand, the signal intensity of all tissues increased rapidly after injection of normal Gd-DTPA 1 and decreased rapidly after 10 min (Fig. 3). The signal intensity of bladder also increased rapidly after injection.

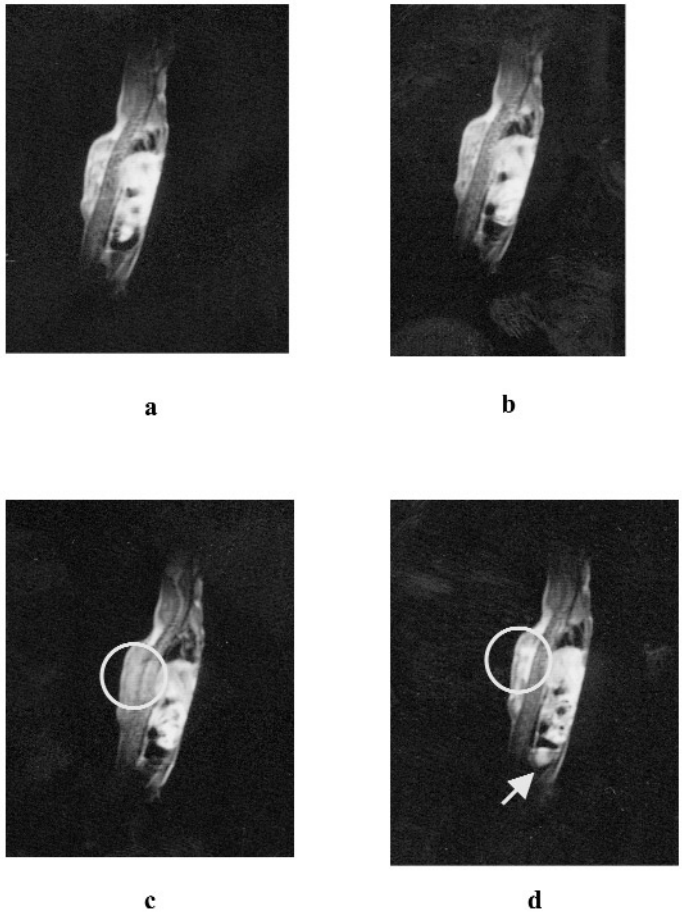

Fig. 1

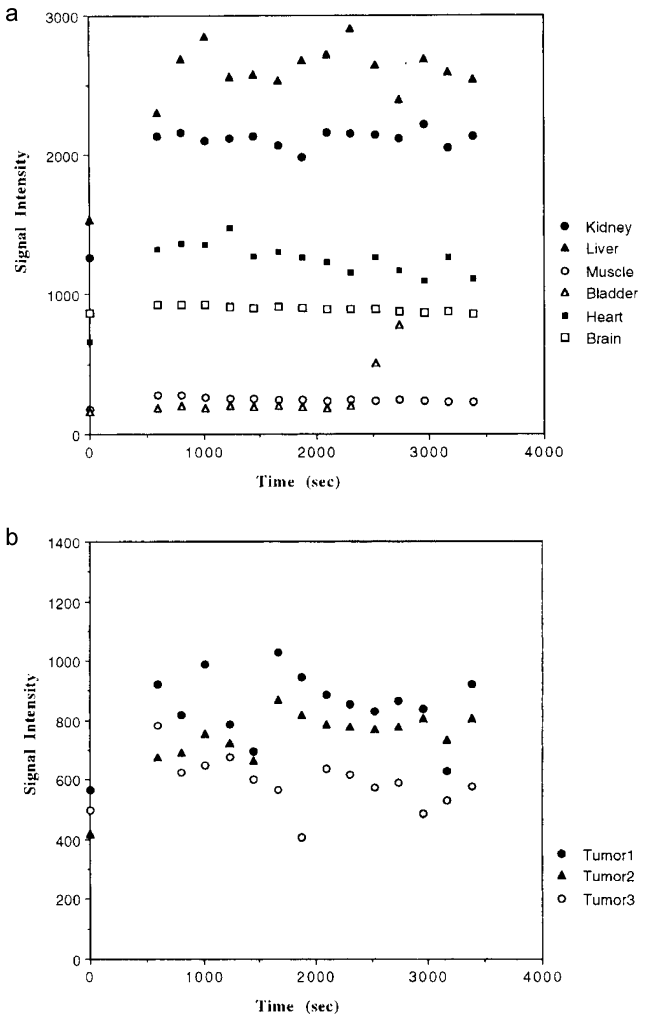

Fig. 2 Gd-carborane 2.

Gd CONCENTRATIONS IN VARIOUS TISSUES OF RATS WITH Gd-CARBORANE COMPLEX 2 USING ICP/AES METHOD

The distribution of gadolinium in the body of rats was investigated with inductively coupled plasma/atomic emission spectroscopy (ICP/AES). The gadolinium concentration in blood was 9.1 ppm at 5 min after injection and then decreased very rapidly. The concentrations in kidney and liver increased after injection, reached a maximum value at 20 min, and then decreased. However, the concentration of gadolinium in tumor and brain was very low.

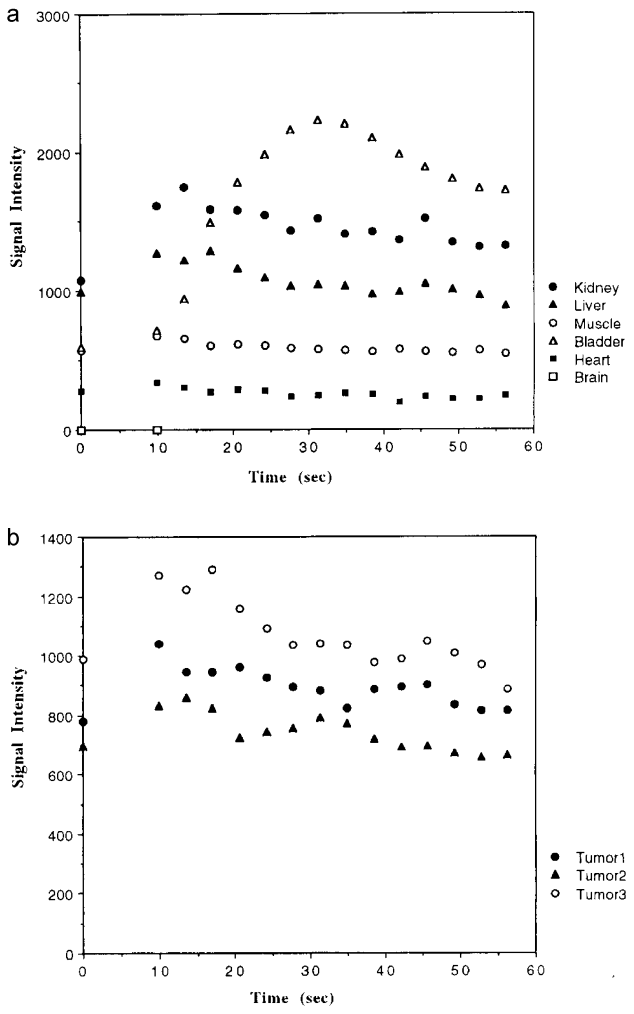

Fig. 3 Gd 1.

BORON DISTRIBUTION IN THE BODY OF TUMOR-BEARING RATS VISUALIZED BY α-AUTORADIOGRAPHY

The α-autoradiography of the rats bearing tumor is shown in Fig. 4. The boron was mainly distributed in the blood pool, and the concentration was relatively high in heart, lung, and kidney at 15 min after injection (Fig. 4a). However, the concentration of boron in the blood decreased, whereas it was still high in the intestines and kidney at 60 min after injection (Fig. 4b). Although the boron concentration in the tumor was relatively low at 15 min, higher accumulation of boron was visualized in the center of the tumor tissue and in the intestines at 60 min.

DISCUSSION

It is important to investigate whether gadolinium complex is stable in the body or gadolinium is dissociated from the boronated DTPA scaffold. We tried to determine the boron concentrations in various tissues of rats. However, it was difficult to measure them by ICP/AES since unidentified strong signals and the boron signals overlapped each other, which made difficult to observe precise and correct the

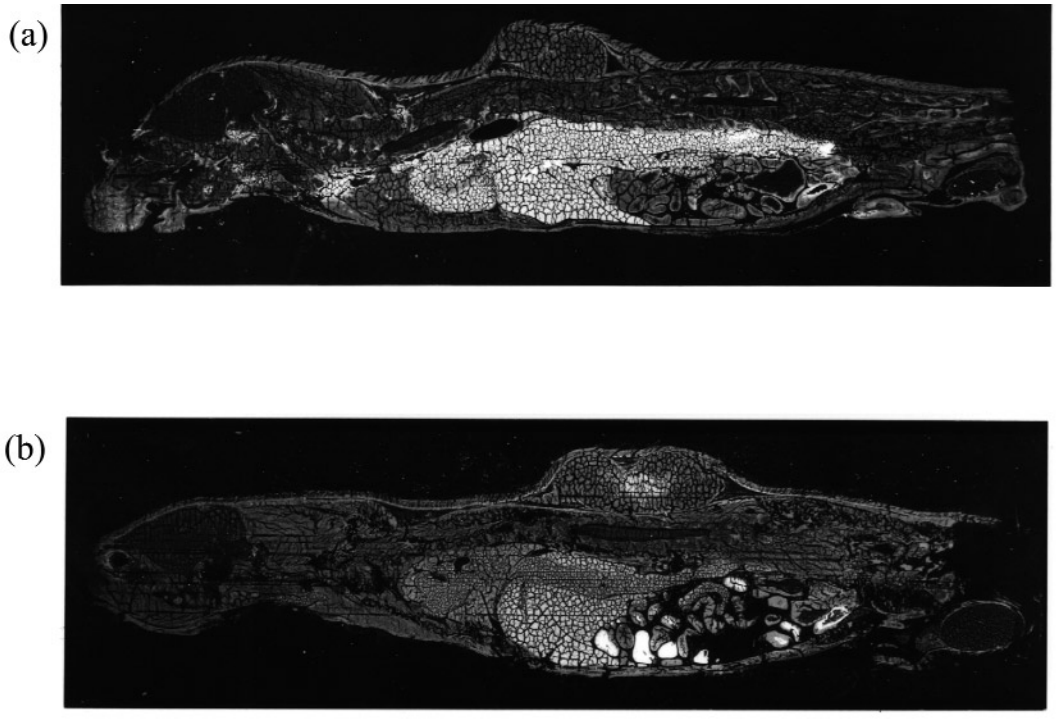

Fig. 4

boron concentration. Nevertheless, under these difficult conditions, we determined the boron concentrations in the brain tissue; as 17 ppm at 20 min and 12 ppm at 60 min. However, its gadolinium concentration was too low to be detected. There are two possibilities for explaining this strange observation. First, gadolinium was dissociated from the boronated DTPA scaffold in the body and only boron was incorporated in the tissue. Second, the values of boron concentration were wrong and perhaps no boron existed in the tissue. The experiment using α-autoradiography clearly indicates that the second possibility is correct and the boron is not accumulated into the brain part (see Fig. 4). Therefore, the data of the boron concentration obtained from the ICP/AES experiment are not reliable. Thus, only the gadolinium concentration determined by ICP/AES experiment is discussed in this paper.

The visible contrast enhancement effected by **2** was obtained from the MRI experiment. The compound **2** is distributed in the necrotic inner part of tumor tissue (Figs. 1c–d and 2b). The same tendency is observed in Fig. 4. These different observations result from which part of tissue is measured. Actually, the outer part (not the necrotic part) of tumor tissue was removed and used for the ICP/AES experiment. Thus, the low gadolinium concentration is obtained in tumor tissue. The outside of necrotic part of tumor is not visualized by the α-autoradiography in Fig. 4, which supports the results obtained from ICP/AES experiment. The tumor/blood ratio of the compound is very low (0.075 at 20 min after injection) and the higher ratio is required for boron carriers (e.g., the tumor/blood ratio of BSH, which is clinically utilized for brain tumor, is ~1). The compound **2** is also incorporated into kidney and liver, and excreted gradually (Figs. 2), whereas Gd-DTPA **1** is excreted rapidly from the body (Fig. 3). It is considered that the lipophilic functional group, carborane, attached to the molecule makes the Gd-DTPA complex stay longer in the tissues. The intestines are visualized at 60 min in Fig. 4, which indicates that **2** is also metabolized via the liver and excreted in the bile.

CONCLUSION

Carborane-containing Gd-DTPA **2** has been synthesized as a dual labeled probe for MRI and neutron capture therapy. It is clear from the MRI experiment that **2** is effective for contrast enhancement and stays in the body for a long period of time in comparison with ordinary Gd-DTPA **1**. Although the selective accumulation into the tumor tissue has not been observed from these experiments, the present findings provide a promising result that the distribution of the boron carrier in the body can be followed in real time by using MRI.

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