11C-Coenzyme Q10: A New Myocardial-Imaging Tracer for Positron Emission Tomography

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Coenzyme Q_{10}(CoQ_{10}) is a redox carrier in the respiratory chain of a mitochondrial electron transfer system[4], and its content is high in the heart, liver and adrenal in mammals.[2] In clinical aspect, coenzyme Q_{10} has been established to be an effective therapeutic agent for various heart diseases.[16] It has been considered that exogenous CoQ_{10} act as a trigger to activate deteriorated mitochondrial energy liberation. In fact, exogenous CoQ_{10} was incorporated into the inner membrane of myocardial mitochondria in rats at longer periods after the administration.[12] Therefore CoQ_{10} labeled with positron-emitting nuclide is expected to become a new positron tracer for diagnosing heart disease.

Because of high liphophilisity of CoQ_{10} with 10 five-carbon isoprenoid units, the CoQ_{10} injection was prepared by the different emulsifying methods, and different tissue distributions were reported in the animal experiments.[5,6,9,17] In previous papers, we synthesized ^{11}C-CoQ_{10} as a myocardial imaging tracer, and emulsified it with polyoxyethylene hydrogenated caster oil(HCO-60). But, biodistribution showed that the ^{11}C-CoQ_{10} was present in the highest concentration in the blood but in low concentration in several organs including the heart for 0.5 h after the injection.[14,15] On the other hand, Yuzuriha et al. showed that ^{14}C-CoQ_{10} in the form of an ethanol/water emulsion was incorporated mainly into the liver and spleen, and to a lesser extent into the heart and adrenal for the first 2 h.[17] However, their preparation does not have enough property to be applied the ^{11}C-labeled CoQ_{10} to the myocardial imaging because of long period required for the myocardial accumulation.

Many investigations have been reported with respect to liposomes as a carrier to deliver drugs or enzymes to target organs.[7,11] Liposomes are composed of lipid bilayer and have different characteristics for biodistribution by changing their composition.[3,13] Therefore, we applied this technique to the ^{11}C-labeled CoQ_{10}. In this paper we compared biodistributions of two kinds of ^{11}C-CoQ_{10} preparations emulsified with HCO-60 and liposomes and indicated the usefulness of the ^{11}C-CoQ_{10} emulsified with liposomes as the potential positron myocardial imaging tracer.

Materials and Methods

Preparation of ^{11}C-CoQ$_{10}$

^{11}C-CoQ$_{10}$ with specific activities of 4-5 Ci/mmol was synthesized by the reaction of 3-demethyl coenzyme Q$_{10}$ with $^{11}CH_3I$ as described previous papers[14,15], and emulsified by two methods(Scheme). In the first method, ^{11}C-CoQ was emulsified in saline with HCO-60 as described in the previous method.[15] In the second method, ^{11}C-CoQ$_{10}$ was emulsified with phospholipids solution as liposomes. Phospholipids solution was a kind gift of the Esai Co, Ltd. and its compositions are as follows: 1 ml Tris-citrate(pH6.5) solution contains 1.4 mg yolk and soybean phospholipids, 0.4 mg soybean oil, 30 mg polyethylene glycol and 45.0 mg D-solbitol. Finally, ^{11}C-CoQ$_{10}$(HCO-60) was filtered through a 0.22 μm filter and ^{11}C-CoQ$_{10}$(liposomes) was filtered through a 0.05, 0.22, 0.45 or 1.0 μm filter. Membrane filters with 0.22 or 0.45 μm pore size were obtained from Millipore Co. and other filters were obtained from Nuclepore Co.

Animal experiments

Biodistribution of ^{11}C-CoQ$_{10}$ were measured in three groups of Wistar rats, that is, adult male rats, pregnant rats in the period 18th day of gestation and new born rats in the 3th or 7th day. Male rats and pregnant rats were injected with each ^{11}C-CoQ$_{10}$ preparation(about 100 μCi/20 nmol) through a dosal vein. New born rats were injected intraperitoneally. At various times, tissues were dissected and washed with saline. The ^{11}C radioactivity was measured with an auto-well γ-ray counter (Packard, AUTO-GAMMA 500C) and the tissues were weighted. Uptakes in the tissues were expressed as % dose/g tissue [100×(count/g tissue)/(total injected count)]. In order to assess the placental transfer of the two ^{11}C-CoQ$_{10}$ preparations, the placenta-to-blood ratio and the fetus-to-placenta ratio were measured as described in the previous paper.[8]

Results

Figure 1 shows the biodistribution of the ^{11}C-CoQ$_{10}$(liposomes). Blood clearance was very rapid for the first 5 min, and then the level of concentration remained constant. The liver and spleen showed the rapid accumulation for the first 10 min and very slow clearance. The heart showed the high accumulation at 1 min after the injection, then slow clearance and a constant concentration after 30 min. The adrenal also showed high uptake. In the bone including bone marrow, the uptake was low, but increased with time. The lowest uptake was found in the brain.

Table 1 shows the difference of two ^{11}C-CoQ$_{10}$ preparations in the biodistributions. The ^{11}C-CoQ$_{10}$(HCO-60) was present in the highest concentration in the blood as observed in the mongolian gerbils in the previous report.[15] In the new born rats, the blood concentration was also high but not so much as in the adult rats. The heart uptake was low in the

adult rats, but was high in new born rats. The concentration ratio of heart-to-blood was 1.0 in the new born rats. On the contrary, the ^{11}C-CoQ_{10}(liposomes) was incorporated in the heart in all rats. The fetal heart uptake was the highest among four organs. The brain uptakes of both ^{11}C-CoQ_{10} were low, but the concentration ratio of brain-to-blood was higher in the ^{11}C-CoQ_{10}(liposomes) in both the adult and new born rats than in the ^{11}C-CoQ_{10}(HCO-60). The heart uptakes were compared among the ^{11}C-CoQ_{10}(liposomes) preparations obtained by using different pore size membrane filters(Table 2). The heart uptake was high in the preparation obtained by using a small pore size filter. However, since the blood clearance was slow, the concentration ratio of heart-to-blood was rather small.

Table 3 shows placental transfer of two ^{11}C-CoQ preparations. The fetus uptakes of two ^{11}C-CoQ_{10} preparations were similar levels although the concentration of ^{11}C-CoQ_{10}(HCO-60) in the maternal blood was much higher than that of ^{11}C-CoQ_{10}(liposomes). The placenta-to-blood ratio of ^{11}C-CoQ_{10}(liposomes) were constant for 30 min, but the fetus-to-placenta ratio increased with time. On the contrary, the placenta-to-blood ratio of ^{11}C-CoQ_{10}(HCO-60) increased gradually but the fetus-to-placenta ratio was constant.

Discussion

In the previous paper we could not indicate the usefulness of the $^{11}CoQ_{10}$ for the myocardial imaging tracer because of the highest concentration in the blood for the first 30 min(15). That result is explained by the strong affinity of HCO-60 for the ^{11}C-CoQ_{10} which prevents the transfer of the ^{11}C-CoQ_{10} from the blood to other organs. In this paper we have used the liposomes as a carrier of the ^{11}C-CoQ_{10} in stead of the non-ionic detergent, HCO-60, have compared the biodistribution of two $^{11}CoQ_{10}$ preparations, and have found several characteristics of the liposomes preparation.

The ^{11}C-CoQ_{10}(liposomes) was rapidly cleared from the blood and was rapidly incorporated into the liver and spleen probably by endocytosis which reflects the characteristics of liposomes. In the myocardium, much uptake was observed just after the injection. This is explained as follows. Because of the high affinity of the liposomes themselves to the myocardium, the ^{11}C-CoQ_{10} is entrapped and gradually incorporated into the inner membrane of myocardial mitochondria[12], or the transport of the ^{11}C-CoQ_{10} from the blood to myocardium is very rapid in relation to the fatty acid transport because of CoQ_{10} having 10 isoprenoid units. It has been indicated that small liposomes are cleared more slowly from the blood stream than larger liposomes.[10] In fact, the ^{11}C-CoQ_{10}(liposomes) prepared by using the smallest pore size filter showed high concentration in the blood and also showed higher uptake in the myocardium(Table 2). But the ratio of heart-to-blood in this preparation is rather lower than those in other preparations by using 0.45 μm or 0.22 μm

filter. Therefore the smallest size preparation is less beneficial for PET study. Although the fetus uptakes of the two ^{11}C-CoQ_{10} preparations were prevented from the placenta in spite of its lipophilic propertity compared with other metabolic substrated[8], the transfer of placenta(the ratio of fetus-to-blood) was improved by using the liposomes in stead of HCO-60(Table 3). Also, the brain uptakes were low, but the transfer through the blood-brain barrier(the ratio of brain-to-blood) was improved in the $^{11}CoQ_{10}$(liposomes), especially in the new born rats because of the immature blood-brain barrier.[1]

For clinical application, CoQ_{10} has been effective for heart diseases such as ischemia, heart failure and arrhythmia.[16] Since CoQ_{10} is an essential co-factor in the respiratory chain, the application of ^{11}C-labeled CoQ_{10} for the study on ischemic heart together with several tracers estimating glucose and fatty acid metabolism and/or blood flow will give useful information.

Acknowledgments

We are grateful Drs. S. Ohsawa and K. Shibusawa in Research Laboratorys of Technological Development, Eisai Co., Ltd. for a kind gift of phospholipid solution and useful advice in preparation of liposomes.

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Table 1. Tissue distrubution of the two ^{11}C-coenzyme Q_{10} preparations in rats. Two kinds of ^{11}C-CoQ preparations were filtered through a 0.22 μm membrane filter. *In experiment at each time, one pregnant rat was injected with ^{11}C-CoQ(liposome). The organs of five fetuses were combined and the uptakes were measured. The fetus uptake was indicated in the Table 3.

Preparation	Rat	Time (min)	Uptake % dose/g tissue Tissue/Blood					
			Blood	Heart	Liver	Spleen	Lung	Brain
^{11}C-CoQ (liposomes)	adult male(3)	30	0.16±0.02 1.0	2.2±0.4 13.7	7.6±0.7 47.4	3.1±0.6 19.3	0.29±0.04 1.8	0.014±0.004 0.09
	new born(3) 7th day	30	0.77±0.54 1.0	4.0±0.9 5.2	21.2±7.8 27.5	25.2±4.4 32.7	4.8 ±1.1 6.3	0.77 ±0.54 1.0
	fetus(5)*	30		0.059	0.027		0.015	0.019
^{11}C-CoQ (HCO-60)	adult male(3)	30	9.6 ±1.4 1.0	1.1±0.3 0.12	1.0±0.3 0.10	3.9±0.1 0.40	2.3 ±0.6 0.24	0.25 ±0.07 0.03
	new born(3) 3th day	30	3.2 ±3.2 1.0	3.3±1.7 1.01	4.4±2.7 1.3		2.3 ±0.6 0.71	0.54 ±0.38 0.07

Table 2. Heart uptakes of ^{11}C-coenzyme Q_{10} prepared with in male adult rats at 30 min after the injection(n=3). (a)^{11}C-CoQ(liposomes) preparations were filtered through indicated pore size membrane filters.

Preparation[(a)]	Uptake, % dose/g tissue Tissue/Blood			
	Blood	Heart	Liver	Spleen
1.0 μm	0.31±0.14 1.0	2.1±0.0 6.7	11.9±3.1 38.4	9.6±5.4 31.0
0.45 μm	0.18±0.02 1.0	2.1±0.4 11.8	8.2±1.1 45.6	4.1±0.2 22.7
0.22 μm	0.16±0.02 1.0	2.2±0.4 13.7	7.6±0.7 47.4	3.1±0.6 19.3
0.05 μm	0.66±0.06 1.0	3.4±0.4 5.2	10.9±1.6 16.5	10.9±2.2 16.5

Table 3. Placental transfer of two ^{11}C-coenzyme Q_{10} preparations. In experiment at each time, one rat was used and the fetus uptake was measured as the average of five fetus uptakes. Two ^{11}CoQ preparations were filtered through a 0.22 μm filter. (a) These data were quoted from our previous report(8).

Preparation	Time	Fetus Uptake	Concentration Ratio	
	min	% dose/ g tissue	Placenta/Blood	Fetus/Placenta
^{11}C-CoQ(liposome)[a)]	10	0.015	0.33	0.056
	30	0.022	0.34	0.135
^{11}C-CoQ(HCO-60)	5	0.014	0.20	0.0071
	10	0.017	0.29	0.0069
	30	0.017	0.34	0.0070

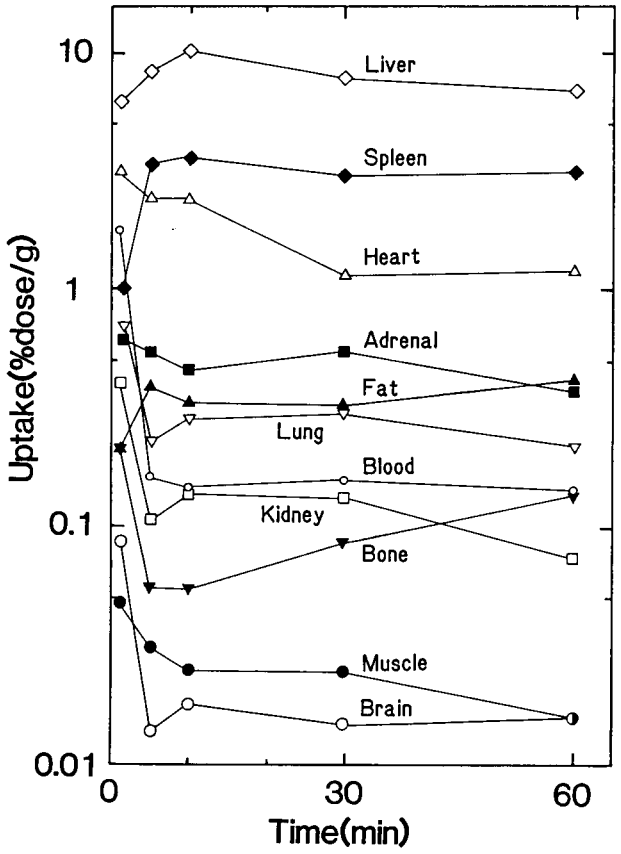

Fig. 1. Tissue distribution of ^{11}C-coenzyme Q_{10} prepared with liposomes in rats.

Scheme