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Thermochimica Acta 250 (1995) 305–318

thermochimica acta

From whole body to molecule: an integrated approach to the regulation of metabolism and growth ☆

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Received 11 June 1994; accepted 8 July 1994

Abstract

This paper considers the use of whole-body calorimetry in a wide context, as one of a range of techniques available for advancing our knowledge of the regulation of energy metabolism and growth. This integrated approach should lead to a greater depth of understanding by investigating the mechanisms by which responses of the whole animal depend on events at the tissue, cellular and molecular levels.

Two critical stages of mammalian development, the perinatal and early postnatal periods, are discussed. Particular attention is paid to skeletal muscle and the extent to which myofibre differentiation and hypertrophy, and hence muscle function and energetic efficiency, can be modified by nutrition and the thermal environment. In view of the crucial roles of thyroid hormones, growth hormone and insulin-like growth factor-I in regulation of metabolism and growth, the role of the endocrine system is also considered. These studies have important implications for survival and optimal health of humans and other animals.

Keywords: Calorimetry; Growth; Metabolism; Whole-body calorimetry

☆ Presented at the Ninth Conference of the International Society for Biological Calorimetry, Berlin-Schmerwitz, 27–31 May 1994, and dedicated to Ingolf Lamprecht on the occasion of his 60th birthday.

SSDI 0040-6031(94)01967-3

1. Introduction

The relation between food intake, energy expenditure and growth is encapsulated in the first law of thermodynamics, namely that energy is conserved

$$\text{Energy}_{\text{intake}} = \text{Energy}_{\text{output}} + \text{Energy}_{\text{stored}}$$

Thus the energy stored, which includes growth, is clearly dependent on the level of energy intake, as food, and energy output, as metabolic rate. The entire field of energy metabolism in mammals has been assessed comprehensively in a number of publications [1–3], while the application of whole-body calorimetry to studies of energy exchange in man and animals has also been reviewed recently [4]. In the latter review, particular attention was paid to the relative merits of direct and indirect calorimetry, problems associated with inappropriate methodology, and the modifying effects of nutrition, thermal environment and physical activity on energy expenditure. Energy can be stored not only as tissue growth but also heat, high energy bonds and ion gradients. In growing infants, it has been speculated that the 7% greater heat production (indirect calorimetry) compared with heat loss (direct calorimetry) could be due in part to the energy cost of growth, because energy needed to form high energy bonds and osmotic gradients requires the oxidation of food energy and is not released as heat [5].

The pioneering studies of McCance, Widdowson and their co-workers established the principle of critical periods of development, and related developmental physiology and nutrition to later consequences [6]. More recent studies have clearly identified the fetal and early postnatal periods as particularly critical stages during which the long-term development of the individual can be affected; thus, retardation of growth during these periods is closely linked to the development of adult degenerative disease [7,8]. Skeletal muscle is essential for a wide range of functions, including thermogenesis, breathing, locomotion and maintenance of posture. Defects in normal muscle development during the perinatal period could impair any of these functions and may also have important long-term consequences for the individual. For example, increased energetic efficiency and reduced motor activity in early life could result in an increased risk of obesity and impaired mental development [9,10].

The endocrine system plays a central role in the control of metabolism and growth, and particularly important in this respect are thyroid hormones (TH), growth hormone (GH) and insulin-like growth factor-I (IGF-I) [11–15]. The aim of this paper is to consider work we have carried out on the regulation of thermogenesis and growth in the fetal and early postnatal periods, with particular emphasis on muscle development, and the roles of nutrition, thermal environment and endocrine status.

2. Perinatal development

Many investigations using direct and indirect calorimetry have revealed the importance of nutrition in determining resting metabolic rate (RMR) throughout

postnatal life [4]. For example, in adult human subjects, there is a clear positive relation between energy intake and energy expenditure, even after only one day of altered food intake [16]. More recently, we have investigated the role of low birth-weight and perinatal undernutrition in modifying thermogenesis and growth, and our studies on the relation between perinatal thyroid status and development have highlighted a major role for TH in the control of neonatal metabolism and growth at the whole body, tissue and mitochondrial levels.

2.1. Low birth-weight

An infant may be born with a low birth-weight because of a shortened period of gestation and/or retarded growth in utero. By one year of age, infants born small-for-gestational age (SGA) remain smaller and lighter than individuals born at term with a weight appropriate-for-gestational age (AGA) [17]. The young pig makes an excellent model for human growth, development and metabolism; the two species having a similar critical temperature, zone of thermal neutrality and a relatively sparse external insulation [18]. Furthermore, the SGA piglet provides a naturally occurring form of intrauterine growth retardation which is ideal as a model for investigating the influence of prenatal undernutrition on subsequent development. Its birth-weight of approximately 0.7 kg is only about half that of its control littermates, and factors such as reduced placental blood supply and position in the uterine horn all reflect the altered availability of nutrients to the developing young, while local tissue hypoxia may also be important. The capacity for growth is impaired in SGA piglets, with circulating IGF-I levels at birth being approximately 30% lower than in AGA controls (Fig. 1) [19]. Furthermore, by 2 weeks of

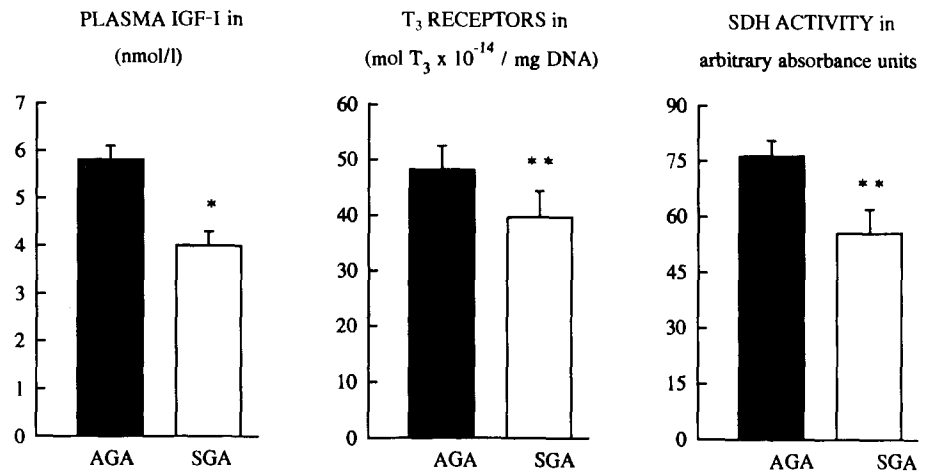

Fig. 1. Comparison between appropriate-for-gestational age (AGA) and small-for-gestational age (SGA) new-born piglets, weighing approximately 1.4 and 0.7 kg respectively. Mean values ± SEM are given for plasma concentrations of insulin-like growth factor-I (IGF-I), nuclear 3,5,3′-triiodothyronine (T_3) receptors in skeletal muscle, and succinate dehydrogenase (SDH) activity in muscle. Statistical analysis: **, $P < 0.01$; *, $P < 0.05$. See Refs. [19], [27] and [21] respectively, for details.

age, if food has been provided ad libitum, SGA animals still have lower plasma and hepatic levels of IGF-I than do controls [20].

At birth, SGA piglets have a lower rate of resting metabolism (when expressed as heat production in J $kg^{-0.67}$) than control AGA animals, at environmental temperatures both within and below the zone of thermal neutrality [21]. When expressed as J kg^{-1}, values in the two groups are similar, because of the smaller size of the SGA animals. However, whichever method of expressing the metabolic rate is used, the results lead to the same conclusion with respect to the maintenance of homeothermy: the smaller SGA animals have a larger surface area to body weight ratio, lose heat faster and have a progressively lower deep body temperature, than the larger AGA animals [21]. Findings in the human infant concur with those in piglets, because although SGA neonates have slightly higher metabolic rates per kg body weight than AGA infants, their lower body temperatures in a cool environment indicate that the increase in metabolic rate is not enough to account for their greater heat loss [22,23].

During postnatal life, animals on a low food intake or with a high metabolic demand have fewer nuclear 3,5,3′-triidothyronine (T_3) receptors in muscle than animals on a high energy intake or with a low metabolic demand [24–26]. The finding of fewer nuclear T_3 receptors in SGA compared with AGA littermates (Fig. 1) [27] suggests that SGA animals are responding to undernutrition in utero in a manner similar to that induced by postnatal undernutrition. A reduction in T_3 receptors probably reduces the response of the individual to TH and hence limits metabolic capacity. These effects of TH could be mediated in part via changes in respiratory enzymes and the lipid composition of the inner mitochondrial membrane [11,28]. At thermal neutrality, RMR is determined in part by the efficiency of substrate oxidation and ADP phosphorylation, and the increased proton motive force of hepatic mitochondria from hypothyroid rats [29] suggests that at least part of the reduced RMR associated with low thyroid status stems from an alteration in mitochondrial heat production.

The reduced metabolic response of SGA animals to the cold must be related to a reduced intensity of shivering, because new-born pigs have no detectable brown adipose tissue [30] and no significant metabolic response to noradrenaline [31]. Lower respiratory enzyme activities in skeletal muscle of new-born SGAs would be a limiting factor in this respect, and we have found the activities of three key respiratory enzymes in skeletal muscle, succinate dehyrogenase, NADH diaphorase and cytochrome oxidase, to be significantly reduced in SGA compared with AGA neonates (Fig. 1) [21]. This seems to be a specific effect on skeletal muscle, because no difference is observed in either heart or diaphragm. In new-born SGA individuals, it seems likely that both the retarded growth and reduction in metabolic capacity stem from the same cause. Undernutrition is likely to be a major factor but the precise mechanism now needs to be established.

2.2. Roles of thyroid and growth hormones

2.2.1. Fetal hypothyroidism

To determine the precise role of TH in the early postnatal regulation of thermogenesis and growth, experimental models with altered thyroid status in the perinatal

period are required. In collaboration with colleagues in France, we have studied the effects of fetal hypothyroidism induced by feeding the sow a high glucosinolate diet during gestation [32–34]. After glucosinolates are metabolized by the sow, their derivatives cross the placenta and depress fetal synthesis of TH, and by late gestation, these piglets have an enlarged thyroid gland, lower plasma TH levels and lower hepatic 5′-deiodinase activity than euthyroid controls. At birth, the hypothyroid piglets have a reduction in summit metabolism and impaired thermostability, in that deep body temperature in a cold environment is lower than in controls [32]. This impaired thermogenic function of hypothyroid compared with control piglets at birth can be explained in part by a reduction in oxidative capacities of liver and rhomboideus muscle, assessed from cytochrome oxidase activity [33,34].

The ontogeny of GH receptors represents a critical stage in the regulation of growth and metabolism, and GH binding to hepatic receptors is regulated post-natally by both GH itself and TH [14,35,36]. We have recently investigated the perinatal ontogeny of hepatic and muscle GH receptor gene expression in fetal and neonatal pigs and assessed the role of TH in this process [37]. There was a striking tissue-specific effect of TH on the control of GH receptor gene expression: hypothyroidism resulted in a down-regulation in liver GH receptor and an equally marked up-regulation in skeletal muscle (Fig. 2), and these differences may have been related to differences in the abundance of nuclear T_3 receptors in the two tissues [38]. Our results also indicated a marked difference in the normal ontogeny of GHR in liver and muscle (Fig. 2): hepatic expression is initiated very late in gestation, whereas in muscle it occurs much earlier, suggesting different roles for GH in the two tissues. Assuming a direct correlation between mRNA levels and protein, the high muscle gene expression of GH receptor as early as 80 days' gestation, together with high plasma GH levels, suggests an important role for GH in controlling differentiation, hypertrophy and metabolism of muscle at this critical stage of development.

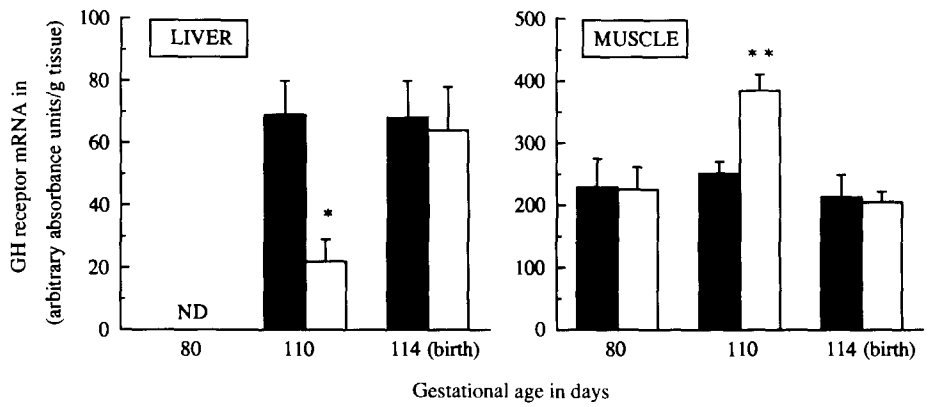

Fig. 2. Late prenatal ontogeny of growth hormone (GH) receptor mRNA expression in liver and skeletal muscle from control (shaded bars) and hypothyroid (open bars) piglets during the last 5 weeks of gestation. Statistical analysis: **, $P < 0.01$; *, $P < 0.05$. See Refs. [32,33,37] for details.

2.2.2. Postnatal hypothyroidism

A 50% reduction in energy intake causes a similar reduction in plasma TH levels [11] and we have recently investigated the extent to which this change in thyroid status affects cellular development of several tissues including muscle [39] and small intestine [40]. Thyroid hormones are one of the major endocrine influences on the concentration of Na^+,K^+-ATPase/Na^+,K^+-pump in skeletal muscle [41], with hypothyroidism inducing a marked down-regulation in pump numbers (Fig. 3). This plasma membrane-bound ATPase plays an essential role in regulation of Na^+,K^+-homeostasis, and skeletal muscle contains a major proportion of the Na^+,K^+-pumps in the body. The pump may also make a small but significant contribution to resting metabolic rate, although its precise role in regulatory thermogenesis remains to be established [42].

Oral administration of methimazole and iopanoic acid to piglets during the first 2 weeks of life was used to induce a reduction in plasma TH concentration similar to that caused by a low food intake [39]. These substances block TH synthesis by the thyroid gland and peripheral conversion of thyroxine (T_4) to T_3, respectively, and the treatment resulted in a 50% reduction in plasma TH levels. Otherwise these animals were healthy and had a good appetite. Euthyroid controls were pair-fed the intake of their hypothyroid littermates and at 14 days, animals were killed humanely for tissue sampling. In the hypothyroid group, there was a significant 15% reduction in Na^+,K^+-pump concentration of both the slow-twitch soleus and fast-twitch longissimus dorsi muscles [43]. This down-regulation of the pump would have two important consequences: impaired fatigue-resistance of muscle, with an associated slowness of movement, and a reduction in the quantity of ATP hy-

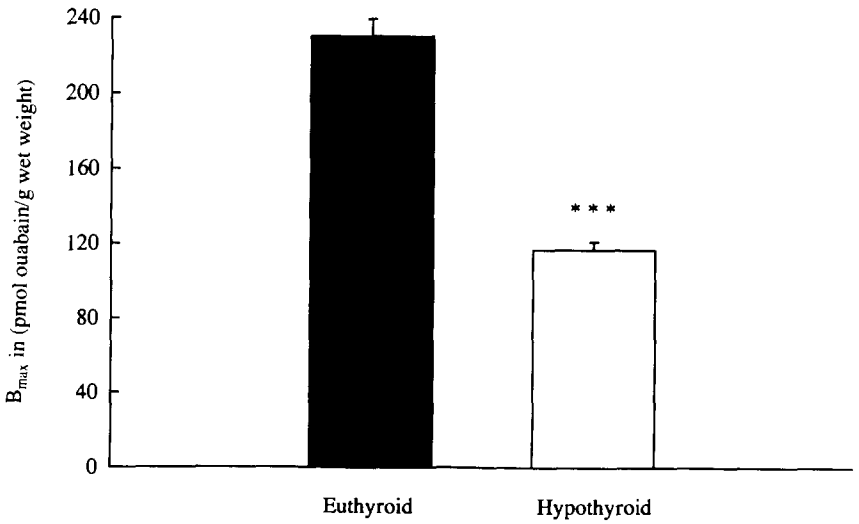

Fig. 3. Concentration of Na^+,K^+-ATPase, estimated from maximal ^3H-ouabain binding capacity (B_{max}) in skeletal muscle from euthyroid control and hypothyroid pigs aged 8 weeks and provided with the same level of food intake. Statistical analysis: ***, $P < 0.001$. See Refs. [56,68] for details of methods.

drolysed to maintain Na^+,K^+-homeostasis per unit time, resulting in improved energetic efficiency. Both factors would be of considerable importance, not only in individuals with mild hypothyroidism but also in children suffering from undernutrition.

3. Early postnatal development

3.1. Role of energy status: interaction between nutrition and temperature

In homeotherms, the energy available for growth will be determined not only by energy intake and the requirements of maintenance, but also by the energy demands of regulatory thermogenesis. Nutrition and thermal environment thus have marked influences on whole body energy expenditure and growth, and we have investigated interactions between these two variables and developed models in the young pig which allow their actions to be assessed at the levels of whole body, tissue, cell and molecule [44]. Fig. 4 shows RMR, at a series of test temperatures, of littermates which had been living at a warm or cold temperature on a high or low level of energy intake. RMR is affected by both temperature and diet, with the effect of food being more pronounced at a cold than a warm temperature [45]. Thermostability is also altered: animals in the cold maintain higher peripheral temperatures at a given test temperature, while those in the cold on a low food intake maintain a deep body temperature which is several degrees lower than littermates in the

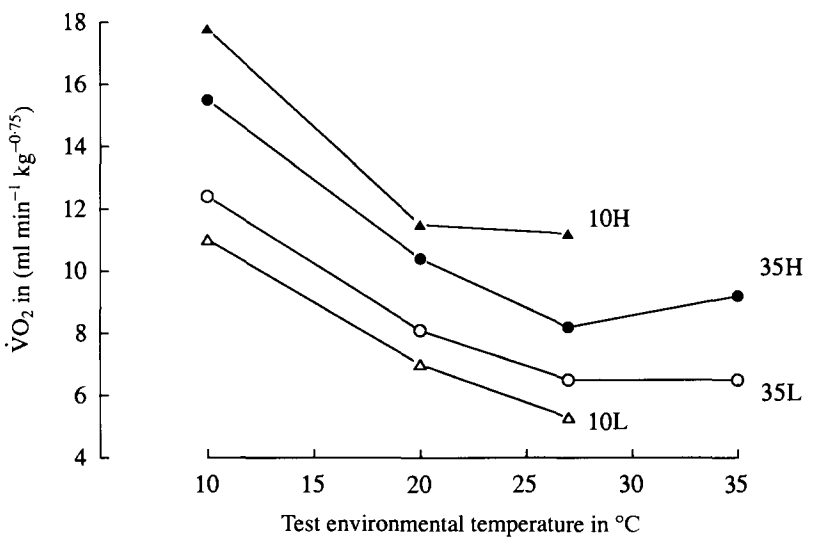

Fig. 4. Resting oxygen consumption ($\dot{V}O_2$) measured 22–24 h after the last meal, at a series of test temperatures, in 8-week-old pigs which had been living at 35 or 10°C on a high (H) or low (L) energy intake (where H = 2L). Statistical analysis: H vs. L, $P < 0.001$ at all test temperatures; 35 vs. 10, not significant. See Ref. [45] for details.

warm or on a high energy intake [45]. The increased peripheral temperatures probably act to prevent tissue damage, at the expense of additional expenditure of energy, while the lower core temperature acts to conserve energy when intake is low and demand is high.

The interaction between energy intake and energy expenditure in determining energy status, and hence growth rate, is clearly demonstrated in littermate pigs which have been living at thermal neutrality (26°C) or in a cool environment (10°C), on a high (H) or low (L) food intake (where H = 2L). At 7 weeks of age, after 3–4 weeks of treatment, body weights (kg; mean ± SEM; $n = 6$ per treatment group) are 26H = 12.5 ± 0.3, 26L = 8.7 ± 0.6, 10H = 9.8 ± 0.3, and 10L = 6.3 ± 0.4. At the extremes, a high intake and low thermoregulatory demand thus result in animals with a body weight approximately twice that of littermates with low intake and high energy expenditure. There are no clear-cut differences in plasma concentrations of GH, because values tend to be high both at a warm temperature and on a low food intake [46]. Instead, the modifying effects of diet and thermal environment on growth are probably mediated in part by marked differences in circulating and tissue levels of IGF-I and its binding proteins, the values of which are altered in animals with low energy status [47–49]. These reductions in plasma and hepatic levels of IGF-I could be mediated by differences in GH action on the liver, the major site for synthesis of endocrine IGF-I, because low energy status causes a marked reduction in specific binding of GH by hepatic membranes [14] and in the mRNA of the hepatic GH receptor [50–52].

By contrast with these effects on liver, we have recently found that expression of the GH receptor gene in skeletal muscle shows a marked up-regulation under conditions where energy availability for growth is limited because of either a reduced intake or an increased themoregulatory demand (Fig. 5) [51,52]. This

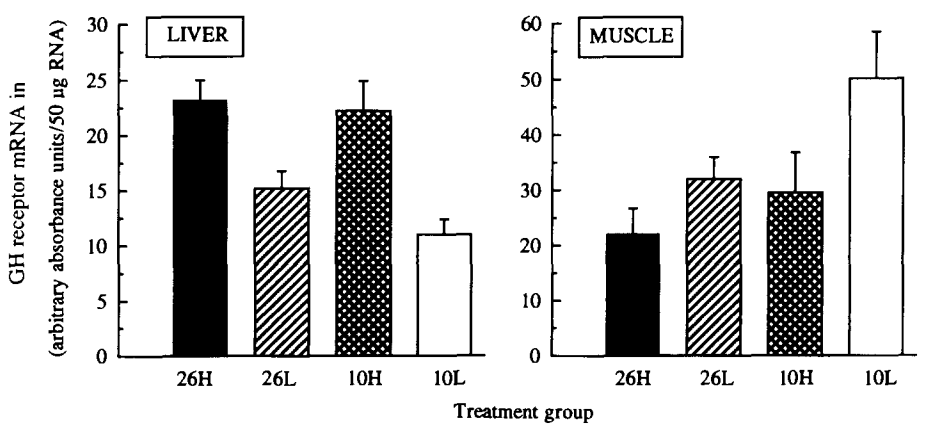

Fig. 5. Growth hormone (GH) receptor mRNA expression in liver and skeletal muscle from 7-week-old pigs which had been living at 26 or 10°C on a high (H) or low (L) energy intake (H = 2L). Statistical analysis: (i) liver: H vs. L, $P < 0.001$; 26 vs. 10, not significant; (ii) muscle: H vs. L, $P < 0.02$; 26 vs. 10, $P < 0.04$. See Ref. [51] for details.

emphasizes the key metabolic role of GH in conditions where energy status is poor [14]. An increase in GH receptor in muscle could be important in increasing fatty acid oxidation while limiting glucose utilization, via the lipolytic and diabetogenic actions of GH. Furthermore, an increase in muscle GH receptors may also play a role in increasing the proportion of slow-twitch oxidative fibres in muscle [53].

Energy intake has a marked effect on circulating TH levels and there is a clear positive relation between the two variables [11,54]. By contrast, in the long term there is no such effect of temperature: TH levels remain elevated in a cold environment only if the subjects eat ad libitum; when food intake is restricted to that of controls at thermal neutrality, the high TH levels are not maintained [11,44,55]. Nuclear TH receptors are also down-regulated both in the cold and on a low food intake [24]. This suggests a mechanism for conservation of fuel supplies, by limiting the metabolic responsiveness of the individual to TH, when energy is restricted.

By contrast with the effect of temperature on TH, a low environmental temperature induces an up-regulation of the Na^+,K^+-pump in muscle [56,57], which could be driven in part by the increased muscular activity associated with shivering. This increase in pump concentration may play a small but important role in non-shivering thermogenesis in animals at a low temperature with a restricted supply of energy. The proportion of oxidative fibres and the activities of key respiratory enzymes are also elevated in muscle of young animals living in a cold environment [58]. The effect on respiratory enzymes, and hence on mitochondrial density, is observed not only in longissimus dorsi muscle but also in muscle from the diaphragm [59], suggesting that these changes are not due entirely to differences in muscular activity associated with shivering. Furthermore, differences in growth rate and hence in myofibre size do not explain these results entirely, and the possibility is that changes in thyroid status induced by nutrition and environment could be important in modulating the functional and morphological development of muscle.

3.2. Myofibre differentiation and hypertrophy

We have recently used enzyme histochemistry, immunocytochemistry and gel electrophoresis to evaluate more completely the extent to which nutrition and environment can influence the contractile (slow/fast) and metabolic (oxidative/glycolytic) properties of skeletal muscles with widely different morphological and functional characteristics, in young growing animals [60,61; A.P. Harrison, A.M. Rowlerson and M.J. Dauncey, unpublished]. In adult human subjects, there is a selective reduction in the size of fast-twitch fibres during undernutrition, whereas in slow-twitch fibres there is a better preservation of size. This would be energetically advantageous because the energy expenditure per unit tension developed is lower in slow- than in fast-twitch fibres [62,63]. However, we have found that during growth, such a mechanism does not appear to operate: all fibres tend to be smaller in young pigs on a low compared with a high energy diet. By contrast, there are striking effects on fibre type distribution in specific muscles. Fig. 6 shows that in the interscapular "red" rhomboideus muscle, a low energy intake results in a greater

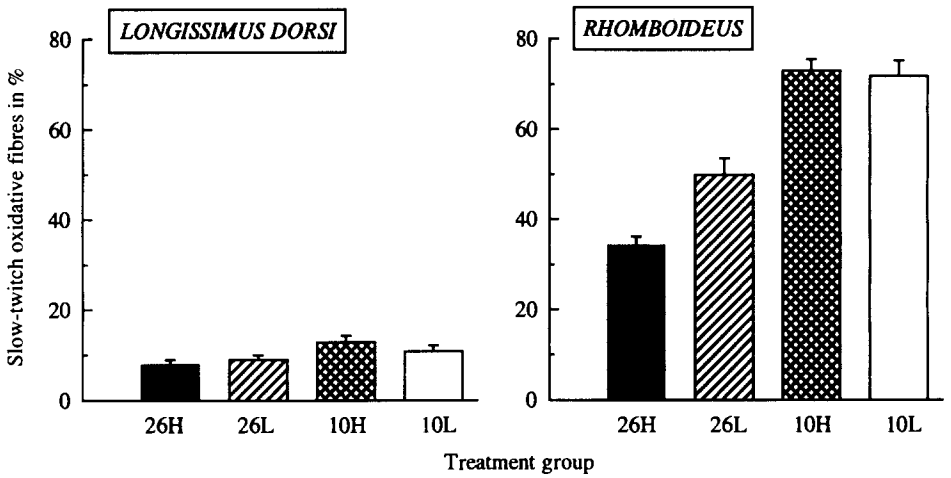

Fig. 6. Proportion of type I slow-twitch oxidative fibres from two different skeletal muscles of 7-week-old pigs which had been living at 26 or 10°C on a high (H) or low (L) energy intake (H = 2L). Statistical analysis: (i) longissimus dorsi: H vs. L, not significant; 26 vs. 10, $P < 0.05$; (ii) rhomboideus: 26H vs. 26L, $P < 0.005$; 26 vs. 10, $P < 0.001$. See Refs. [60,61] for details.

proportion of type I slow-twitch oxidative fibres and fewer type II fast-twitch oxidative/glycolytic fibres, whereas there is no such effect on the lumbar "white" longissimus dorsi muscle or the postural "red" soleus muscle [60]. From this study we concluded that, by contrast with adult life, energy restriction in the early postnatal period does not result in selective preservation of fibre area but can significantly influence the differentiation of myofibres. The changes in rhomboideus muscle would improve the energetic efficiency of contraction on a reduced food intake.

Furthermore, a low ambient temperature resulted in a slight but significant increase in the proportion of slow-twitch oxidative fibres in longissimus dorsi muscle, but a very marked increase in slow-twitch fibres in rhomboideus muscle (Fig. 6) [61]. Two dominant regulators of muscle differentiation are thyroid status and contractile activity. Thyroid hormones enhance the conversion of slow- to fast-twitch myofibres [64], and the reduced thyroid activity of animals on a low food intake could therefore be particularly important in determining the increased proportion of slow-twitch fibres in rhomboideus. Both endurance training and long-term electrical stimulation enhance the conversion from fast- to slow-twitch myosin isoforms [65,66]. Shivering can be compared, to some extent, to these activities and the possibility is that at a low temperature, the effects of sustained contractile activity associated with shivering could play an important role in increasing the proportion of slow-twitch fibres. These changes in myofibre differentiation will tend to conserve energy in animals on a low food intake, because slow-twitch fibres have a greater contractile efficiency than fast-twitch fibres. They will also facilitate the prolonged low frequency contraction of shivering, which is

required for regulatory thermogenesis at a low environmental temperature. The rhomboideus muscle is located in the interscapular region, close to the temperature-sensitive neurones of the spinal cord. It is thus in the same region as a major depot of brown adipose tissue in small rodents and the new-born of some species. Our findings, together with those in animals fed ad libitum [67] lend strong support to the hypothesis that rhomboideus muscle plays a key role in thermoregulation, particularly in those individuals which do not rely on brown adipose tissue for regulatory thermogenesis.

4. Concluding remarks

These studies have highlighted the role of whole-body calorimetry as one of the many techniques available for investigating the underlying mechanisms which regulate metabolism and growth. Our results suggest that the perinatal and early postnatal periods are particularly critical stages for development of muscle, and that nutritional, thermal and endocrine environment can markedly affect its functional ability. The extent to which these environmental factors can alter long-term development of muscle, including its thermogenic, postural, respiratory and cardiac functions, now needs to be investigated.

Acknowledgements

I acknowledge the excellent and enthusiatic collaboration of the many colleagues who have taken part in these studies; their names are mentioned throughout the list of references. I should also like to thank Prof. Dr. I. Lamprecht, Dr. R.B. Kemp, and the Organizing Committee of the International Society for Biological Calorimetry for giving me the opportunity of presenting this paper at the 9th ISBC Conference, Berlin-Schmerwitz, Germany.

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