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Invited commentary

The influence of undernutrition on skeletal muscle development

The work described in the present issue of the *British Journal of Nutrition* by Bayol *et al.* (2004) adds to the body of evidence indicating that undernutrition during critical stages of pregnancy alters skeletal muscle development in a variety of species. But why does this matter? Maternal undernutrition has been shown to result in a reduction in the numbers of muscle fibres of offspring, which in most mammalian species (except rodents) is fixed at the time of birth (see Brameld *et al.* 2003). Hence, the number of fibres in any particular muscle does not change during postnatal life: they simply get bigger (hypertrophy). Does the number of muscle fibres matter? Studies in a variety of species have indicated that high muscle fibre number is associated with increased growth rates and decreased amounts of adipose tissue. Thus, from an agriculture point of view, high muscle fibre number is desirable since the animals will tend to reach market weight quicker, but will also produce a more desirable carcass quality (increased lean and decreased fat). However, the human health implications may be even more important.

Skeletal muscle plays a central role in whole-body energy metabolism (see Helge *et al.* 1999). It is estimated to account for 20 % total energy expenditure in man, stores substantially more glucose (in the form of glycogen) than the liver and is the major tissue of insulin-stimulated glucose uptake. Skeletal muscle also utilises substantial amounts of fatty acids for energy and contains significant triacylglycerol stores. It is therefore possible that changes in the numbers and/or types of fibres present in a skeletal muscle may contribute to the risk of developing type 2 diabetes (insulin resistance) and/or obesity (excess adipose tissue) in later life. This obviously relates to the Barker hypothesis and so-called fetal (or nutritional) programming of adult disease.

Although Bayol *et al.* (2004) found no effect of maternal undernutrition on numbers of fibres in the semitendinosus muscle, the reduction in the number of nuclei in the 40 % undernutrition group does indicate a reduction in muscle cell proliferation. The gene expression studies have investigated the lightest- and heaviest-birth-weight pups and demonstrated differences in the gastrocnemius. The lightest pup in a litter will have experienced greater undernutrition than the heaviest pup, and therefore it would have been interesting to see the muscle fibre number and nuclei content results split similarly for both muscles studied.

Earlier, I stated that rodents were the exception among mammals in that the number of fibres in a muscle can be affected to some extent after birth. Wilson *et al.* (1988) demonstrated that restoration of normal nutrition during the suckling period in rats was able to overcome the reduction in number of fibres induced by undernutrition during pregnancy in the lumbrical muscle, but not in soleus muscle. Hence muscles develop at different times, with the number of fibres in some rat muscles (e.g. soleus) being fixed at the time of birth, whereas in other muscles this occurs between birth and weaning. This begs the question of whether the muscles studied by Bayol *et al.* (semitendinosus and gastrocnemius) are still developing during suckling. Since the mothers were re-fed to control levels after birth, this could account for the lack of effect on numbers of fibres in the semitendinosus and some of the effects on gene expression observed.

We have conducted a number of studies investigating changes in gene expression during differentiation of fetal sheep myoblasts, both *in vitro* (Brameld *et al.* 1999) and *in vivo* (Fahey *et al.* 2003). These studies indicate that expression of insulin-like growth factor (IGF)-II increases at the same time as increases in myogenin expression (*in vivo*; Fahey *et al.* 2003) and creatine kinase activity (*in vitro*; Brameld *et al.* 1999). Myogenin is a transcription factor that plays a major role in inducing expression of all the muscle specific proteins and is thought to be important in inducing differentiation of myoblasts into muscle fibres (see Brameld *et al.* 1998, 2003). Creatine kinase is a muscle-fibre-specific protein often used as a means of quantifying myoblast differentiation. Thus, local IGF-II expression matches the initiation of differentiation and could be involved in the induction process, since elimination of local IGF-II expression (using antibodies or antisense) results in inhibition of differentiation of myoblasts *in vitro* (see Brameld *et al.* 1998, 2003). It would have been interesting to monitor both myogenin and IGF-II expression in the studies by Bayol *et al.* (2004). Interestingly, in both our *in vitro* and *in vivo* studies in sheep, IGF-I expression also increased with differentiation, but there was a lag after the increases in IGF-II, myogenin and creatine kinase, suggesting that increased IGF-I is a consequence of the differentiation (Brameld *et al.* 1999; Fahey *et al.* 2003). The increased expression of IGF-I in gastrocnemius of both light and heavy pups from the 50 % undernutrition group (Bayol *et al.* 2004) may indicate an increase in muscle differentiation, which as the authors indicate could also account for some of the other effects described. This increased local IGF-I expression may then be the mechanism for the positive relationship between numbers of muscle fibres and growth rates.

The 50 % undernutrition group (Bayol *et al.* 2004) is interesting, since a degree of compensatory growth appears

to have occurred. This suggests that both the level of undernutrition and the timing of that undernutrition are critical. The 50 % undernutrition group had increased growth and cell proliferation, but the authors quite rightly point out that not all the nuclei in muscle relates to muscle cells. It would be interesting to allow these animals to grow and investigate the phenotype in later life, particularly comparing the light and heavy littermates. Does the increased growth rate persist? Are there differences in the cells present and do these lead to differences in muscle composition (e.g. fibre type, amount of intramuscular fat, etc.)?

As a model for man, the rat has drawbacks, not least because the number of muscle fibres present is not fixed at the time of birth. However, we already know the time at which the different populations of fibres develop in a variety of species, including rats, guinea-pigs, pigs, sheep, cattle and man (see Brameld *et al.* 2003). Rats, due to their short gestation period (21 d) and time to maturity, serve as a useful model for initial investigations in this area and can then be followed-up using other, possibly better, models for man (e.g. sheep, pigs).

Most studies in this area have demonstrated effects of nutrition on the numbers of secondary muscle fibres. These develop after and around the primary fibres. The primary fibres tend to form type I (slow oxidative) fibres, whereas the secondary fibres tend to form faster type II fibres (e.g. type IIB, fast glycolytic or the intermediate type IIA, fast oxidative glycolytic). However, a degree of plasticity occurs postnatally, such that slow fibres can become faster in a fast muscle and fast fibres can be come slower in slow muscles. Hence, changes in the numbers of particular fibre types may then alter the metabolism of the muscle and thereby relate to changes in insulin sensitivity and energy expenditure. Studies in rats demonstrate increased insulin resistance in 15-month-old male pups born to mothers exposed to a low-protein diet (80 *v.* 200 g/kg) throughout pregnancy and lactation (Ozanne *et al.* 2003). This was associated with reduced soleus muscle mass, but no change in body weight. The numbers and types of muscle fibres present appear not to have been studied. Glucose uptake has been shown to be positively correlated with percentage of type I fibres and negatively correlated with percentage of type IIB fibres in adult men (Lillioja *et al.* 1987). Similarly, the percentage of type I fibres is negatively correlated with percentage body fat in human subjects (Helge *et al.* 1999) and rats prone to developing obesity on a high-fat diet have a higher percentage of faster type II fibres than obesity-resistant rats (Mrad *et al.* 1992). In contrast, rats bred to have an increased proportion of fast fibre types have been shown to be resistant to developing obesity even when fed a high-fat diet (Suwa *et al.* 2002). However, these rats had increased numbers of type IIA fibres (which are intermediate, fast oxidative glycolytic fibres) and similar numbers of type I (slow oxidative) and type IIB (fast glycolytic) fibres compared with controls (Suwa *et al.* 1999), suggesting that the overall oxidative capacity was increased. Hence, it is not clear whether it is the number or the type of fibres that is important. In larger animals, decreased numbers of muscle fibres are generally associated with decreased growth rates and increased adiposity (e.g. runted pigs).

There are a variety of studies linking either insulin resistance or obesity to characteristics of skeletal muscle metabolism, as well as linking maternal undernutrition during critical stages of muscle development to numbers and types of muscle fibres formed. Whether the two are inter-related, and thereby indicate a mechanism for nutritional programming of type 2 diabetes and/or obesity, is yet to be determined.

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