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SUPPRESSION OF COLD-INDUCED THERMOGENESIS IN FULL-TERM PREGNANT RATS

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SUMMARY

1. Thermoregulation against cold exposure was studied in rats during pregnancy and early lactation, and compared with that of virgin rats.

2. When exposed to 0 °C for 60 min, rats which were within 24–48 h of parturition (pre-1-day rats) and those within 24 h of parturition (pre-0-day rats) showed significantly larger falls of colonic temperature (T_{co}) than virgin rats. The temperature decrease was greatest in the pre-0-day rats, being $4{\cdot}1 \pm 0{\cdot}4$ °C (mean ± S.E.M.) at the end of cold exposure, compared with a decrease of $1{\cdot}7 \pm 0{\cdot}3$ °C in the virgin rats. The tail skin temperature fell to 0 °C during cooling in all virgin rats and in pregnant rats at each gestational stage.

3. During cold exposure at 10 °C for 30 min, pre-0-day rats also showed significantly larger falls in T_{co} ($1{\cdot}8 \pm 0{\cdot}6$ °C) than virgin ($0{\cdot}4 \pm 0{\cdot}2$ °C), pre-1-week ($0{\cdot}8 \pm 0{\cdot}3$ °C), post-0-day ($0{\cdot}3 \pm 0{\cdot}3$ °C) or post-1-week rats ($0{\cdot}4 \pm 0{\cdot}3$ °C). Although body weights in pre-0-day rats were far larger than those in virgin rats, the increase in oxygen consumption per animal during cold exposure was 50% lower in pre-0-day rats ($2{\cdot}2 \pm 0{\cdot}5$ ml/min) than in virgin rats ($5{\cdot}3 \pm 0{\cdot}3$ ml/min). There was no difference in basal oxygen consumption per animal between the late pregnant and virgin rats.

4. Within 24 h after parturition, both the decrease of T_{co} and the increase of oxygen consumption during cold exposure returned to the values observed in virgin rats.

5. The present results demonstrate clearly that cold-induced thermogenesis is significantly suppressed in rats at a late stage of pregnancy.

INTRODUCTION

Pregnancy is accompanied by a number of physiological changes which proceed very rapidly and which animals do not otherwise undergo during their lives. As pregnancy progresses, body weight, body surface area and blood flow to the placenta all rapidly increase. In all homothermic animals during homothermy, body temperature is regulated within a relatively narrow temperature range by central

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control of heat production and heat loss. Both are related to body mass, body surface area and distribution of circulatory blood. Therefore, it seems likely that the rapid changes in these variables occurring in pregnant animals might influence body temperature regulation.

We have observed a large fall of colonic temperature in full-term pregnant rats exposed to cold. This fall was larger than that in any non-pregnant female rats. Surveying the previous reports, however, we found no systematic study of the thermoregulatory ability of pregnant rats exposed to cold. Therefore, we performed this study to investigate when, during pregnancy, colonic temperature in rats falls markedly during cold exposure and what the underlying mechanism of this fall might be. We report here that fall in body temperature due to cold exposure gradually becomes larger with the process of pregnancy. The largest fall is observed just before parturition. We also report that the fall in body temperature in full-term pregnant rats exposed to cold is caused by a significant decrease in heat production, not only per unit body weight but also per individual animal.

METHODS

Animals

Pregnant Wistar rats, which had been mated at the age of 12 weeks, at 10 days of gestation (parturition at gestational day 21) and the same-aged virgin Wistar rats (Japan SLC Inc.), were reared at 25 °C in a light–dark cycle, with lights on from 07.00 to 19.00 h, and fed a standard laboratory chow (Oriental Yeast Co., Ltd) *ad libitum*. The animals experienced the experimental set-up (insertion of the thermocouple into the colon, cold exposure and other experimental conditions) at least once before the experiments were performed.

Experimental procedures

Experiment 1. To compare the cold resistance of pregnant rats at different stages of gestation, the colonic temperatures (T_{co}) and tail skin temperatures (T_{tail}) of six pregnant and eight virgin rats were continuously measured in a cold environment. In the pregnant rats, experiments were carried out at 6, 4, 2 and 1 days before giving birth, on the day of birth before (pre-0 day) and after parturition (post-0 day), and 1 day after giving birth. The measurements were started at 12·00 h. A Cu–Co thermocouple was inserted 5 cm beyond the anus and fixed by surgical tape at the base of tail. Another thermocouple, for the measurement of T_{tail}, was placed on the tail skin 4 cm behind the anus and covered with surgical tape. The wire of the thermocouple was protected by a covering of flexible, stainless-steel spring tubing. For the experiments, rats were placed individually in metal, meshed cages where they could move freely, at an ambient temperature (T_a) of 25 °C. When their T_{co} had stabilized at the T_a of 25 °C, and after at least 30 min, the rats were transferred in their cages to a climatic chamber with T_a of 0 °C for 60 min.

Experiment 2. The results of experiment 1 showed that the largest decrease of T_{co} induced by cold exposure occurred in rats within 24 h before parturition (pre-0 day). Therefore, the oxygen consumption ($\dot{V}_{O_2}$) as well as T_{co} during cold exposure was measured one week before parturition (pre-1 week), pre-0 day, post-0 day, and one week after parturition (post-1 week) in six pregnant rats and in six virgin rats. A thermocouple was inserted into the colon, as in experiment 1, and each rat was placed in a polyethylene cylinder (inside diameter, 8 cm; length, 25 cm) in order to measure $\dot{V}_{O_2}$. Air was pulled from the cylinder by a pump at a flow rate of 3 l/min. The difference in oxygen concentration between room air and the sampled air was continuously monitored by an oxygen analyser (Toray Engineering Co.) and recorded with a pen writer. Recordings of T_{co} and $\dot{V}_{O_2}$ were made at a temperature of 25 °C (inside the cylinder) for at least 30 min. When T_{co} and $\dot{V}_{O_2}$ were stable, the cylinder containing the rat was immersed into a temperature-controlled bath. The temperature of the cylinder interior was kept at 10 °C for 30 min, and T_{co} and $\dot{V}_{O_2}$ were continuously recorded. The post-0-day and post-1-week rats were caged with their pups except for the time of experiment.

Statistical analysis

Data were sampled every 1 min. The pre-cold exposure T_{co} and $\dot{V}_{O_2}$ were evaluated by a mean T_{co} and $\dot{V}_{O_2}$ for the last 5 min at T_a of 25 °C.

Mean values ± S.E.M. were calculated for the responses of each test group. The data were analysed using analysis of variance and Bonferroni's multiple comparison test. Atypical data were excluded on one occasion using the Smirnov test (Grubbs, 1950). A $P < 0.05$ level of significance was set for all statistical analyses.

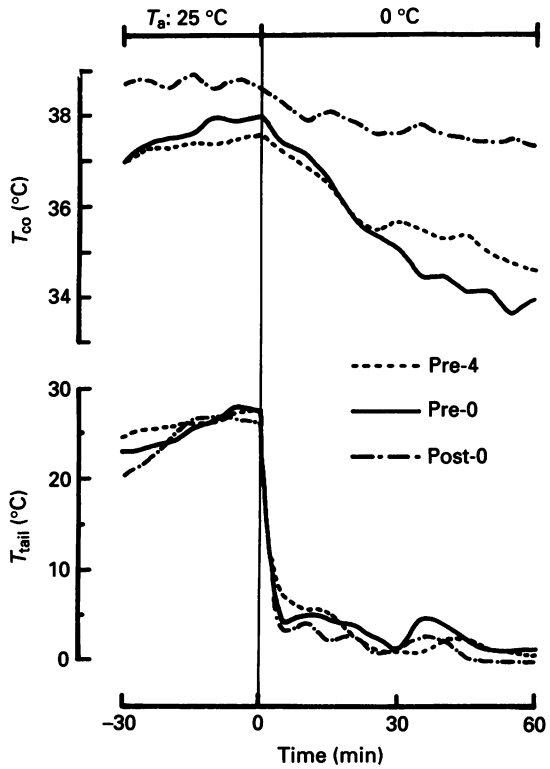

Fig. 1. Changes in colonic and tail skin temperatures during cold exposure in a rat 4 and 0 days before (pre-4 and pre-0) and 0 days after (post-0) parturition.

RESULTS

Experiment 1

Figure 1 shows a typical example of changes in T_{co} and T_{tail} during cold exposure (0 °C) at three different gestational stages of a pregnant rat. T_{co} decreased more during cold exposure as pregnancy progressed. However, the fall of T_{tail} to near T_a was similar for each stage of pregnancy. In other pregnant rats as well, fall of T_{co} due to cooling became larger as pregnancy progressed, while T_{tail} decreased to near T_a regardless of stage during pregnancy.

The time courses of change in T_{co} during cold exposure in six pregnant and eight virgin rats are shown in Fig. 2. At T_a of 25 °C, T_{co} in pregnant rats were lower than in virgin and post-partive rats.

The mean drop in T_{co} during cold exposure from the pre-cold exposure T_{co} was calculated for each group and each stage of pregnancy. T_{co} in virgin rats had fallen by $1{\cdot}7 \pm 0{\cdot}3$ °C (mean ± S.E.M. of eight rats) by the end of 60 min cold exposure. The magnitude of decrease in T_{co} gradually became larger later in pregnancy. Until two

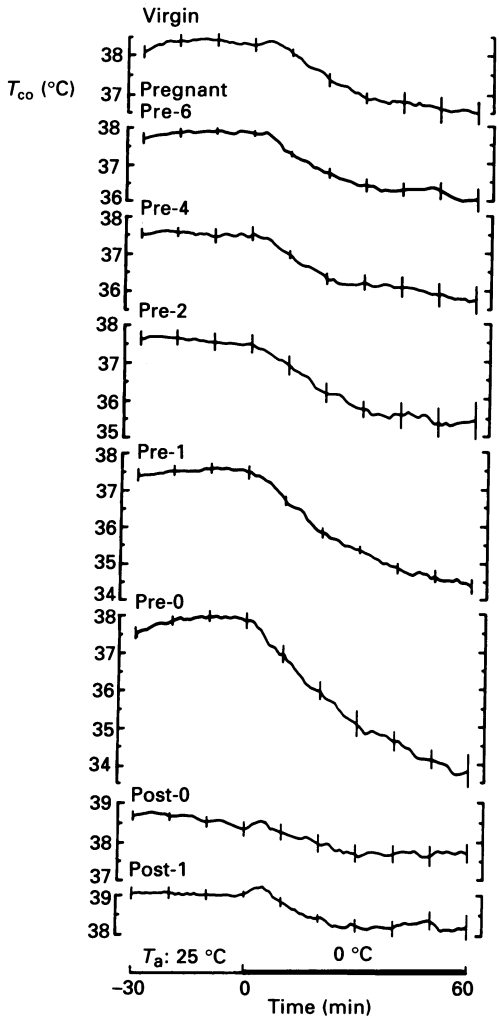

Fig. 2. Time course of changes in colonic temperature (T_{co}) (mean ± S.E.M.) at 25 °C for 30 min and 0 °C for 60 min (experiment 1). Pre- (or post-) 0, 1, 2, 4 and 6 are 0, 1, 2, 4 and 6 days before (or after) parturition, respectively.

days before parturition, however, the decrease of T_{co} in pregnant rats at the end of cold exposure was not significantly different from that in virgin rats. In pre-1-day and pre-0-day pregnant rats, the decrease of T_{co} was significantly larger than that in virgin rats. T_{co} decreased by $3{\cdot}2 \pm 0{\cdot}3$ °C in pre-1-day ($n = 6$) and $4{\cdot}1 \pm 0{\cdot}4$ °C in pre-0-day rats ($n = 5$; data from one rat were excluded by application of the Smirnov test (Grubbs, 1950)).

All pregnant rats except one showed the largest fall in T_{co} at 0 or 1 day before parturition, and for each of these rats the drop in T_{co} became much smaller just after parturition. However, on day 0 before parturition, one animal had a remarkably different T_{co} change from the other five rats. The decrease of T_{co} in this rat during cold

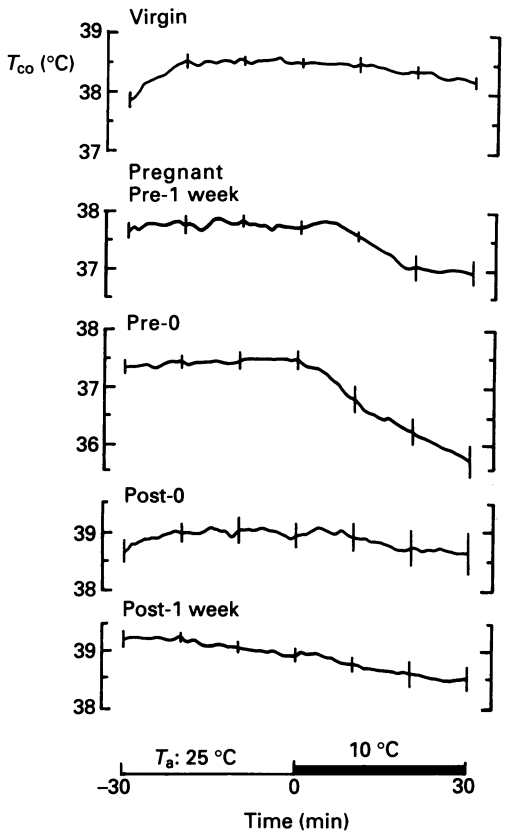

Fig. 3. Time course of T_{co} changes (mean ± S.E.M.) at 25 °C for 30 min and 10 °C for 30 min (experiment 2). Pre-1 week, pre-0, post-1 week and post-0 represent the rat groups 1 week, 0 days before, 1 week and 0 days after parturition, respectively.

exposure was very small in comparison with that observed in the other five rats. The Smirnov test (Grubbs, 1950) could be used to exclude this rat's data from the others, therefore, the mean values of pre-0-day T_{co} in Fig. 2 were calculated from the data of the other five rats only. In the pre-1-day experiment, the decrease in T_{co} of this rat was not different from those of the other rats. Although changes in body weight before and after parturition were similar to those in the other five rats, this rat produced only six pups, while the other mother rats had eight to sixteen pups (eleven pups on average). One day after birth, four of its pups died; the remaining two pups were dead after 5 days. The other five mother rats reared normal, healthy baby rats.

After parturition, the decreases of T_{co} induced by cold exposure became small. The mean decrease of T_{co} in post-0-day rats (0·8 ± 0·2 °C) and post-1-day rats (0·9 ± 0·4 °C) at the end of cooling were significantly smaller than that in pre-2-day, pre-1-day and

TABLE 1. Mean ± S.E.M. of body weight, pre-cold exposure T_{co}, pre-cold exposure $\dot{V}_{O_2}$ and changes of T_{co} and $\dot{V}_{O_2}$ induced by cold exposure (10 °C for 30 min)

	Body weight (g)	Pre-cold exposure T_{co} (°C)	ΔT_{co} (°C)	Pre-cold exposure $\dot{V}_{O_2}$ (ml/(min kg$^{0.67}$))	$\Delta \dot{V}_{O_2}$ during cooling (ml/(min) kg$^{0.67}$))
Virgin	209·6 ± 1·1	38·5 ± 0·1*	0·4 ± 0·2*	23·2 ± 1·3	15·2 ± 0·9*
Pre-1 week	278·8 ± 9·8*†	37·7 ± 0·1†	0·8 ± 0·3*	22·1 ± 1·6	9·6 ± 1·1†
Pre-0	344·1 ± 14·3†	37·5 ± 0·2†	1·8 ± 0·3†	20·2 ± 1·8	4·5 ± 1·0†
Post-0	249·1 ± 13·1*†	39·0 ± 0·2*	0·3 ± 0·3*	18·5 ± 1·3	13·8 ± 1·8*
Post-1 week	256·0 ± 9·2*†	39·0 ± 0·1*	0·4 ± 0·2*	25·4 ± 2·1‡	11·1 ± 2·0*

* Significantly different, $P < 0.05$, from pre-0-day rats.
† Significantly different, $P < 0.05$, from virgin rats.
‡ Significantly different, $P < 0.05$, from post-0-day rats.

pre-0-day rats. In these rats, the decreases of T_{co} were not significantly different from those of virgin rats.

The pre-cold exposure T_{co} (mean T_{co} for the last 5 min pre-cold exposure) in pre-6, pre-4, pre-2, pre-1, pre-0, post-0 and post-1-day rats were $37{\cdot}9 \pm 0{\cdot}1$, $37{\cdot}5 \pm 0{\cdot}2$, $37{\cdot}5 \pm 0{\cdot}3$, $37{\cdot}5 \pm 0{\cdot}2$, $37{\cdot}9 \pm 0{\cdot}2$, $38{\cdot}4 \pm 0{\cdot}2$ and $39{\cdot}1 \pm 0{\cdot}1$ °C, respectively. The pre-cold exposure T_{co} in pre-4, pre-2 and pre-1-day rats were significantly lower than those in post-0- and post-1-day rats.

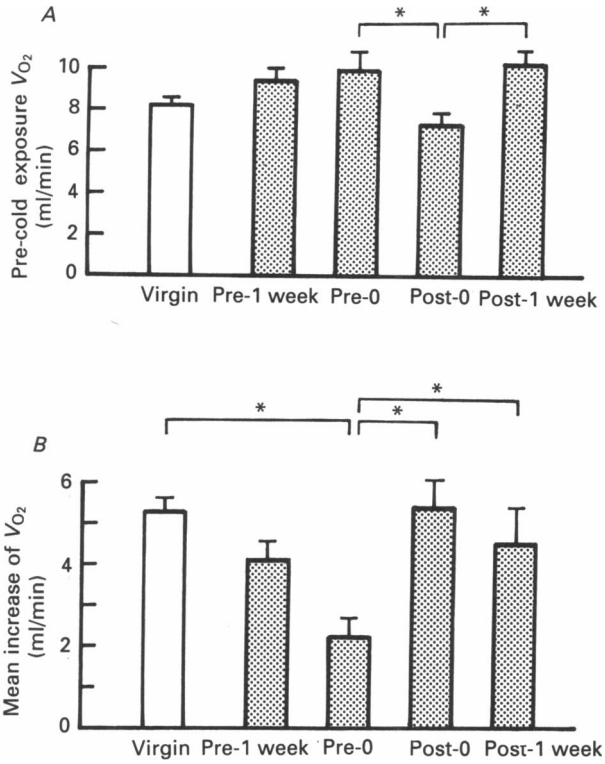

Fig. 4. Pre-cold exposure $\dot{V}_{O_2}$ (*A*) and the mean increases of $\dot{V}_{O_2}$ during cold exposure (*B*) per animal in virgin and pre-1-week, pre-0-day, post-0-day and post-1-week rats. $*P < 0{\cdot}05$.

Experiment 2

Figure 3 shows the time courses of T_{co} changes during the less stressful conditions of experiment 2 in which rats were exposed to 10 °C for 30 min. At the end of cooling T_{co} was significantly lower in pre-0-day rats than in all other rats (Fig. 3 and Table 1). The decreases of T_{co} in pre-1-week, post-0-day, post-1-week and virgin rats were not significantly different within each group. The pre-cold exposure T_{co} was significantly lower in pre-1-week and pre-0-day pregnant rats than in virgin, post-0-day and post-1-week rats (Table 1). There were no significant differences between virgin and post-partive rats.

The group means of pre-cold exposure $\dot{V}_{O_2}$ per animal are shown in Fig. 4*A*. There

were no significant differences except between post-0-day rats and pre-0-day or post-1-week rats. The mean increases of $\dot{V}_{O_2}$ for the 30 min during cooling were 4·1 ± 0·5 ml/min (pre-1-week rats), 2·2 ± 0·5 ml/min (pre-0-day), 5·4 ± 0·7 ml/min (post-0-day), 4·5 ± 0·9 ml/min (post-1-week) and 5·3 ± 0·3 ml/min in virgin rats (Fig. 4*B*). The increase in $\dot{V}_{O_2}$ in pre-0-day rats was less than half that in virgin and post-partive rats. Increases of $\dot{V}_{O_2}$ induced by cooling in the other rats were not significantly different from those in virgin rats.

The mean increases of $\dot{V}_{O_2}$/(kilogram body weight)$^{0·67}$ during cooling are summarized in Table 1. Compared with the mean increase of $\dot{V}_{O_2}$/(body weight)$^{0·67}$ in virgin rats, those in pre-1-week and pre-0-day rats were significantly less. The increase of $\dot{V}_{O_2}$/(body weight)$^{0·67}$ in pre-0-day rats was also significantly less than that in post-partive rats. The pre-cold exposure $\dot{V}_{O_2}$/(body weight)$^{0·67}$ comparing all rats except for post-1-week rats were not significantly different.

DISCUSSION

This study has shown that rats in late pregnancy are less able to maintain body temperature during acute cold exposure than middle-term pregnant or post-partive rats. Among rats exposed to 0 °C for 60 min, decreases in T_{co} were largest for those in the last two days of pregnancy. Within 24 h of parturition, the decrease in T_{co} was maximal, being 4·1 °C at the end of cold exposure. Full-term pregnant rats under less stressful conditions, exposed to 10 °C for 30 min, also failed to maintain T_{co}. Since post-partive rats appeared to regulate body temperature normally, it seems unlikely that their decreased ability to maintain body temperature during late pregnancy was due to repeated exposure to stressful cold; it seems rather to be related to their stage of pregnancy.

A second experiment showed that increase of oxygen consumption during cold exposure was significantly lower in pre-1-day rats than in the virgin rats, whether or not it was calculated per unit (body weight)$^{0·67}$ or per animal. The pre-cold exposure $\dot{V}_{O_2}$ per animal were the same in virgin, pre-1-week and pre-0-day rats. Although the pre-0-day rats had the highest body weight, among them, cold-induced increase in $\dot{V}_{O_2}$ per animal was less than half of that in virgin rats. It is uncertain whether the pregnant rats lost heat through insufficient cutaneous vasoconstriction. T_{tail} decreased to near T_a during cold exposure in all rats. Therefore, the large decrease of T_{co} in rats at a late stage of pregnancy probably was caused by reduced heat production rather than by excessive heat loss. However, even assuming comparable cutaneous vasoconstrictive tone in pregnant and virgin rats, the possibility cannot be excluded that the large body surface area of the full-term pregnant rats dissipated more heat than that of other rats.

In the present study, we could not evaluate separately the contributions of the brown adipose tissue (BAT) (non-shivering thermogenesis) and shivering to the total, cold-induced thermogenesis. Biochemical studies on rat BAT have demonstrated that GDP binding to BAT dropped at day 18–20 of gestation and remained low throughout lactation (Tatelman & Winick, 1986). Similarly, it is known that BAT lipoprotein lipase activity and lipogenesis start to decrease on day 18–20 of gestation and remain at low levels throughout lactation (Villarroya & Mampel,

1986), and that basal and noradrenaline-induced iodothyronine 5′-deiodinase activity are relatively low in the BAT of 20-day pregnant and lactating rats (Giralt, Villarroya, Mampel & Iglesias, 1986). These findings suggest that BAT thermogenic activity starts to decrease in the late stage of pregnancy and decreases further during lactation. It has also been shown in the mouse that BAT thermogenesis is suppressed more in the mid-lactating period than in the pregnant period (Trayhurn, Douglas & McGuckin, 1982). In our study, cold-induced thermogenesis per animal was lowest in pre-0-day rats but quickly recovered to normal within 24 h of parturition. If the BAT biochemical changes mentioned above were principal reasons for the decreased cold-induced thermogenesis in pre-0-day rats, then thermogenesis should not have recovered to normal in the post-0-day rats. Therefore, the suppression of cold-induced thermogenesis in pre-0-day pregnant rats could not have been due only to decreased BAT thermogenic capacity. A compensatory relationship has been demonstrated between non-shivering thermogenesis and shivering (Brück & Wünnenberg, 1970). Within the present study, if BAT thermogenesis in full-term pregnant rats was insufficient to maintain body temperature, shivering should have occurred and should have maintained heat production and normal body temperature. There seems to be a general suppression of shivering and non-shivering thermogenesis in full-term pregnant rats exposed to cold. This suppression may be under the integrated control of the central nervous system. Shivering is known to be mediated by the motor nervous system (Hensel, 1981), while BAT thermogenesis is controlled by the sympathetic nervous system (Smith & Horwitz, 1969; Perkins, Rothwell, Stock & Stone, 1981).

The physiological significance of the suppression of cold-induced thermogenesis in full-term pregnant rats is unclear at present. However, observation of one exceptional case suggests that suppression of cold-induced thermogenesis is necessary for normal pregnancy and lactation. The rat, mentioned above, which maintained its body temperature well against the cold on the last day of pregnancy had fewer pups than the other rats and could not keep them alive longer than 5 days. One possible physiological 'use' for inhibition of cold-induced thermogenesis in full-term pregnant rats might be the maintenance of a high rate of uteroplacental blood flow. Animals exposed to cold usually increase blood flow to thermogenic tissues (Foster & Frydman, 1979). However, in late-pregnant animals, placental blood flow is maximum (Ahokas, Anderson & Lipshitz, 1983) and must be maintained in order to constantly supply oxygen and nutrition to the fetus. It has been reported that the intravenous injection of noradrenaline induces maternal placental vasoconstriction (Leduc, 1972). Thus, increase of noradrenaline in the blood induced by cold exposure might be dangerous for a fetus. When a pregnant animal is exposed to a cold environment, competition is likely to occur between the maintenance of blood supply to the placenta and an increase in blood supply to thermogenic tissue. Late-term, pregnant rats may maintain a high rate of uteroplacental blood flow during exposure to cold, even at the cost of blood flow to thermogenic tissues or reduced body temperature. If a pregnant rat maintained its body temperature during cold without accounting for placental blood flow need, the oxygen demand of the fetus, which is affected by its body temperature, might exceed the amount supplied. In such cases, irreversible hypoxic damage might occur in the fetus.

In previous studies, fetal body temperature has been shown to parallel maternal temperature (Abrams, Caton, Curet, Crenshaw, Mann & Barron, 1969; Gunn & Gluckman, 1983). Therefore, when the body temperatures of pre-0-day pregnant rats in the present study dropped by 4 °C in the cold, fetal temperature probably decreased correspondingly. Although it has been reported that maternal hyperthermia causes fetal death and fetal brain defects (Shah, 1956; Macfarlane, Pennycuik & Thrift, 1957; Edwards, Penny & Zevnik, 1971), maternal hypothermia might not be as dangerous for the fetus. Fetuses seem to be resistant to cold; newborn animals, for example, can withstand lower environmental temperatures than adults (Adolph, 1951; Conklin & Heggeness, 1971; Alexander, 1975). Neonatal rats can survive hypothermia with rectal temperatures as low as 1 °C (Alexander, 1975).

The mechanism of the suppression of cold-induced thermogenesis remains to be clarified. At the time of parturition, hormones including luteinizing hormone, progesterone, and prolactin show dramatic changes (Morishige, Pepe & Rothchild, 1973). These hormones act not only on the peripheral organs, but also on the central nervous system to produce normal delivery, lactation and maternal behaviour. The brain also influences endocrine systems; such neuro-hormonal interactions may be the underlying cause of the suppression of cold-induced thermogenesis in full-term pregnant rats.

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