—Review—

Fetal and Neonatal Thermoregulation

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Abstract

The metabolic rate of the fetus per tissue weight is relatively high when compared to that of an adult. Moreover, heat is transferred to the fetus via the placenta and the uterus, resulting in a 0.3℃ to 0.5℃ higher temperature than that of the mother. Therefore, fetal temperature is maternally dependent until birth. At birth, the neonate rapidly cools in response to the relatively cold extrauterine environment. Thus, the neonatal temperature rapidly drops soon after birth. In order to survive, the neonate must accelerate heat production via nonshivering thermogenesis (NST), which is coupled to lypolysis in brown adipose tissue. Heat is produced by uncoupling ATP synthesis via the oxidation of fatty acids in the mitochondria, utilizing uncoupled protein.

Thermogenesis must begin shortly after birth and continue for several hours. Since thermogenesis requires adequate oxygenation, a distressed neonate with hypoxemia cannot produce an adequate amount of heat to increase its temperature.

In contrast to the neonate, the fetus cannot produce extra heat production. This is because the fetus is exposed to inhibitors to NST, which are produced in the placenta and then enter the fetal circulation. The important inhibitors include adenosine and prostaglandin E2, both of which have strong anti-lypolytic actions. The inhibitors play an important role in the metabolic adaptation of a physiological hypoxic fetus because NST requires adequate oxygenation. Furthermore, the presence of NST inhibitors allows the fetus to accumulate an adequate amount of brown adipose tissue before birth.

The umbilical circulation transfers 85% of the heat produced by the fetus to the maternal circulation. The remaining 15% is dissipated through the fetal skin to the amnion, and is then transferred through the uterine wall to the maternal abdomen. As long as fetal heat production and loss are appropriately balanced, the temperature differential between the fetus and the mother remains constant (heat clump). However, when the umbilical circulation is occluded for any reason, the fetal temperature will rise in relation to the extent of the occlusion. The fetal temperature may elevate to the hyperthermic range in cases of acute cord occlusion; if this occurs, fetal growth, including brain development, may be impacted. Experimentally induced cord occlusion, which is recognized as a significant cause of brain damage, results in a rapid elevation of body temperature; however, the brain temperature tends to remain constant. This is considered to be a cerebral thermoregulatory adaptation to hypoxemia, which has the physiologic advantage of protecting the fetus from hyperthermia, a condition that predisposes the fetus to hypoxic injury (cerebral hypometabolism).

A number of thermoregularatory mechanisms are in place to maintain normal fetal and

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neonatal growth. Data has primarily been collected from animal studies; aside from the strict thermal control provided in the newborn nursery, little information exists concerning these mechanisms in the human fetus and neonate. Probably further information on thermoregulation is necessary specially to improve perinatal management for hypoxic fetuses.
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Key words: thermogenesis, heat production, fetus, neonate

1. Introduction

Fetuses develop in the uterus, which provides a relatively stable thermal environment. The maternal body constantly supplies an appropriate amount of heat to the amnion via the placental surface and the umbilical circulation; thus, the intrauterine environment is thermally stable. The fetal temperature is usually 0.3℃ to 0.5℃ higher than the maternal temperature; therefore, it is generally thought that fetal thermoregulation is immature and that the fetal temperature is completely dependent on the maternal temperature. However, central thermoregulatory mechanisms are well differentiated well before birth.

Immediately after birth, thermal conditions dramatically change. The ambient temperature in a delivery room is 26℃ to 27℃, which is about 10℃ less than the intrauterine temperature. In order to survive, the newborn, whose thermoregulation was dependent on the mother inside the uterus, must rapidly elevate its heat production. This increased heat production is a response to birth in a cold environment; mammalian newborns increase heat production within minutes after birth. This article reviews fetal and neonatal thermoregulation as described above.

Most information addressed here has been collected from animal experiments. Thus, data obtained from human fetuses and neonates have been scanty. However, we have to understand thermoregulatory alterations in human fetuses and neonates who are distressed or hypoxic. It is important for clinicians to manage such patients, since brain temperature predisposes their brain to damage.

2. Fetal Thermoregulation

a. Fetal Heat Production

During intrauterine life, the fetus is warmed by its own metabolic processes. Power et al measured fetal heat production in sheep[1]. Heat production of fetal sheep was found to be about 3.3 watts/kg of fetal tissue. This equals 47 calories/minute, which is approximately twice an adult's heat production, per unit of body weight.

Fetal heat production has generally been estimated by measuring oxygen consumption. Asakura et al. directly measured oxygen consumption in the fetal lamb, which was oxygenated after occlusion of the umbilical cord[2]. Fetal oxygen consumption was 6.7 m*l*/kg/min, which is 1.5 fold higher than an adult lamb. Other researchers measured fetal oxygen consumption by different methods, and the values ranged between 5 and 8 m*l*/kg/min. These studies indicated that the basal metabolic rate of the fetus is higher than that of an adult, resulting in significant fetal heat is produced. Furthermore, the amount of the heat produced by the placenta and the uterine wall is reported to be approximately 2.1 watts/kg of tissue[3]. This heat also increases the fetal temperature.

b. Intrauterine Temperature Regulation

Fetuses develop and grow within the uterus under aerobic metabolism. Since the fetal metabolic rate is higher with more oxygen consumption than an adult, the fetal temperature constantly remains 0.3℃ to 0.5℃ higher than an adult[3]. The temperature differential between the fetus and the mother is called the "heat clump". The heat clump is relatively constant even when a pregnant woman becomes febrile. Our experiment, in which an

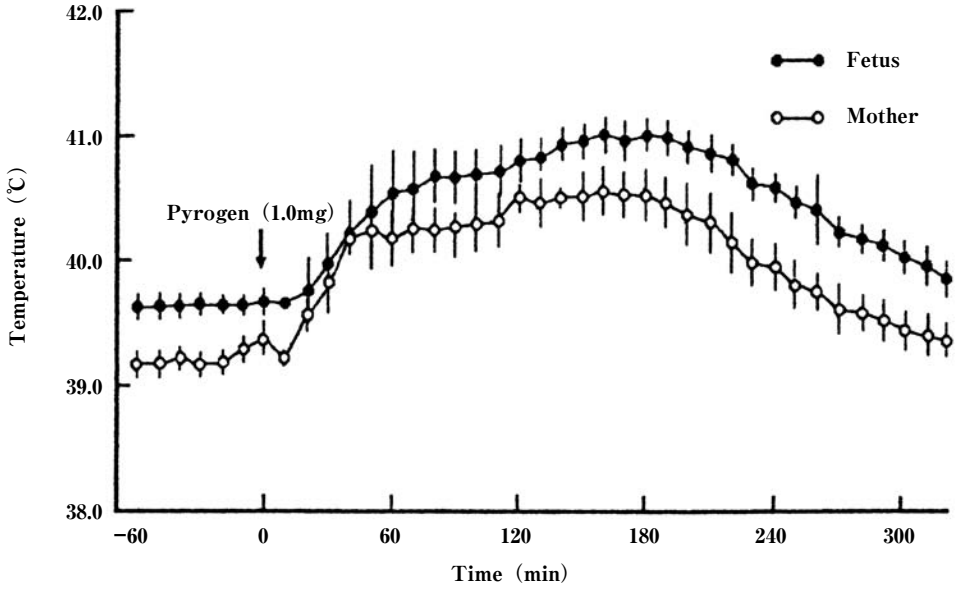

Fig. 1 Time course of maternal and fetal core temperatures after pyrogen (endotoxin) administration in pregnant goats, Mean and SEM are shown. Constant temperature difference is observed before pyrogen administration and relatively constant after maternal temperature rose by the administration[7].

endotoxin was administrated to a pregnant goat, revealed that the heat clump is maintained even when the temperature of the pregnant goat gradually rose (**Fig. 1**)[4]. This indicates that fetal thermoregulation is immature and that fetal thermoregulation is largely dependent on maternal conditions.

c. Dissipation of Fetal Heat to the Mother

Body temperature is defined as the balance between heat production and loss. For example, when heat production increases, body temperature rises. When heat loss increases, body temperature falls. Since the fetal temperature is higher than the maternal temperature, it is physiologic that heat produced by the fetus is transferred to the mother. Gilbert et al. found that in sheep the heat readily passes across the placenta when compared to transfer across the fetal skin. They found that 85% of heat that is produced by fetal lamb is transferred to the mother via the umbilical circulation; the remaining 15% is dissipated through the fetal skin to the amnion, and then passes through the uterine wall and to the maternal abdomen[5].

As long as fetal heat production and loss are appropriately balanced, the temperature differential between the fetus and the mother remains constant (heat clump), and the appropriate amount of heat is transferred to the mother. However, if the heat transfer is disrupted for any reason, the fetal temperature may increase. Since the majority of fetal heat is dissipated via umbilical blood flow, we present cases of alteration of umbilical blood flow. These cases are common clinical situations, which occur during pregnancy and labor. An animal study found that the body temperature of the fetal baboon was elevated by partial occlusion of umbilical cord[6]. Also, the temperature of fetal sheep rose quickly following complete occlusion of the umbilical blood flow[2]. Using tele-thermography, we found that the skin temperature of human newborns shortly after birth was relatively higher if the umbilical cord was coiled[7]. This finding indicates that fetal temperatures rapidly change in response to a disturbance in umbilical blood flow because heat accumulates within the fetus.

The most serious umbilical cord problem for fetal live is prolapse, which may lead to disruption of blood flow, and can result in acute hypoxic ischemic brain damage[8]. Even in this serious clinical situation,

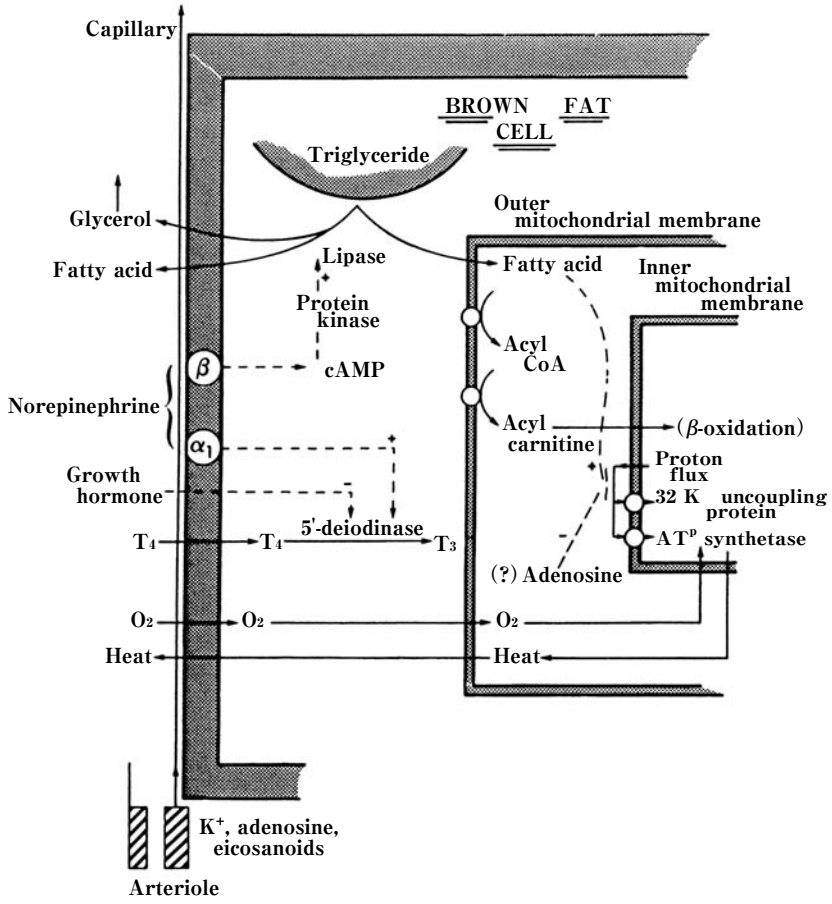

Fig. 2 Metabolic and hormonal control of brown adipose tissue. Control occurs by regulating blood flow to the tissue, altering the activity of lipase, 5'-deionidase, and 32K uncoupling protein and by affecting the permeability of inner mitochondrial membrane to proton. Norepinephrine stimulates thermogenesis through β-and possibly α1-receptors, but its effects are attenuated in utero probably by inhibitors of thermogenesis[3].

the relevance of the fetal temperature is not well understood in the human. It is likely that, as in animal models, human fetal temperature rapidly increases after occlusion of the umbilical cord blood because the heat cannot dissipate via the umbilical circulation.

d. Effect of Fetal Hyperthermia

The effect of maternal fever on fetal temperature should be considered. When a pregnant woman becomes febrile, the temperature of the uterus, amnion, and blood increases; therefore, the amount of heat loss from the fetus to the mother is reduced, and heat accumulates within the fetus. The situation is similar to fetal hyperthermia. Experiments on fetal lamb have indicated that umbilical and uterine arterial blood flow is reduced when the mother becomes hyperthermic[9]. When the maternal temperature rises by 2.5℃, umbilical cord blood flow significantly decreases[10].

When a pregnant woman becomes febrile, increased blood flow to the skin readily dissipates the heat. In this adaptation, blood flow to visceral organs, such as the kidneys, intestine and uterus, decreased. Therefore, maternal hyperthermia may reduce uterine, uteroplacental and umbilical blood flow, resulting in fetal hypoxia or acidosis[11]. These findings suggest that hyperthermia may have serious fetal consequences.

e. Physiological Mechanisms for Fetal Protection in Response to Hyperthermia

Fetal hyperthermia is related not only to pathological events, such as occlusion of the umbilical cord and maternal fever, but also to common daily routines during pregnancy, such as exercise and bathing in hot water. There are several protective mechanisms respond to fetal

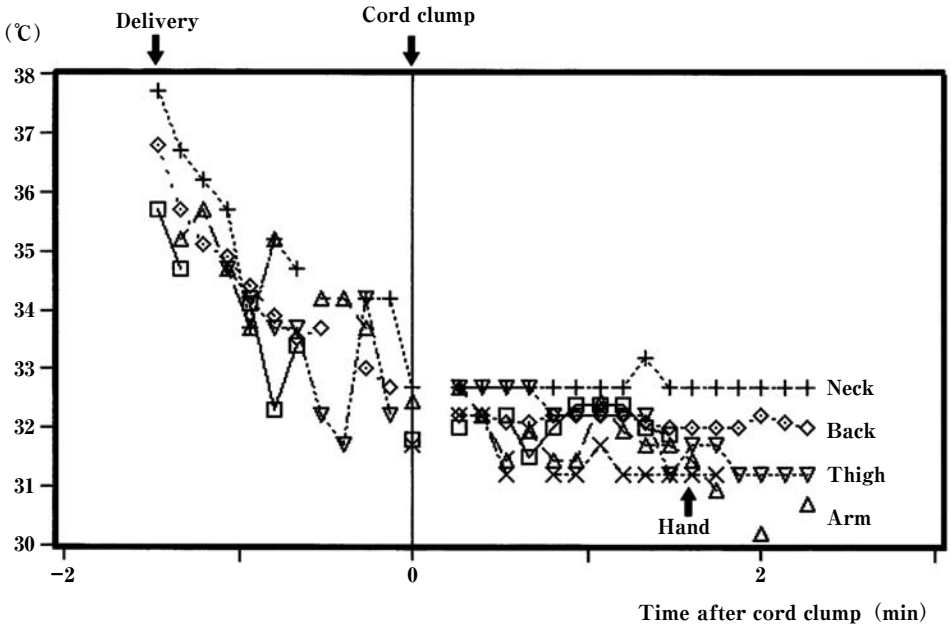

Fig. 3 Time course of human neonatal skin temperatures immediate after delivery by observation with thermography Skin temperatures falls rapidly after birth. However skin temperatures do not fall after cord occlusion, indicating initiation of nonshivering thermogenesis to rise body temperatures.

hyperthermia. One is a right shift of the fetal hemoglobin dissociation curve. As the hemoglobin dissociation curve shifts to the right, fetal oxygenation is facilitated[12]. The second mechanism for fetal protection is blood flow redistribution within the uterus. Although uterine blood flow decreases in response to hyperthermia, only blood flow to the myometrium decreases while placental blood flow remains the same[13]. These mechanisms are present in pregnant sheep with a temperature elevation from exercise. From these experimental results, extremely strenuous exercise should be avoided by pregnant women. In regard to bathing, studies indicate that a normal bath is not harmful to the fetus, although animal experiments have indicated that very hot water produces fetal acidosis.

3. Neonatal Thermoregulation

a. Non-shivering Thermogenesis

At birth, neonatal heat loss is rapid due to removal from the the warm intrauterine environment; in the relatively cold external environment, evaporative heat loss is significant, and the neonatal temperature rapidly drops. Therefore, increased fetal heat production is essential for survival. The thermogenic response begins within minutes of birth and continues for many hours. For example, oxygen consumption and heat production of the human neonate increases two to three fold during cold stress at birth.

Two heat production modalities have been described: (1) The basic heat production as a result of increased cellular metabolic activity; and (2) Extra-heat production when necessary, such as cold stress. Extra-heat production includes nonshivering and shivering thermogenesis which produces heat by shivering skeletal muscles. Since neonatal muscles are relatively immature to produce heat, shivering thermogenesis is an insignificant factor. The significant role of nonshivering thermogenesis (NST) at birth has been well recognized; heat is produced in brown adipose tissue. Brown adipose tissue differs morphologically and metabolically from ordinary white adipose tissue. Brown adipose tissue contains many mitochondria, numerous fat vacuoles, an abundant sympathetic innervation, and an abundant blood supply[14–17].

In the mitochondria of brown adipose tissue, ATP synthesis is uncoupled from the oxidative process by

a protein located in the inner mitochondrial membrane[18]. This protein is called an "uncoupling protein". By uncoupling ATP synthesis from the oxidative process[18], heat is produced as a final product; there is an associated increase in oxygen consumption and elevation of free fatty acids in serum as a result of the lypolysis of brown adipose tissue (**Fig. 2**).

In newborns of species, such as the lamb, the rabbit, and the rat, significant NST begins in the brown adipose tissue shortly after birth. In human newborns, the response is not as pronounced but still clearly evident. Brown adipose tissue constitutes only 1.4% of the body mass of human newborns over 2,000 grams[19]. Brown adipose tissue is prominent in nuchal subcutaneous tissue, the intrascapular region, the mediastinum, surrounding the spinal cord, and around the kidneys. Therefore, initiation of NST in brown adipose tissue elevates core body temperature.

b. Thermographic Observation of Human NST

Using thermography, we observed the neonatal back skin temperatures and heat dissipation from interscapular skin where brown adipose tissue is rich. Heat from interscapular region reflects thermogenesis of brown adipose tissue. We established time course of NST in normal newborns for the first 24 hours of life.

NST was promptly initiated when the umbilical cord occluded at a delivery room (**Fig. 3**). Afterwards, NST continued to acitivate and the activity of NST continued by 6 hours after birth (**Fig. 4**). During 6 hours after delivery, skin temperatures of neonates rose rapidly. Furthermore, a positive correlation between the umbilical PO2 and the intensity of NST was found (**Fig. 5**)[20]. Although it is known that NST is strongly influenced by oxygenation, NST activates in accordance with oxygenation even under usual postnatal conditions. Using thermography, we found that bathing of the neonates elicited NST. Particularly on the day of birth, activity of NST was maximal; therefore, it is of clinical relevance that a neonate should not be bathed until the stability of neonatal oxygen status is confirmed.

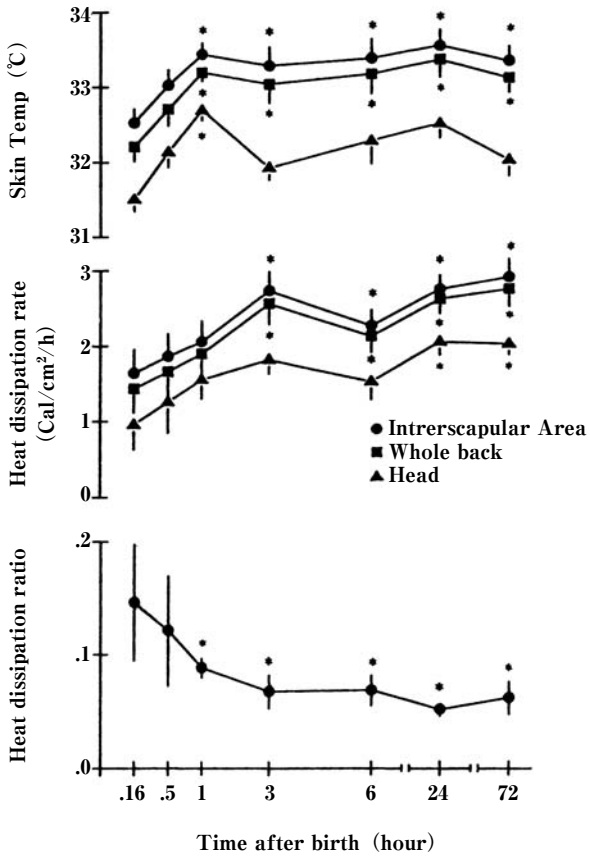

Fig. 4 Time course of changes in temperature (top), heat dissipation rate (midpanel), and heat dissipation ratio (bottom) after birth[20].
Heat dissipation ratio is defined as heat dissipated from interscapular region divided by mean heat dissipated from whole back area. This ratio indicates nonshivering thermogenic activity from interscapular region.

4. NST in Preterm Newborns and Small for Gestational Age (SGA) Infants

In order to survive thermally stressful extrauterine life, a fetus must accumulate brown adipose tissue in utero. Since the fetal brown adipose tissue accumulates later in gestation, premature infants have minimal ability to initiate NST in response to a cold extrauterine environment. This may be also true for SGA infant who has decreased subcutaneous adipose tissue. Thermographic observations demonstrated that infants delivered prior to 30 weeks did not exhibit any NST activity on their dorsal surface. SGA infants did show NST but at a markedly decreased level. Moreover, these

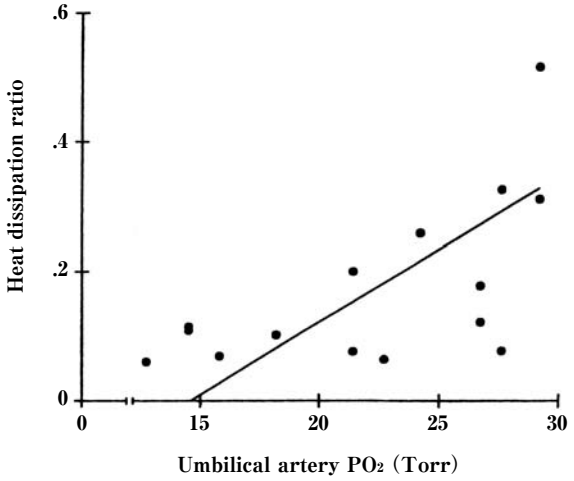

Fig. 5 Correlation of fetal heat dissipation ratio at 6 hours from birth and PO_2 of umbilical artery at birth ($r = 0.627$, $p < 0.01$)[20].

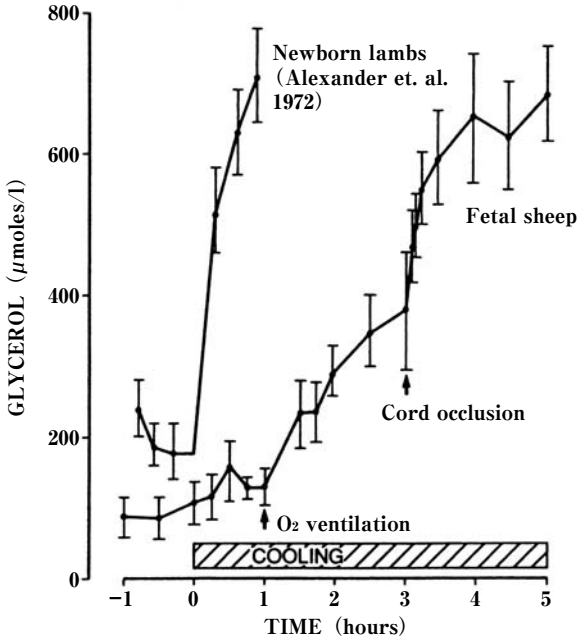

Fig. 6 Plasma glycerol, an index of nonshivering thermogenesis, rises rapidly when newborn lambs are exposed to cold. Fetal responses to cooling are minimal and remain modest even when supplemental oxygen is given. Cord occlusion triggers a near maximal thermogenic response. Thermogenic response of neonatal lamb to cooling (Alexander et al.) is shown as a reference[3].

infants have a thin skin layer, which readily transmits heat to the external environment. Therefore, warm thermal conditions should be maintained for these infants with immature thermoregulation. The appropriate temperature management for these infants is clinically well established. In regard to NST, infants do not produce enough heat to respond to cold extra uterine life until the third trimester[20].

5. Thermogenic Inactivity of the Fetus

Both shivering and non-shivering thermogenesis are minimally evident in utero. Fetal sheep shiver during cooling; however, it has not measurable thermogenic efficacy in utero. Power established an animal experimental model, which produced fetal NST in utero[3]. To initiate NST for a fetus subjected to cooling, supplemental oxygen is administered to the fetus and the umbilical cord is occluded (**Fig. 6,7**). Intrauterine cooling of the fetus by circulating cold water through a plastic coil surrounding the fetus decreased the fetal core temperature by 2℃; however, the plasma concentration of glycerol and free fatty acids, which are indices of NST, did not rise. After supplemental oxygen was administered, half of the neonatal level of glycerol was produced, and when the umbilical cord was occluded, thermogenic responses, including glycerol, free fatty acids, oxygen consumption and core temperature, all increased the neonatal level. The phenomenon were interpreted as initiation of NST like neonatal sheep.

Since NST requires a large amount of oxygen, it is understandable that NST does not occur in utero. Exposure of the fetal lamb to cold does not initiate NST. Administration of a high level of oxygen to the fetus also does not initiate NST. To clarify this phenomenon, Power' et al. established the hypothesis that inhibitory substances for NST are produced in the placenta and that such substances enter the fetal circulation and inhibit NST.

6. Possible Mechanisms Initiating NST at Birth

NST rarely occurs in utero, perhaps because the oxygen level of the brown adipose tissue is inadequate or because of a lack of circulating cathecolamines and thyroid hormones, which are essential for the initiation of NST. Several hypotheses have been proposed, and currently, the

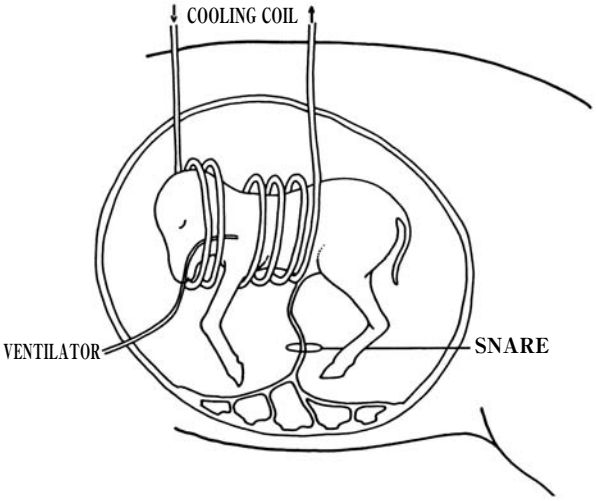

Fig. 7 Animal model to initiate non-shivering thermogenesis in fetal lamb[3]. Intrauterine cooling of the fetus by circulating cold water through a plastic coil surrounding the fetus decreased the fetal core temperature by 2℃. Then supplemental oxygen is ventilated and the umbilical cord was occluded to initiate thermogenic responses.

concept of an inhibitor of thermogenesis is the most likely. Sawa et al. investigated the relationship between plasma concentrations of adenosine and NST. They found that occlusion of the umbilical cord in the fetal lamb, which had been subjected to cold and supplied with oxygen, resulted in a dramatic reduction of adenosine concentrations in the fetal plasma; this reduction is closely related to the initiation of NST. They concluded that placental adenosine is a likely candidate for an inhibitory substance[22]. Like adenosine, prostaglandin E_2 has an inhibitory effect on NST[23,24].

Physiologically active substances, such as adenosine and PGE_2, have strong anti-lypolytic actions on brown adipose tissue. These substances are produced by placental tissue and their concentrations are high in fetal plasma. The physiologic benefit of the inhibition of fetal NST is considered to be the conservation of fetal oxygen and accumulation of brown adipose tissue in the fetus.

For example, intrauterine growth retarded (IUGR) fetuses have a high level of circulating adenosine[25] to inhibit lypolysis. This may be a physiological adaptation to the minimal accumulation of subcutaneous fat.

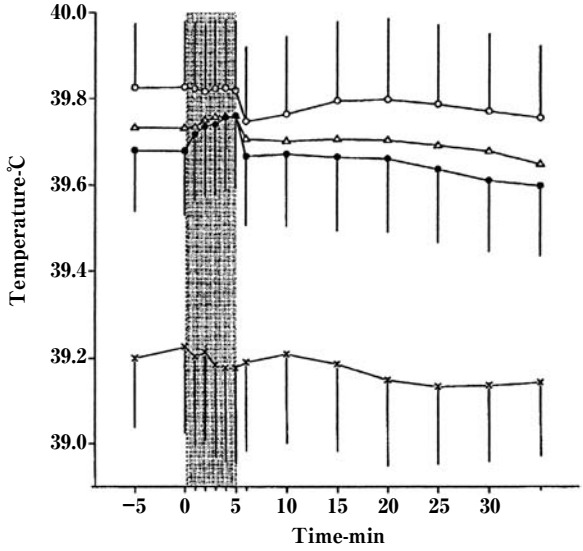

Fig. 8 Time course of temperature changes of fetal brain tissue (open circles), ascending aorta (solid circles) and internal juglar vein (open triangles) in response to the cord occlusion in fetal sheep. Symbols (X) indicate temperature of carotid artery of pregnant sheep. Shaded vertical band indicates the period of umbilical occlusion. By the occlusion, temperatures of ascending aorta and juglar vein increased, while brain temperature did not increase[34]. This may be due to hypometabolic adaptation during hypoxemia.

7. Brain Temperature and Thermoregulation

Recently, a relationship between hyperthermia and brain damage has been established; therefore, acute umbilical cord occlusion, such as cord prolapse, might result in fetal brain damage[26,27]. To clarify this mechanism of fetal brain damage, we must determine the serial changes of fetal temperature during cord occlusion. Brain temperature is particularly important because relatively small changes affect its sensitivity to hypoxic injury[28,29]. In newborns and adult animals, for instance, small decreases in brain temperature reduce ischemic brain damage, whereas relatively small increase predisposes to hypoxic injury[30,31]. In their experiments in which 30 minutes of uteroplacental ischemia was instituted, hyperthermia produced severe symmetrical intrauterine growth retardation, while hypothermia did not affect fetal growth. However, the effect of thermal conditions on fetal

brain development was similar[32].

An association exists between fetal brain damage and umbilical cord occlusion[26,33]. As described earlier, disturbances of umbilical blood flow may lead to abnormal fetal temperatures, which might induce brain damage[30-32]. Kubonoya et al. found that changes in brain temperatures of fetal lambs in response to a five minute occlusion of the umbilical cord produced ischemia and hypoxemia. They found that the brain temperature did not increase while body core temperature rapidly rose in response to umbilical cord occlusion (**Fig. 8**)[34]. Other investigators obtained similar results[35], and theorized that the lack of a rise in brain temperature may be due to a decrease in heat production by brain tissue concomitant with an increase in cerebral blood flow.

A marked decrease in cortical electricity activity occurs during and following cord occlusion. Since electrical activity is a major consumer of oxygen and producer of metabolic heat, oxygen consumption in the brain decreases during cord occlusion. Furthermore, if cerebral blood flow markedly increases during partial cord occlusion, the brain temperature will not increase significantly because of the more effective removal of metabolic heat from brain. However, after complete cord occlusion for five minutes, cerebral blood flow is not elevated[27]. Thus, the relationship between cerebral blood flow and constant brain temperature depends on the experimental design. Rapid induction of cerebral hypometabolism during hypoxemia has the physiologic advantage of protecting against damaging hyperthermia that predispose to hypoxic injury. To reduce the risk of neonatal brain damage, further investigation is indicated for the measurement of the metabolic status of the brain in sick newborns.

Cord occlusion induces hypoxic-ischemic injury of the fetal brain. Experimental data shows that a 10-minute occlusion of the umbilical cord damages the hipppocampus, although there is metabolic protection for hyperthermia when the cord is occluded as described earlier. Cooling the brain and body is reported to be effective to prevent hypoxic-ischemic injury of fetal brain. This is an artificial thermoregulation, which does not produce neurotoxic substances such as excitatory amino acids, NO and oxygen radical species[36]. However, currently, an appropriate newborn cooling methodology has not been defined in regard to type, when it should be instituted, and when it should be discontinued. Therefore general use of this technique for human newborns should not be instituted until physiological data and pilot studies answer these questions.

Conclusion

I have reviewed the physiology of fetal and neonatal thermoregulation. The data has been primarily obtained from animal studies; therefore, research using human subjects is indicated to improve the clinical care of fetuses and neonates. We understand the thermoregulatory mechanisms of fetuses and neonates; however, the clinical management of their thermoregulation is not well established beyond the customary thermal care of neonates. For example, when we encounter a severely distressed fetus or neonate due to occlusion of umbilical cord in utero, we currently have not defined the most appropriate treatment to prevent brain damage. As described earlier, the body temperature of a fetus or a neonate can be elevated while the brain temperature remains normal. However, body temperature drops promptly after delivery, and because a severely distressed neonate is hypoxic, adequate oxygen and heat are essential to elevate temperature via NST. Do we cool the brain to prevent damage? When do we initiate brain cooling? These are a sampling of unanswered clinical questions.

By uncoupling protein, brown adipose tissue can produce adequate heat for neonates at birth. Recently, a number of sub-types of uncoupling protein have been found in many organs; therefore, currently, the role of uncoupling protein has been limited not only to thermoregulation, as previously described, but also to energy expenditure[37]. This is suggested in pregnant women as Asakura et al. pointed out[38].

Since uncoupling proteins have been found in many species, including mammals, birds, insects, and

plants, the role of these proteins have been interpreted to be essential for life. Further study of uncoupling proteins may lead to increased understanding of fetal and neonatal physiology.

References

1. Power GG, Schroder H, Gilbert RD: Measurement of fetal heat production using differential calorimetry. J Appl Physiol 1984; 57: 917–922.
2. Asakura H, Ball KT, Power GG: Interdependency of arterial PO_2 and O_2 consumption in fetal sheep. J Dev Physiol 1990; 13: 205–213.
3. Power GG: Biology of temperature: the mammalian fetus. J Dev Physiol 1989; 12: 295–304.
4. Tanaka K, Kawamura T, Asakura H, Araki T: Effect of maternal injection of endotoxin on prostaglandin production and uterine contraction in late gestational pregnant goats. J Nippon Med Sch 1997; 64: 42–47.
5. Gilbert RD, Schroder H, Kawamura T, Dale PS, Power GG: Heat transfer pathways between fetal lamb and ewe. J Appl Physiol 1985; 59: 634–638.
6. Morishma HO, Yeh M, Niemann WH, James LS: Temperature gradient between fetus and mother as an index for assessing intrauterine fetal condition. Am J Obstet Gynecol 1977; 129: 443–448.
7. Asakura H: Thermogenesis in fetus and neonate. J Nippon Med Sch 1996; 63: 171–172 (Author's translation).
8. Arulkumaran S, Skurr B, Tong H, Kek LP, Yeoh KH, Ratnum SS: No evidence of heating loss due to fetal acoustic stimulation test. Obstet Gynecol 1991; 78: 2
9. Oakes GK, Walker AM, Ethenkranz RA, Cefalo PC, Chez RA: Uteroplacental blood flow during hyperthermia with and without respiratory alkalosis. J Appl Physiol 1972; 41: 197–492.
10. Cefalo RC, Hellenger AE: The effects of maternal hyperthermia on maternal and fetal cardiovascular and respiratory function. Am J Obstet Gynecol 1987; 131: 687–693.
11. Abrams R, Caton D, Clapp J, Baron DH: Thermal and metabolic features of life in utero. Clin Obstet Gynecol 1970; 13: 549–564.
12. Lottergerin FK, Gilbert RD, Longo LD: The interaction of exercise and pregnancy; a review. Am J Obstet Gynecol 1984; 149: 560–568.
13. Hohiner AR, Bissonnette JM, Metacaffe J, Mckean TA: Effect of exercise on cardiac output and distribution of uterine blood flow in the pregnant pygmy gout. Am J Physiol 1984; 26: H207–212.
14. Dawkins MJR, Hull D: Brown adipose tissue and the response of new-born rabbits to cold. J Physiol London 1964; 172: 216–238.
15. Girardier L: Brown fat: an energy dissipating tissue. Mammalian thermogenesis (Giradier L, Stock MJ, eds), 1983: pp50–57, Chapmann and Hall, London-New York.
16. Heim D, Hull D: The blood flow and oxygen consumption of brown adipose tissue in the newborn rabbit. J Physiol 1966; 186: 42.
17. Rylander E, Prybiliva H, Lind J: A thermographic study of infants exposed to cold. Acta Paediat Scand 1972; 61–42.
18. Nicholls D, Locke R: Cellular mechanisms of heat dissipation. Mammalian thermogenesis (Girardier L, Stock MJ, eds), 1984: pp8–42, Chapmann and Hall, London-New York.
19. Merklin RJ: Growth and distribution of human fetal brown fat. Anat Rec 1974; 178: 637–646.
20. Oya A, Asakura H, Koshino T, Araki T: Thermographic demonstration of nonshivering thermogenesis in human newborns after birth: its relation to umbilical gases. J Perinat Med 1977; 25: 447–454.
21. Okken A: Postnatal adaptation in thermoregulation. J Pediat Med 1991; 19 (suppl 1) : 67–73.
22. Sawa R, Ball KT, Asakura H, Power GG: Changes in plasma adenosine during simulated birth of fetal sheep. J Appl Phsiol 1991; 70: 1524–1528.
23. Ball KT, Takauchi M, Power GG: Role of prostaglandins I_2 and E_2 in the initiation of nonshivering thermogenesis during the simulation of birth in utero. Reprod Feril Dev 1995; 7 : 65–119.
24. Takeuchi M, Yoneyama Y, Power GG: Role of prostaglandin E_2 and prostacyclin in nonshivering thermogenesis during simulated birth in utero. Prosta Leukotr and Essential Acids 1994; 51: 373–380.
25. Yoneyama Y, Wakatsuki M, Sawa R, Kamoi S, Takahashi H, Shin S, Kawamura T, Power GG, Araki T: Plasma adenosine concentration in appropriate and small-for-gestational-age fetus. Am J Obstet Gynecol 1994; 170: 684–688.
26. Mallard EC, Williams CE, Johnston BM, Gunning MI, Davis S, Gluckman PD: Repeated episodes of umbilical cord occlusion in fetal sheep lead to preferential damage to the striatum and sensitize the heart to further insults. Pediatr Reserch 1995; 37: 6707–6713.
27. de Haan HH, Gunn AJ, Williams CE, Heymann MA, Gluckman OD: Magnesium sulfate therapy during asphyxia in near-term fetal lambs does not compromise the fetus but does not reduce cerebral injury. Am J Obstet Gynecol 1997; 176: 18–27.
28. Bristo R, Dietrich WD, Globus MY, Valdes I, Scheinberg P, Grinsberg MD: Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. J Cereb Blood Flow Metab 1987; 7 : 729–738.
29. Minamisawa H, Smith ML, Sesjo BK: The effect of mild hyperthermia and hypothermia on brain damage following 5, 10, and 15 minutes of forebrain ischemia. Ann Neurol 1990; 28: 26–33.
30. Chopp M, Knight R, Tidewell CD, Helpern JA, Brown E, Welch KMA: The metabolic effects of mild hyperthermia on global cerebral ischemia and recirculation in cat: comparison to normothermia and hyperthermia. J Cereb Blood Flow Metab 1989; 9 : 141–148.
31. Dietrich WD, Busto R, Valdes I, Loor Y: Effects of normothermic and mild hyperthermic forebrain

ischemia in rats. Stroke 1990; 21: 1318–1325.
32. Asakura H, Nakai A, Power GG, Araki T: Short-tem effects of different thermal conditions during uteroplacental ischaemia on fetal growth of Sprague-Dawley rats. Reprod Fertile Dev 2002; 14: 355–361.
33. Clapp JF, Peress NS, Wesley M, Mann LI: Brain damage after intermittent partial cord occlusion in chronically instrumented fetal lamb. Am J Obstet Gynecol 1988; 159: 504–509.
34. Kubonoya K, Yoneyama Y, Sawa R, Araki T, Power GG: Brain temperature and metabolic responses during umbilical cords occlusion in fetal sheep. Pluger Arch-Eur Physiol 1998; 436: 667–672.
35. Lotgering FK, Bishai JM, Struijik PC, Blood AB, Hnter CJ, Power GG, Longo LD: Ten-minute umbilical cord occlusion markedly reduces cerebral blood flow and heat production in fetal sheep. Am J Obstet Gyenecol 2003; 189: 233–238.
36. Thoresen M: Cooling the newborn after asphyxia-physiological and experimental background and its clinical use. Semin Neonatol 2004; (1) : 61–73.
37. Argyropoulos G, Harper ME: Molecular biology of thermoregulation, Invited review: uncoupling proteins and thermoregulation. J Appl Physiol 2002; 92: 2187–2198.
38. Asakura H, Nakai A, Araki T: Correlations between interscaplar deep temperature and plasma free fatty acid levels in pregnant women with hyperemesis gravidarum. Arch Gynecol Obstet 2003; 268: 35–40.

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