SPECIAL ARTICLE

Does Thermoregulatory Feeding Occur in Newborn Infants? A Novel View of the Role of Brown Adipose Tissue Thermogenesis in Control of Food Intake

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Abstract


The physiological significance of the extensive deposits of brown adipose tissue (BAT) in newborn human infants has been the subject of much experimentation and discussion. Because of its large thermogenic capacity, its function has usually been viewed as preparing the infant for producing heat in response to cold exposure at birth. Newborn infants are indeed capable of precise thermoregulation for a limited time over a rather limited range of ambient temperatures, from thermoneutrality (32-34°C) down to common “room” temperatures (24-28°C). During such mild “cold-exposure”, in response to a decrease in their skin temperature, their sympathetic nervous system activity increases, and they can more than double their resting metabolic rate, principally by thermogenesis in their BAT. This review puts forward an entirely new role for BAT thermogenesis in the cyclic feeding pattern of newborn infants during their first months of life. BAT thermogenesis is proposed to be an integral element in a physiological thermoregulatory feeding control mechanism in which extended periods of very gradual cooling are interspersed with episodes of increased sympathetic nervous system activity, increased heating via BAT thermogenesis, arousal, and feeding. The cry with which the baby attracts its mother’s attention is an integral part of the mechanism, as is the nutritive suckling reflex and the behavior of the mother. Initiation of feeding is attributed to a transient dip in blood glucose concentration that is due to stimulation of glucose utilization in the BAT. Termination of feeding is attributed to the high temperature brought about by the stimulated BAT thermogenesis. The duration of the urge to feed extends from the time of the cry to the time of the peak rise in temperature, when feeding stops. There is no clear circadian rhythm in core temperature in newborn infants, and meals occur at fairly frequent intervals both day and night in infants that are fed on demand. These physiological mechanisms are consistent with the limited information on phenomena attending spontaneous feeding in the newborn human infant and with what is known about the physiological control of feeding in rats. In rats, thermoregulatory feeding is defined as a feeding episode that occurs during a transient but marked increase in sympathetic nervous system activity that has several consequences. It stimulates BAT thermogenesis and increases body temperature. It produces a transient decline in blood glucose concentration secondary to the increased uptake of glucose by the stimulated BAT; this signals the initiation of the feeding episode. Subsequently the high temperature induced by BAT thermogenesis signals termination of the feeding episode. The size of the meal is determined by the balance between the capacity for BAT thermogenesis (heat production) and ambient temperature (heat loss).

BAT thermogenesis is here viewed as an integral part of a physiological feeding control mechanism that links thermal balance with energy balance. The phenomenon is referred to as thermoregulatory feed-
Feeding is initiated by the dip in blood glucose concentration. This is probably sensed, directly or indirectly, by the hypothalamus and possibly involves the release of neuropeptide Y (NPY).

5. Blood glucose level is restored to normal by counterregulatory processes in liver.

6. Body temperature continues to rise until, about 1°C higher, it reaches a set level. Sensing of this high level brings into play measures to prevent hypothermia. Feeding stops. Sympathetic nervous system activity decreases and BAT thermogenesis is switched off. Core temperature stops rising and starts to fall.

7. Core temperature continues to fall gradually until it reaches a level that activates the sympathetic nervous system, and initiates another thermoregulatory feeding episode. Time to the next meal depends on the size of the previous meal eaten, i.e., on the thermic effect of the food, and on the ambient temperature.

Evidence for Thermoregulatory Feeding in Rats

Evidence is available for the separate occurrence in rats of all the events listed above. Rats living in a constant environment with regular periods of light and dark, with a temperature below thermoneutrality (29°C to 30°C) and with constant access to a monotonous food supply spontaneously eat nine to 12 discrete meals per day, mostly during the dark phase (34,49,50). Pulsatile increases in sympathetic nervous system activity occur in rats (51). Pulsatile increases occur in core temperature (13), indeed in temperature of all organs including
BAT in which it exceeds that in other organs (11). So do pulsatil increases in whole body nonshivering thermogenesis (5). Pulsatile release of noradrenaline in the hypothalamus has been described (14). For all these pulsatil events, the frequency corresponds approximately to the usual frequency of feeding episodes in rats, i.e., 9 to 12 per day. An episode of feeding occurs during the rising phase of core temperature, starting some time after its onset and ceasing when it reaches 39.3°C (starting and finishing at lower temperatures during the light phase) (13). A transient dip in blood glucose concentration has been observed prior to the time of meal onset in rats and proposed as part of the initiation signal (8-10). Attempts to attribute such a dip to pulsatil insulin secretion have not proved entirely successful (47) and its cause has remained obscure. BAT is known to be a major site of glucose utilization when its thermogenesis is stimulated (53,54); the major fate of the glucose used is conversion to lactate (35). The return of blood glucose concentration to a normal level after the dip is most probably due to increased glycogenolysis in liver, known to occur in association with an episode of feeding in rats (19,32) and to increased gluconegenesis in liver, using the lactate exported by the BAT (23-25). The thermoregulatory feeding hypothesis proposes the sequence and linkage of all these different pulsatil events before and during a feeding episode.

**Does Thermoregulatory Feeding Occur in Newborn Infants?**

The purpose of the present review is to extend the hypothesis for thermoregulatory feeding in rats to the control of feeding in newborn babies. It will review the limited evidence available, mostly indirect, that in new-
Newborn infants the sequence of events enumerated above might, indeed, occur, during the first few weeks of life.

Evidence is obviously more difficult to obtain for newborn infants than for adult rats, and much of that required is not available. The review will dwell on information presently available, draw attention to areas where more evidence is needed, and propose experimental approaches by which it might be obtained.

Some Characteristics of Feeding Behavior in Newborn Infants

Newborn breast-fed babies fed on demand do not eat continuously. They ingest roughly 8 to 12 meals per day. They have no clear circadian rhythm in their feeding. Meals are taken at intervals both night and day. The meals are sometimes large (of long duration) and sometimes small (of short duration). Demand is indicated by arousal and crying. The baby sleeps most of the rest of the time. If a meal is missed, the baby tends to sleep again until a next meal would be expected, i.e. the "window of opportunity" is missed. Sometimes the baby falls asleep during a meal, frustrating the nursing mother. Arousal and feeding are readily provoked by unwrapping swaddling blankets at a room temperature of 22°C to 24°C. These features of feeding behavior will be incorporated into the description of thermoregulatory feeding outlined below.

Thermoregulation in Newborn Infants

Characteristics of Thermoregulation in Newborn Infants

Thermoneutrality for unclothed newborn infants is about 32°C to 34°C. Exposing them to temperatures of 24°C to 28°C (common "room" temperatures) induces restlessness, crying, and a substantial and rapid increase in metabolic rate (more than doubled) (6,7,22,28). Shivering does not occur in newborn infants and the increase in metabolic rate has been attributed solely to nonshivering thermogenesis (6). If left for several hours at a temperature below thermoneutrality, they eventually develop hypothermia. The increase in metabolic rate begins long before any fall in rectal temperature and declines on return to a warm environment long before the recovery of a normal rectal temperature (6). The changes in metabolic rate are thus believed to be mediated by cold receptors in the skin (6). Even exposing only the facial skin to 20°C to 22°C can evoke a large increase in metabolic rate in a newborn infant (37). Over the wide range of ambient temperatures handled by an adult, newborn infants are imperfect homeotherms. They are, nonetheless, capable of precise short-term thermoregulation without becoming hypothermic over a rather limited range of ambient temperatures. The thermoneutral temperature is higher for premature babies than for babies born at term; it decreases slightly in all babies during the first few weeks of life but remains rather high for many months (22,41).

Newborn infants do not exhibit the circadian pattern of body temperature seen in older children and adults (20,21). No pattern is discernible at all during the first days. Slowly over 1 to 3 months a slight lowering of temperature occurs at night and between 3 and 6 months a definite rhythm is established. Maximum amplitude of the circadian variation is reached only at between 2 to 5 years of age (1,2,20,21). The similar time scale in the development of a circadian rhythm in heart rate (21) suggests that both are attributable to a slow development of a circadian rhythm in sympathetic nervous system activity.

Early workers paid great attention to physical activity of the newborn as a cause of the cold-induced increase in metabolic rate. In general, it appears that physical activity itself has rather little effect on metabolic rate of the neonate, although of course the cold-induced increase in metabolic rate is usually associated with an increase in physical activity. Muscle is rather poorly developed in the neonate. Since muscle contributes to only 6 percent of resting metabolic rate (15), even at 6 months of age, it is unlikely that even a doubling of its use of oxygen could change the metabolic rate by the 100% to 150% seen in the infant exposed to a temperature slightly below thermoneutrality.

Role of Noradrenaline in the Thermogenic Response to Cold

If the cold-induced increase in metabolic rate is due to nonshivering thermogenesis, it would be expected to be mediated by noradrenaline secreted by the nerves of the sympathetic nervous system. Indeed, such a large increase in excretion of noradrenaline in the urine in association with the increase in metabolic rate has been demonstrated in newborn infants exposed to 18°C to 20°C (43,48). In one premature infant in which no increase in metabolic rate was observed there was also no increase in noradrenaline excretion (48). Moreover, infusion of noradrenaline into newborn infants can raise the resting metabolic rate, decrease the respiratory quotient, increase the level of plasma free fatty acids and raise rectal temperature (30,31,43).

Development of Brown Adipose Tissue in Fetal and Neonatal Life

Newborn infants are endowed with an abundant supply of brown adipose tissue (4,6,27,36,38). This would be expected in view of their large capacity for noradrenaline-mediated nonshivering thermogenesis that underlies the cold-induced increase in metabolic
rate. On gross dissection some discretely located deposits of BAT are clearly visible, particularly one large brown body at the nape of the neck. On histological examination, further depots of multilocular BAT cells can be readily seen, both in the fetus and the newborn. The amount of BAT increases during the last months of gestation to attain a maximum size by about 34 to 35 weeks of gestation. A recent study demonstrates that in BAT there is also a sharp increase in the concentration of uncoupling protein by 30 to 32 weeks of gestation (26). This increase is preceded by, and probably facilitated by, an increase in thyroxine 5'-deiodinase activity (26). Thus, BAT of the newborn infant has a substantial thermogenic potential similar to that of a cold-acclimated rat. Newborn infant BAT expresses β3-adrenoceptors at a level greatly in excess of their level in adult human adipose tissue, indeed comparable with that in rat BAT (17). This all indicates its capability for a sustained thermogenic response to endogenous noradrenaline.

Role of Brown Adipose Tissue in the Thermogenic Response to Cold

The presence of abundant brown adipose tissue with a high thermogenic capacity in newborn infants, the increased sympathetic activity that occurs in newborn infants during exposure to cold and the large capacity of newborn infants for a thermogenic response to infused noradrenaline all suggest that brown adipose tissue is the major site of nonshivering thermogenesis in cold-exposed newborn infants (3,7). Since the resting metabolic rate can more than double in response to mild cold-exposure, most of the oxygen presumably being used in the brown adipose tissue, and since approximately 50% to 60% of the resting metabolic rate occurs in brain (15), it can be concluded that the capacity of brown adipose tissue to consume oxygen is greater than that of the brain in the newborn infant and many times that of muscle. A decrease in respiratory quotient during exposure to cold and during infusion of noradrenaline suggests that fatty acids are the main fuel consumed by BAT for the increase in heat production. In addition, and by analogy with what is known about metabolism of stimulated brown adipose tissue in rats, one would expect that in the newborn the stimulated brown adipose tissue likewise considerably increases its utilization of glucose, converting it to lactate (23-25), perhaps even competing with the brain for the scarce supplies of glucose in the newborn infant.

Evidence for the Occurrence in Newborn Infants of the Events Associated with Thermoregulatory Feeding in Rats

A summary of such limited evidence as is available for the sequence of events in operation during an episode of thermoregulatory feeding in a newborn infant is presented below. (Numbers correspond to those listed in the Introduction).

1. There is no evidence for the occurrence of ultradian oscillations in sympathetic nervous system activity in human infants.

2. An increase in rectal temperature during feedings has been described in one study (A. Gyllenswärd, unpublished work described in (29)). The researcher measured rectal temperature in a 3-month old infant continuously over 24 hours and observed sleeping, crying, and feeding. Four episodes during which rectal temperature rose rapidly to 37.5°C were associated with feeding. Whether the peak of temperature, uniformly 37.5°C, actually coincided with cessation of feeding and whether the initiation of the rise occurred before the onset of feeding cannot be discerned from the data presented. There was one similar episode of a rise in temperature when the baby was awake, but feeding was not described (possibly an error in the figure). One very brief feeding period late at night, perhaps instigated by the mother, since the baby was not awake, was not associated with any increase in temperature. The infant studied was 3 months of age, and might be expected to have begun to develop a circadian rhythm in body temperature and feeding (20,21). Meals and temperature fluctuations did all occur during the day time period, and a gradual decline in temperature at night is apparent in this study.

3. Influx of glucose into brown adipose tissue of newborn infants has not been assessed and transient dips in blood glucose concentration before meals have not been reported. Newborn infants are subject to hypoglycemia, particularly during the time shortly before feeding (12,16). Described as “asymptomatic hypoglycemia” or “early transient hypoglycemia” (12,16), its true incidence is unknown because it has been detected only during routine checks and appears not to have been systematically studied. It does not appear to impair heat production (18). It may be relevant in this context that noradrenaline infusion promotes arousal, just as does cold exposure (30,31); unfortunately the only study in which blood was collected (43) did not measure glucose.

4. Whether transient hypoglycemia triggers a feeding episode in a newborn infant, via NPY or via some other mechanism, is unknown.

5. Since there appears to be spontaneous recovery from hypoglycemia in the newborn, either feeding or endogenous counterregulatory mechanisms presumably return the level of glucose to normal.

6-7. The peak rectal temperature of 37.5°C reached during meals in the one infant studied was remarkably consistent, suggesting the repeated invoking of some...
A New Look at the Role of Brown Adipose Tissue in Newborn Infants

Why do newborn babies possess BAT? The growth of BAT in fetal life has usually been regarded as preparing the baby to produce heat in response to the cold-exposure that inevitably occurs at birth (6,7,18,26,39). However, BAT thermogenesis can help maintain normothermia to only a limited extent at ambient temperatures that are only slightly below thermoneutrality. During the first days of life normothermia and a maximum rate of heat production, about double the resting rate at thermoneutrality, are achieved for a short time at an ambient temperature of 23°C by a lightly clothed newborn baby. While presumably of transient usefulness, this small degree of protection against hypothermia would appear to be of only limited long-term adaptive importance and could not be expected to provide much protection against accidental development of hypothermia. The increase in metabolic rate could also mitigate against maintenance of energy balance and a normal growth rate if the exposure is prolonged. Another, recently proposed function for fetal development of BAT is to provide for peripheral deiodination of thyroxine by virtue of the high level of thyroxine 5-deiodinase in it and thus to be responsible for the sympathetic-mediated increase in triiodothyronine level after birth (26).

The proposed role of BAT in thermoregulatory feeding outlined in this review provides a different and novel concept of the significance of BAT thermogenesis in newborn infants. Most of the evidence needed is not available, but such limited information as is available is consistent with the hypothesis. BAT thermogenesis proposed to be an integral part of a physiological feeding control mechanism. The large capacity for BAT thermogenesis, present at birth, allows the occurrence of extended periods of gradual cooling interspersed with episodes of heating during which meals occur. It is perhaps not a coincidence that the fetal development of thermogenically competent BAT, which occurs between 30 to 32 weeks and reaches a maximum by 36 weeks of gestation (26), slightly precedes the ability of the premature infant to feed by nutritive sucking, which appears at 32 to 34 weeks and is properly coordinated by 37 weeks (16). The cry with which the aroused baby attracts its mother's attention is an integral and necessary part of the mechanism, as is the mother's behavior on hearing the cry. The window of opportunity for feeding spans the time of the cry to the peak of the temperature increase. Whether the cry precedes or follows the initiation of stimulated BAT thermogenesis, i.e., whether it is signaled by the increase in sympathetic nervous system activity, or whether it is triggered by a dip in blood glucose concentration that triggers feeding only after BAT thermogenesis has started, is unknown.

Brick (6), in his extensive studies of thermoregulation in newborn infants, described cold-induced BAT thermogenesis as "the 'natural' or 'primitive' reaction in thermoregulation, which later disappears, perhaps because the microclimate created by civilization does not put a greater stress on temperature regulation." It emphasizes the use of behavioral measures in thermoregulation in adult humans (donning more clothes, turning up the thermostat) that are not available to the newborn infant. Being unable to use behavioral measures in their thermoregulation, newborn infants cry, thereby inducing indirect behavioral thermoregulation measures through the parent (6,7). The view of the role of BAT thermogenesis in feeding presented here extends this view of indirect control by the infant of behavioral thermoregulation to indirect control of feeding as well. The concept becomes obvious once enunciated, yet strangely appears not to have been recognized previously.

In the novel view proposed here, the role of BAT thermogenesis is seen to be part of a "natural" or "primitive" feeding control mechanism that is essential for the survival of newborn infants, allowing them to "communicate" with their mother at a time when their communication skills are at a very early stage of development. Once the human skills of learning and communication are acquired, plus the learned pattern of intake of food at regular mealtimes, the "primitive" feeding mechanism involving BAT becomes atrophied, as does the BAT itself. Thus, the function of BAT is not simply that of a furnace, to keep newborn infants warm. The function is, rather, to ensure that feeding occurs at regular intervals, matching energy needs for thermoregulation, for main-
Evidence Needed to Support the Thermoregulatory Feeding Hypothesis

For rats, it would be feasible, although technically difficult, to gather experimental evidence to support the occurrence of thermoregulatory feeding. This would need minute to minute recording of temperature at various internal locations (e.g., interscapular BAT, perirenal BAT, liver, brain, rectum), of substrates available in the blood (glucose, free fatty acids, lactate), of noradrenaline in the blood (a index of sympathetic nervous system activity), of feeding behavior (with an exact assessment of time of meal onset, time of meal termination and size of meal) and of neurotransmitter release in brain areas involved in thermoregulation and in feeding. All of this would need to be done throughout twenty-four hours, during both light and dark phases, in free-living rats adapted to a regular light-dark cycle.

An experimental approach feasible for gathering evidence for thermoregulatory feeding in a rat is obviously not appropriate for a free-living newborn infant being fed on demand. Some simple non-invasive measurements could be made. Minute to minute skin temperature changes at various locations could readily be measured continuously before, during and after feeding episodes. These locations should include those directly above BAT depots (nape of the neck, middle of the back) that have been demonstrated to maintain their temperature better than others during mild exposure to cold (41,42,46). Measurement of metabolic rate could be achieved before the onset of a feeding episode and correlated with changes in skin temperature, but obviously could not be achieved during the feeding episode itself. Information requiring more invasive procedures, such as collection of blood samples or recording of internal temperatures, could probably not readily be obtained for the healthy newborn infant born at term and undisturbed except for its internally driven spontaneous feeding episodes.

Implications of the Thermoregulatory Feeding Hypothesis for the Care and Nutrition of Newborn Infants

Does the thermoregulatory feeding hypothesis have any implications for the care and nutrition of newborn infants? In these days, when the healthy infant born at term is either born at home or discharged from hospital after only one day, the parents are very much on their own to care for it. New parents are usually ill-equipped to understand the virtually complete lack of circadian rhythms in their offspring or the degree of cold-exposure achieved if, lightly clothed, it is exposed to common room temperatures (22-26°C). The only discernible, and somewhat variable, rhythm that governs their baby’s behavior is the periodic burst of sympathetic activity that attempts to initiate a thermoregulatory feeding episode by inducing a bout of crying. Since the intake of food demanded by the physiological mechanism at these times is nutritionally essential, not only for thermoregulatory needs for also for maintenance and growth, it is clearly important that the physiologically-determined behavior of the baby govern the behavior of the caregiver, whether the mother who is breast feeding or either parent who is feeding formula. The current practice of “feeding-on-demand” is thus seen to be entirely in accord with the physiological needs of the baby, matching energy needs, determined to a large extent by the ambient temperature, to energy requirements. As the baby’s nervous system matures, circadian rhythms develop and become entrained by the daily events in the surroundings. The capacity for food ingestion in a single meal increases as the baby grows. As these events occur, the baby’s thermoregulatory needs at night become less, both because body temperature is regulated at a lower level and because the last meal was larger, so that the frequency of feeding at night diminishes spontaneously. Thus, on the one hand it is futile and frustrating for parents to attempt to train a newborn infant to take meals at convenient times before the appropriate physiological rhythms have matured. On the other hand, since a newborn infant realizes fairly rapidly that mealtimes and the attention they bring are enjoyable, and learns how to entrain its parents to its rhythms, parents need to realize in their turn that a normal circadian rhythm in body temperature does develop in the first few months and should be taken advantage of.

That a failure of the thermoregulatory feeding system might occur and result in a lack of the normal BAT-mediated signal for arousal and feeding, should be borne in mind in considering causes of neonatal cold-injury, of malnourishment, and of sudden infant death syndrome. Such a failure might occur, for example, due to exhaustion of available substrate after prolonged exposure to mild cold, or due to hypoglycemia for any reason, or...
due to chronic hypoxemia and consequent lack of sufficient oxygen for maximum thermogenesis.

Thermoregulation in the premature newborn has been very extensively studied and results of such studies have important implications for the care of premature or sick infants in incubators (7,16,40,44). The improved survival of premature infants housed in incubators at close to thermoneutrality was established in a series of studies some 30 to 40 years ago (40,45). It is not clear whether thermoregulatory feeding could occur under these conditions. In any case, such infants are usually fed on a fixed schedule. Cyclic oscillations every 2 to 3 hours in abdominal skin temperature have been observed in premature newborn infants housed in incubators (52). In the report of this study (52) the author questions whether the use of incubators might mask an underlying rhythm of physiological importance and goes on to ask whether incubators could be operated in a way that allows such temperature rhythms to occur and to permit "environmentally sensitive care that is contingent upon infant cues." The thermoregulatory feeding hypothesis suggests that detecting endogenous oscillations in temperature in premature infants housed in incubators and feeding these infants during the rising phase of the oscillations, and as frequently as these oscillations occur, might be more appropriate for their physiological needs than feeding on a fixed schedule.

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References

25. Himms-Hagen J. Role of brown adipose tissue thermogenesis in control of thermoregulatory feeding in rats: a new hypothesis that links thomostatic and glucostatic


