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Autoradiographic Evidences on the Perilobular Distribution of Dehydrocorydaline-^{14}C in the Mouse Liver[1)]

Heterogeneous "reticular" distribution of radioactivity was observed in the macro-autoradiogram of mouse liver after intravenous administration of dehydrocorydaline-^{14}C. Microautoradiography revealed that this is due to the perilobular localization of label in the liver.

Dehydrocorydaline, one of alkaloids isolated from *Corydalis bulbosa*,[2)] has anti-ulcerous and gastric anti-secretory activities.[3)] In the course of its disposition studies utilizing ^{14}C-labeled compound, a kind of "reticular" distribution of the label (Fig. 1) was found in the liver of mice and rats on their macro-autoradiograms after oral and intravenous administrations, indicating that the distribution of the drug in the liver is identical whether it was transported from interlobular portal vein or hepatic artery. The "reticular" distribution itself is not a rare case, since rather many compounds have been reported to show this type of distribution in the liver by macro-autoradiography (*e.g.*, ref. 4). Although several speculations were made to characterize this phenomenon, there has not yet been reported any histological evidences. Therefore we attempted to perform histological characterization by micro-autoradiography on this drug-localization in the liver, with a view to elucidate this localization mechanism.

Dehydrocorydaline-^{14}C (Chart 1) dissolved in physiological saline was injected into the tail vein of male ICR-JCL mice weighing about 30 g in a dosage of 186 μCi/6.8 mg/kg. One hr. after dosing, one mouse was subjected to macro-autoradiography as described by Matsuoka and Kashima[5)] using Autocryotome (Nakagawa Works Co., Ltd., Tokyo). Another mouse was decapitated and the liver was dissected out rapidly, chopped into small pieces and frozen in dry ice–acetone. Frozen 8 μm thick sections were prepared in a cryostat (Slee Co., Ltd., London), dried and contacted with emulsion-precoated slide by modified dry-mount technique described by Stumpf.[6)] Detailed procedures for micro-autoradiography and preparation of labeled compound will be reported elsewhere.

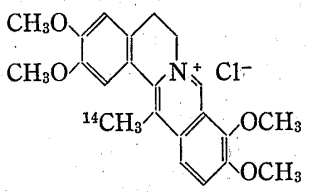

Chart 1. Dehydrocorydaline-^{14}C

The result obtained from macro-autoradiography is shown in Fig. 1, where radioactivity in the liver is localized "reticularly." Small blood vessels can be seen in the center of the labeled portion. This suggests that radioactivities were concentrated around certain blood vessels of hepatic tissue. Further, the size of "reticular" structure was estimated by counting crossing frequency of the "reticular" label along any one-centimeter straight lines to be 10—20, suggesting that the label is localized in limited portions of hepatic lobule to form the "reticular" localization with length of 500—1000 μm.

1) This study was in part presented at the 95th annual meeting of Pharmaceutical Society of Japan held at Nishinomiya in 1975.

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3) Y. Soji, T. Kadokawa, Y. Masuda, K. Kawashima, and K. Nakamura, *Folia Pharmacol. Japon.*, **65**, 194 (1969); Y. Soji, K. Kawashima, and M. Shimizu, *ibid.*, **70**, 425 (1974).
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5) O. Matsuoka and M. Kashima, *Radioisotopes* (Tokyo), **15**, 195 (1966).
6) W.E. Stumpf, *Acta Endocrinol., Suppl.*, **153**, 205 (1971).

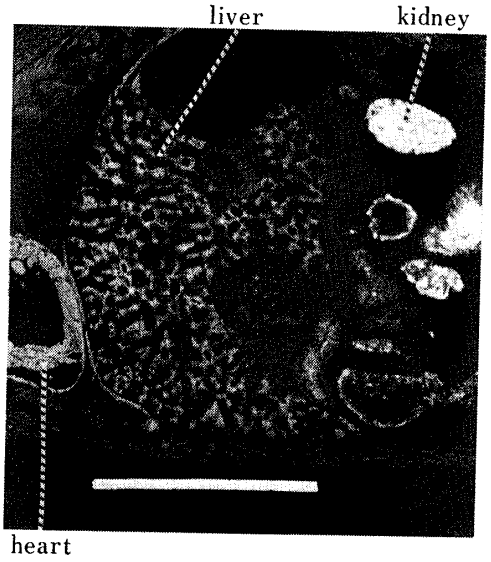

Fig. 1. Enlarged Macro-autoradiogram of Mouse Liver

Macro-autoradiography was performed as described in the text. A 40 μm-thick section was contacted with a SAKURA X-ray film (Industrial, Type N) for 5 days. The white line in lower portion indicates 1 cm.

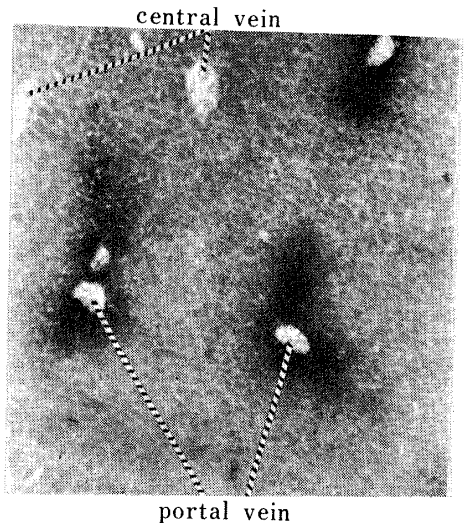

Fig. 2. Micro-autoradiogram Showing the Distribution of Radioactivity in the Hepatic Lobule

The emulsion used was SAKURA NR-M 2. The silver grains are concentrated in the perilobular areas. Magnification; ×100. Giemsa stained.

The above estimation can be proved by a microscopic autoradiogram of the liver given in Fig. 2. The silver grains were concentrated in the periportal space whereas few grains can be seen in the central area of the lobule. This fact accounts for the observations mentioned above on macro-autoradiogram. That is, under the condition employed, the radioactivities were concentrated in the peripheral area of hepatic lobules (their diameters are 500—1000 μm), resulting in the "reticular" distribution macroscopically. In other words, the macroscopic distribution of radioactivity is corresponded to that of periportal spaces in the mouse liver.

As mentioned, a considerable number of water soluble small molecules show this "reticular" distribution in the liver.[4] Based on the careful observations of the macro-autoradiograms, some authors[4a] proposed that the distribution is cetrilobular and other,[4b] perilobular. Unfortunately it seems that they lack the clear-cut evidence bearing with such considerations and discussions. In the present study, it became evident that the heterogeneous distribution of radioactivity in the liver is due to the perilobular localization after dehydrocorydaline-^{14}C administration. However, even when the localization be limited in the centrilobular area, a macroscopic "reticular" distribution can be obtained. Characterization of "reticular" distribution should therefore be proved microscopically since it is conceivably difficult to distinguish macroscopically the difference between perilobular and centrilobular localizations.

The perilobular localization of the drug in the present study would be due to its kinetic disposition that the rate of the drug influx into liver cells from sinusoidal blood streams exceeds the rate of the drug transport to the central vein of the hepatic lobule. However, the exact mechanism remains to be solved.

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