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^{19}F NMR CHEMICAL SHIFT IMAGING OF ANESTHETICS IN MODEL MEMBRANES

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The images of fluorinated anesthetics in the lipid dispersions were obtained by ^{19}F NMR method using a commercial spectrometer with a satisfactory resolution in space and molecular species.

The information of drug dynamics in the tissues of intact animals is essential for the in vivo biochemical study. The use of radioisotope labels is certainly the most sensitive and reliable method for the drug distribution maps. However, a safe and noninvasive techniques which do not require the synthesis of radioactive compounds are awaited. The NMR imaging method using proton has now been utilized to the level of clinical diagnosis, where the proton spin relaxation times provide crucial information to distinguish the tissues. On the other hand, NMR imaging combined with information of chemical shifts to differentiate the molecular species is now widely under developing, for example, with nuclei like ^{1}H,[1] ^{31}P,[2] ^{1}H and ^{13}C,[3] and ^{14}N.[4] The knowledge of ^{19}F NMR in the field of biochemistry is increasing.[5] The ^{19}F NMR surface coil method has recently been reported for the noninvasive monitoring of anesthetics.[6] In this work, we made an investigation of ^{19}F NMR chemical shift imaging of fluorine compounds in the medium of lipid dispersions as a model of molecules adsorbed to tissues.

The anesthetics 2-bromo-2-chloro-1,1,1-trifluoroethane(halothane) and 2,2-dichloro-1,1-difluoro-ethyl methyl ether(methoxyflurane) were injected into 8 cm^3 tubes containing 0.2 cm^3 of multilamellar dispersions(150 g/dm^3) of egg yolk total lipids. The tube was kept standing quietly for 4 h at room temperature for complete equilibration. Two sealed capillaries containing the mixtures were placed in a 5 mm sample tube to constitute a phantom(Fig. 1a). ^{19}F NMR was taken by JEOL FX-100 standard FT spectrometer operated at 94 MHz at ambient temperature(24 °C). The final concentrations of the samples were determined by signal intensities. These samples gave only the signals characteristic of the fluorine compounds adsorbed to lipid[7] as shown in Fig. 1b. The spectra from 20 directions were taken for image construction under the static field gradient of 4 μT/mm.

The image made by the projection-reconstruction method[8] is shown in Fig. 1c. A sufficient chemical shift difference of these two compounds, 990 Hz, made it possible to distinguish two anesthetics under the experimental condition of the mentioned field gradient. The positions and the concentrations of the samples were well resolved. The spread of spin density beyond the two sample positions may come partly from the insufficient projection number and partly from the intrinsic line width of the lipid-bound molecules as seen in Fig. 1b.

The total observation time of the experiment was 1030 s. The concentration

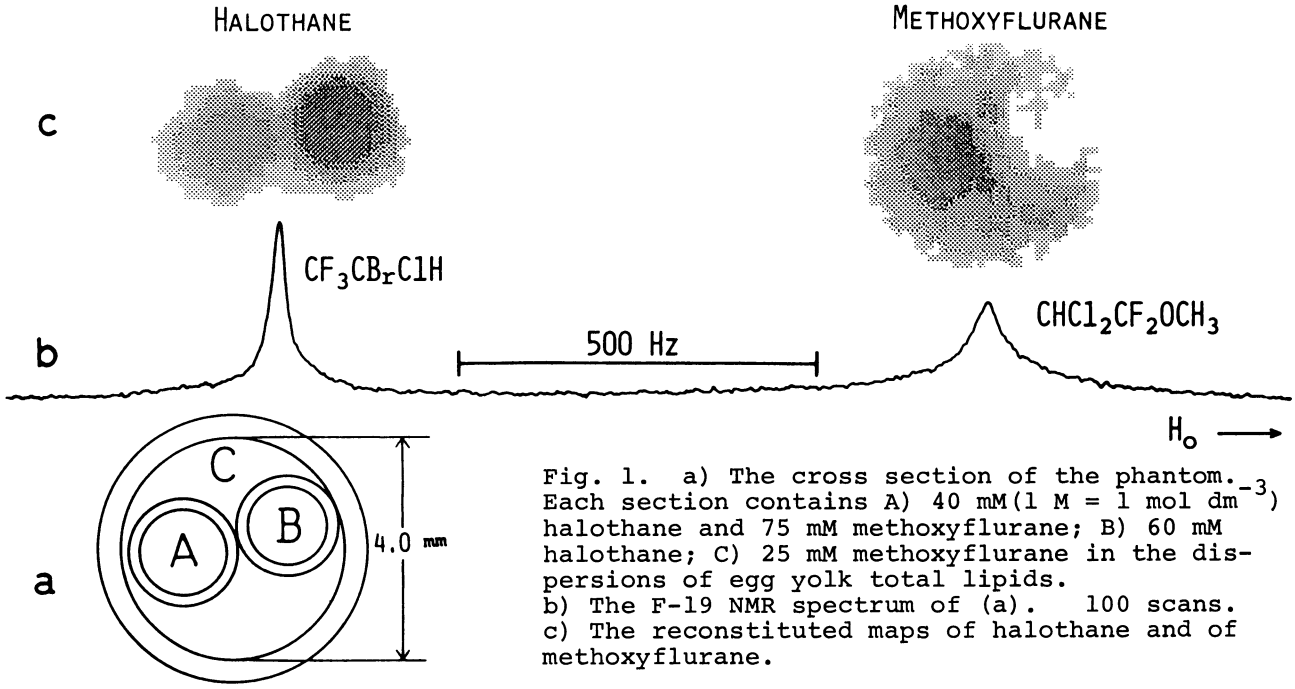

Fig. 1. a) The cross section of the phantom. Each section contains A) 40 mM(1 M = 1 mol dm^{-3}) halothane and 75 mM methoxyflurane; B) 60 mM halothane; C) 25 mM methoxyflurane in the dispersions of egg yolk total lipids.
b) The F-19 NMR spectrum of (a). 100 scans.
c) The reconstituted maps of halothane and of methoxyflurane.

of fluorine compounds in the normal living animals must be some orders of magnitude lower than that in this model experiment. A calculation of the observation time of CF_3-compound of 1 mM concentration was made at the optimum condition according to the relation given by Mansfield and Morris.[9] The result was 1000 s for a sample of 50 mm diameter with the resolution of 2 x 2 x 2 mm^3 at the frequency of 94 MHz and S/N of 4, which seems to be an acceptable examination time for animals. A drastic reduction in the observation time will be achieved with higher magnetic field, for example, to only 33 s at 250 MHz under the same experimental conditions.

In order to create the clear NMR images of rare substances in the intact lives, it is advantageous to use a nuclear species not inherently abundant in tissues such as fluorine. Moreover, the wide spread of chemical shift distribution of ^{19}F NMR could be utilized to separate metabolites from their original compound. ^{19}F NMR chemical shift imaging is thus shown to be quite promising in the field of biochemistry in vivo as well as physiology and medical diagnosis.

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References

1) P. C. Lauterbur, D. M. Kramer, W. V. House, Jr., and C.-N. Chen, J. Am. Chem. Soc., 97, 6866 (1975).
2) P. Bendel, C.-M. Lai, and P. C. Lauterbur, J. Magn. Reson., 38, 343 (1980).
3) L. D. Hall and S. Sukumar, J. Magn. Reson., 50, 161 (1982).
4) Y. Kanazawa and H. Kamei, Chem. Lett., 1984, 353.
5) C. T. Burt, R. R. Moore, and M. F. Roberts, J. Magn. Reson., 53, 163 (1983).
6) A. M. Wyrwics, M. H. Pszenny, J. C. Schofield, P. C. Tillman, R. E. Gordon, and P. A. Martin, Science, 222, 428 (1983).
7) K. A. Koehler, M. K. Jain, E. E. Stone. E. T. Fossel, and L. S. Koehler, Biochim. Biophys. Acta, 510, 177 (1978).
8) P. C. Lauterbur, Nature, 242, 190 (1973).
9) P. Mansfield and P. G. Morris, "NMR Imaging in Biomedicine," Academic Press, New York (1982).

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