Placental Transfer of Positron-emitting Metabolic Substrates

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Positron-emitting radiopharmaceuticals have been developed explosively for several years as the in vivo radio-tracers to diagnose metabolic functions or drug distribution in human by positron emission tomography. But, these tracers have not been applied to pregnant women in term of studies about the metabolic functions or placental transfer because of the risk of radiation exposure to the fetus. However, the positron-tracers will be also very useful for the animal studies in this region. Placental transfer of drugs during early human pregnancy have been studied[1], but the informations about the placental transfer of metabolic substrates have not been obtained adequately.[2] In this paper, we report the placental transfer and the fetal brain uptake of the positron-emitting metabolic substrates and analogues, and discuss the feto-maternal relationship about these compounds during pregnancy.

Materials and Methods

A mixture of ^{11}C-glucose and ^{11}C-fructose(^{11}C-Glc/Frc) was synthesized from $^{11}CO_2$.[3] ^{11}C-methionine(^{11}C-Met) was synthesized from $^{11}CH_3I$.[4] ^{11}C-coenzyme Q_{10}(^{11}C-CoQ) and ^{11}C-S-adenosyl-L-methionine(^{11}C-SAM) were also prepared from $^{11}CH_3I$ by the modified methods of Takahashi et al.[5] and Gueguen et al.[6], respectively. ^{11}C-D,L-leucine(^{11}C-Leu)[4] and ^{11}C-adenine(^{11}C-Ade)[7] were synthesized from $H^{11}CN$. ^{18}F-2-fluoro-2-deoxyglucose(^{18}F-FDG)[8] and ^{18}F-5-fluoro-2'-deoxyuridine(^{18}F-FdUrd)[9] were synthesized from $^{18}F_2$.

Pregnant rats in the period 16-19th day of gestation were injected with 50-200 μCi of ^{11}C- or ^{18}C-labeled compound through a tail vein. At various time intervals up to 30 min after injection, rats were killed by cervical dislocation and heart puncturing. Uterus was removed immediatly. Then the maternal and fetal organs were removed and washed with saline. The radioactivity was measured with a well-type γ-counter and the tissues were weighted. Uptakes in the tissues were expressed as % dose/ g tissue [100×(count/g tissue)/(total injected count)]. For study of ^{18}F-FDG, three rats were used at each experiment, and one rat was used for studies of other compounds. Uptakes in the fetus and its organs were expressed as the average of 4-5 fetal distributions. Placental uptake was shown as the average of 4-5 pieces.

Results and Discussion

The nutritional requirements of neonatal rabbits were studied by using ^{14}C-labeled compounds such as adenine, arginine, choline, tryptophan and lactate which indicated the benificial inclution of these compounds for the developing central nervous system.[10] The feto-maternal relationship is important for normal development of fetus and especially for the fetal brain in term of nutritional or energy supply from maternal side. We investigated the biodistribution and the placental transfer of ^{11}C- and ^{18}F-labeled metabolic substrates in pregnant rats. Table 1-4 show the distributions in the maternal and fetal organs and tissues. These compounds were usually cleared from the blood quickly. Excretion pattern of these compounds was observed in the maternal visceral organs except for ^{11}C-Leu, ^{11}C-Met and ^{11}C-SAM in the liver. There were increased uptake with time in the maternal brain of ^{18}F-FDG, ^{11}C-Glc/Frc, ^{18}F-FdUrd and ^{11}C-SAM. But the uptakes of ^{18}F-FdUrd and ^{11}C-SAM were very low. The concentration of sugars and amino acids in the placenta usually increased with time. The uptakes in the fetus and its organs usually increased with time in order of amino acids, sugars, ^{11}C-Ade, ^{18}F-FdUrd, ^{11}C-SAM and ^{11}C-CoQ. The concentrations of sugars and amino acids in the fetal organs were similar to those in the maternal organs. The concentrations of ^{11}C-Ade, ^{11}C-SAM and ^{11}C-CoQ were much smaller in the fetal organs than in the maternal organs. Interestingly enough, the fetal heart showed the highest uptake of ^{18}F-FDG, and the fetal lung showed the higher uptakes of ^{18}F-FDG and ^{11}C-Glc/Frc. Increased uptake of amino acids was not observed in the fetal liver which was present in the maternal liver. Uptakes of ^{11}C-SAM and ^{11}C-CoQ were relatively higher in the fetal brain than in the maternal brain. As far as the ^{11}C-CoQ in the fetal organs, the concentration in the heart and liver increased with time but decreased in the brain and lung.

In order to assess the placental transfer of metabolic compounds, two different ratios of the concentrations of these compounds were measured; ratio A, concentration in the placenta to that in the blood, and ratio B, concentration in the fetus to that in the placenta(Fig. 1). As far as the ^{11}C-Glc/Frc, the ratio A and the ratio B increased with time to a similar extent, which supported the facilitated transport of glucose.[2] But the ratio A for the ^{18}F-FDG increased more rapidly than the ^{11}C-Glc/Frc and the ratio B was less than 1.0 without any changes in 30 min. These results probably indicate the presence of the glucose metabolism in the placenta because the ^{18}F-FDG was trapped as the ^{18}F-FDG-6-phosphate in the tissues. Amino acids were transported easily through the placenta and the ratio B was always over 1.0, which supported the active transport of amino acids.[2] For other four compounds the ratio B increased with time in order of ^{18}F-FdUrd, ^{11}C-Ade, ^{11}C-SAM and ^{11}C-CoQ. The ratio B was almost the same as the ratio A for the ^{18}F-FdUrd. The ^{18}F-FdUrd transfered through the placenta more easily than the ^{11}C-Ade, probably because of the ribose moiety of nucleoside. However, for other three compounds the

ratio B was smaller than the ratio A, and the transfer from blood to fetus were virtually inhibited by the placenta in spite of these compounds being metabolic constituents.

Table 5 shows the relative uptakes in the maternal and fetal brains at 30 min after injection. Much amounts of sugars and amino acids were incorporated into the maternal brain. Contrarily, all compounds were incorporated into the fetal brain to the different extent. This result suggests an immature blood-brain barrier. However, Nau and Liddiard described the possible existance of a blood-brain barrier in the fetal brain.[1] Therefore, it could be conceivable that the high accumulation of these compounds reflects the nutritional requirements of the fetal brain in addition to the immature blood-brain barrier possibly.

A comlicated pregnancy is one of the causes of intrauterine growth retardation, which is associated with nutritional problems at times and results in a fetal distress syndrome. The placental blood flow is also involved to cause the lower transport through the placenta of these biological constituents. The presented technique may be applied to the further studies to elucidate the pathogenesis of intrauterine growth retardation associated with nutritional problems or low energy metabolism due to intrauterine hypoxia.

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Table 1 Tissue distribution of ^{18}F-2-deoxy-2-fluoroglucose and ^{11}C-glucose/fructose

Tissue	^{18}F-2-deoxy-2-fluoroglucose Uptake(%Dose/g)			^{11}C-glucose/fructose Uptake(%Dose/g)			
	5 min	10 min	30 min	1 min	5 min	10 min	30 min
Blood	0.68 ± 0.04	0.54 ± 0.07	0.40 ± 0.02	2.07	1.31	1.39	0.75
Brain	0.50 ± 0.05	0.56 ± 0.06	0.70 ± 0.05	0.46	0.71	1.06	1.06
Heart	0.56 ± 0.05	0.48 ± 0.11	0.57 ± 0.03	0.93	1.19	0.68	0.49
Lung	0.80 ± 0.05	0.65 ± 0.12	0.68 ± 0.04	1.32	0.98	0.95	0.51
liver	0.91 ± 0.08	0.76 ± 0.13	0.58 ± 0.04	2.85	2.51	2.35	1.35
Placenta	0.62 ± 0.10	0.63 ± 0.17	0.95 ± 0.03	0.39	0.55	0.67	0.64
Fetus	0.40 ± 0.07	0.41 ± 0.09	0.61 ± 0.01	0.11	0.21	0.40	0.74
Fetal Brain	0.40 ± 0.08	0.41 ± 0.11	0.47 ± 0.03	0.13	0.27	0.43	0.69
Fetal Heart	0.96 ± 0.20	1.19 ± 0.45	1.87 ± 0.02				
Fetal Lung	0.40 ± 0.07	0.42 ± 0.15	0.71 ± 0.06		0.44	0.95	2.27
Fetal Liver	0.41 ± 0.05	0.37 ± 0.06	0.49 ± 0.03	0.22	0.42	0.74	0.98

Table 2 Tissue distribution of ^{11}C-L-methionine and ^{11}C-D,L-leucine in pregnant rats.

Tissue	^{11}C-L-methionine Uptake(%Dose/g)				^{11}C-D,L-leucine Uptake(%Dose/g)		
	1 min	5 min	10 min	30 min	5 min	10 min	30 min
Blood	0.64	0.64	0.33	0.26	0.57	0.67	0.36
Brain	0.31	0.35	0.33	0.37	0.33	0.30	0.31
Heart	0.80	0.68	0.66	0.57	0.79	0.75	0.56
Lung	1.03	0.89	0.64	0.64	0.73	0.76	0.60
Liver	2.14	3.96	3.54	3.58	1.75	1.78	2.73
Placenta	0.30	0.39	0.28	0.45	0.33	0.39	0.45
Fetus	0.33	0.42	0.29	0.73	0.46	0.50	0.59
Feral Bran	0.13	0.24	0.21	0.45	0.30	0.40	0.55
Fetal Lung	0.26	0.47	0.43	0.55	0.45	1.00	1.08
Fetal Liver	0.29	0.61	0.44	0.84	0.56	0.70	1.02

Table 3 Tissue distribution of ^{11}C-adenine and ^{18}F-5-fluoro-2'-deoxyuridine in pregnant rats

Tissue	^{11}C-adenine Uptake(%Dose/g)			^{18}F-5-fluoro-2'-deoxyuridine Uptake(%Dose/g)		
	1 min	10 min	30 min	5 min	10 min	30 min
Blood	2.24	1.21	0.98	0.27	0.38	0.30
Brain	0.098	0.075	0.055	0.018	0.032	0.035
Heart				0.26	0.39	0.19
Lung	2.30	2.18	2.08	0.29	0.37	0.23
Liver	0.98	0.57	0.35	0.71	2.82	4.19
Placenta	0.41	0.58	0.51	0.11	0.25	0.17
Fetus	0.016	0.11	0.16	0.034	0.11	0.13
Fetal Brain	0.010	0.030	0.024	0.028	0.038	0.038
Fetal Heart				0.11	0.17	0.10
Fetal Lung				0.13	0.12	0.087
Fetal Liver	0.024	0.13	0.13	0.18	0.31	0.54

Table 4 Tissue distribution of ^{11}C-S-adenosyl-L-methionine and ^{11}C-coenzyme Q_{10} in pregnant rats

Tissue	^{11}C-S-adenosyl-L-methionine Uptake(%Dose/g)			^{11}C-coenzyme Q_{10} Uptake(%Dose/g)	
	5 min	10 min	30 min	10 min	30 min
Blood	0.69	0.69	0.48	0.83	0.48
Brain	0.029	0.033	0.045	0.040	0.023
Heart	0.32	0.25	0.21	5.31	3.48
Lung	0.73	0.47	0.36	0.46	0.16
Liver	0.26	0.29	0.55	8.32	8.39
Placenta	0.54	0.41	0.29	0.27	0.17
Fetus	0.014	0.028	0.065	0.015	0.022
Fetal Brain	0.011	0.023	0.042	0.021	0.019
Fetal Heart	0.038	0.043	0.068	0.010	0.059
Fetal Lung	0.047	0.039	0.068	0.017	0.015
Fetal Liver	0.013	0.027	0.073	0.014	0.027

Table 5 Relative brain uptake in pregnant rat at 30 min

compounds	Uptake (%Dose/total brain) maternal brain	fetal brain	fetal brain / maternal brain
^{18}F-2-deoxy-2-fluorodeoxyglucose	2.53	4.4	1.8
^{11}C-glucose/fructose	0.86	6.6	7.7
^{11}C-L-methionine	0.74	6.9	9.3
^{11}C-D,L-leucine	0.53	6.2	11.7
^{11}C-adenine	0.10	0.5	5.0
^{18}F-5-fluoro-2'-deoxyuridine	0.06	1.3	21.7
^{11}C-S-adenosyl-L-methionine	0.052	6.3	121
^{11}C-coenzyme Q_{10}	0.034	5.2	153

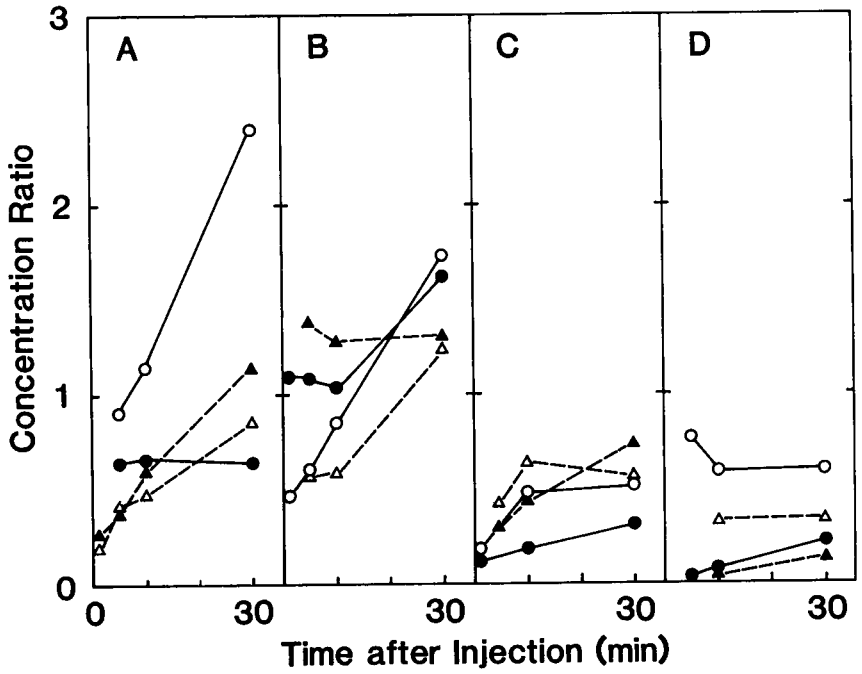

Fig. 1. Placental transfer of positron-emitting compounds. The ratio of concentration in the placenta to that in the blood and the ratio of concentration in the fetus to that in the placenta are shown as open symbols and closed symbols, respectively.
A: ○,●; [^{18}F]FDG△,▲; [^{11}C]Glc/Frc. B: ○, ●; [^{11}C]Met, △, ▲; [^{11}C]Leu.
C: ○,●; [^{11}C]Ade, △,▲; [^{18}F]FdUrd. D: ○, ●; [^{11}C]SAM, △, ▲; [^{11}C]CoQ_{10}.