Maternal and environmental influences on thermoregulation in the neonate

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In precocious mammalian species such as man and sheep which do not benefit from the protection of a higher local environmental temperature due to huddling in a nest, the ability to alter metabolic rate in response to changes in ambient temperature at birth is a prerequisite for survival. A principal tissue involved in metabolic adaptation to the extra-uterine environment in both precocious and altricial species such as rodents is brown adipose tissue (BAT), which has the ability to rapidly generate large amounts of heat and also converts thyroxine to triiodothyronine (T_3), the dominant hormone regulating metabolic rate. Heat generation in BAT is a result of the electron transport chain becoming uncoupled from ATP synthesis, an effect mediated by a unique mitochondrial protein, uncoupling protein or thermogenin (see Cannon & Nedergaard, 1985).

In both infants and lambs BAT comprises 1–2% of birth weight (Merklin, 1974; Alexander & Bell, 1975) and is found predominantly in the axillary and perirenal region in infants and perirenal–abdominal area in sheep (Alexander, 1978). Infants, however, are rarely exposed to a cold environment and are completely dependent on non-shivering thermogenesis, whilst newborn lambs can generate appreciable amounts of heat from shivering as well as non-shivering thermogenesis (see Mellor & Cockburn, 1986). This contrasts with neonatal pigs which do not possess BAT and are entirely dependent on shivering thermogenesis to maintain heat production during cold exposure. In both infants and lambs, therefore, the amount and activity of BAT is likely to have a significant effect on thermoregulation. Over the first weeks of life in sheep (Gemmel *et al.* 1972) or months of life in man (Naeye, 1974) BAT is gradually replaced by white adipose tissue and as a result shivering rather than non-shivering thermogenesis is the principal response to cold exposure. An apparent failure to utilize BAT during neonatal development is associated with unexpected death (Naeye, 1974; Symonds *et al.* 1989) and may be an important factor contributing to the annual lamb mortality of 1–4 million in the British sheep industry (Slee, 1979).

FETAL BAT DEVELOPMENT

The thermogenic capacity of BAT, as measured from GDP-binding to thermogenin in mitochondrial preparations or the presence of mRNA for thermogenin, appears to remain low throughout gestation (Casteilla *et al.* 1987, 1989) and then peak at birth. Growth and development of BAT in the fetus can be divided into three distinct phases: (1) tissue growth as a result of hyperplasia and hypertrophy, (2) differentiation and the ability to generate T_3, (3) expression of thermogenin during late pregnancy and birth.

The multilocular cells which are characteristic of BAT first appear at mid-gestation in both human (Moragas & Toran, 1983), and sheep fetuses (Gemmel & Alexander, 1978). In the ovine fetus there then follows an increase in cell volume, tissue weight (see Vernon, 1986), lipid content (Alexander, 1978) and proliferation of mitochondria (Gemmel & Alexander, 1978) with the growth of perirenal adipose tissue being linear to

that of the whole body up to 120 d of gestation in *ad lib*.-fed ewes. The principal substrates for fatty acid synthesis at this stage of gestation are acetate, glucose and lactate (Vernon *et al.* 1981), although the in vivo contribution of these lipogenic substrates has yet to be determined. Between 120 d of gestation and term (147 d) the in vitro rates of fatty acid production from all these lipogenic substrates fall dramatically and the rate of lipid accumulation in BAT drops (Alexander, 1978) as an increasing proportion of acetate taken up by BAT is oxidized (Vernon *et al.* 1981). At this stage of pregnancy insulin treatment can stimulate the in vitro rate of glucose conversion to lipid in BAT (Fain *et al.* 1984).

Although only a small amount of BAT growth occurs in the last month of gestation in comparison with total growth of the ovine fetus, there are major morphological and enzymic changes within BAT cells which appear to be crucial with respect to the tissue's ability to generate heat. These include the development of sympathetic innervation (Gemmel & Alexander, 1978), a rise in the activity of 5'-monodeiodinase (*EC* 3.8.1.4; Wu *et al.* 1990) which converts thyroxine to T_3 and expression of genes for thermogenin and lipoprotein lipase (*EC* 3.1.1.34; Casteilla *et al.* 1989; Giralt *et al.* 1990). Ovine BAT appears to contain two distinct 5'-monodeiodinases (Wu *et al.* 1990), a type I which has a Michaelis constant (K_m) for T_4 and reverse T_3 in the micromolar range and type II with a K_m in the nanomolar range. Bovine fetal BAT only possesses the type I form of 5'-monodeiodinase and its activity rises after 150 d of gestation but then falls 2–3 weeks before birth (270 d of gestation). A decrease in type II 5'-monodeiodinase activity has also been observed immediately before birth in fetal rat BAT (Giralt *et al.* 1990) but not in sheep (Wu *et al.* 1990). This change in activity of 5'-monodeiodinase may be regulated by the sympathetic nervous system as observed in adult rats (Silva & Larson, 1983) with the local production of T_3 being essential for full expression of thermogenin (Bianco & Silva, 1987).

The induction of thermogenin gene expression in bovine fetal BAT commences at approximately day 200 of gestation and is associated with maximal activity of 5'-monodeiodinase (Casteilla *et al.* 1989; Giralt *et al.* 1989). It is not known if this effect is mediated via an increased rate of T_3 production within BAT because inhibition of 5'-monodeiodinase activity over the last 4 d of pregnancy in rat pups fails to prevent the first appearance of mRNA for thermogenin (Giralt *et al.* 1990). Other factors present *in utero* may, therefore, be responsible for thermogenin gene expression towards the end of pregnancy. This could include noradrenaline which regulates the overall thermogenic activity of BAT in adult rats (Mory *et al.* 1984) or insulin which is necessary for BAT retention in growing mice (Geloen & Trayhurn, 1990). Nerves are first seen in ovine fetal BAT at day 130 of gestation and their numbers increase towards term (Gemmel & Alexander, 1978) by which stage BAT is endowed with insulin receptors. Also the observation that BAT growth, in ovine fetuses, is stimulated following fetal hypophysectomy at 112 d of gestation (Stevens & Alexander, 1986) is indicative of a negative influence by the pituitary on BAT development. The possible role of the sympathetic nervous system and pancreatic or pituitary hormones on fetal BAT differentiation remains to be explored.

MATERNAL MANIPULATION OF BAT DEVELOPMENT

Maternal undernutrition of species where placental transport of fatty acids is low (i.e. sheep and rats) results in a decrease in BAT deposition, independent of effects on fetal

growth (Alexander, 1978; Higham *et al.* 1984). In sheep this response is likely to be caused by significant reductions in the rate of maternal supply of both glucose and acetate to the growing fetus (Lindsay & Ford, 1964; Leury *et al.* 1990). This effect can be exacerbated by a reduction in placental size (Mellor, 1983) or its ability to transport glucose (Leury *et al.* 1990) during maternal undernutrition. Diets low in protein, fed to pregnant rats, also decrease BAT weight and its thermogenic activity (Tyzbir, 1984).

Cold stress during late pregnancy stimulates the in vivo capacity for non-shivering thermogenesis in newborn lambs (Stott & Slee, 1985) and BAT deposition in neonatal rats (Hyvarinin *et al.* 1976). Chronic cold exposure, induced by winter-shearing twin-bearing pregnant ewes approximately 8 weeks prepartum, also improves lamb survival and lamb birth weight, independent of changes in maternal feed intake (Rutter *et al.* 1971; Symonds *et al.* 1986). This increase in lamb birth weight from shorn ewes is likely to be a consequence of elevated fetal plasma concentrations of glucose and insulin (Thompson *et al.* 1982), since maternal glucose entry-rate and plasma concentration of glucose are increased over the final 2–4 weeks of pregnancy (Symonds *et al.* 1988*a*,*b*). Glucose infusion directly into the fetus during this period has a greater stimulatory effect on BAT growth compared with that of the whole body (Stevens *et al.* 1990). BAT sampled from lambs born from shorn ewes possesses a 40% higher thermogenic activity and these lambs exhibit an 18% increased rate of oxygen consumption (per kg body-weight) over the first day of life compared with those born from unshorn ewes (Symonds *et al.* 1991). Consequently an increase in glucose supply to the late-gestation fetus in conjunction with a rise in fetal insulin levels appears to stimulate the growth of BAT *in utero* (Stevens *et al.* 1990) and its thermogenic activity postnatally (Symonds *et al.* 1991).

METABOLIC ADAPTATION AT BIRTH

Premature delivery of lambs is associated with an apparent failure to generate heat via non-shivering thermogenesis (Alexander *et al.* 1972) similar to that observed following chemical sympathectomy of the fetus (Alexander & Stevens, 1980). This is indicative of BAT not being functional, despite appearing normal histologically. A similar situation appears to pertain in human infants as the rise in heat production during cold exposure is lower in premature deliveries compared with term babies (Heim, 1981). Some premature infants even lose their ability to respond to moderate cold exposure over the first week of life (Hey & Katz, 1969).

The fetus is unable to generate heat via non-shivering thermogenesis in BAT *in utero*, and it has been proposed that the onset of thermogenesis is limited by a placental factor because thermogenesis rises after cord-clamping (see Power, 1989). One putative candidate for this role is adenosine for which the plasma concentration falls dramatically following cord-clamping (Sawa *et al.* 1991). The interpretations of these experiments, however, must be made with caution because direct measurements of the thermogenic capacity of BAT were not made. There is a two–fivefold increase in the levels of mRNA for thermogenin within hours of birth in calves (Casteilla *et al.* 1989) and rats (Giralt *et al.* 1990). In rat pups this increase in thermogenin mRNA is a result of exposure to cold environment after birth and is dependent on 5′-monodeiodinase activity (Giralt *et al.* 1990). The ability of BAT to synthesize large amounts of mRNA following parturition may, therefore, be regulated by the sympathetic nervous system.
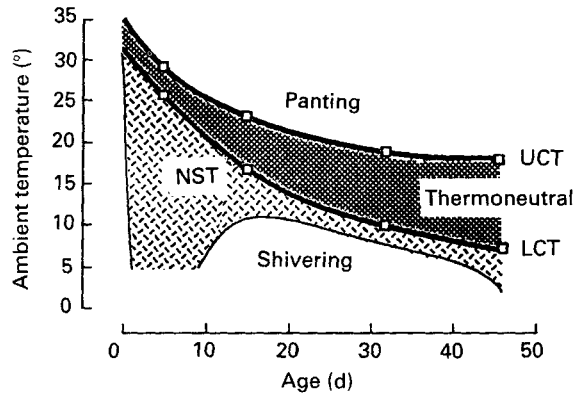
Fig. 1. Metabolic adaptation over the first 45 d of life in the neonatal lamb. UCT, upper critical temperature, i.e. occurrence of panting; LCT, lower critical temperature, i.e. significant rise in oxygen consumption or the ocurrence of shivering, or both; NST, non-shivering thermogenesis. Adapted from Symonds *et al.* (1989).

Irrespective of the adaptations to birth which initiate the onset of non-shivering thermogenesis in BAT there appears to be a gradual increase in its activity over the first days of neonatal life in human infants. The metabolic response to cold exposure or to noradrenaline infusion rises over the first few hours (Smales & Kime, 1978) and days of life (Hill & Rahimtulla, 1965; Karlberg *et al.* 1965), in both small and normal-weight infants (Hey, 1969). A gradual increase in the thermogenic activity of BAT could explain why in a newborn baby rectal temperature falls by 2° following exposure to an ambient temperature of 23° for 30 min within 1 h of birth, but only by 0·5° by 3 h post partum (Rylander, 1972). It has yet to be determined how a change in activity of BAT at birth can affect the longer-term control of thermoregulation in developing infants.

THERMOREGULATORY DEVELOPMENT AND ITS MANIPULATION BY THE ENVIRONMENTAL TEMPERATURE

Over the first 45 d of life in the lamb there is a widening of the thermoneutral zone as the neonate adjusts to the extrauterine environment which is summarized in Fig. 1. (Symonds *et al.* 1989). This metabolic adaptation is associated with a decrease in the plasma concentration of T_3 but not thyroxine (Symonds *et al.* 1989) and occurs as BAT is converted to white adipose tissue (Gemmel *et al.* 1972). The rate at which BAT is depleted can be delayed by hyperthyroidism (Alexander *et al.* 1970) and by rearing at cold ambient temperatures in both young ruminants (Gemmel *et al.* 1972; Casteilla *et al.* 1989; Darby *et al.* 1992) and rat pups (Mouroux *et al.* 1990). The net effect of this environmental manipulation is for BAT to retain a higher thermogenic activity and delay the onset of shivering thermogenesis (see Table 1). Environmental temperature is also important in human infants because warm rearing (abdominal skin temperature maintained at 36·5°) between 1 and 3 weeks of life results in a decreased metabolic response to cold (28°), suggesting a loss of thermogenic activity in BAT (Glass *et al.* 1968). These responses are dependent on adequate nutrition and growth of the infant because the rate of lipid depletion in BAT is accelerated in malnourished sick infants

Table 1. *Effect of warm (25°) or cold (15°) rearing on the thermogenic capacity of brown adipose tissue (BAT) on days 7–9 of life in neonatal lambs*

(Mean values with their standard errors)

| | Perirenal adipose tissue wt (g) | | Mitochondrial protein (mg) | | GDP binding (pmol/mg protein) | | V_{O_2} (ml/min per kg W) | | | | No. of lambs shivering |
| | | | | | | | 26° | | 12° | | |
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	
Warm-reared (n 8)	24·0*	3·3	422	50	123**	21	14·4*	0·7	19·7	1·9	7
Cold-reared (n 8)	16·5	2·3	441	78	189	31	16·8	1·0	20·4	1·0	3

V_{O_2}, oxygen consumption; W, body-weight.
Mean values were significantly different from those for cold-reared animals: *$P<0.05$; **$P<0.01$.

born prematurely at 34 weeks of gestational age and nursed at room temperature of 22–27° in comparison with a group born after 30 weeks of gestation and nursed in an incubator at 34–35° (Heim *et al.* 1968).

During neonatal development there is an important link between T_3 and non-shivering thermogenesis via BAT, because lambs of normal birth weight with a low plasma concentration of T_3 (0·34–1·73 nM) respond to acute cold exposure (2–3 h at 5–10°) by shivering whilst other lambs with high plasma levels of T_3 (2·06–3·69 nM) exhibit non-shivering thermogenesis (Symonds *et al.* 1989). Lambs with low T_3 levels can become hypothermic and subsequently die, an effect which is more pronounced in lambs born prematurely (Cabello, 1983). An impairment in the thermogenic capacity of BAT in conjunction with an inability to generate T_3 could be linked to the absence of a single major gene which enables BAT to respond to noradrenaline despite BAT being normal in its histological appearance (Slee & Simpson, 1991). The ability of BAT to produce T_3 is essential in maintaining its normal thermogenic response (Bianco & Silva, 1987) and at the same time BAT can contribute 30–60% of total T_3 production in cold-exposed rats (Fernandez *et al.* 1987). This is more than equal to the contribution of peripheral tissues to whole-body production rate of T_3 in neonatal lambs (Klein *et al.* 1980) which includes that of the liver (Polk *et al.* 1986). Successful metabolic adaptation by the neonate following birth, therefore, appears to be linked to normal BAT function in conjunction with the maintenance of elevated T_3 levels.

The function of BAT in neonatal thermoregulation may be implicated in the control of breathing. Over the period in which BAT is replaced by white adipose tissue, minimal metabolic rate decreases in conjunction with a fall in breathing frequency in the lamb (Andrews *et al.* 1991a). Exposure of infants and lambs to warm ambient conditions close to the upper limit of thermoneutrality can cause irregular breathing and prolonged apnoeas (Adams *et al.* 1964; Daily *et al.* 1969; Andrews *et al.* 1991b). Impaired BAT activity and exposure to warm ambient temperatures in conjunction with a high degree of thermal insulation may explain why the latter environmental conditions are associated with sudden infant death syndrome (SIDS; Fleming *et al.* 1990). This contrasts with the

observation that BAT depletion is significantly delayed in SIDS victims (Naeye, 1974). It is not known if this is caused by either a failure of BAT to respond to thermogenic stimulae as recorded in neonatal lambs (Slee & Simpson, 1991) or of an increased stimulation of BAT activity in association with chronic hypoxaemia (Naeye, 1980).

In conclusion, the evidence cited clearly shows that BAT plays a critical role in neonatal thermoregulation in infants, ruminants and rodents. Research into mechanisms regulating fetal and neonatal BAT development in these species is likely to provide opportunities for improving neonatal survival and viability, despite the diverse conditions in which they are reared.

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