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HEPATECTOMY-NEPHRECTOMY EFFECTS IN THE PREGNANT RAT AND FETUS

Teresa Mampel*, Francesc Villarroya* and Emilio Herrera**

Cátedra de Fisiología General, Facultad de Biología, Universidad de Barcelona*
Departamento de Investigación, Centro Ramón y Cajal, 28034-Madrid**, Spain

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SUMMARY Levels of circulating glucose, glycerol, and FFA concentrations were determined before and after hepatectomy-nephrectomy in 20 day pregnant rats and virgin controls. After evisceration, blood glucose levels decreased in a parallel way in both groups whereas in pregnant rats, the blood glycerol level increased less and plasma-FFA rose more than in controls. Maternal evisceration caused reduced blood glucose and enhanced glycerol levels in fetuses, whereas fetal plasma-FFA levels were unmodified. Results indicate that extrahepatic glucose utilization remained stable in the late pregnant rat. Fetal levels of circulating glycerol, but not of FFA, appeared directly dependent on maternal levels. It is proposed that under normal conditions, glycerol availability to the fetus is low, due to its preferential utilization by maternal gluconeogenic organs which reduced the amount available for possible placental transfer.

Functional hepatectomy and nephrectomy in the rat decrease circulating levels of glucose (1-3) due to both lack of synthesis of glucose and its increased use by extrahepatic tissues. In conditions of reduced hepatic function this hypoglycemia is partially compensated for by the activation of adipose tissue lipolysis (4,5) which in addition to reductions in the use of its normal products, FFA and glycerol, causes increments in their respective circulating levels (2,3,6,7). The late pregnant rat is hypoglycemic and has increased

**To whom correspondence should be addressed.

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circulating levels of both FFA and glycerol (8,9) due to enhanced adipose tissue lipolysis (10,11). These effects occur in spite of the mother's active hepatic metabolic state, as shown by her augmented gluconeogenesis, specially from glycerol (8,9,12). These changes in the pregnant mother are also influenced by transfer to the fetus of glucose, glycerol and FFA which occurs through different mechanisms and in different degrees of efficiency (for a review see ref.13). The purpose of the present study was to investigate the effects of hepatectomy and nephrectomy on circulating metabolites in the late pregnant rat and their potential effects on the fetus.

MATERIALS AND METHODS

Female Wistar rats fed ad libitum purina chow were mated when weighing 160-180 g, and gestation was timed from the day spermatozoids appeared in vaginal smears. Animals were studied at day 20 of gestation and compared to age- and sex-matched virgin controls. They were anesthetized with sodium nembutal (40 mg intravenously/Kg body weight) and subjected to functional hepatectomy and nephrectomy following the method of Russell (1) and Higgins and Anderson (14), as previously described (2,3). When indicated, sham-operated controls were studied in parallel. Blood samples were collected in heparinized syringes from the inferior cava vein at 0, 5 and 10 min after hepatectomy-nephrectomy and after deproteinization (15), glucose (16) and glycerol (17) were measured in the supernatants. Plasma was obtained from other blood aliquots and used for FFA estimation (18). After the last blood collection, fetuses were excised and rapidly decapitated for blood collection into heparinized receptacles to measure glucose, glycerol and FFA as above. Results are expressed as means + SEM, and comparisons between groups were performed with the Student's "t" test.

RESULTS

As shown in Table 1, blood glucose levels were significantly lower in pregnant than in virgin animals. Hepatectomy-nephrectomy produced a significant and

Table 1. Effects of hepatectomy-nephrectomy on blood glucose and glycerol and plasma FFA in virgin and 20-day pregnant rats

Min after evisceration:	0	5	10
Virgin rats			
Glucose, mg/dl	119±3	90±1^{c}	87±6^{c}
% time 0	100	82±6^{b}	72±6^{c}
Glycerol, umoles/dl	13±1	22±3^{a}	33±3^{c}
% time 0	100	179±10^{c}	227±20^{c}
FFA, mmoles/l	3.3±0.5	4.2±0.8	6.1±1.0^{a}
% time 0	100	155±27^{a}	178±10^{c}
Pregnant rats			
Glucose, mg/dl	77±2^{f}	66±3^{b,f}	58±2^{c,f}
% time 0	100	87±4^{b}	73±1^{c}
Glycerol, umoles/dl	20±1^{e}	31±3^{b}	36±4^{b}
% time 0	100	167±15^{c}	174±11^{c,d}
FFA, mmoles/l	4.7±0.7^{e}	8.7±0.7^{b,e}	10.7±1.2^{a,e}
% time 0	100	181±34^{d}	238±11^{c,e}

a,b,c= significance versus time 0 (a=p<0.05, b=p<0.01, c=p<0.001); d,e,f= significance of pregnants versus virgins (d=p<0.05, e=p<0.01, f=p<0.001); n=7-8 rats/group.

progressive decrease in blood glucose values in both groups, and levels remained significantly lower in pregnant than in virgin animals . The hypoglycemic effect produced by evisceration did not differ in the two groups, as indicated by their similar percentual reduction of blood glucose levels (Table 1). Under basal conditions (time 0, Table 1), blood glycerol levels were significantly higher in pregnant than in virgin animals . Values increased in both groups after hepatectomy-nephrectomy but the change was significantly less in pregnant than in virgin animals as shown by the percentual glycerol values at 10 min (Table 1). Plasma FFA concentration was also significantly higher in pregnant than in virgin animals under basal conditions and hepatectomy-nephrectomy enhanced this parameter more in pregnant than in virgin animals, as indicated by the significantly greater percentual FFA change 10 min after evisceration in the pregnant group (Table 1). To

determine how these changes in the eviscerated mother affect the fetus, circulating levels of the same metabolites were studied in fetuses and their respective mothers 10 min after either hepatectomy-nephrectomy or a sham operation . As shown in Table 2, in sham-operated late pregnant rats, blood glucose levels were significantly lower in fetuses than in their mothers. Maternal hepatectomy-nephrectomy produced parallel decreases in blood glucose levels of mothers and fetuses and the fetal/maternal glucose ratio remained stable (Table 2). Glycerol concentrations, which were significantly lower in fetal than in maternal blood, rose in parallel in hepatectomized mothers and their fetuses whereas the fetal/maternal glycerol ration was not modified in sham-operated animals. FFA levels were significantly lower in fetal than in maternal plasma in the sham-operated rats. Plasma levels rose in hepatectomized mothers but not in their fetuses in which this value was similar to that of fetuses from sham-operated mothers (Table 2), and the fetal/maternal plasma

Table 2. Blood glucose and glycerol and plasma FFA in 20-day pregnant rats and their fetuses 10 min after hepatectomy-nephrectomy or sham-operation

	Glucose (mg/dl)	Glycerol (umoles/dl)	FFA (mM)
Sham-operated			
Mothers	97±6	26±2	6.5±0.8
Fetus	48±5	6.9±0.8	3.5±0.5
p	<0.001	<0.001	<0.01
Fetus/Mother	0.50±0.04	0.27±0.05	0.54±0.05
Hepatectomyzed-nephrectomyzed			
Mothers	58±2[c]	36±4[a]	10.7±1.2[a]
Fetus	35±3[a]	14±3[a]	3.6±0.3
p	<0.001	<0.001	<0.001
Fetus/Mother	0.58±0.04	0.36±0.06	0.33±0.04[b]

a,b,c= Significance of eviscerated versus sham-operated (a=p<0.05, b=p<0.01, c=p<0.001): n = 7-8 rats/group

FFA ratio appeared significantly lower in hepatectomized than in sham-operated animals (Table 2).

DISCUSSION

Present results show that evisceration of late pregnant or virgin rats causes a similar decrease in their blood glucose levels, indicating that extrahepatic utilization of glucose is not modified by pregnancy, in agreement with previous proposals based on glucose turnover studies (19). Evisceration in the virgin rats produced an increase in circulating levels of both glycerol and FFA , confirming earlier studies (2,3), whereas in the pregnant animals the glycerol and FFA increases were respectively less and more pronounced than in virgin animals. After evisceration the fetal/maternal blood glucose ratio remained unchanged. This finding together with our previously reported linear correlation between maternal glycemia and placental glucose transfer in the diabetic rat (20) indicate that independently of its directional change, fetal glucose availability is directly dependent on maternal plasma glucose concentrations. Enhanced adipose tissue lipolysis in the pregnant rat (10,11) may account for her augmented circulating levels of glycerol and FFA as compared to virgin controls. The lower increment in blood glycerol levels in pregnant versus virgin animals produced after evisceration may be a consequence of placental glycerol transfer to the fetus. In normal conditions, very litle maternal glycerol crosses the placenta (21) but this could be due to its efficient use as gluconeogenic substrate in the mother (9,12), which leaves isufficient glycerol for its

transfer to the fetus. Present findings support this hypothesis as a functional block in maternal gluconeogenic organs doubled fetal blood glycerol levels, indicating that in this condition, the metabolite efficiently crosses the placental barrier. The greater increase of maternal plasma FFA than glycerol after evisceration is probably the result of their known difficulties in crossing the placenta (22), which could account for the lack of change in FFA levels in fetal plasma. The possibility that adipose tissue lipolytic response to evisceration differs in pregnant and nonpregnant animals remains to be determined and may be an additional factor influencing some of the observed differences.

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