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Effects of Meluadrine Tartrate on Maternal Metabolic Responses and Fetal Hemodynamics in Pregnant Goats

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ABSTRACT—This study was designed to elucidate the effects of meluadrine tartrate on maternal metabolic responses and fetal hemodynamics in unanesthetized, chronically instrumented pregnant goats. After the administration of meluadrine tartrate to pregnant goats or directly to fetuses, changes in heart rate (HR), arterial blood pressure and arterial blood pH, gasses, electrolytes and metabolic responses were measured. The constant administration of meluadrine tartrate (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) to pregnant goats resulted in the increases of maternal HR, glucose and free fatty acid and the decrease of maternal blood K^+ concentration. The direct escalating administration of meluadrine tartrate (0.01, 0.03 and 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) did not increase the fetal HR, while ritodrine hydrochloride (0.3, 1 and 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) to fetuses increased the fetal HR dose-dependently. The present study suggests that meluadrine tartrate has a mild influence relative to the effects of ritodrine to the maternal metabolic responses and fetal cardiovascular function.

Keywords: Fetus, Heart rate, Meluadrine tartrate, Pregnant goat, Ritodrine hydrochloride

Meluadrine tartrate is a selective β_2-adrenoceptor agonist, which has been developed as a tocolytic agent for the treatment of premature labor. It has been reported that meluadrine tartrate has a potent tocolytic activity, which inhibited spontaneous or oxytocin-induced uterine contraction and showed a good selectivity against the effect on maternal heart rate (HR) in pregnant rats (1 – 3). In the previous study, we demonstrated that meluadrine tartrate inhibited oxytocin-induced uterine contraction and showed a mild influence on maternal HR and uterine arterial blood flow (UBF) in pregnant goats (4).

There are several clinical reports that ritodrine hydrochloride causes fetal tachycardia during its administration (5, 6). However, the effects of meluadrine tartrate on the maternal metabolic responses and fetal circulation are not well understood.

The present study was designed to elucidate the effects of meluadrine tartrate on fetal circulation as well as maternal metabolic responses in unanesthetized, chronically instrumented pregnant goats.

Long-term administration is practical in the clinical situation, and consequently, it is considered necessary to investigate the long-term exposure of meluadrine tartrate in animal studies. Before the long-term study, however, we have been considering that it is necessary to study the "short-term" effects of meluadrine tartrate in comparison with ritodrine hydrochloride, for which there have been many animal studies employing short-term administration (7 – 10).

MATERIALS AND METHODS

Drugs and chemicals

The following drugs were used: meluadrine tartrate ((−)-(*R*)-2-*tert*-butylamino-1-(2-chloro-4-hydroxyphenyl)ethan-1-ol mono-(2*R*,3*R*)-tartrate; Hokuriku Seiyaku Co., Ltd., Katsuyama) and ritodrine hydrochloride (Sigma Chemicals, St. Louis, MO, USA). Meluadrine tartrate and rito-

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drine hydrochloride were dissolved in saline and sterilized by the filtration via a Millex™ filter (0.22 μm; Nihon Millipore Ltd., Tokyo).

Animal preparation

Experiment 1 was performed on six pregnant Japanese Saanen goats weighing from 25 to 32 kg, between 110 and 125 days (term = 145 days) of gestation. These goats were cared for in accordance with the guidelines approved by the Department of Veterinary Medicine of Kagoshima University for the care and use of animals. The animals were fasted for 24 h before surgery.

They were intubated, and anesthesia was maintained using O_2 (2 L/mix), N_2O (2 L/mix) and isoflurane (1.5%). 4.7 F polyethylene catheters (PE160; Imamura Co., Tokyo) were inserted into the femoral artery and vein. An incision was made in the peritoneum, and a blood flow meter probe (FH020T, FC-040T; Nihon Kohden Co., Tokyo or 3S859, Perivascular Flow probe; Transonic Systems Inc., Ithaca, NY, USA) with an inner diameter of 2 – 4 mm was mounted on the middle uterine artery. After this, the gravid uterus was exposed, and the fetal head was exteriorized through a small hysterotomy incision. A 3.8 F polyethylene catheter (PE90, Imamura Co.) was inserted into the fetal carotid artery. The fetus was returned to the amniotic cavity and the uterine and peritoneal incisions were closed.

The animals were allowed to recover for at least 72 h after surgery.

The preparation for Experiment 2 was carried out on eight pregnant Japanese Saanen goats weighing from 25 to 35 kg, between 115 and 130 days of gestation. The operation was performed like in Experiment 1 except a 3.8 F polyethylene catheter was also inserted into the fetal jugular vein as well as the carotid artery.

Experimental protocol 1

On the day of the experiment, the animal was allowed to stand quietly in her cage. Following the control period (Cont), pregnant goats received a steady infusion of meluadrine tartrate via the catheter placed in the femoral vein at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 4 h. Recovery was observed for 2 h after the termination of the drug infusion. According to the data of the previous experiment, we selected this dosage (4).

Maternal blood pressure, HR, arterial blood sampling for pH, gasses, glucose, free fatty acid (FFA), electrolytes, lactic acid (LA) and meluadrine concentration analysis, and fetal blood pressure and HR were obtained immediately before the start of the drug infusion (Cont); at 1 (60), 2 (120), 3 (180) and 4 h (240) after the start of the drug infusion; and at 60 (R-60) and 120 min (R-120) after the termination of the drug infusion. The mean UBF value was calculated as the mean of three UBF measurements for each 5-min interval between 10 min before and each above-mentioned time point. Fetal arterial blood sampling for pH, gasses, glucose, electrolytes and meluadrine concentration analysis were obtained immediately before the start of the drug infusion (Cont), at 2 (120) and 4 h (240) after the start of the drug infusion, and at 120 min (R-120) after the termination of the drug infusion.

Experimental protocol 2

On the day of the experiment, the animal was allowed to stand quietly in her cage. After a 60-min control period (Cont), six fetuses received an escalating infusion of meluadrine tartrate via the jugular vein beginning at 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the first 30 min and then the dose was increased to 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the last 30 min. Individual doses of 0.01, 0.03 and 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 30 min totaled 1.5 h of infusion period. Six fetuses, including four fetuses who received meluadrine tartrate 2 days before or after the experiment day, received an escalating infusion of ritodrine hydrochloride beginning at 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the first 30 min and then the dose was increased to 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the last 30 min. Individual doses of 0.3, 1 and 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 30 min totaled 1.5 h of infusion period. Recovery was observed for 2 h after the termination of the drug infusion.

Maternal blood pressure, HR, arterial blood sampling for pH, gasses and meluadrine concentration analysis, and fetal blood pressure and HR were obtained immediately before the start of the drug infusion (Cont); at 30 (D-1), 60 (D-2) and 90 min (D-3) after the start of the drug infusion; and at 60 (R-60) and 120 min (R-120) after the termination of the drug infusion. Fetal arterial blood sampling for pH and gasses was obtained immediately before the start of the drug infusion (Cont); and at 30 (D-1), 60 (D-2) and 90 min (D-3) after the start of the drug infusion; and at 120 min (R-120) after the termination of the drug infusion. To reduce the sampling volume from a fetus, the measurement of plasma drug concentration was limited to that at 90 min (D-3) after the start of the drug infusion.

Measurements of physiologic parameters

Maternal and fetal HR and aortic blood pressure were measured continuously via the catheters, which were connected to the previously calibrated, sterile pressure transducers (4-327-C; Bell & Howell, Los Angeles, CA, USA), an amplifier (7747; San-ei Co., Tokyo) and a tachometer (N4778, San-ei Co.). The UBF meter probe was connected to the electromagnetic blood flow meter (MFV-1200, Nihon Kohden Co. or T206, Transonic Systems, Inc.), which was then balanced. All the above data were recorded on the pensillograph (8K24-1-L, San-ei Co.).

The maternal and fetal arterial blood pH and blood gasses were measured by the blood gas analyzer (AVL995;

AVL Scientific Co., Roswell, GA, USA), and corrected for body temperature.

The maternal arterial blood glucose, FFA (acyl-CoA synthetase-acyl-CoA oxidase-1-(4'-sulfonyl)-3-carboethoxy-5-pyrazolone (ACS-ACOD-SCEP) method, model 705; Hitachi, Tokyo); LA (lactate oxidase method, model 705; Hitachi); Na^+, K^+ (flame photometry method, model 710; Hitachi) and Ca^{2+} concentration (ortho-cresolphthalein complexone (OCPC) method, model 705; Hitachi) were measured. The fetal arterial blood glucose and electrolytes were also measured.

Determination of the plasma concentration

The plasma samples were kept frozen until the assay of meluadrine concentration in maternal and fetal arterial blood (4).

Statistical analyses

All values are expressed as the mean ± S.E.M. Statistical differences between meluadrine tartrate- and ritodrine hydrochloride-treatment groups in the various parameters were analyzed by 2-way ANOVA followed by Tukey Kramer's method. The dose-dependency in each treatment group was analyzed by Williams' multiple range test. Differences in *P* value less than 0.05 were considered to be statistically significant.

RESULTS

Experiment 1

Effect on maternal hemodynamics, arterial blood pH and gasses

Maternal HR gradually increased after starting the infusion of meluadrine tartrate at a rate of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. It reached an approximately 20% higher level than the control value (Cont) at 1 h after the start of the infusion (60) and then was maintained at the same level for 4 h. The HR value began to recover after cessation of meluadrine tartrate-infusion (Fig. 1). Compared with the "Cont", the values of HR were significantly different at time points of 1, 2, 3 and 4 h after the start of the infusion. The infusion of meluadrine tartrate at a rate of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 4 h did not influence maternal systolic, diastolic and mean blood pressure, arterial blood pH, P_{o_2}, P_{co_2}, HCO_3^- and base excess (Table 1).

Effect on maternal arterial blood glucose, FFA, LA and electrolytes

Maternal arterial blood glucose tended to increase after starting the infusion of meluadrine tartrate (Table 2). It reached a 66% higher level than the control value at 4 h after the start of the infusion. Maternal arterial blood FFA increased at 1 h after starting the infusion of meluadrine tartrate. It was gradually recovered even though the infu-

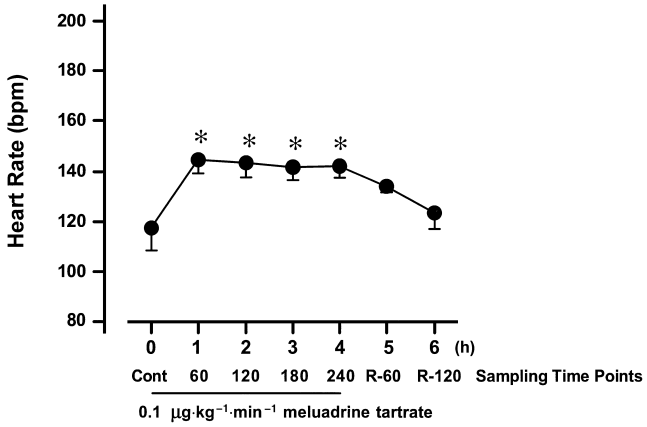

Fig. 1. Effect of meluadrine tartrate on maternal heart rate in pregnant goats. Meluadrine tartrate at a steady infusion rate of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was administered to the maternal vein for 4 h (see text). Values are the mean ± S.E.M. **P*<0.05, compared with "Cont" value.

Table 1. Effect of meluadrine tartrate on the maternal systolic, diastolic and mean blood pressure in pregnant goats

Time points		Cont	60	120	180	240
Systolic	(mmHg)	111 ± 7	108 ± 9	110 ± 9	114 ± 8	109 ± 9
Diastolic	(mmHg)	64 ± 5	60 ± 6	64 ± 8	66 ± 7	64 ± 7
Mean	(mmHg)	79 ± 6	76 ± 7	79 ± 8	82 ± 7	79 ± 7
pH		7.426 ± 0.013	7.411 ± 0.014	7.405 ± 0.024	7.418 ± 0.017	7.413 ± 0.012
P_{o_2}	(mmHg)	113.6 ± 4.6	113.7 ± 4.1	109.8 ± 5.7	111.2 ± 5.2	114.9 ± 3.1
P_{co_2}	(mmHg)	31.4 ± 1.4	31.4 ± 0.7	32.2 ± 1.1	30.7 ± 1.8	31.1 ± 1.2
HCO_3^-	(mM)	19.7 ± 0.9	19.1 ± 0.6	19.4 ± 1.2	19.0 ± 1.3	19.0 ± 0.9
Base excess	(mM)	–2.0 ± 0.9	–2.9 ± 0.8	–2.8 ± 1.5	–2.8 ± 1.3	–2.9 ± 1.0

Experimental conditions are the same as Fig. 1. Values are the mean ± S.E.M. Abbreviations in the line of "Time points" stand for that before the start (Cont) and at 1 (60), 2 (120), 3 (180) and 4 h (240) after the start of meluadrfine tartrate at a steady infusion rate of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Table 2. Effect of meluadrine tartrate on the maternal arterial blood glucose, FFA, LA and electrolytes in pregnant goats

Time points		Cont	60	120	180	240
Glucose	(mg/dl)	52.7 ± 10.7	56.3 ± 11.7	62.0 ± 12.0	76.0 ± 16.0	87.2 ± 20.3
FFA	(μEq/l)	1226 ± 164	1954 ± 140*	1710 ± 146*	1516 ± 142*	1472 ± 166*
LA	(mg/dl)	25.7 ± 3.7	25.3 ± 3.1	27.0 ± 3.4	25.9 ± 1.9	23.7 ± 2.5
K^+	(mEq/l)	4.50 ± 0.28	4.22 ± 0.35	4.00 ± 0.30	3.86 ± 0.31	3.84 ± 0.36
Na^+	(mEq/l)	152.5 ± 1.6	152.5 ± 1.8	152.3 ± 1.8	152.0 ± 1.7	151.9 ± 1.7
Ca^{2+}	(mg/dl)	8.3 ± 0.3	7.9 ± 0.3	7.8 ± 0.2	7.8 ± 0.3	8.0 ± 0.2

Experimental conditions are the same as Fig. 1. Values are the mean ± S.E.M. *P<0.05, compared with "Cont" value. Abbreviations in the line of "Time points" are the same as Table 1.

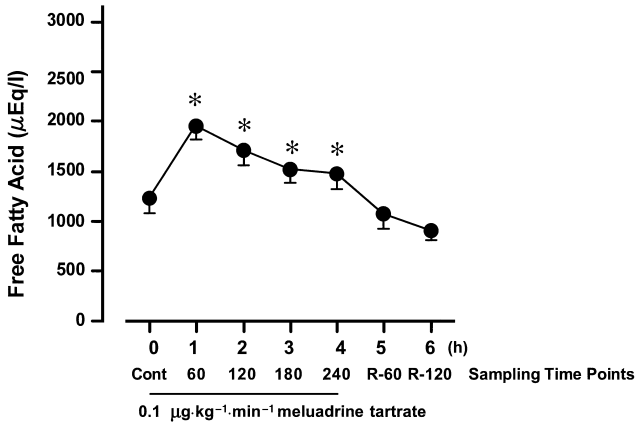

Fig. 2. Effect of meluadrine tartrate on FFA concentration of the maternal arterial blood in pregnant goats. Experimental conditions are the as same as Fig. 1. Values are the mean ± S.E.M. *P<0.05, compared with "Cont" value.

sion was continued (Fig. 2 and Table 2). Maternal arterial blood LA was not influenced during the infusion of meluadrine tartrate for 4 h (Table 2). Although blood K^+ concentration tended to decrease, the change was not statistically significant (Table 2). Blood Na^+ and Ca^{2+} concentrations were not influenced (Table 2).

Effect on UBF, fetal hemodynamics, arterial blood pH and gasses

The mean UBF value was not influenced during the infusion of meluadrine tartrate at a rate of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 4 h (238.8 ± 35.8 and 250.0 ± 36.6 ml/min). Fetal HR (172 ± 9 and 172 ± 15 bpm) and systolic (58 ± 6 and 57 ± 5 mmHg), diastolic (38 ± 5 and 35 ± 5 mmHg) and mean (45 ± 5 and 42 ± 5 mmHg) blood pressure, arterial blood pH (7.327 ± 0.022 and 7.304 ± 0.019), HCO_3 (23.2 ± 1.4 and 21.4 ± 1.5 mM), base excess (–2.0 ± 1.6 and –4.0 ± 1.6 mM), Po_2 (23.0 ± 2.4 and 22.4 ± 2.1 mmHg), Pco_2 (46.4 ± 2.1 and 45.0 ± 2.1 mmHg), K^+ (6.05 ± 0.82 and 5.75 ± 1.08 mEq/l), Na^+ (145.3 ± 3.1 and 140.9 ± 3.9 mEq /l) and Ca^{2+} (10.7 ± 0.6 and 9.8 ± 0.5 m/dl) were not influenced by the infusion of meluadrine tartrate to the maternal vein at a rate of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 4 h.

Effect on fetal arterial blood glucose and electrolytes

The control values of arterial blood glucose were lower than the detectable limit (20 mg/dl) in 5 out of 6 fetuses. In one fetus, the arterial blood glucose level was not influenced by the infusion of meluadrine tartrate to the maternal vein: 26, 25 and 27 mg/dl at the time points of 0, 2 and 4 h after the start of the infusion, respectively. In the other 2 fetuses, the arterial blood glucose level became detectable by the infusion of meluadrine tartrate to the maternal vein: 24 and 43 mg/dl at the time points of 2 and 4 h after the start of the infusion in one case and 21 mg/dl at the time point of 4 h after the start of the infusion in another case. In the other 3 cases, the arterial blood glucose levels were lower than the detectable limit (20 mg/dl) even though meluadrine tartrate was infused to the maternal vein. The fetal electrolytes were not influenced by the infusion of meluadrine tartrate to the maternal vein for 4 h.

Plasma concentrations of meluadrine in fetal and maternal arterial blood

The mean plasma concentration of meluadrine in maternal arterial blood reached a plateau at 2 h (120) after the start of meluadrine tartrate infusion. At 4 h (240) after the start of the infusion, the mean maternal and fetal arterial plasma concentrations of meluadrine were 1.235 and 0.395 ng/ml, respectively.

Experiment 2

Effects on fetal hemodynamics

There is no statistically significant difference in "Cont" value between the ritodrine hydrochloride- and meluadrine tartrate-treated groups.

The fetal HR was significantly higher in the ritodrine hydrochloride-treatment group than in the meluadrine tartrate-treatment group (P<0.001, by 2-way ANOVA).

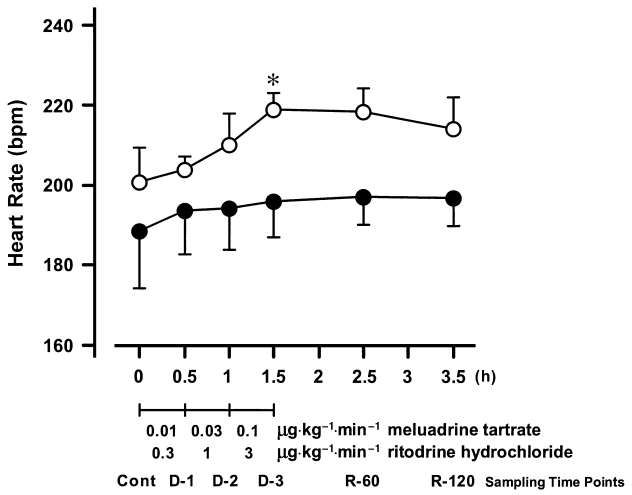

Fig. 3. Effects of meluadrine tartrate (filled circle, n = 6) and ritodrine hydrochloride (open circle, n = 6) on the fetal heart rate in pregnant goats. Meluadrine tartrate in doses ranging from 0.01 to 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or ritodrine hydrochloride in doses ranging from 0.3 to 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was administered in an escalating manner to the fetal vein at 30-min intervals (see text). Values are the mean ± S.E.M. *P<0.05, compared with "Cont" value.

The change in the ritodrine hydrochloride-treatment group was dose-dependent and statistically significant at a dose of 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (Fig. 3). The infusion of meluadrine tartrate or ritodrine hydrochloride did not influence fetal systolic, diastolic, and mean blood pressure (Table 3).

Effects on fetal arterial blood pH and gasses

The fetal arterial blood pH, P_{o_2}, P_{co_2}, HCO_3 and base excess in both the meluadrine tartrate and ritodrine hydrochloride-groups were within the normal range (Table 4).

Effects on maternal hemodynamics, maternal arterial blood pH and gasses

The maternal HR; systolic, diastolic and mean blood pressure; arterial blood pH; and gasses were not influenced in either the meluadrine tartrate group or the ritodrine hydrochloride group.

Plasma concentration of meluadrine in maternal and fetal arterial blood

At 30 min after the start of the final dose infusion, the mean plasma concentration of meluadrine in fetal arterial blood was 0.532 ng/ml. The mean maternal arterial plasma concentration of meluadrine was lower than the detectable limit (0.02 ng/ml) at any time point.

DISCUSSION

The aim of this study was to determine if there is any possibility of influencing the fetal cardiovascular function when meluadrine tartrate was infused into the mother or the fetus. Using a chronic preparation model of pregnant goats, we studied the changes in HR, arterial blood pressure, arterial blood pH, gasses, metabolic responses and electrolytes (Na^+, K^+ and Ca^{2+}) in fetuses, as well as in pregnant goats.

Continuous infusion of meluadrine tartrate at the rate of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which produced sufficient inhibition on the oxytocin-induced uterine contraction, resulted in a mild increase in maternal HR in pregnant goats (4).

In the present study, meluadrine tartrate infusion increased the maternal blood glucose level and FFA (11). This observation is compatible with the effects of other β-adrenoceptor agonists such as salbutamol and terbutaline (12 – 14). Goldberg et al. (13) reported that FFA levels rose by bolus doses of intravenous salbutamol to nine male volunteers, and oral practolol, known as a selective β_1-

Table 3. Effects of meluadrine tartrate and ritodrine hydrochloride on the maternal fetal systolic, diastolic and mean blood pressure in pregnant goats

Time points		Cont	D-1	D-2	D-3
Meluadrine tartrate					
Systolic	(mmHg)	60 ± 2	60 ± 4	58 ± 4	57 ± 3
Diastolic	(mmHg)	37 ± 3	36 ± 4	34 ± 4	34 ± 3
Mean	(mmHg)	45 ± 3	44 ± 4	42 ± 4	42 ± 3
Ritodrine hydrochloride					
Systolic	(mmHg)	61 ± 3	62 ± 3	62 ± 2	61 ± 3
Diastolic	(mmHg)	37 ± 2	35 ± 2	36 ± 2	35 ± 2
Mean	(mmHg)	45 ± 2	44 ± 2	45 ± 2	44 ± 2

Experimental conditions were the same as in Fig. 3. Values are expressed as the means ± S.E.M. Abbreviations in the line of "Time points" stand for that before the start of (Cont) and at 30 (D-1), 60 (D-2) and 90 min (D-3) after the start of escalating infusion of meluadrine tartrate or ritodrine hydrochloride.

Table 4. Effects of meluadrine tartrate on the fetal blood pH and gasses in pregnant goats

Time points		Cont	D-1	D-2	D-3
Meluadrine tartrate					
pH		7.341 ± 0.011	7.349 ± 0.008	7.343 ± 0.007	7.336 ± 0.008
P_{o_2}	(mmHg)	20.7 ± 1.4	21.8 ± 1.9	20.5 ± 1.5	18.4 ± 1.3
P_{co_2}	(mmHg)	37.5 ± 1.5	39.3 ± 0.9	38.7 ± 1.2	39.3 ± 2.3
HCO_3^-	(mM)	19.3 ± 0.6	20.6 ± 0.3	20.0 ± 0.6	20.0 ± 1.2
Base excess	(mM)	–4.7 ± 0.6	–3.5 ± 0.4	–4.0 ± 0.5	–4.3 ± 1.0
Ritodrine hydrochloride					
pH		7.362 ± 0.010	7.371 ± 0.009	7.366 ± 0.011	7.364 ± 0.014
P_{o_2}	(mmHg)	22.8 ± 1.7	22.6 ± 2.1	24.3 ± 3.2	22.9 ± 2.4
P_{co_2}	(mmHg)	40.2 ± 2.1	37.3 ± 1.6	37.4 ± 1.4	37.4 ± 2.4
HCO_3^-	(mM)	21.7 ± 0.9	20.6 ± 0.9	20.4 ± 0.9	20.5 ± 1.7
Base excess	(mM)	–2.2 ± 0.7	–2.9 ± 0.8	–3.1 ± 0.9	–3.1 ± 1.7

Experimental conditions were the same as Fig. 3. Values are expressed the mean ± S.E.M. Abbreviations in the line of "Time points" are the same as Table 3.

adrenoceptor antagonist, did not prevent it, thus suggesting β_2-adrenergic control. Massara et al. (14) reported that the increase in blood glucose and FFA induced by salbutamol, a primarily β_2-adrenergic stimulant, might be mediated by β_1- and β_2-receptors, respectively. Haffner et al. (12) mentioned that the increase in plasma glucose might be mediated by β_2-receptors and the increase in plasma FFA might involve both routes through β_1- and β_2-receptors, from the observation of administration of terbutaline, a specific β_2-adrenoceptor agonist and of xamoterol, a partial β_1-adrenoceptor agonist with β_2-adrenoceptor blocking activity. According to a result of the study using ritodrine hydrochloride in fetal sheep, Bassett and Symonds (15) suggested that ritodrine might activate peripheral brown adipose tissue through activation of β_2-receptors alone and/or through β_3-receptors and result in increasing lipolysis and high plasma FFA concentration. The increases in the maternal blood glucose level and FFA by meluadrine tartrate infusion is thought to be caused through β-adrenoceptors. However, it is unclear which receptor subtypes are involved in the mechanisms.

These metabolic changes returned to the control levels soon after the cessation of administration in this study, which may be acceptable in clinical use.

Under this condition, the change of fetal HR did not occur. This may be derived from the observation that UBF was not reduced by the infusion of meluadrine tartrate at the rate of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to pregnant goats, a result similar to the previous data obtained to evaluate the effects on the oxytocin-induced uterine contraction in pregnant goats (4).

The mean plasma concentration of meluadrine in fetal arterial blood was 0.395 ng/ml at 4 h after the infusion. The ratio of fetal to maternal plasma concentration of meluadrine was approximately 0.3. The value of 0.3 is thought to show that meluadrine tartrate has poor placental transfer. It is comparable to that of ritodrine hydrochloride, which has been reported as 0.1 or less in pregnant sheep (16). The low ratio of fetal to maternal plasma concentration of hydrophilic substances like as ritodrine hydrochloride was reported to be due to the low lipophilicity especially in species, such as sheep and goat, that have epitheliochorial placenta (17, 18). The explanation may be adapted to meluadrine tartrate since the partition coefficients (1-octanol /pH 7.4 Sörensen Buffer, 37°C) of meluadrine tartrate (1.39) is similar to that of ritodrine hydrochloride (2.25).

When the fetus directly received the escalating doses (0.01, 0.03 and 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ every 30 min) of meluadrine tartrate, fetal HR did not increase significantly even at the end of the final dose (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The mean plasma concentration of meluadrine in fetal arterial blood was 0.532 ng/ml, which seemed to be a sufficient exposure level to the fetus according to the following observations. In the previous study, we determined that the mean plasma concentration of meluadrine in arterial blood of pregnant goats was 0.318 to 0.931 ng/ml when the oxytocin-induced uterine contraction was adequately suppressed by an escalating infusion of meluadrine tartrate (4). At a range of concentrations, meluadrine completely inhibited spontaneous and oxytocin-induced contraction of the uterine preparation isolated from pregnant rats (1 – 3). Meluadrine tartrate is thought to have poor placental transfer. On the contrary, ritodrine hydrochloride increased in the fetal HR significantly when the fetus directly received doses up to 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which was equivalent to efficacious infusion rate of meluadrine tartrate (4). Gamissans et al. (19), Spellacy et al. (5) and Black et al. (6) reported that ritodrine hydrochloride caused a significant fetal tachycardia. Therefore, the present result seems to show the possibility that

meluadrine tartrate may have an advantage over ritodrine hydrochloride for the future clinical use. However, the response in immature goat fetus is unclear. Further study is needed to clarify the developmental differences in the effect of meluadrine tartrate.

In conclusion, the present study in pregnant goats clearly revealed that meluadrine tartrate with a potent tocolytic activity had a mild influence on the fetal cardiovascular function in comparison with ritodrine hydrochloride.

Further study is needed to clarify the effect of long term administration of meluadrine tartrate on the fetal hemodynamics and blood gas status.

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