Placental Transfer of 18F-2-Deoxy-2-Fluoroglucose and 14C-4-Iodoantipyrine in Hypoxic Rats

III. 10 Placental Transfer of ^{18}F-2-Deoxy-2-Fluoroglucose and ^{14}C-4-Iodoantipyrine in Hypoxic Rats

Matsui A., Sakuragawa N., Matsuzaka T., Kono Y., Ido T.*, Ishiwata K.* and Kawashima K.*
National Center for Nervous, Mental and Muscular Disorders, Tokyo
Cyclotron and Radioisotope Center, Tohoku University*

Normal fetal development results from good function of materno-feto-placental unit. Although placental transfer of drugs during early pregnancy has been studied[1], informations about the placental transfer of metabolic substrates has not been adequately obtained.[2] Recently Ishiwata et al[3] reported placental transfer of several metabolic substrates labeled with short half life nuclides; sugars and amino acids transferred easily through the placenta but there was a certain placental barrier against ^{11}C-adenine, ^{11}C-coenzyme Q_{10} and ^{11}C-S-adenosyl-L-methionine.

Recent progress in perinatal medicine such as monitoring system and neonatal intensive care decreased the incidence of fetal distress syndrome and neonatal asphyxia. But there seems to be a pathophysiology to be elucidated in terms of perinatal insults due to nutritional problems or low energy metabolism from intrauterine hypoxia. In this communication, we report the glucose metabolism using ^{18}F-2-deoxy-2-fluoroglucose(^{18}F-FDG) of pregnant rats and fetuses in experimental hypoxia with a special attention to placental function.

Materials and Methods

^{18}F-FDG was synthesized from $^{18}F_2$ by the method of Iwata et al.[4] [N-Methyl-^{14}C]4-iodoantipyrine (^{14}C-IAP) was purchased from Ammersham Co. (specific activity, 53 μCi/mmol).

Pregnant Wistar rats, 18-20 days of gestational age, were used. Mean maternal body weight was 252 g, mean litter size 10.5 and mean fetal body weight 1.8 g. Experimental studies of hypoxia were carried out using rats placed in a box where 10 % oxygen gas with nitrogen gas was ventilated constantly to maintain the oxygen concentration at 9-11 % by O_2 monitor. In order to measure arterial pO_2, an anesthesized pregnant rat with intraperitoneal injection of sodium pentobarbital (50 mg/kg) received canulation into femoral artery. Arterial blood was obtained from a rat before and after exposing to this hypoxic condition.

For the experiment of acute hypoxia, pregnant rats were anesthesized and exposed up to 60 minutes to the hypoxic environment described above. Rats were sacrificed by cervical dislocation 5, 10 and 30 minutes after intravenous

^{18}F-FDG injection. Maternal and fetal organs and tissues were obtained as soon as possible and weighted. The radioactivity of each organs and tissues was measured by auto-well γ-counter (Packard 500 C). And appropriate decay collection was made. As far as the experiment of chronic hypoxia, pregnant rats without anesthesia were placed in a box maintained oxygen concentration at 10-11 % for 11-12 hours before ^{18}F-FDG injection under anesthesia. Control pregnant rats were anesthesized and kept in room air throughout the experiment. Otherwise, pregnant rats received the same treatment and preparation.

The organ distribution of ^{18}F-FDG was expressed as percent ratio of radioactivity per gram of organ to total radioactivity initially injected (%Dose/g). In addition, percent ratio of total radioactivities of the whole organ to initially injected dose (%Dose) was calculated to compare with each other.

In order to make the double-tracer autoradiography of ^{18}F-FDG and ^{14}C-IAP at anesthesized rats, control and hypoxic, were injected with ^{18}F-FDG and ^{14}C-IAP. 30 minutes and 1 minutes, respectively, before ligation of vessels circulation to uterine of rats. Pairs of placenta and fetus were removed, frozen in crushed dry ice, and cut 200 μm thickness in a cryostat. Sections were exposed to X-ray film twice; for the first hours to get the image of ^{18}F and for following seven days after decay of ^{18}F to get the image of ^{14}C.

Results

The arterial blood pO_2 of control pregnant rats ranged about 116.6 ± 5.0 mm Hg and fell down to 56.9 ± mm Hg 15 minutes after exposure to hypoxic condition. Its value in hypoxia was almost constant at least for one hour.

The distribution ratio of ^{18}F-FDG as expressed as each organ per blood and plotted against time (Fig. 2). This ratio increased with time in the maternal brain, placenta and fetus. The increment of this ratio became more prominant in acute and chronic hypoxia than controls. In other words, ^{18}F-FDG uptake increased with time in these organs of control rats and enhanced in hypoxic condition. In addition, the maternal heart in chronic hypoxia showed more drastic increase of this ratio. The uptake of ^{18}F-FDG into the fetal organs also increased with time in controls and enhanced in the hypoxic condition.

The autoradiograms of ^{18}F-FDG and ^{14}C-IAP in placenta and fetus of control and hypoxia were shown in Figure 3 and 4. ^{14}C-IAP autoradiogram represented the high accumulation of ^{14}C mainly in the maternal side of placenta of control rats with clear boundary between maternal and fetal side of placenta. However, the low accumulation was recognized in the fetal side of placenta and fetus itself. Interestingly enough, ^{14}C-IAP autoradiogram revealed the heterogeneous accumulation in both placenta and fetal organs of rats in hypoxia without clear demarcation between maternal and fetal side of

placenta. ^{18}F-FDG autoradiogram demonstrated high accumulation in the maternal side and low accumulation in the fetal side of control placenta. Marked changes of accumulation pattern in the hypoxia were observed in the fetal brain where ^{18}F-uptake increased drastically.

The placental transfer of ^{18}F-FDG was studied using the ratio of %Dose in placenta per blood and fetus per placenta. The accumulation of ^{18}F-FDG uptake in the placenta of control rats increased with time, which became more prominant in hypoxic condition. However, the ratio of placental transfer of ^{18}F-FDG, expressed as the ratio of %Dose in placenta per fetus, was constant in control and hypoxic rats during examination.

Discussion

Fetal distress due to the intrauterine hypoxia during delivery needs urgent treatment of obstetrician to remove the causes of hypoxia. In addition, the changes of energy metabolism due to hypoxia in the fetus should bear in mind for the medical treatment because lactate and pyruvate increased and ATP decreased in the hypoxic brain. Glucose as a metabolic fuel is main energy source for the fetus and plays an important part of materno-feto-placental unit in hypoxic condition. Judging from our experiments, glucose uptake into the maternal brain, heart, placenta and fetus was higher in hypoxia than that in the controls which indicated that the demands of energy source in these organ increased in hypoxia. However, the supply of glucose from the placenta or placental transfer of glucose into the fetus appeared to be constant in the hypoxic condition which was not related to the duration of hypoxia.

Double autoradiography of ^{18}F-FDG and ^{14}C-IAP in control placenta and fetus indicated the presence of reguratory transporting mechanism in the placenta against the glucose and ^{14}C-IAP. The changes of ^{14}C-IAP uptake in hypoxia may indicate the destruction of this barrier system of placenta against ^{14}C-IAP metabolism. However, the difference in the autoradiographical images of ^{18}F-FDG and ^{14}C-IAP in control and hypoxia may suggest the different placental transport mechanism between ^{18}F-FDG and ^{14}C-IAP. We interpret these data to suggest that the placental dysfunction in transporting energy sources in a most important factor of various pathogeneses of fetal asphyxia. We should bare in mind of the placental function in dealing with perinatal anoxia and design a new approach to treat the brain damage due to fetal distress.

Reference

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Table 1. The ratio of placenta per blood means the ratio of %Dose/g of placenta and that of blood. The ratio of fetus per placenta indicates the ratio of %Dose of fetus and that of placenta.

MATERNAL -FETAL RELATIONSHIP.

	PLACENTA/BLOOD			FETUS/PLACENTA		
	5 min	10 min	30 min	5 min	10 min	30 min
CONTROL	0.72	1.02	2.14	3.49	4.27	3.25
ACUTE HYPOXIA	1.28	1.78	4.43	3.03	3.42	3.03
CHRONIC HYPOXIA	1.04	1.39	3.20	3.72	3.89	4.61

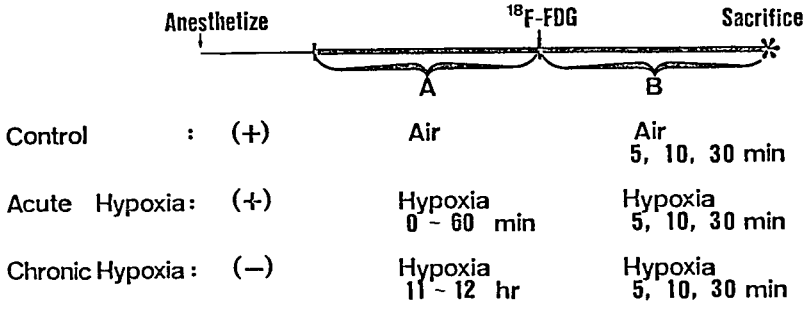

Fig. 1. Time schedule for preparation of hypoxic pregnant rats.

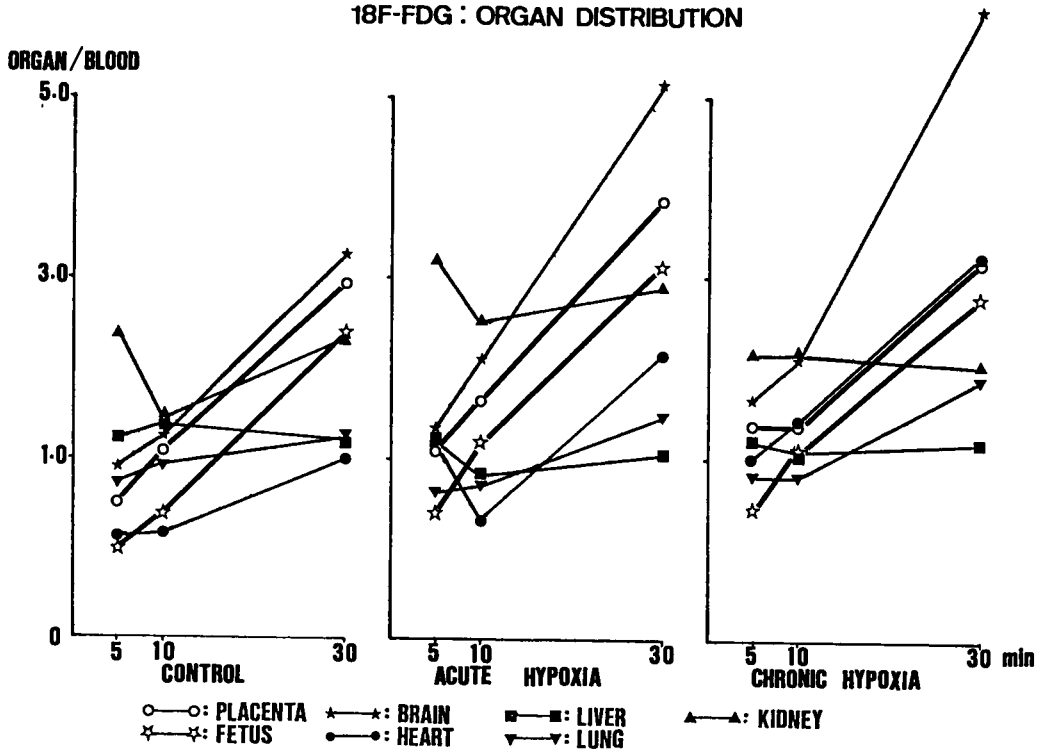

Fig. 2. Organ distribution of ^{18}F-FDG was expressed as the ratio of %Dose/g of each organ against that of blood.

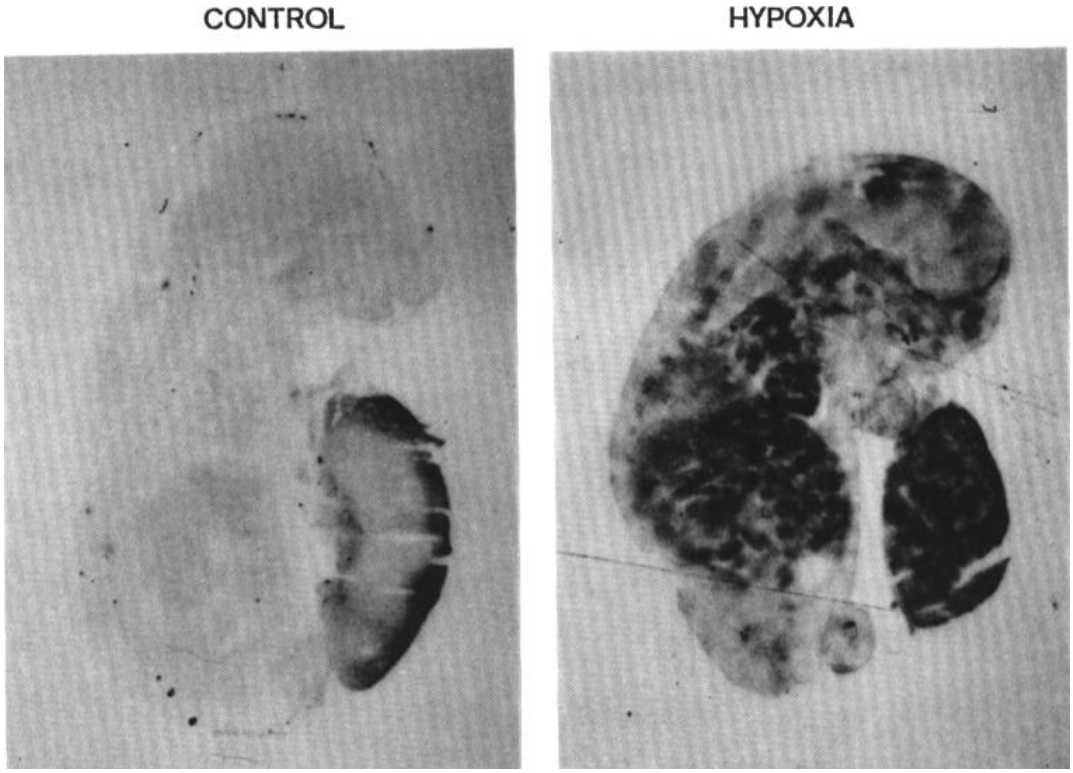

Fig. 3. Autoradiogram of ^{14}C-IAP in the placenta and fetus, control and hypoxic.

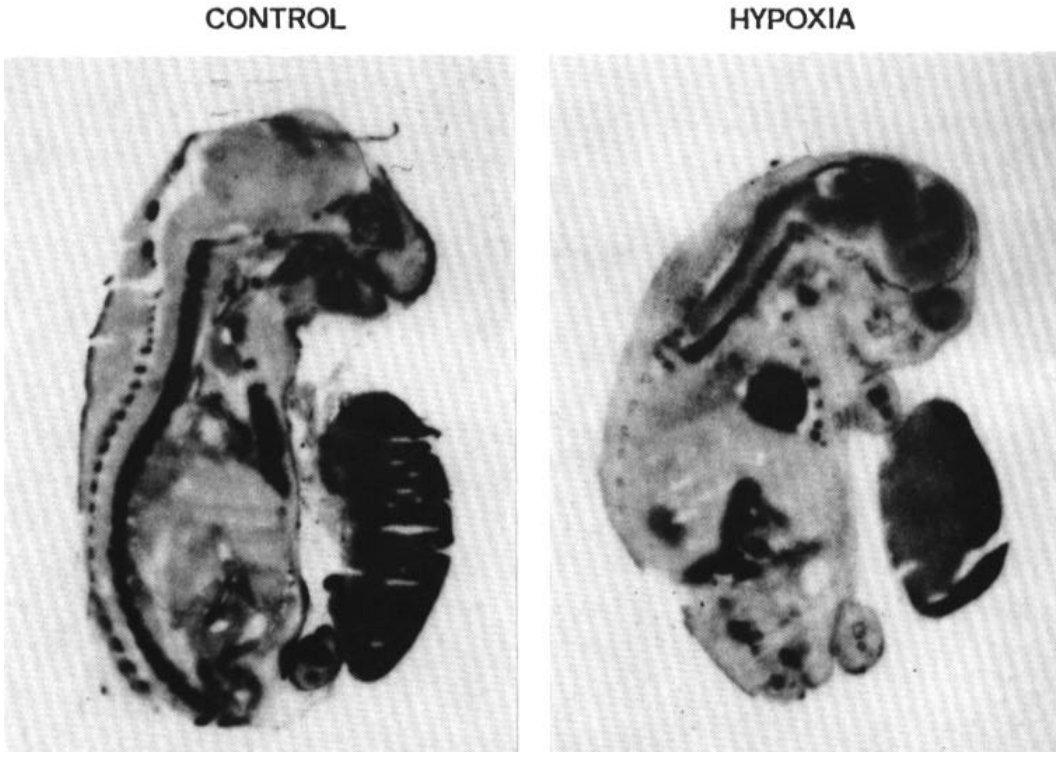

Fig. 4. Autoradiogram of ^{18}F-FDG in the placenta and fetus, control and hypoxic.