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Research Article

Diabetes mellitus in pregnancy is associated with neonatal respiratory distress syndrome due to impaired synthesis of fetal lung surfactant. Pharmacologic agents that promote fetal lung maturity are diabetogenic and have limited use in the management of diabetic pregnancy for prevention of respiratory distress syndrome. Maternal administration of a thyroid analog 3,5-dimethyl-3'-isopropyl-L-thyronine (DIMIT) results in significant enhancement of fetal lung phospholipid synthesis and accelerated lung maturity. We therefore studied the effects of DIMIT (0.5 mg/kg per d, s.c.) administration to pregnant alloxan-diabetic rabbits on days 25 and 26 of gestation. DIMIT treatment of diabetic maternal rabbits (DD) was associated with reduction of maternal blood glucose (115 +/- 13 vs. 275 +/- 72 mg/dl, P less than 0.05) and fetal glucose (64 +/- 6 vs. 274 +/- 47 mg/dl, P less than 0.001) compared with saline-injected diabetic (D) mothers. Reduction of fetal insulin levels was also associated with maternal DIMIT therapy in diabetic rabbits (56 +/- 5 (D) vs. 24 +/- 4 microunits/ml, P less than 0.001). Maternal diabetes resulted in significant reduction of fetal lung weight (370 +/- 20 vs. 520 +/- 30 mg, P less than 0.005) and lung protein content (6.5 +/- 0.7 vs. 8.7 +/- 0.7 mg/gm, P less than 0.005), which were restored to normal in offspring of DIMIT-treated diabetic rabbits. Maternal DIMIT administration caused significant reduction […]

3,5-Dimethyl-3′-Isopropyl-L-Thyronine Therapy in Diabetic Pregnancy

STIMULATION OF RABBIT FETAL LUNG PHOSPHOLIPIDS

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ABSTRACT Diabetes mellitus in pregnancy is associated with neonatal respiratory distress syndrome due to impaired synthesis of fetal lung surfactant. Pharmacologic agents that promote fetal lung maturity are diabetogenic and have limited use in the management of diabetic pregnancy for prevention of respiratory distress syndrome. Maternal administration of a thyroid analog 3,5-dimethyl-3′-isopropyl-L-thyronine (DIMIT) results in significant enhancement of fetal lung phospholipid synthesis and accelerated lung maturity. We therefore studied the effects of DIMIT (0.5 mg/kg per d, s.c.) administration to pregnant alloxan-diabetic rabbits on days 25 and 26 of gestation. DIMIT treatment of diabetic maternal rabbits (DD) was associated with reduction of maternal blood glucose (115±13 vs. 275±72 mg/dl, $P < 0.05$) and fetal glucose (64±6 vs. 274±47 mg/dl, $P < 0.001$) compared with saline-injected diabetic (D) mothers. Reduction of fetal insulin levels was also associated with maternal DIMIT therapy in diabetic rabbits (56±5 (D) vs. 24±4 μU/ml, $P < 0.001$).

Maternal diabetes resulted in significant reduction of fetal lung weight (370±20 vs. 520±30 mg, $P < 0.005$) and lung protein content (6.5±0.7 vs. 8.7±0.7 mg/gm, $P < 0.005$), which were restored to normal in offspring of DIMIT-treated diabetic rabbits. Maternal DIMIT administration caused significant reduction in fetal lung glycogen content in control (62±5.8 vs. 25±5.9 μg/mg protein, $P < 0.001$) and diabetic (56±7 vs. 34±5 μg/mg protein, $P < 0.02$) offspring. Whereas maternal diabetes was associated with reduction of all major phospholipid species in fetal lung-comprising surfactant, these were restored with DIMIT therapy. The results demonstrate that short-term maternal administration of DIMIT in pregnant diabetic rabbits not only promotes fetal lung phospholipid synthesis, but also appears to ameliorate maternal hyperglycemia. Thus, DIMIT is of potential benefit in the management of diabetic pregnancy.

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INTRODUCTION

Poorly controlled diabetes mellitus during pregnancy results in fetal hyperinsulinemia and is associated with neonatal respiratory distress syndrome (RDS) (1). This is probably due to the direct inhibition of surfactant production in fetal lung by insulin (2, 3). Although strict control of maternal diabetes has resulted in a reduction in the prevalence of RDS, this disorder still occurs with significantly greater frequency in diabetic pregnancies (4). Although glucocorticoids (5) and aminophylline (6) promote fetal lung maturity and prevent fetal RDS when administered to the mother before delivery, these agents are insulin antagonists and diabetogenic and are of limited use in the treatment of diabetic pregnancies (7). Thyroid hormones have been shown to stimulate fetal lung maturation (8, 9); however, they do not effectively cross the rabbit or human placenta and maternal administration of these hormones does not result in thyromimetic effects on the fetus (10). Although a preliminary report suggested that intraamniotic T_4 administration accelerated human fetal lung maturity (11), the practical use of this method

[1] *Abbreviations used in this paper*: C, control mothers; CD, DIMIT-treated control mothers; D, alloxan-diabetic mothers; DD, DIMIT-treated diabetic mothers; DIMIT, 3,5-dimethyl-3′-isopropyl-L-thyronine; DSPC, disaturated phosphatidylcholine; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PG, phosphatidylglycerol; PI, phosphatidylinositol; PS, phosphatidylserine; RDS, respiratory distress syndrome; SM, sphingomyelin; T_3, L-Triiodothyronine; and T_4, L-thyroxine.

of T_4 administration in vivo is cumbersome and involves a surgical procedure.

Recent reports have shown that the synthetic nonhalogenated thyroid hormone analogue 3-5-dimethyl-3'-isopropyl-L-thyronine (DIMIT) (12) effectively crosses the rat (13), rabbit (14), and primate (15) placentas. Ballard et al. (14) has recently shown that DIMIT administration to maternal rabbits resulted in significant enhancement of lung maturation by promoting phospholipid synthesis. DIMIT exerted thyromimetic effects in the primate fetus, and suppressing fetal pituitary-thyroid axis function and improving amniotic fluid lecithin/sphingomyelin (L/S) ratios (15).

Because the beneficial effects of DIMIT on fetal lung development in vivo were associated with little metabolic effect in the mother, we investigated the effects of DIMIT administration to diabetic pregnant rabbits on fetal lung maturation. We have found that this agent improved maternal hyperglycemia and promoted fetal lung maturity.

METHODS

Materials

DIMIT, synthesized by the late Dr. Eugene Jorgensen (12), was kindly supplied by Dr. Ralph Somack, University of California, San Francisco. The hormone was dissolved in 0.9% NaCl containing 0.2 N NaOH (vehicle) immediately before injection.

Animal preparation. Pregnant New Zealand rabbits were used for the experiments. Alloxan (60 mg/kg) was administered intravenously to the pregnant mothers on day 14 of gestation at a time that has been shown to permit normal development of fetal islet cells (16). The does were allowed access to 10% dextrose in water for 24 h. Their random blood sugar concentrations remained between 200 and 400 mg/dl until delivery. Alloxan treatment during pregnancy enabled the animals to carry litters to term and has alleviated the problem of decreased fertility and fetal wastage observed in animals rendered diabetic before gestation (16).

Experimental procedure

On days 25 and 26 of gestation, nondiabetic (control) does in pairs received subcutaneous injections of either vehicle or DIMIT (0.5 mg/kg × 2 doses). Similarly, alloxan-diabetic rabbits in pairs received vehicle or DIMIT on the designated days. Animals were killed on day 27, as described (16). Maternal blood was collected by cardiac puncture. After delivery by hysterotomy, fetuses were decapitated, trunk blood collected, and serum was separated and stored at −70°C for subsequent assay. Lung tissue was harvested from individual fetuses and weighed and frozen for subsequent tissue analyses.

Tissue analyses

Lung tissue was washed with buffer (Krebs-Ringer phosphate, pH 7.4) and total lipids were extracted according to Folch et al. (17). The total lipid was dissolved in 1 ml of 4:1 chloroform/methanol, and aliquots were applied to Merck Silica Gel 60-high performance plates (Merck Sharp & Dohme Div., West Point, Pa.). The plates were developed in a one-dimensional system using a solvent system consisting of petroleum ether/chloroform/methanol/acetic acid (3.5:5:1.5:1) by volume, as described by Kolin et al. (18). This method distinguished the major primary phospholipids, phosphatidylcholine (PC), sphingomyelin (SM), phosphatidylinositol (PI), phosphatidylserine (PS), phosphatidylethanolamine (PE), and phosphatidylglycerol (PG). Disaturated phosphatidylcholine (DSPC) was isolated and quantitated after reaction with osmium tetroxide, as described by Mason et al. (19). The spots were visualized with iodine vapor, identified in ultraviolet light, and phospholipid content was quantitated by the method of Raheja et al. (20). After lipid extraction the remaining tissue pellets were analyzed for glycogen (21) and DNA content (22). Glucose analyses of plasma samples were performed by ferricyanide reduction. Insulin was determined on all serum samples by the double antibody method radioimmunoassay (16). Unless otherwise noted, all values are expressed as mean±SE. Statistical significance was evaluated by unpaired t test, or analysis of variance where appropriate (23).

RESULTS

DIMIT administration to pregnant diabetic rabbits resulted in marked metabolic changes in both mother and fetus (Table I). DIMIT treatment of control mothers did not change maternal blood sugar levels, [93±11 (C) vs. 66±23 mg/dl (CD)], but diabetic mothers did show a significant decrease in their blood glucose levels after DIMIT treatment (275±72 (D) vs. 115±13 (DD) mg/dl, $P < 0.05$). Birthweight of D fetuses was significantly lower than control (31±0.8 vs. 26.9±1.3 g (D), $P < 0.05$). DIMIT treatment was associated with lowered birthweights in control (CD), but did not further reduce weights in offspring of treated diabetic mothers. Blood glucose values were significantly elevated in D fetuses (274±48 vs. 48±4 mg/dl, $P < 0.001$) reflecting maternal hyperglycemia; treatment of D mother with DIMIT (0.5 mg/kg per d) for 48 h before sacrifice resulted in a marked reduction in fetal blood sugar levels from 274±48 to 64±6 mg/dl, $P < 0.001$. The elevated insulin levels found in D fetuses (56±5 μU/ml) were also markedly lowered by DIMIT (25±4 μU/ml, $P < 0.001$). The net weights of D fetal lungs (370±20 mg) were significantly lower than C fetal lung (520±30 mg, $P < 0.005$) and were increased with DIMIT treatment to 480±20 mg (Table II). Maternal diabetes resulted in significant reduction of lung protein content (6.5±0.7 vs. 8.7±0.7 mg/gm, (C) $P < 0.05$), which was restored to normal with DIMIT treatment (9.3±1.2 mg/gm, $P < 0.05$ vs. D). Lung DNA content was not affected by either maternal diabetes or hormone treatment. DIMIT therapy did, however, result in a significant reduction of lung tissue glycogen content in both C and D fetuses.

Results of lung phospholipid analyses are detailed in Table III. Maternal diabetes was associated with a reduction of all major lung phospholipid species. DSPC, an essential component of surfactant, rose from

TABLE I
*Metabolic Effects of DIMIT Administration (0.5 mg/kg/d) to Pregnant Diabetic Rabbits on Days 25 and 26 of Gestation**

	Maternal			Fetal			
		Glucose	Insulin		Glucose	Insulin	Birth weight
	n	*mg/dl*	*μU/ml*	*n*	*mg/dl*	*μU/ml*	*g*
C	5	93±11	13±2	30	48±4	32±4	31±0.8
CD	2	66±23	21±15	18	46±6	29±4	26.7±0.5§
D	5	275±72	4±1	32	274±48§	56±5§	26.9±1.3‡
DD	3	115±13	3±1	20	64±6‖	25±4‖	29.6±1.6

* Mothers were sacrificed on day 27 and immediate hysterotomies were performed.
‡ $P < 0.05$ vs. C.
§ $P < 0.001$ vs. C.
‖ $P < 0.001$ vs. D.
C = Control mothers; CD = DIMIT-treated control mothers; D = alloxan-diabetic mothers; DD = DIMIT-treated diabetic mothers.

335±9 (D) to 481±66 (DD) μg/mg DNA, ($P < 0.05$), in D fetuses receiving DIMIT treatment. Phosphatidylglycerol (PG), a surfactant stabilizer which was reduced in D fetuses rose to C levels after DIMIT administration to diabetic mothers ($P < 0.05$). Maternal DIMIT treatment in diabetic animals was associated with an overall increase in fetal lung phospholipids, with significant enhancement of PC, PS, and SM. No change in total lung phospholipids or individual phospholipid species were noted in fetuses of DIMIT-treated control mothers.

DISCUSSION

Maternal diabetes was associated with significant reductions in fetal birthweight, lung wet weight and lung protein content. All of these abnormalities were restored toward normal with DIMIT treatment of diabetic does. Furthermore, the results demonstrate stimulation of fetal lung phospholipid synthesis in diabetic pregnancy by maternal DIMIT treatment. The enhanced production of certain phospholipid species, notably DSPC and PG, seen with DIMIT treatment would be expected to result in mature lung surfactant and thus prevent neonatal respiratory distress syndrome (24, 25). In accord with previous studies, no significant change in fetal lung phospholipids was noted in control animals receiving DIMIT (14). Although glucocorticoids are used in the antenatal period to prevent RDS, they are of limited use in diabetic pregnancy (5). Fetal hyperinsulinemia diminished lung phospholipid synthesis (3) and also blocked

TABLE II
*Fetal Lung Net Weights, Protein, DNA and Glycogen Content**

	Lung net weight	Lung protein	Lung DNA	Lung glycogen
	mg	*mg/g*	*mg/mg tissue*	*μg/mg protein*
C (16)‡	520±30	8.7±0.7	4.98±0.41	62±5.8
CD (18)	560±50	8.7±0.7	4.95±0.45	25±5.9
D (11)	370±20	6.5±0.71	5.10±0.32	56±7.0
DD (20)	480±20	9.3±1.2	5.23±0.48	34±5.0
P values				
C vs. CD	NS	NS		<0.001
C vs. D	<0.005	<0.001		NS
D vs. DD	<0.001	<0.05		<0.02

* C = control mothers; CD = DIMIT-treated control mothers; D = alloxan-diabetic mothers; DD = DIMIT-treated diabetic mothers.
‡ ( ) = number of fetuses in each group.

TABLE III

Fetal Lung Phospholipid Analyses

Group	SM	PC	PL	PS	PE	PG	DSPC	Total PL
				μg/mg DNA				*mg/mg DNA*
C (16)*	146±32	908±53	66.5±5	103±8	327±28	21±7	544±96	2.17±0.17
CD (16)	118±8	946±72	61.5±2	104±12	285±24	18±4	534±73	2.58±0.27
D (11)	68±15	534±37	55±7	51±9	228±17	10±1	335±9	1.75±0.09
DD (20)	148±25	790±53	49±8	77±10	267±10	20±4	481±66	1.96±0.12
P values								
C vs. D	<0.05	<0.001		<0.001			<0.05	<0.05
C vs. CD								
D vs. DD	<0.02	<0.001				<0.05	<0.05	

SM = sphingomyelin, PC = phophatidylcholine, PL = phophatidylinositol, PS = phosphatidylserine, PE = phosphatidylethanolamine, PG = phosphatidylglycerol, DSPC = disaturated phosphatidylcholine.
* ( ) = number of fetuses in each group.

the stimulatory effect of cortisol on lecithin synthesis in fetal lung (2). Administration of betamethasone to pregnant alloxan diabetic rabbits resulted in aggravation of maternal diabetes, fetal hyperinsulinemia, and stillbirth (26). These findings were not unexpected in view of the known diabetogenic effects of glucocorticoids. Although no data is currently available on the use of aminophylline in preventing RDS in diabetic pregnancy, it would be expected from its known sympathomimetic properties to further aggravate maternal diabetes, exaggerate fetal hyperinsulinemia, and consequently impair fetal lung phospholipid synthesis (7).

It is most likely that DIMIT is acting as a thyromimetic agent (27). Thyroid hormones promote phospholipid synthesis in fetal lung (8). T_4, when administered directly in utero, was shown to enhance the lung maturation of fetal rabbits (8). In cultured fetal rabbit lung cells, T_4 enhanced the rate of choline incorporation into lecithin, a major constituent of lung surfactant (9). Thyroidectomized fetal sheep had lowered tracheal fluid L/S ratios, associated with morphological evidence of lung immaturity (28). Human studies have shown a correlation between low fetal thyroid hormone at birth and respiratory distress syndrome (29). Preliminary reports in humans have indicated that either intraamniotic T_4 administration (11) or prophylactic T_4 administration to the fetus immediately after birth have resulted in accelerated fetal lung maturation and a lowering of infant mortality in premature infants (30). Ballard et al. (14) showed increased activity of phosphatidic acid phosphatase in fetal rabbit lung after administration of DIMIT to pregnant rabbits, associated with increased incorporation of [^{14}C]choline into surfactant. Both fetal and adult rabbit lung have been shown to contain specific nuclear binding sites for T_3 (31). DIMIT was only 0.15% as active as T_3 for binding to fetal lung nuclei, but at sufficiently high concentrations was able to completely displace T_3. These data suggest that the fetal lung is a target organ for DIMIT.

Antenatal DIMIT treatment of pregnant rabbits also resulted in increased fetal levels of corticosteroids in fetal offspring (14). Glucocorticoids stimulate the breakdown of fetal lung glycogen, which serves as a precursor of surface active phospholipids (32). As lung glycogen content was significantly reduced in DIMIT-treated fetuses, enhanced corticosteroid action might partially account for the results observed in this study.

An unexpected finding was that glucose levels in DIMIT-treated diabetic does were lowered, although no change in glucose was seen in control animals receiving DIMIT. Reduction in fetal insulin levels accompanying the restoration of maternal euglycemia (33) appears to have contributed to the enhancement of phospholipid synthesis in DD fetal lungs.

These observations suggest that DIMIT is of potential benefit in the management of diabetic pregnancy and the prevention of RDS associated with maternal diabetes.

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