

Lactate Production and Absence of Gluconeogenesis from Placental Transferred Substrates in Fetuses from Fed and 48-H Starved Rats

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ABSTRACT. Fed and 48-h starved rats were infused on day 21.5 of gestation for 20 min through the left uterine artery with [U-¹⁴C]-D-glucose, [U-¹⁴C]-glycerol, or [U-¹⁴C]-L-alanine. The mother and fetuses from both uterine horns were processed separately for radioactivity measurements in plasma and liver. Differences in radioactivity values between fetuses from the left and the right sides are used as indexes of placental transference of the infused tracers prior to their distribution and transformation in the maternal circulation. After infusion of [U-¹⁴C]-D-glucose, [U-¹⁴C]-glycerol, or [U-¹⁴C]-L-alanine, plasma radioactivity values and specific activities corresponding to the respective infused tracer appeared much higher in fetuses from the left than the right uterine side. Plasma ¹⁴C-lactate values also were higher in the left than the right fetuses indicating that fetoplacental structures produced lactate from those placentally transferred ¹⁴C-metabolites. No difference in plasma ¹⁴C-glucose between left and right uterine horn fetuses was observed after maternal infusion with either [U-¹⁴C]-glycerol or [U-¹⁴C]-L-alanine, either in fed or 48-h starved rats. In the mother both [U-¹⁴C]-glycerol and [U-¹⁴C]-L-alanine were efficiently converted to ¹⁴C-glucose, and this process was significantly enhanced with starvation. ¹⁴C-fatty acids present in fetal liver after maternal infusions with either [U-¹⁴C]-D-glucose or [U-¹⁴C]-glycerol were decreased by starvation whereas no fatty acid synthesis from [U-¹⁴C]-L-alanine was detected. Much less ¹⁴C-glyceride glycerol was found in fetal liver after maternal infusions of [U-¹⁴C]-D-glucose than [U-¹⁴C]-glycerol, and its incorporation was unaffected by maternal starvation. Results show the significant production by the fetoplacental unit of lactate from transferred maternal substrates and the absence of gluconeogenesis in the rat fetus even after 48 h of maternal food deprivation. Lack of gluconeogenesis occurred even above the triose phosphate step and despite the fact that glycerol phosphorylation is active in fetal liver, indicating that maternal glucose is the only source of this metabolite for the normal rat fetus. (*Pediatr Res* 22: 6-10, 1987)

absent and develops only after birth (5-8) as a consequence of the induction of cytosolic phosphoenolpyruvate carboxykinase (1, 9). Due to the conversion of administered [1-¹⁴C]-glycerol to ¹⁴C-glucose (10) it has been proposed that the gluconeogenic pathway is functional in the rat fetus above the triose phosphate step, but in other studies gluconeogenesis from glycerol was not detected in *in vitro* (11) or *in vivo* (12) rat fetus preparations. Maternal fasting has been reported to induce gluconeogenesis prematurely in the rat fetus (13-15), but this finding has not been consistent and no change in fetal liver gluconeogenic activities were reported after 48 h of maternal fasting (16). In addition, no changes were detected in fetal liver lipogenic enzymes after maternal fasting (16) whereas fetal lipogenesis from ³H₂O was inhibited (17). In order to clarify these controversies, the present study was performed to determine the comparative *in vivo* metabolic fate of D-glucose, L-alanine, and glycerol in fetuses from fed and 48-h starved late pregnant rats. Labeled substrates were infused through the maternal left uterine artery according to our recently described technique (18) for placental transfer studies which allows determination of the metabolic fate of substrates in the rat fetus independently of interconversions occurring in the mother.

METHODS

Wistar female rats, mated when weighing 170-190 g, were studied at day 21.5 of gestation (estimated by the appearance of spermatozooids in vaginal smears) comparing fed and 48-h food-deprived animals. Rats were anesthetized with sodium pentobarbital (33 mg/kg body weight, intravenous) and operated according to our previously reported surgical procedure (18). Briefly, a PE-10 cannula (Intramedic) was introduced counter current into the left external iliac artery to the beginning of the superior vesical artery which was clamped distal to the left uterine artery exit level. The infusion medium introduced through the cannula therefore combines with the blood circulating through the left uterine artery. Rats were infused for 20 min at a constant rate of 12.5 μl/min with 250 μl of a 0.9% NaCl solution containing 10 μCi of [U-¹⁴C]-D-glucose, [U-¹⁴C]-L-alanine, or [U-¹⁴C]-glycerol (The Radiochemical Center, Amersham, England) (specific activity 257, 10 and 171 mCi/mmol, respectively).

After collection of blood from the maternal aorta into heparinized syringes, placentas and fetuses from the left and right uterine horns were immediately excised. Fetuses were decapitated and blood collected into heparinized receptacles. All fetal blood from each uterine side was pooled separately. Fetal livers were immediately placed in liquid N₂. Plasma aliquots were deproteinized with 10% perchloric acid and neutralized with saturated potassium bicarbonate. Protein-free supernatants were used for esti-

In the rat fetus unlike several other species including the guinea pig (1), rabbit (2), sheep (3), and man (4) gluconeogenesis is

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mation of glucose (19), alanine (20), glycerol (21), and lactate (22). In experiments with infusions of [U-¹⁴C]-D-glucose or [U-¹⁴C]-L-alanine, labeled plasma glucose, alanine, and lactate were purified (23) from 100- μ l aliquots of deproteinized supernatants, using microcolumns made with AG 1 \times 8 200–400 chloride and AG 50 W-8 200–400 H⁺ (Bio-Rad Laboratories, Richmond, CA) rinsed with distilled water, 0.5 M formic acid, and 2 N ammonium hydroxide for ¹⁴C-glucose, ¹⁴C-lactate and ¹⁴C-alanine elutions, respectively. Eluates were collected in counting vials and lyophilized for counting. Recoveries for [U-¹⁴C]-D-glucose added to plasma before precipitation were 97 \pm 2% in the first eluate, 88 \pm 3% for [U-¹⁴C]-L-lactate in the second eluate, and 91 \pm 2% for [U-¹⁴C]-L-alanine in the third eluate. Tracer recoveries in the noncorresponding eluates were always below 0.4%.

In experiments with [U-¹⁴C]-glycerol infusions, labeled plasma glycerol, glucose, and lactate were purified by ascending paper chromatography, the eluent being the upper phase resulting from the butanol-water-methanol-formic acid mixture (320:320:80:1) (v/v) (24). The spots were identified by running purified standards in parallel and cutting them into small pieces for introduction into counting vials. Recoveries of labeled glycerol, glucose, and lactate were 86 \pm 0.5%, 92 \pm 1%, and 90 \pm 0.5%, respectively. Labeled lipids in fetal liver were extracted (25) and saponified in ethanolic 1 N potassium hydroxide for fatty acid and glyceride glycerol fractionation (26). Radioactivity counting was done by means of a Normascint-22 cocktail (Scharlau, Barcelona, Spain) in a LS 3800 Beckman counter. Radioactivity values were corrected by considering 1 \times 10⁶ dpm as the total infused radioactivity per rat. Results were expressed as means \pm SD and statistical comparison between groups was performed by the Student's *t* test.

RESULTS

Pregnant rats in the 21.5 day of gestation were infused for 20 min with tracer amounts of three different labeled metabolites through the left uterine artery to determine their appearance and potential transformation in the respective fetuses. The steady state concentration in plasma of these metabolites and lactate was measured in mothers and their fetuses at the end of the infusions and values are shown in Table 1. Plasma glucose and glycerol concentrations were higher and alanine and lactate levels were lower in fed and 48-h starved mothers than in their respective fetuses. Maternal starvation caused a decrease in maternal plasma glucose and alanine and a slight increase in plasma glycerol concentrations whereas in fetuses the only change detected with starvation was a significant reduction in plasma alanine (Table 1).

After infusion of labeled metabolites through the left maternal uterine artery, radioactivity in fetuses from the left uterine side comprised the amounts transferred from directly infused tracer and coming from the maternal circulation; whereas in fetuses from the right uterine side radioactivity corresponded only to

the amount coming from maternal circulation, *e.g.* the infused tracer diluted in general maternal circulation and labeled products of metabolization. The difference between radioactivity values in left and right fetuses therefore provides an index of direct availability to the fetus of placentally transferred substrates from the infused medium.

These values and those of maternal plasma after the infusion with [U-¹⁴C]-D-glucose, [U-¹⁴C]-glycerol, or [U-¹⁴C]-L-alanine through the left uterine artery are shown in Tables 2 to 4, respectively. After maternal infusion with [U-¹⁴C]-D-glucose, plasma ¹⁴C-glucose level and its specific activity were much higher in fetuses from the left uterine side than from the right side (Table 2). Similarly, the amount of ¹⁴C-lactate and its specific activity in fetal plasma were significantly greater in the left than in the right fetuses. Interestingly, ¹⁴C-lactate plasma values in left fetuses were much higher than the mother's (Table 2). Maternal starvation did not modify these relationships although it significantly increased the amount of ¹⁴C-glucose present in maternal plasma and its specific activity (Table 2). As shown in Table 3, when [U-¹⁴C]-glycerol was the tracer infused through the maternal left uterine artery both ¹⁴C-glycerol and ¹⁴C-lactate plasma values and their specific activities were significantly higher in the left than in the right fetuses whereas ¹⁴C-glucose levels and ¹⁴C-glucose specific activity did not differ between fetuses from both sides (Table 3).

Much more radioactivity appeared as ¹⁴C-glucose than as ¹⁴C-glycerol in maternal plasma after maternal infusion with [U-¹⁴C]-glycerol and this difference was even greater in the 48-h starved rat (Table 3). Plasma ¹⁴C-glucose values did not differ between fetuses from either side whereas both ¹⁴C-glycerol and ¹⁴C-lactate levels and their respective specific activities were significantly higher in fetuses from the left *versus* the right uterine side in both the fed and the starved condition after maternal infusion with [U-¹⁴C]-glycerol (Table 3). As shown in Table 4, after maternal infusion of [U-¹⁴C]-L-alanine through the left uterine artery, plasma ¹⁴C-alanine levels appeared higher in fetuses from the left uterine side than in their mothers either fed or starved. Left fetuses showed higher plasma ¹⁴C-alanine and ¹⁴C-lactate values as well as ¹⁴C-alanine specific activity than the right ones after maternal infusion with [U-¹⁴C]-L-alanine when either fed or starved. On the contrary, ¹⁴C-glucose levels in fetuses were very low and no differences were observed between those from the left and the right uterine sides (Table 4). As it occurred with [U-¹⁴C]-glycerol, after the infusion with [U-¹⁴C]-L-alanine, maternal ¹⁴C-glucose values and specific activity were significantly higher in 48-h starved than in fed rats (Table 4).

Labeled lipid levels in fetal liver after maternal infusion of the labeled metabolites were measured and values are summarized in Table 5. [U-¹⁴C]-D-glucose and [U-¹⁴C]-glycerol produced higher radioactivity values of both ¹⁴C-fatty acids and ¹⁴C-glyceride glycerol in the liver of fetuses from the left *versus* the right uterine horn (Table 5). Maternal starvation diminished ¹⁴C-fatty

Table 1. Glucose, glycerol, alanine, and lactate* concentrations in mother's and fetus' plasma after maternal infusion with D-[U-¹⁴C]-glucose, [U-¹⁴C]-glycerol, or L-[U-¹⁴C]-alanine, respectively, in 21.5-day pregnant rat

	Fed rats			48-h starved rats		
	Mothers	Fetuses	<i>p</i> †	Mothers	Fetuses	<i>p</i>
Glucose (mmol/liter)	4.9 \pm 0.7 (6)‡	3.9 \pm 0.4 (6)	<0.05	4.1 \pm 0.2§ (6)	3.6 \pm 0.2 (6)	<0.01
Glycerol (μ mol/liter)	155 \pm 40 (6)	113 \pm 29 (6)	NS	182 \pm 58 (6)	122 \pm 20 (6)	NS
Alanine (μ mol/liter)	479 \pm 47 (6)	1667 \pm 425 (6)	<0.001	292 \pm 82 (5)	1072 \pm 280§ (5)	<0.001
Lactate (mmol/liter)	3.2 \pm 1.2 (18)	13.2 \pm 4.1 (18)	<0.001	3.0 \pm 0.8 (17)	13.0 \pm 6.4 (17)	<0.001

* Lactate values correspond to all animals studied.

† Statistical comparisons between mothers and fetuses.

‡ Mean \pm SD. Numbers in parentheses are numbers of rats/group.

§ Statistical comparisons between fed and 48-h starved rats: § *p* < 0.05; || *p* < 0.01.

Table 2. Plasma radioactivity values in mothers and fetuses after maternal infusion through left uterine artery with D-[U-¹⁴C]-glucose in 21.5-day pregnant rat

	Fed rats				48-h starved rats			
	Mothers	Left fetuses	Right fetuses	<i>p</i> *	Mothers	Left fetuses	Right fetuses	<i>p</i>
¹⁴ C-glucose (dpm/ml)	4479 ± 562†	4495 ± 1238	1236 ± 300	<0.001	6038 ± 1070‡	6984 ± 4315	1528 ± 734	<0.01
¹⁴ C-glucose specific activity (dpm/μmol)	915 ± 161	1289 ± 562	347 ± 138	<0.001	1472 ± 281‡	1786 ± 803	374 ± 190	<0.01
¹⁴ C-lactate (dpm/ml)	818 ± 112	5296 ± 807	1355 ± 341	<0.001	833 ± 408	7111 ± 3334	1271 ± 575	<0.001
¹⁴ C-lactate specific activity (dpm/μmol)	305 ± 94	495 ± 156	133 ± 29	<0.001	288 ± 127	370 ± 172	123 ± 94	<0.05

* Statistical comparisons between left and right fetuses.

† Mean ± SD of six rats/group.

Statistical comparisons between fed and 48-h starved rats: ‡ *p* < 0.05.

Table 3. Plasma radioactivity values in mothers and fetuses after maternal infusion through left uterine artery with [U-¹⁴C]-glycerol in 21.5-day pregnant rat

	Fed rats				48-h starved rats			
	Mothers	Left fetuses	Right fetuses	<i>p</i> *	Mothers	Left fetuses	Right fetuses	<i>p</i>
¹⁴ C-glycerol (dpm/ml)	630 ± 212†	569 ± 366	47 ± 60	<0.01	768 ± 294	835 ± 493	40 ± 54	<0.01
¹⁴ C-glycerol specific activity (dpm/μmol)	4045 ± 2139	4780 ± 2393	390 ± 335	<0.001	4355 ± 1376	6044 ± 2201	371 ± 504	<0.001
¹⁴ C-glucose (dpm/ml)	3387 ± 386	691 ± 120	550 ± 96	NS	4625 ± 743‡	926 ± 288	877 ± 190‡	NS
¹⁴ C-glucose specific activity (dpm/μmol)	685 ± 69	170 ± 45	166 ± 69	NS	1190 ± 143§	268 ± 47	230 ± 45	NS
¹⁴ C-lactate (dpm/ml)	878 ± 185	1954 ± 299	922 ± 201	<0.001	1019 ± 274	1733 ± 314	982 ± 281	<0.001
¹⁴ C-lactate specific activity (dpm/μmol)	373 ± 149	129 ± 18	87 ± 36	<0.001	705 ± 314	133 ± 29	89 ± 25	<0.05

* Statistical comparisons between left and right fetuses.

† Mean ± SD of six rats/group.

Statistical comparisons between fed and 48-h starved rats: ‡ *p* < 0.01; § *p* < 0.001; || *p* < 0.05.

Table 4. Plasma radioactivity values in mothers and fetuses after maternal infusion through left uterine artery with L-[U-¹⁴C]-alanine in 21.5-day pregnant rat

	Fed rats				48-h starved rats			
	Mothers	Left fetuses	Right fetuses	<i>p</i> *	Mothers	Left fetuses	Right fetuses	<i>p</i>
¹⁴ C-alanine (dpm/ml)	1021 ± 321†	6697 ± 2533	433 ± 87	<0.001	1177 ± 296	5463 ± 2518	441 ± 98	<0.001
¹⁴ C-alanine specific activity (dpm/μmol)	2152 ± 664	3647 ± 1628	304 ± 74	<0.01	4346 ± 1634‡	4232 ± 1290	514 ± 112‡	<0.01
¹⁴ C-glucose (dpm/ml)	627 ± 76	286 ± 89	274 ± 40	NS	1582 ± 160§	480 ± 150	417 ± 94	NS
¹⁴ C-glucose specific activity (dpm/μmol)	97 ± 38	51 ± 16	66 ± 9	NS	292 ± 56	135 ± 122	119 ± 40	NS
¹⁴ C-lactate (dpm/ml)	861 ± 96	6535 ± 2611	819 ± 132	<0.001	896 ± 76	4160 ± 2158	829 ± 208	<0.001
¹⁴ C-lactate specific activity (dpm/μmol)	212 ± 47	341 ± 167	58 ± 18	<0.01	346 ± 212	260 ± 122	70 ± 28	<0.05

* Statistical comparisons between left and right fetuses

† Means ± SD of six (fed) or five (starved) rats/group.

Statistical comparisons between fed and 48-h starved rats: ‡ *p* < 0.01; § *p* < 0.001; || *p* < 0.05.

acids without affecting ¹⁴C-glyceride glycerol (Table 5). Following infusion of [U-¹⁴C]-D-glucose in fed pregnant rats, the radioactivity level was higher in liver fatty acids than in glyceride glycerol of left fetuses whereas this relationship was reversed when the mother was starved. Infusion of [U-¹⁴C]-glycerol produced a much higher proportion of ¹⁴C-glyceride glycerol than ¹⁴C-fatty acids in fetal liver; this difference was more pronounced in fetuses from the left than from the right uterine horn (Table 5). Negligible amounts of radioactivity were found in fetal liver when the infused tracer was [U-¹⁴C]-L-alanine, and no differences in values were detected in fetuses from the left and right uterine horns.

DISCUSSION

Present results in rat fetuses from 21.5-day pregnant fed or 48-h starved mothers support three basic conclusions: 1) significant gluconeogenesis does not occur from either glycerol or L-alanine; 2) a high proportion of these substrates and also D-glucose, when transferred from maternal circulation, reach the fetus in the form of lactate; and 3) the fetus responds to maternal starvation by decreasing liver fatty acid synthesis from transferred D-glucose and glycerol but not from L-alanine which is practically negligible as a lipogenic substrate for the rat fetus. Differences in radioac-

Table 5. Labeled fatty acids and glyceride glycerol in fetal livers after maternal infusion through left uterine artery with D-[U-¹⁴C]-glucose, [U-¹⁴C]-glycerol, or L-[U-¹⁴C]-alanine in 21.5-day pregnant rat

	Fed rats			48-h starved rats		
	Left fetuses	Right fetuses	<i>p</i> *	Left fetuses	Right fetuses	<i>p</i>
Infusion with D-[U- ¹⁴ C]-glucose						
¹⁴ C-fatty acids (dpm/g)	86 ± 49†	24 ± 16	<0.05	4 ± 4‡	1 ± 2‡	NS
¹⁴ C-glyceride glycerol (dpm/g)	48 ± 20	21 ± 11	<0.05	34 ± 7	8 ± 4§	<0.001
Infusion with [U- ¹⁴ C]-glycerol						
¹⁴ C-fatty acids (dpm/g)	91 ± 42	40 ± 16	<0.05	19 ± 18‡	5 ± 2‡	NS
¹⁴ C-glyceride glycerol (dpm/g)	385 ± 149	86 ± 60	<0.01	471 ± 252	45 ± 13	<0.01
Infusion with L-[U- ¹⁴ C]-alanine						
¹⁴ C-fatty acids (dpm/g)	27 ± 29	19 ± 20	NS	18 ± 16	3 ± 2	NS
¹⁴ C-glyceride glycerol (dpm/g)	23 ± 13	22 ± 13	NS	50 ± 42	28 ± 26	NS

* Statistical comparisons between left and right fetuses.

† Mean ± SD of five to six rats/group.

Statistical comparisons between fed and 48-h starved rats: ‡ *p* < 0.01; § *p* < 0.05.

tivity between left and right fetuses for ¹⁴C-glucose, ¹⁴C-glycerol, and ¹⁴C-alanine after maternal infusion through the left uterine artery with the respective uniformly ¹⁴C-labeled tracers, and the magnitude of these differences (the larger corresponding to ¹⁴C-alanine and the smaller to ¹⁴C-glycerol) are in agreement with the way it is known they cross the placenta (10, 27, 28). Plasma-specific activities of the respective tracers in fetuses from the left uterine side were also significantly higher than in those from the right ones, indicating that the infused tracer directly reached fetuses from the left side whereas it reached those from the right side after its dilution in maternal circulation. This explanation also justifies the fact that specific activities of infused metabolites were always lower in right fetuses than in their mothers. Present findings validate the technique used and reflect its suitability for the study of metabolic fate of placental transferred substrates in the rat.

After maternal infusion with [U-¹⁴C]-glycerol or L-[U-¹⁴C]-alanine a significant proportion of the label was converted into glucose by maternal tissues as indicated by the appearance of ¹⁴C-glucose in maternal plasma; the process was enhanced with starvation as expected. Glycerol was always a more efficient gluconeogenic substrate even when values were corrected by their respective specific activities in maternal plasma, substantiating previous findings in the late pregnant rat (29). In contrast, from either substrate no incorporation of ¹⁴C-atoms into glucose occurred in fetuses. Despite the fact that the amount of radioactivity of the infused tracers (¹⁴C-glycerol or ¹⁴C-alanine) and their specific activities were much higher in plasma of left than of right fetuses, ¹⁴C-glucose values were statistically equal in fetuses from both sides (Tables 3 and 4). It may be concluded that fetal ¹⁴C-glucose is derived exclusively from the maternal circulation and that no fetal gluconeogenesis occurred either in the fed or the starved condition.

This conclusion is in agreement with reports based on different methodologies (5–8) but is in contradiction with results of other studies (10, 13, 15), most of which (13, 15) used 4-day rather than 2-day starvation periods indicating that fetal gluconeogenesis is only induced after prolonged maternal food deprivation. In one study, in which the rat diet was not specified (10), gluconeogenesis from labeled glycerol was detected in the fetuses, but the tracer was injected into the fetus when exteriorized from the uterus. This greatly altered the environmental condition and the immediate and abnormally high glycerol load to the fetus could induce premature gluconeogenesis. Absence of gluconeogenesis in the rat fetus is probably a consequence of its limited phosphoenolpyruvate carboxykinase and glucose-6-phosphatase activities in the liver (7, 30), and when using L-alanine as substrate, reduced alanine aminotransferase activity (16) should also be taken into consideration.

Lack of ¹⁴C-glucose synthesis in the rat fetus is clearly in contrast with the efficient incorporation of ¹⁴C-atoms from either labeled glucose, glycerol, and alanine into fetal lactate which was shown in the present study by the much higher levels of ¹⁴C-lactate in the plasma of fetuses from the left than in those from the right side after maternal infusions through the left uterine artery. Findings indicate that ¹⁴C-lactate is synthesized from maternal transferred substrates by fetoplacental structures. Recently we reported the ability of rat placenta to synthesize lactate from both D-glucose (31) and L-alanine (32). Production of placental lactate from L-alanine seems to be involved in the mechanism of the maternofetal transfer of the amino acid (32) and is consistent with the reported presence of alanine aminotransferase in rat placenta (16, 33). The level of labeled lactate in fetal plasma after infusion through the maternal left uterine artery was much lower with [U-¹⁴C]-glycerol than with the other substrates studied. This may be due to the limited placental transfer of glycerol as compared with either D-glucose or L-alanine (34) as a result of the low concentration of glycerol in maternal circulation. Because of the rapid and efficient conversion of maternal glycerol into glucose (29), only a limited amount of glycerol is consequently available for transfer to the fetus, as previously proposed (35). Placental production of lactate from maternal transferred substrates is physiologically important as it contributes to the high lactate levels present in fetal plasma, and also because lactate is used by the rat fetus as an energy fuel (36, 37). As pointed out by Kraan and Dias (38), the excess of lactate produced by fetal structures is efficiently cleared through the placenta to the mother and converted into glucose.

In view of the quality change detected in fetal plasma after maternal infusion of any labeled compound studied, it is not possible to attribute the appearance of labeled lipids in fetal liver to their direct and unique use as lipogenic substrates. It is evident from present results, however, that [U-¹⁴C]-L-alanine is not used by the rat fetus as a substrate for labeled fatty acid or glyceride glycerol synthesis, perhaps due to the low alanine aminotransferase activity found in fetal liver (16). This hypothesis is not in disagreement with the observed appearance of ¹⁴C-lactate in fetus plasma after maternal ¹⁴C-alanine infusion since this conversion occurs in the placenta rather than in fetal tissues (32). Unlike L-alanine, after maternal infusions through the left uterine artery of either ¹⁴C-D-glucose or ¹⁴C-glycerol, labeled lipids appeared in fetal liver. Since this value was higher in livers of fetuses from the left than from the right uterine horn it may be concluded that the lipids were directly synthesized from the placental transferred substrate. Maternal starvation caused a reduction in the synthesis of ¹⁴C-fatty acids from both labeled D-glucose and glycerol, in agreement with the similar effect reported using ³H₂O as tracer (17). This effect seems to occur independently of a

change in fetal liver lipogenic activities which have been shown to be unmodified by maternal starvation (16). It may therefore be caused by the reduced fetal availability of maternal substrates, cosubstrates, and/or effectors for this pathway which occurs in fetuses of starved mothers as a result of diminished placental metabolite transfer, which depends on maternal circulating levels and uterine blood flow.

In contrast with lipogenesis, ^{14}C -glyceride glycerol synthesis was much greater in liver of fetuses from mothers infused with $[\text{U-}^{14}\text{C}]$ -glycerol than with $[\text{U-}^{14}\text{C}]$ -D-glucose and it was unmodified by maternal starvation. This finding indicates that this process occurs through the direct esterification of glycerolphosphate formed by the glycerol kinase catalyzed reaction, which is known to be active in fetus liver at late gestation (11), rather than by glycerolgenesis. In adults, glycerolgenesis from different substrates is directly correlated with gluconeogenesis (23, 39). Therefore the negligible glycerolgenesis found in fetal liver further supports the main conclusion of the present study concerning the absence of gluconeogenesis from either L-alanine and glycerol and even from lactate in the fed and 48-h starved rat fetus.

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