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Responses to nutrients in farm animals: implications for production and quality

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It is well known that any quantitative (energy and protein levels) and qualitative (nature of the diet, nutrient dynamic) changes in the feeding of animals affect metabolism. Energy expenditure and feed efficiency at the whole-body level, nutrient partitioning between and within tissues and organs and, ultimately, tissue and organ characteristics are the major regulated traits with consequences on the quality of the meat and milk produced. Recent progress in biology has brought to light important biological mechanisms which explain these observations: for instance, regulation by the nutrients of gene expression or of key metabolic enzyme activity, interaction and sometimes cross-regulation or competition between nutrients to provide free energy (ATP) to living cells, indirect action of nutrients through a complex hormonal action, and, particularly in herbivores, interactions between trans-fatty acids produced in the rumen and tissue metabolism. One of the main targets of this nutritional regulation is a modification of tissue insulin sensitivity and hence of insulin action. In addition, the nutritional control of mitochondrial activity (and hence of nutrient catabolism) is another major mechanism by which nutrients may affect body composition and tissue characteristics. These regulations are of great importance in the most metabolically active tissues (the digestive tract and the liver) and may have undesirable (i.e. diabetes and obesity in humans) or desirable consequences (such as the production of fatty liver by ducks and geese, and the production of fatty and hence tasty meat or milk with an adapted fatty acid profile).

Keywords: metabolism, nutrients, production, quality, tissues

Introduction

In the context of increased globalisation and competitiveness, producers of animal products have been the most affected, with considerable reductions in profit margins. Research on nutrition in farm animals is therefore still needed to reduce the production costs by increasing metabolic efficiency. To achieve this goal, the aim is to control animal performance accurately by improving quantification of animal requirements, specifying feed evaluation and evaluating animal responses to varying nutritional inputs. At the same time, the farming and agri-food sectors are faced with a general saturation of food markets in Europe and with an increasing demand by consumers for high-quality meat and dairy products. This has also led to specific research in nutrition, which aims to optimise the metabolic activity of muscles and mammary gland to produce meat and dairy products of the desirable composition. Farm animal responses increasingly require multicriteria evaluation.

This paper aims to address this important question: how animal nutrition may help to optimise metabolic efficiency and product quality? In humans, due to the development of obesity and diabetes, the question can be reworded as: how human nutrition may help to optimise metabolic efficiency and individual health? Today, both questions need a better knowledge of tissue and organ requirements and of nutrient fate within tissues and organs. Furthermore, new concepts and techniques such as genomics and modelling are available to decipher mechanisms that were impossible to address adequately a few years ago with the ultimate objective of gaining a greater understanding of mammal response to nutrition.

In the present paper, we describe the nutritional regulation of metabolism based on basic knowledge and more recent results arising, for example, from genomics and modelling. Only a few selected and representative examples of research are given to support this trend in research. They

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concern the effects of feeding level, the nature of nutrients and the rate of nutrient delivery. We also highlight the key role of insulin in the nutritional regulation of energy and protein metabolism. The last part of this paper focuses on target tissues and organs (namely, muscles and mammary gland), which control at least in part the quantitative and qualitative production of meat and milk in farm animals.

New approaches for studying the nutritional regulation of energy and protein metabolism

Progress in understanding nutrient absorption and metabolism regulation was achieved by different and sequential approaches. Some decades ago, the calorimetry approach was developed in order to build up a database of energy expenditure measurements. Then, the use of cannulation techniques was used to measure nutrient flow from the digestive tract. The apparent absorption of nutrients into the portal vein and the use of nutrients by the major organs and tissues were then quantified with the help of multicatheterisation techniques on live animals, with the combination of the blood flow measurement with venous–arterial differences and nutrient labelling techniques providing a better understanding of nutrient fate within the body and within tissues (Drackley *et al.*, 2006). In parallel, the development of *in vitro* (tissue or cell culture) and *ex vivo* (enzyme activities, gene expression) approaches has provided knowledge about control mechanisms. It has been shown that, besides the 'mass action' when substrate availability changes, a fundamental response to nutrient supply is indeed a change in the signals that regulate metabolism either indirectly through hormones or directly by the action of nutrients on gene expression and on enzyme activities. So far, numerous studies have focused on the expression analysis of the candidate genes that control the activity of key metabolic enzymes. The advent of high throughput genomic techniques (transcriptomics, proteomics, metabolomics) nowadays allows studies of thousands of genes, proteins and metabolites simultaneously to get a more precise picture of biological mechanisms (see review by Hocquette, 2005).

A new challenge for modern biology is to integrate knowledge with the aim of understanding the whole metabolism in complex biological systems based on our understanding of the parts. Generally speaking, there may be a conflict between the analytic approach (i.e. understanding a specific molecular mechanism) and the integrated work (i.e. a relevant combination of different mechanisms). A key question is to identify the elementary mechanisms that have an important impact both quantitatively and qualitatively on the final integrated processes. To evaluate the quantitative importance of mechanisms, *in vivo* fluxes of metabolites through metabolic pathways are among those important mechanisms which must be measured accurately. Those approaches made indeed a real effort to be quantitative. There are, however, limitations, particularly relating to the small size of the venous–arterial difference and large blood flow numbers that are hard to measure on catheterised animals. Metabolomics tools (using for instance quantitative mass spectrometry techniques) are other approaches suitable for measuring metabolic fluxes with accuracy, and automation (Hellerstein, 2003). To identify the key metabolic changes, transcriptomics and proteomics are high throughput techniques to measure gene and protein expression.

More and more examples based on genomics studies are being published in Animal Science. For instance, in order to get a global view of the metabolic regulation of either liver or mammary metabolism, transcriptomic studies have been performed to identify genes regulated as a result of nutrient restriction. Restricting cow energy intake during the dry period induces an upregulation of some liver genes involved in fatty acid oxidation, gluconeogenesis and cholesterol synthesis. Conversely, *ad libitum* feeding favours the expression of some genes associated with fat synthesis. In addition, overfeeding might render the cow liver more susceptible to oxidative stress and DNA damage through changes in gene expression. In other words, overfeeding predisposes cows to fat accumulation in the liver and to health problems, thereby demonstrating the importance of nutrition planning for dairy cows (Loor *et al.*, 2006). Although these conclusions were, at least in part, previously known through physiological approaches, the global transcriptomic approach has the merit of assessing these biological adaptations by studying genes on a large scale. In other respects, transcriptomics has demonstrated that food deprivation for 48 h alters goat mammary transcriptome simultaneously with milk production and composition. The expression of 161 genes was altered, in particular genes that might be responsible for a slowdown of mammary cell proliferation and differentiation as well as an orientation of mammary cells towards programmed cell death, which could correspond to an early step in mammary gland involution. In addition, genes involved in the drop in milk component secretion were downregulated, such as genes encoding milk proteins and genes involved in lipid metabolism and transport (Ollier *et al.*, 2007). Other examples of genomic results will be indicated in the last section of this paper related to product eating quality.

Finally, the increasing need to combine numerous experimental results obtained at similar and different levels of organisation to evidence general metabolic processes relies on the development of modelling. The marriage of all these approaches from 'omics' approaches to modelling through *in vivo* approaches will undoubtedly lead to a greater understanding of nutrient responses in energy and protein metabolism.

Effect of nutrition level

Metabolic regulation at the animal level

It is well known that metabolisable energy utilisation increases with energy intake (as does protein deposition

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with protein intake), but feed efficiency varies depending on the feeding level. For instance, in growing cattle, feed efficiency expressed as retained energy/supplied energy increases to reach a maximum with increasing food supply and then decreases at high-energy level (Geay and Robelin, 1979). Different mechanisms may explain this observation. One of them is of course the partitioning of fuels between protein deposition in muscles and fat storage in adipose tissue; this process will be illustrated in the sections that follow. Another important mechanism is the variable contribution of the metabolic activity of liver and portal-drained viscera (PDV) to total energy expenditure.

The liver and the PDV indeed have a great importance in total energy expenditure since their metabolic rates are up to 20 and six times higher, respectively, than that of the hind limb (composed approximately of two-thirds muscle). Thus, despite their lower mass relative to muscles, PDV and liver contribute to 17% and 13% to total energy expenditure *v.* 18% for muscles in pre-ruminant calves. However, due to the development of the digestive tract and the high ingestion of forages, relative contributions are 16% and 29%, 17% and 31%, 18% and 20% for PVD, liver and muscles, respectively, in weaned, growing and adult ruminants (for review, see Ortigues and Doreau, 1995; Bauchart *et al.*, 1996; Chilliard *et al.*, 1998). Similar findings have been reported with regard to the contribution of different tissues to whole-body protein synthesis, with for example relative contributions of 18%, 24% and 25% for intestine, liver and muscles, respectively, in the rat (Waterlow, 1984). Consequently, the metabolic fate of nutrients in the splanchnic tissues is of prime importance to control nutrient supply and use in peripheral tissues. Splanchnic tissue energy expenditure is greatly influenced by the level of nutrition. In ruminants, the increment in whole-animal energy expenditure with increased intake originates mainly from the PDV (17% to 61%) and the liver (16% to 44%) rather than from the muscle mass (5% to 7%) (Figure 1). Modelling approaches are now being applied to these results and clear curvilinear response equations of splanchnic energy expenditure to increasing intake have been quantified in sheep and cattle (Bermingham *et al.*, 2007).

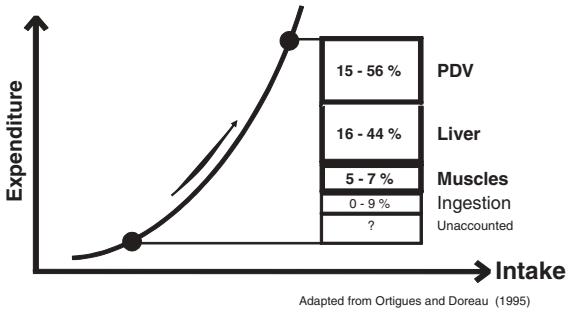

Figure 1 Origins in the increase in whole-body energy expenditure with increasing food intake in ruminants.

Increases in the weights of splanchnic tissues with increasing intake are primarily responsible for this effect although metabolic rates can also be modified (Lobley, 1991). For instance, in the PDV metabolic rate increases postprandially by approximately 20% as a result of digestion, nutrient absorption and metabolism in pre-ruminants and to a lower extent in ruminants (for review, see Ortigues and Doreau, 1995 also Bauchart *et al.*, 1996). Changes in metabolic rates are also associated with changes in the balance among nutrients supplied, and response equations of nutrient absorption to increasing intake are starting to be established (Bermingham *et al.*, 2007).

For example, undernutrition is mediated by changes in nutrient supply (low dietary energy and protein intake), by changes in nutrient balance (increased muscle use of non-esterified fatty acids (NEFAs) and ketone bodies at the expense of acetate and glucose) and by changes in the hormonal status (low thyroid hormone, insulin and insulin-like growth factor-1 (IGF-1) plasma levels, high growth hormone (GH), glucocorticoid and epinephrine plasma concentrations) (for review, see Chilliard *et al.*, 1998).

One animal type that is unique due to its very high-energy requirement is the dairy cow. Indeed, the huge energy demand for lactation in high-producing dairy cows largely overwhelms the energy expended for maintenance or for physical activity (for review, see Chilliard, 1999). For instance, maintenance energy requirement can be estimated at about no more than 25% of the total energy requirement of a cow producing 45 kg of milk per day compared with 60 to 80% in humans and rats, or in a dry, non-pregnant cow. This makes the dairy cow an important model for studying the response to nutrients at the whole-body level in terms of food intake and metabolic regulation. Firstly, it has been shown that cereal grains that are highly digestible in the rumen can depress food intake in lactating cows compared with starch digestion in the small intestine. It is likely that the high production of propionate associated with starch intake causes satiety. The mechanisms explaining the regulation of intake by propionate are not known. A great deal of research suggests, however, that feeding behaviour is regulated by the hepatic oxidation of fuels (Allen *et al.*, 2005). A reduction in feed intake in the periparturient period is a significant problem in dairy cows, which increases the risk of a high negative energy balance with associated body lipid mobilisation and metabolic diseases. However, a relatively slow increase in feed intake could also be seen as a safety mechanism allowing the development, over a longer period, of the digestive and metabolic adaptations necessary for the use of large amounts of nutrients at the time (Bareille *et al.*, 1997). One mechanism limiting feed intake may be associated with the increased lipolysis which liberates a high amount of fatty acids taken up by the liver. The reduction in insulin and adenosine and increase in β-adrenergic sensitivities of adipose tissues associated with low insulin and high GH levels favour lipolysis (Chilliard *et al.*, 2000 and 2001; Allen *et al.*, 2005). Furthermore, negative energy balance and low

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insulinaemia make the liver IGF-1 secretion resistant to the GH stimulation (Chilliard *et al.*, 2001). This GH resistance allows the catabolic effects of this hormone to take priority over its anabolic effects in extra-mammary tissues and the occurrence of its galactopoietic effects in the mammary gland.

To better understand the biological mechanisms explaining the metabolic regulation at the animal level, we need to study the effects of nutrients more deeply. These effects are complex and involve different direct and indirect mechanisms, for instance, acute or long-term enzyme regulation or a stimulation of the secretion of some hormones, i.e. insulin by specific nutrients (mainly glucose). It is noteworthy that insulin is a major regulator of glucose metabolism, but is also the primary hormone known to regulate protein metabolism: insulin exerts its action through the two components of protein turnover which determine protein accretion or loss (i.e. protein synthesis and proteolysis). Insulin regulates protein metabolism in animals by clearly decreasing *in vivo* proteolysis (for review, see Tesseraud *et al.*, 2007). Interestingly, studies using clamp techniques have demonstrated that the ability of physiological insulin to inhibit protein degradation is enhanced during early lactation (greater sensitivity of proteolysis to insulin; Tesseraud *et al.*, 1993): this adaptation may provide a mechanism limiting excessive mobilisation of body protein and preserving lean mass despite the significant diversion of amino acids towards mammary gland protein synthesis. This mechanism originates from an amino acid deficit during early lactation since hyperaminoacidaemia abolishes the phenomenon (amino acids are no longer limiting in hyperaminoacidaemia). Therefore, insulin plays a major role during early lactation, since this hormone has an 'amino acid sparing' effect in a physiological situation where the dietary requirements are very high. Such a mechanism is complementary to the fine and complex regulation described above for energy metabolism.

Despite the fact that insulin clearly stimulates protein synthesis *in vitro* (Grizard *et al.*, 1999; Tesseraud *et al.*, 2007), the effects of insulin on protein synthesis are much more difficult to demonstrate *in vivo*. A positive insulin effect has been reported only in studies performed in young postabsorptive or food-deprived monogastric mammals. In these animals, plasma insulin concentrations are low in the fasting state and relatively high after a meal. In contrast, ruminants have more constant nutrient absorption and insulinaemia, which may limit the anabolic response to exogenous insulin. Results obtained by Wester *et al.* (2004) further support these concepts since elevation of insulin failed to stimulate muscle protein synthesis in fasted lambs. The hypothesis of protein synthesis that is very sensitive to insulin, with maximal responses observed at relatively low insulinaemia, has been confirmed by transiently decreasing insulinaemia in rodents with diazoxide injection: postprandial insulin suppression greatly decreased protein synthesis, suggesting that insulin plays a major role in regulating protein synthesis *in vivo* (Sinaud *et al.*, 1999; Balage *et al.*, 2001; Prod'homme *et al.*, 2005). Similar findings have also been reported in pigs using somatostatin to block endogenous insulin (O'Connor *et al.*, 2003a and 2003b). However, even under these particular conditions, the role of insulin is a matter of debate and interactions between insulin and amino acids have to be considered: for instance, the positive effect of insulin on *in vivo* skeletal muscle protein synthesis is more marked in the presence of amino acids (Garlick and Grant, 1998). Interestingly, recent studies have suggested that a minimum level of insulin is required for the stimulation of protein synthesis by refeeding or the absorption of amino acids across the PDV (reviewed by Kimball *et al.*, 2002). Insulin may thus have a permissive effect for the amino acid-induced stimulation of protein synthesis.

Hepatic metabolism

The liver is characterised by a very intense metabolic rate with both elevated anabolic and catabolic activities and particularly high rates of protein turnover. Generally speaking, increased hepatic oxidation of fuels likely causes satiety (thus reducing food intake), whereas increased clearance of fuels from the blood is expected to cause hunger (Allen *et al.*, 2005). In addition, a high food intake increases liver energy expenditure and favours esterification of fats at the expense of their oxidation. In ruminants, unlike in other species, a high food intake also favours the hepatic gluconeogenic rate due to a high dietary supply of propionate (a major glucose precursor). These changes result from short-term mechanisms of regulation through the action of metabolites and by long-term mechanisms of regulation through changes in gene expression. Gluconeogenesis is also highly regulated by hormonal factors such as insulin (Drackley *et al.*, 2001).

With respect to fat metabolism, the liver is able to synthesise fatty acids (although much less in ruminants and pigs than in other species) and oxidise them. The balance between these two processes is of prime importance for the delivery of energy in the form of fat (short-chain fatty acids, ketone bodies, long-chain fatty acids (LCFAs)) to other tissues. When a high mobilisation of fat occurs from adipose tissue (in the case of energy deficiency), the liver, which is faced with a high uptake of fatty acids, oxidises more fats. The enzyme called carnitine palmitoyltransferase I (CPT I) catalyses the rate-limiting step of fat oxidation because it controls LCFA transfer into mitochondria. It is thus also involved in the control of ketone body production. CPT I activity is inhibited by malonyl-CoA, an intermediate in LCFA synthesis from acetyl-CoA, the synthesis of which is enhanced by insulin, which stimulates lipogenesis (i.e. the conversion of acetyl-CoA into malonyl-CoA). Consequently, any change in insulin secretion or in LCFA supply to the liver modifies the balance of fat within the liver and therefore the supply of fat to peripheral tissues (for review, see Hocquette and Bauchart, 1999). Other studies have shown that oxidation of fatty acids provides ATP needed for

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gluconeogenesis supporting strong interrelationships between glucose and fatty acid metabolism in the liver (Drackley *et al*., 2001).

Fat metabolism is also of interest in avian species since *de novo* lipogenesis is essentially hepatic in these animals (Pearce, 1977). Farmers have taken advantage of this species specificity to produce fatty liver from ducks and geese following overfeeding of the animals. In the liver of ducks, overfeeding with a carbohydrate-rich diet induces a significant increase in the activity of the main enzymes involved in lipogenesis from glucose (glucokinase, glucose-6-phosphate dehydrogenase, malic enzyme, acetyl CoA carboxylase). Cytochrome-*c* oxydase activity, on the other hand, remains unchanged, indicating that the overall oxidation ability of energy-yielding substrates is not regulated so much. Plasma levels of insulin and triglycerides (TGs) are considerably increased and glycaemia is significantly higher. Some differences exist, however, between genotypes: compared with the Pekin duck, the Muscovy duck probably has a more efficient hepatic lipogenesis (since acetyl-CoA carboxylase activity is higher) but its ability to export lipids is probably lower (since plasma TG levels are lower) (Chartrin *et al*., 2006).

To summarise, an important role of the liver is therefore its participation in the regulation of food intake by contributing to the matching of energy supply to energy use. In addition, all portal vein blood must traverse the liver before reaching the other tissues and the rest of the body and the liver also plays a key metabolic role in converting the different metabolites. Consequently, the liver metabolism has a great impact on the availability of nutrients for other tissues and organs.

Muscle and adipose tissue metabolism

Muscle tissues use carbohydrates and fatty acids as energy sources for the production of free energy (ATP). This general process is regulated by these two classes of nutrients as well as by many hormonal factors, mainly insulin. It is also highly regulated by physical activity (which itself increases muscle insulin sensitivity), but it is outside the scope of the paper.

States of insulin resistance or of reduced potential of glucose use by muscles may impair growth, for instance in calves (for review, see Bauchart *et al*., 1996 also Hocquette and Abe, 2000). Many factors have been shown to be involved in the aetiology of insulin resistance. They include heredity, age, obesity, diet, sex, sedentary life style, etc. (Khan and Safdar, 2003). Impaired glucose transport rate, as well as impaired mitochondrial activity, and higher intramyocellular lipid content were shown in the insulin-resistant offspring of patients with type 2 diabetes (Petersen *et al*., 2004). Recently, total muscle fat oxidative capacity was also shown to be positively correlated with insulin sensitivity (Rimbert *et al*., 2004). In addition, insulin-regulated mitochondrial gene expression is positively associated with glucose flux in human skeletal muscle (Huang *et al*., 1999). Mitochondrial markers, but not muscle fibre type *per se*, may indeed be predisposing factors for obesity (Raben *et al*., 1998). In addition, several nutritional factors regulate the action of insulin. For instance, there is evidence that insulin resistance may be caused by excess nutrient supply (for review, see Proietto *et al*., 1999). Other mechanisms linked to animal management or feeding strategy are thought to regulate glucose metabolism and insulin action: plasma insulin levels are indeed lower in steers at pasture compared with control animals in a shed with similar growth rates (I. Ortigues *et al*., unpublished results).

The effect of nutrient availability on muscle metabolism is subject to variations between animal species. Thus lipoprotein lipase activity, which is related to tissue potential for plasma TG fatty acid uptake, as well as plasma TGs, decreased by underfeeding ewes (Faulconnier *et al*., 2001) or cows (Bonnet *et al*., 2004), contrary to what has been observed in rodents. This peculiarity is likely related to the fact that the ruminant liver is less able than rodent liver to recycle fatty acids mobilised from adipose tissue during undernutrition. Inversely, muscle GLUT4 glucose transporter was less responsive to underfeeding–refeeding in bovines than in rats in parallel to lower relative changes in plasma glucose and insulin (Bonnet *et al*., 2004).

In ducks, muscle overall oxidative ability, estimated by cytochrome-*c* oxydase activity, is increased in *pectoralis major* muscle following overfeeding. Generally speaking, the muscle tissues adapt their energy metabolism to overfeeding, increasing their oxidative metabolism, and decreasing their glycolytic metabolism, particularly in breast muscle (Zanusso *et al*., 2003; Chartrin *et al*., 2006). It has been hypothesised that muscle tissues adapt their metabolism to use more fat as the energy source following overfeeding due to greater fat availability (as demonstrated by higher TG levels in the plasma) and reduce their utilisation of glucose (Chartrin *et al*., 2006).

In cattle, muscle metabolism is more affected by mild nutritional restriction than any other muscle biochemical characteristic. A mild nutritional restriction followed by *ad libitum* feeding affected the metabolism of muscles, although their histological profile was preserved. Interestingly, muscles responded in different directions to refeeding after a restriction period in terms of metabolic activity (Figure 2) and collagen solubility, without any modification of their lipid content or of the characteristics of their proteasome system (Cassar-Malek *et al*., 2004). The muscles reacted differently to the nutritionally induced discontinuous growth path, suggesting that muscle types display a differential nutritional sensitivity. These results confirmed that muscle metabolic characteristics are in a dynamic state and are subject to plasticity in adjusting to feed and hormonal signals.

Generally, increased adipose tissue mass (due for instance to a high feeding level) and insulin resistance in skeletal muscle mass are closely related. Communication between the two tissues is thought to play a major role in the development of insulin resistance. One possible

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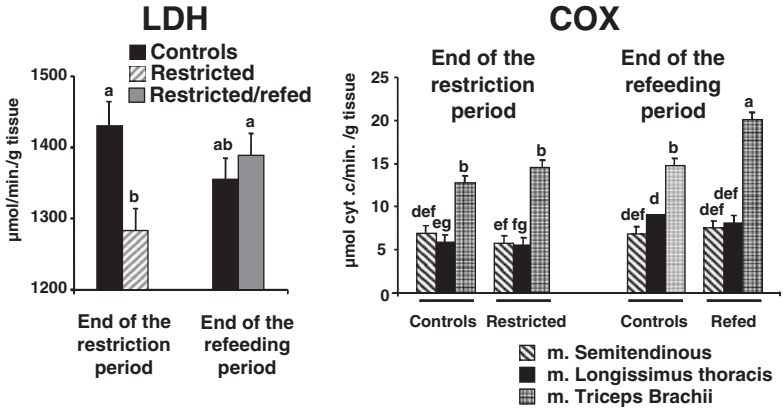

Figure 2 Influence of restriction and refeeding on lactate dehydrogenase (LDH), and cytochrome-*c* oxidase (COX) activities across the three muscles (according to Cassar-Malek *et al.*, 2004). At 9 months of age, steers were fed a restricted diet for 3 months and slaughtered or subject to a 4-month *ad libitum* refeeding period prior to slaughter with the same regimen. Control steers were fed to gain continuously between 9 and 12 months of age and slaughtered (end of the restriction period) or maintained on a continuous feeding protocol through 16 months of age prior to slaughter (end of the refeeding period).

mechanism is associated with free fatty acids and their metabolites. A defective oxidative phosphorylation due, for instance, to a low mitochondrial activity is thought to be the underlying mechanism (Sell *et al.*, 2006). Another mechanism is the release of endocrine and metabolic mediators by adipose tissue. One of these mediators is leptin, whose secretion by adipocytes increases when body fatness and/or sugar intake increases, stimulates energy expenditure and fatty acid oxidation in muscles, liver and adipose tissue and inhibits adipose tissue lipogenesis (Havel, 2004). The development of leptin resistance when body fatness and/or short-term energy intake increases is, however, a limit to this homeostatic regulation (Unger, 2005). The stimulation of energy expenditure by leptin may partly explain why fat ewes lost body lipids, contrary to lean ones, and showed increased basal and adrenergic lipolytic activities in adipose tissue, when fed for a long period at their theoretical maintenance energy requirements (Chilliard *et al.*, 2000). Reciprocally, lactation hypoleptinaemia likely decreases energy expenditure and favours high milk energy secretion during early lactation, as well as body reserve rebuilding after the lactation peak (for a review, see Chilliard *et al.*, 2005).

Effect of the nature of nutrients

Metabolic regulation at the animal level

Many arguments exist to support the idea that energy and protein metabolism are regulated by the nature of nutrients and therefore depend on the type of diet.

In weaned growing ruminants, efficiency of metabolisable energy utilisation for growth is generally low (less than 40%) with forage diets, for which the percentage of energy absorbed as volatile fatty acids (VFA) averages 66% (33% for acetate, 14% for propionate and 19% for butyrate). By contrast, efficiency of energy utilisation is higher (more than 50%) with maize-based diets, which supply about 50% of absorbed energy as VFA (13% by acetate, 18% by propionate and 13% by butyrate). This lower efficiency with forage diets is thought to result from higher heat losses from food fermentation in the rumen, higher energy expenditure of PDV due to an increased PDV mass and an increased PDV motricity as well as lower metabolic efficiency of VFA utilisation (for review, see Ortigues and Visseiche, 1995). When animals are at pasture, a high-energy expenditure of muscles due to physical activity is also likely to contribute to these observations.

Energy metabolism can be specifically regulated by carbohydrates. For instance, glucose is known to be hypophagic in many non-ruminants, but not in ruminants. This is likely to be due to differences in hepatic oxidation of glucose. Indeed, the ruminant liver does not remove a significant part of the circulating glucose. Hypophagic effects of propionate have been well documented in ruminants although inconsistent effects have been observed. Propionate can be used for gluconeogenesis which consumes ATP, or is catabolised as acetyl-CoA, therefore generating ATP. Insulin and glucose are important regulators of fuel partitioning within the liver, especially in monogastrics. When glucose and insulin levels are high, gluconeogenesis is low, propionate is oxidised faster and satiety occurs sooner. Propionate is also an insulin secretagogue and insulin is a putative satiety hormone, thus possibly amplifying the phenomena (Allen *et al.*, 2005). In human beings, it is well known that increased carbohydrate intake will make a person fatter. One mechanism is the well-known higher expression of genes and proteins involved in fat synthesis. The first and quantitatively most important response to a high carbohydrate intake is, however, increased carbohydrate oxidation at the expense of fat oxidation. In addition, hepatic glucose production is higher despite higher insulin levels and lipolysis is reduced. Thus, the liver is more likely to contribute to obesity by overproducing glucose and reducing fat oxidation than by converting glucose into fat (Hellerstein, 2003).

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Again, the dairy cow may be a good model to study the regulation of energy metabolism by the nature of nutrients. Besides the high-energy requirements of dairy cows, feeding strategies specific to this animal type have brought interesting results regarding the metabolic regulations. For instance, fat sources are often added to dairy cow diets to support the high milk production. Furthermore, as in human beings, it has been observed that unsaturated fatty acids decreased food intake. Generally speaking, it is likely that oxidised fat is satiating whereas fat that is stored is not satiating in the short term. Saturated fatty acids are not oxidised as rapidly as polyunsaturated fatty acids (PUFAs). This may explain the differential regulation of food intake according the nature of fatty acids although other mechanisms are likely to occur, such as gut peptide release during meals (Allen *et al*., 2005). The combined effects of an increase in milk energy secretion and a decrease (or no change) in energy intake paradoxically result in lower energy balance and higher body-weight loss in early lactation cows fed supplemental lipids (Chilliard, 1993). Furthermore, unsaturated fatty acids probably increased these effects since postruminally infused plant oil stimulated β-adrenergic lipolytic responses in adipose tissue (Gagliostro and Chilliard, 1991).

Amino acids have also a major effect in controlling metabolism (see Grizard *et al*., 1995 and 1999; Lobley, 1998; Muramatsu, 1990; Nieto and Lobley, 1999; Prod'homme *et al*., 2004 for reviews). They are first substrates for protein synthesis and the lack of even a single essential amino acid causes a decrease in protein synthesis. Amino acid availability affects not only protein synthesis rates, but also proteolysis and amino acid oxidation, therefore affecting various pathways involved in metabolism. Evidence of the action of amino acids in protein turnover has been provided using diets varying in protein or amino acid supplies. For example, protein-deprived diets cause inhibition of protein synthesis, whereas the effect on proteolysis seems to depend on the severity of deficiency. Excess protein appears to have only a minor effect on muscle protein metabolism, except when it is associated with energy restriction. In this case, it results in reduction in protein synthesis. Nevertheless, under some critical conditions, excess proteins can have a positive effect on protein deposition. For example, in young piglets, protein-rich diets prevent the decrease in protein synthesis after early weaning (Seve *et al*., 1986). In 'normal' nutritional situations, whatever the species (man, pig or goat), hyperaminoacidaemia induced by intravenous infusion of amino acids increases muscle protein synthesis, at least when measurements are performed using the constant infusion of labelled amino acids (Bennet *et al*., 1989; Watt *et al*., 1992; Tesseraud *et al*., 1993).

The role of amino acids in regulating protein turnover has also been studied in refeeding conditions, i.e. postprandial regulation. Volpi *et al*. (1996) showed in adult men that amino acids contributed to 90% of the increase in protein synthesis following a meal with balanced levels of lipids, carbohydrates and proteins. The fact that amino acids are essential to postprandial stimulation of protein synthesis has also been demonstrated in rats (Yoshizawa *et al*., 1997 and 1998) and chickens (Yaman *et al*., 2000). Stimulation of protein synthesis by amino acids is thus associated with an increase in translational efficiency. Protein turnover also depends on the supply of specific amino acids, particularly limiting amino acids. Among them, methionine is, for example, the first limiting factor in classical diets used for growing chickens because of a high requirement of sulphur amino acids for the synthesis of feathers whereas poultry diets based on corn and soya-bean meal are deficient in sulphur amino acids without supplementation (Baker, 2006). In this species, the decreased rates of body-weight gain and protein accretion induced by methionine and cysteine deficiency are apparently more pronounced than those recorded with diets deficient in lysine or histidine (Kino and Okumura, 1986). Decreased growth in chickens fed methionine- and cysteine-free diets was primarily caused by lower rates of whole-body protein synthesis associated with lower RNA efficiency, suggesting translational regulation. A positive effect of methionine supplementation on muscle growth has conversely been reported, since the addition of methionine to a methionine-deficient diet, otherwise balanced in terms of other amino acids, increases accretion and synthesis of protein in the *gastrocnemius* and *pectoralis major* muscles in chickens (Barnes *et al*., 1995). Methionine supplementation in a protein-free diet is also effective in increasing protein synthesis of whole-body protein, particularly muscle protein (Muramatsu *et al*., 1985 and 1986). Webel and Baker (1999) found that cysteine supplementation elicits a response similar to or greater than methionine and suggested that the primary need is for cysteine, and not for methionine *per se*; like methionine, cysteine is an important constituent of feather and fur proteins. Wool production is quite a nice example of increasing sulphur amino acid requirements.

Amino acids exert their action in various tissues and organs, including the splanchnic tissues, which are able to control the distribution of nutrients between tissues since they are the first tissues exposed to newly absorbed nutrients due to their anatomical position (first-pass splanchnic extraction; see Nieto and Lobley (1999) for a review). Despite this function and the fact that the portal delivery of amino acids possibly initiates a signal to the liver that increases hepatic amino acid utilisation, i.e. protein synthesis, these findings are not discussed further here. The nutritional regulation of protein metabolism by amino acids has also been intensively studied in skeletal muscle since these nutrients are known as anabolic factors, which induce protein gain by stimulating protein synthesis while inhibiting proteolysis. The aim of the work performed is thus to improve and control muscle growth and meat quality in animal production and to reduce muscle wasting in some physiological (e.g. early lactation) and physiopathological situations (e.g. ageing, infection). Indeed, due to the differences between the amino acid composition of

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acute-phase and muscle proteins, a considerable amount of muscle protein must be degraded to provide the amino acids used in the acute-phase response (Reeds *et al.*, 1994). Understanding the mechanisms by which amino acids regulate protein metabolism is therefore essential to improve control of the use of nutrients and optimise dietary amino acid supply.

Finally, the regulation of insulin sensitivity is an important mechanism by which the nature of nutrients indirectly regulate energy and protein metabolism. Glucose oxidation is usually decreased in insulin-resistant human subjects. An increase in lactose intake increases insulin resistance in preruminant calves (for review, see Hocquette and Abe, 2000) as described in other species (for review, see Hocquette *et al.*, 1998). By contrast, an increase in digestible protein intake at a constant protein-free energy intake decreases insulin resistance unlike the situation in humans. In rats and humans, fat intake has been associated with the development of insulin resistance, and plant oil duodenal infusion lowers glucose tolerance and response to insulin in lactating cows (Chilliard and Ottou, 1995).

Hepatic metabolism

Energy metabolism is regulated by the nature of nutrients at the whole-body level due to tissue- or organ-specific regulations, which are of course important in the liver when strong interrelationships take place between fat and carbohydrate metabolism.

Propionate, which is absorbed in large quantities in ruminants, directly inhibits fatty acid oxidation and, indirectly, entry of LCFA into mitochondria. Indeed, CPT I is inhibited by methylmalonyl-CoA which derives from propionate. In addition, succinyl-CoA generated from propionate inhibits ketogenesis. A low delivery of propionate to the liver, due for instance to a forage-based diet would therefore enhance ketosis in the ruminant liver (for review, see Hocquette and Bauchart, 1999). The majority of absorbed propionate is converted to glucose within the liver. Propionate, however, decreases the utilisation of other gluconeogenic substrates such as lactate (for review, see Brockman, 1993), thus modifying the balance of nutrients supplied to the muscles.

As in avian species, fatty liver may occur in the veal calf depending on nutritional factors, thereby affecting growth and health. One important factor that may regulate hepatic TG metabolism is the nature of dietary fatty acids such PUFAs or medium-chain fatty acids (MCFA). Compared with standard milk replacers for calves, PUFA-rich diets (soyabean oil rich in $C_{18:2n-6}$) or MCFA-rich diets (coconut oil rich in $C_{12:0}$) lead to the development of hepatic TG infiltration (for review, see Bauchart *et al.*, 1996). This may be explained by a modification of LCFA partitioning between esterification and oxidation within peroxysomes and mitochondria (Piot *et al.*, 1999). Insulin resistance also occurs in high-producing dairy cows and is also linked to disturbance in glucose homeostasis. Glucose and LCFA, the major nutrients in monogastrics and in the preruminant calf, were shown to control gene expression in laboratory rodents (for reviews, see Clarke and Abraham, 1992 also Girard *et al.*, 1994). For instance, in rodents, dietary glucose is a key determinant of hepatic transcription rate for several genes encoding various enzymes including phosphofructokinase, acetyl-CoA carboxylase or fatty acid synthase (for review, see Ferré, 1999). By contrast, PUFA are potent inhibitors of the expression of the genes encoding hepatic lipogenic enzymes. Glucose also influences mRNA stability or processing such as the editing of apolipoprotein B. The relative contribution of transcription *v.* transcript stability as determinants of mRNA abundance varies for each transcript and is dependent on specific tissues (for reviews, see Clarke and Abraham, 1992 also Girard *et al.*, 1994). Those regulations are of prime importance in the liver.

Basically, carbohydrate intake results in a high glucose level in plasma, which induces insulin secretion. Insulin in interaction with glucose plays a major role in linking fat and carbohydrate metabolism in the liver. Firstly, insulin suppresses hepatic glucose production. Insulin is also known to directly induce the expression of the transcription factor (sterol regulatory element-binding protein-1c (SREBP-1c)) expression, thereby enhancing the expression of lipogenic enzymes in the liver. However, in mice lacking SREBP-1c, glucose alone can also enhance the expression of lipogenic enzymes through the carbohydrate-responsive element-binding protein (ChREBP), the expression of which is enhanced in carbohydrate-fed rats (for review, see Uyeda and Repa, 2006). This major regulation is altered in insulin-resistant states. Insulin resistance is defined here as the failure of insulin to suppress hepatic glucose production. For instance, in mice, accumulation of intracellular fatty acid metabolites such as long-chain fatty acyl-CoAs reduces the activity of phosphatidylinositol-3′ kinase (PI3K), a key step in the insulin signalling cascade. Conversely, the prevention of fat accumulation reduces hepatic insulin resistance. At a molecular level, insulin is known to suppress the activity of two enzymes involved in the control of gluconeogenesis, namely phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphate. This action is reduced or suppressed in insulin-resistant states. Elevated glucose concentration causes increased insulin secretion and activates the two transcriptional factors SREBP-1c and ChREB. In insulin-resistant states, SREBP-1c blocks hepatic insulin signalling thereby promoting hepatic glucose production (which is not or less inhibited by insulin due to insulin resistance). The failure of insulin to inhibit glucose production increases insulin secretion and causes hyperinsulinaemia. Insulin, SREBP-1c and ChREBP increase the activity of lipogenic enzymes leading to fat accumulation. On the other hand, insulin is known to inhibit fatty acid oxidation, and this occurs to a large extent in insulin-resistant states. Thus, fat accumulation results in fact from both increased fat synthesis and inhibition of fatty acid oxidation in insulin-resistant states due to a positive interaction between glucose level and insulin signalling, thereby altering the

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ability of insulin to reduce glucose production (Weickertt and Pfeiffer, 2006).

PUFAs are also known to interact with nuclear receptor proteins. This is important in human nutrition, since during the last 100 to 150 years, huge nutritional changes of the human population have led to an increase in saturated fats from dairy and meat products, in *trans*-fatty acids from the hydrogenation of vegetable oils and in n-6 fatty acids due to the production of oils from vegetable seeds. Again, the liver is the primary site for the metabolism of essential fatty acids (linoleic and linolenic acids of the n-6 and the n-3 families, respectively). Sequential alternating elongation and desaturation steps lead to PUFA with more carbons. The application of molecular biology techniques has shown that PUFA elicit changes in gene expression that precede changes in cellular composition. This is achieved by directly governing the activity of nuclear transcription factors, the first one which has been discovered being the peroxisome proliferator-activated receptor-α (PPAR-α). This factor plays a role in regulating the genes that control glucose and lipid metabolism. Generally speaking, PUFAs induce fatty acid oxidation and are potent suppressors of fat synthesis through the activation of PPARs. Indeed, a great number of genes involved in fatty acid oxidation or synthesis contain DNA sequences that are recognised by PPARs. Besides the action of PPAR-α, it was also shown that PPAR-γ induces the expression of lipoprotein lipase and fatty acid transporters. Other transcriptional factors (SREBP, liver X receptors) were shown to be involved in the action of PUFA on gene expression. For instance, liver X receptors act through the regulation of SREBP-1c, with PUFA suppressing the nuclear content of this factor. PUFA also suppress the enhancer activity of hepatic nuclear factor-4 (HNF-4), which is known to enhance the expression of some lipogenic enzymes (Benatti *et al.*, 2004).

Muscle and adipose tissue metabolism

The muscle metabolism is highly regulated by hormonal factors, especially insulin, and several nutritional factors regulate the action of insulin. Firstly, increased muscle TG content, or a high proportion of saturated fats within muscles, is inversely related to insulin action (for review, see Hocquette *et al.*, 1998). Secondly, some dietary micronutrients may also modify the action of insulin. For instance, severe iron deficiency in veal calves induces an increase in glucose use by muscle directed to glycolysis and lactate production (for review, see Bauchart *et al.*, 1996). Chronic hyperglycaemia is also a cause of insulin resistance, for instance in intensively milk-fed calves. Studies in rats showed that a high rate of intracellular formation of hexosamine from glucose decreases glucose uptake, but has inconsistent effects on glycogen accumulation (Virkamaki *et al.*, 1997).

Muscle and adipose tissue metabolism is also regulated by the nutrients themselves. For instance, lipogenesis has been shown to be regulated *in vivo* by glucose infusion in sheep (Ballard *et al.*, 1972). More recent research focused on facilitative glucose transporters, mainly the insulin-sensitive isoform, GLUT4, which controls extraction of plasma arterial glucose by muscle. The rate-limiting role of glucose transport in glucose homeostasis and muscle metabolism has been demonstrated by several *in vivo* and *in vitro* approaches. Indeed, the change in the nature of nutrients which occur at weaning has huge consequences for insulin action and hence muscle metabolism. For instance, in rats, the fat-rich milk is replaced by a high-carbohydrate diet characteristic of the adult. This change induces a higher insulin responsiveness of glucose utilisation and glucose transport rate in adipose tissues and muscles. These changes have been shown to be explained by a higher expression of GLUT4 (Girard *et al.*, 1992). The situation in ruminants is not the same: the contribution of carbohydrates to total energy dietary supply decreases from the suckling period to adult nutrition since carbohydrates are degraded by the rumen micro-organisms which develop at weaning. Therefore, the enhanced regulation of GLUT4 does not occur at weaning in ruminants as it does in monogastrics (Hocquette *et al.*, 1997), which is in agreement with observations on the species-specific effects of underfeeding–refeeding on muscle metabolism and plasma metabolites and hormones reported in the previous section.

Finally, muscle energy metabolism is regulated by the interactions between carbohydrate and fatty acid metabolisms. High intracellular levels of NADH, ATP and acetyl-CoA derived from LCFA or acetate oxidation decrease glucose catabolism, mainly by inhibiting the pyruvate dehydrogenase activity. This biological mechanism is known as 'the Randle cycle'. However, this competitive interaction between nutrients might not be as marked in the case of increased energy requirements resulting from higher rates of protein synthesis and deposition. Conversely, stimulation of carbohydrate catabolism, for instance by insulin, may inhibit LCFA oxidation (for review, see Faergeman and Knudsen, 1997 also Hocquette *et al.*, 1998).

Metabolism is regulated by energetic nutrients, and also by amino acids with major consequences on muscle and adipose tissue development. Among amino acids, lysine is probably one of those exerting the most specific effects on carcass composition and muscle growth. In chickens, a particularly drastic effect has been observed on breast muscle development (Tesseraud *et al.*, 1996b). It is worthwhile noting that neither threonine nor valine exhibits as pronounced an effect as lysine on body composition, as was observed in an experiment in which these three amino acids were studied together in similar conditions (Leclercq, 1998). Interestingly, preliminary results have also shown that increasing lysine can improve chicken breast muscle quality by increasing its ultimate pH and water holding capacity (Berri *et al.*, 2004), but the underlying mechanisms are still unknown.

Lysine supplementation to a lysine-deficient diet otherwise balanced in terms of other amino acids significantly increased the amounts of protein synthesised and degraded in chicken skeletal muscle (Tesseraud *et al.*, 1992, 1996a, 1996b and 2001). Similar results have been demonstrated

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in the growing pig (Salter *et al.*, 1990) and in humans (Conway *et al.*, 1980; Meredith *et al.*, 1986). Studies performed using lysine-deficient diets have also revealed the possibility of a major effect of dietary amino acid levels on protein degradation: the fractional rates of proteolysis (values expressed as % per day) measured in the breast muscle of growing chickens are always higher in the lysine-deprived animals, irrespective of age or genotype (Tesseraud *et al.*, 1996a and 2001). It is probable that the breast muscles of chickens represent a major reservoir of body protein that can be mobilised in deficiency states. Increased proteolysis in such conditions provides free amino acids that are used for protein synthesis. A specific role of amino acids on proteolytic pathways has also been demonstrated. For example, *in vitro* studies have clearly shown that amino acid deficiency stimulates autophagic (lysosomal degradation) and proteasome-mediated proteolysis (Meijer and Dubbelhuis, 2004; Yang *et al.*, 2005; Bechet *et al.*, 2005; Hamel *et al.*, 2004). Autophagic and ubiquitin-proteasome-dependent proteolysis are two major pathways responsible for skeletal muscle proteolysis (Attaix *et al.*, 2001 and 2005). In particular, ubiquitin–proteasome-dependent proteolysis degrades the bulk of muscle proteins, including myofibrillar proteins, after their targeting by ubiquitin.

With regard to protein synthesis, studies conducted over the last 10 years indicate that, in addition to be substrates for protein synthesis amino acids act as mediators of metabolic pathways in the same manner as certain hormones (e.g. insulin) (Kimball and Jefferson, 2004 and 2006; Dann and Thomas, 2006; Tesseraud *et al.*, 2006). Thus, amino acids, particularly the branched-chain amino acid leucine in skeletal muscle, modulate the activity of the intracellular protein kinases involved in the control of mRNA translation, such as 4E-binding protein (4E-BP1) and 70 kDa ribosomal protein S6 kinase (p70S6K, also called S6K1). p70S6K and, similarly, 4E-BP1 are phosphorylated in response to insulin via a signal transduction pathway involving PI3K and the mammalian target of rapamycin (mTOR) (Proud, 2006). Amino acid signalling also originates from mTOR, and activates p70S6K and 4E-BP1 (Kimball and Jefferson, 2004 and 2006; Dann and Thomas, 2006; Tesseraud *et al.*, 2006). It is noteworthy that the role of amino acids as a nutrient signal appears to be important for cell functions and metabolic pathways other than those directly concerning protein turnover. For example, overstimulation of mTOR/p70S6K by amino acids mediates a feedback loop promoting insulin resistance (i.e. inhibition of insulinstimulated glucose transport; see Um *et al.*, 2006; Tremblay *et al.*, 2005). Nevertheless, despite this increased knowledge on the role of amino acids, many questions still remain and the underlying mechanisms need to be elucidated.

Effect of nutrient delivery

Another important factor that regulates energy and protein metabolism is the rate of nutrient delivery. Dietary nutrients can be divided into slow and fast types according to the speed at which they are digested and according to the proportion of nutrients absorbed from the gut. For instance, studies in humans indicate that a slow rate of dietary protein digestion as with casein may promote postprandial protein deposition unlike a rapid rate of dietary protein absorption, as with whey (Boirie *et al.*, 1997). In calves, the coagulation of milk caseins in the abomasum results in the retention of dietary proteins and TGs in an insoluble clot for several hours. This delays the absorption of amino acids and fatty acids. As a consequence, the postprandial hormonal status is altered, thereby affecting protein metabolism: insulin secretion is lower with milk replacers rich in proteins which do not curdle in the abomasum (for review, see Hocquette and Bauchart, 1999). Furthermore, with a non-clotting diet, we observed an orientation of the muscle tissue towards a more oxidative type and indications of a lower efficiency of amino acids for protein deposition (Ortigues-Marty *et al.*, 2003).

Several studies were conducted to study the effect of nutrient synchrony on the regulation of energy metabolism, with nutrient synchrony being defined as the matching of nutrient availability with body and tissue requirements within a day. The veal calf was used as a model since this type of animal is commonly fed twice daily and nutrient absorption is expected to occur twice per day.

In a first experiment with a quickly hydrolysable protein source, it was shown that an increased feeding frequency at the same feeding level enhanced the efficiency with which protein and energy were utilised. In particular, fat deposition increased (Van den Borne *et al.*, 2006a). It can be hypothesised that the higher energy expenditure of gastrointestinal tissues associated with big meals may explain the low fat deposition when calves are fed less frequently. Furthermore, feeding the milk supply in more than five meals avoids the hyperglycaemia and glucosuria characteristics of veal calves and results in an endocrine pattern potentially more favourable for anabolism: indeed, lower responses to a meal of plasma glucose and insulin levels were observed postprandially with a high feeding frequency; in other words, insulin to glucose ratios indicate that insulin sensitivity and glucose homeostasis improve with increased feeding frequency.

In a second experiment, calves fed twice a day were assigned to different degrees of nutrient synchrony by modifying protein and lactose amounts in each meal. In other words, for the same feed level, the most asynchronous treatment was when the calves received 85% of the daily protein supply in one meal and 15% in the other meal. Unlike in pigs, heat energy production decreased and energy retained as fat increased with decreasing nutrient synchrony (Van den Borne *et al.*, 2006b). It was also shown that oxidative enzyme activities and intramuscular fat content increased with decreasing nutrient synchrony in skeletal muscles of the oxidative type only (Van den Borne *et al.*, 2007). Furthermore, simultaneous ingestion of lactose and protein results in a much larger insulin secretion

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compared with the low insulin response to a meal in case of nutrient asynchrony. Nutrient asynchrony is thus thought to improve insulin sensitivity.

Implications for product quality

Effect of pasture on beef quality

The influence of two production systems (pasture *v.* maize silage indoors) on muscle properties and gene expression was studied in 30-month-old Charolais cattle. Transcriptomic analyses (Cassar-Malek *et al.*, 2005) revealed that most of the genes differentially expressed in muscles between the two production systems were involved in metabolic and contractile properties. An interesting finding was the downregulated expression of the selenoprotein W (an antioxidant) in steers grazing on pasture, most probably linked to the selenium availability in the diet. It was also shown that the muscles from Charolais beef grazing on pasture group had more oxidative characteristics than those of steers fed maize silage indoors. In an another experiment, the separate effects of the nature of diet and grazing mobility on the metabolic potential of muscles were determined from beef grazing on pasture or fed a cut grass diet or maize silage, with half of each feeding regime group being submitted 7 days/week to a daily 5.2 km walk. It was observed that the more oxidative metabolic orientation of muscles in grazing steers originates from a combination of two separate effects: an increased mobility at pasture and a grass-based diet (Jurie *et al.*, 2006). Together with the muscle changes observed with alterations in growth path (refer to a previous section), these responses to grazing production system indicate a critical role for postnatal nutrition in regulating muscle phenotype and plasticity and hence meat quality. Indeed, the more oxidative metabolism will primarily affect meat colour, mostly by enhancing the red meat colour, which is the first characteristic the consumer takes into account to evaluate meat quality. In addition, the more oxidative muscles may also affect, to a lesser extent, the flavour, juiciness and tenderness of beef meat (for a review, see Hocquette *et al.*, 1998).

Regulation of intramuscular fat and glycogen deposition

Energy restriction was shown to affect muscle characteristics. In rabbits, energy restriction decreases intramuscular fat contents and some lipogenic activities without any change in muscle fibre types (Gondret *et al.*, 2000). These results confirm the general view that mitochondria in skeletal muscles can undergo rapid changes as a consequence of modifications in environmental conditions (Hoppeler and Martin, 2003). Generally, muscle fat content variation has been proven to result from a reciprocal balance between catabolic and anabolic fatty acid fluxes, and cannot be assigned to one specific energy pathway (Gondret *et al.*, 2004).

It has also been postulated that diets in ruminants which promote both (i) maximal fermentation in the rumen to produce gluconeogenic precursors (propionate) and (ii) which maximise starch digestion in the small intestine, might increase intramuscular fat deposition (Pethick *et al.*, 2004). One underlying mechanism is that such diets would promote increased levels of the anabolic hormones (insulin) known to stimulate lipogenesis. In addition, such diets would also deliver increased levels of net energy for lipogenesis. Finally, there is evidence that marbling adipocytes show a preference for glucose/lactate carbon while subcutaneous adipose tissue in ruminants uses mainly acetate as a source of acetyl units for lipogenesis (Smith and Crouse, 1984; Hocquette *et al.*, 2005), which could explain that G6PDH activity is well related to marbling in steers (Bonnet *et al.*, 2007).

Intramuscular level of glycogen is also a very important parameter since it determines the ultimate pH of meat which itself affects many meat quality attributes. There is evidence from studies performed in pigs, poultry and bovines that achieving an optimal pH is required to avoid meat quality defects such as acidic or dark-cutting (or dark firm dry) meat. The general view is that animal management, genotype and nutrition play an interacting role in determining the initial level of intramuscular glycogen at slaughter. For example, stress at slaughter induces a glycogen mobilisation thereby inducing a too high meat ultimate pH and dark cutting in beef. In this species and in pork, the genetic effect acts by modifying the proportion of the different muscle fibre types which contain more or less glycogen and are differently sensitive to stress. In chicken, muscle glycogen reserves at death are also significantly related to bird genotype, but without changes in muscle fibre types (Berri *et al.*, 2005). In bovine, the nutritional effect has been evidenced by a strong seasonal influence on glycogen concentration in bovine muscles in Australia with low levels in winter and summer, and high levels in spring. The low glycogen level is explained, at least in part, by low pasture availability and quality. It was concluded that a growth rate of above 1 kg day is needed to ensure a minimum level of glycogen in muscles and hence to ensure a normal pH of beef thereby reducing the occurrence of dark cutting for grazing cattle in Australia. For more details about the nutritional regulation of glycogen level in muscles, the reader is invited to refer to Pethick *et al.* (2000).

Nutritional regulation of milk composition

Feed deprivation for 2 to 4 days in cows or goats strongly decreased the yields of milk water, lactose, protein and fat; however, only milk lactose concentration decreased (lactose secretion decreased more than water secretion), whereas protein and, more markedly, fat concentrations increased (protein and fat secretion decreased less than water secretion) (Sauvant *et al.*, 1983; Ollier *et al.*, 2007; Table 1). This illustrates the key role of lactose, which is the major component regulating milk osmotic pressure, and the fact that the ability to mobilise some protein and more

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Table 1 *Responses (% of control) to underfeeding or physical activity in lactating ruminants*

Treatment	48-h food deprivation[†]	Walking[‡]
Dry-matter intake	−100	−15
Milk yield	−84	−21
Lactose yield	−89	−20
Protein yield	−75	−19
Fat yield	−45	−8
Plasma NEFA[§]	+506	+252

[†]In dairy goats (Ollier *et al.*, 2007).
[‡]In dairy cows, 9.6 km walking per day (Coulon *et al.*, 1998).
[§]Abbreviation is: NEFA = non-esterified fatty acids.

markedly fat reserves make it possible to maintain, at least in the short term, the secretion of other milk components. The same types of responses, although less extreme, were observed when *ad libitum*-fed cows were forced to walk 9.6 km/day, due to the decreased energy balance caused by the combined effects of appetite decrease and energy expenditure increase (Coulon *et al.*, 1998; Table 1). During periods of negative energy balance, including early lactation in well fed ruminants, the milk fatty acids are changed, with an increase in the percentages of stearic (18:0) and oleic (c9-18:1) acids inversely proportional to the energy balance value, which is related to the fact that these two fatty acids are largely represented in ruminant adipose tissues (Chilliard *et al.*, 1991 and 2003). However, over the longer term, energy deficiency decreases both milk yield and protein content (Coulon and Rémond, 1991), reflecting the limitation of the extent to which body protein reserves can be mobilised to sustain milk protein secretion (for a review, see Chilliard *et al.*, 1998).

Changing diet composition is well known to modify largely milk fat composition, although the composition of caseins and other proteins are not, or very slightly, responsive (Coulon *et al.*, 2001). The main factors changing milk fat content and fatty acid composition are the forage : concentrate (or fibre : starch) ratio and the lipid content (or supplementation) of the diet (Bauman and Griinari, 2003). Increasing concentrate percentage above 50% to 60% of diet dry matter decreases milk fat content and the concentrations of 14:0, 16:0 and 18:0 and increases *trans*-18:1 isomers (particularly the *trans*-10 isomer), c9,t11-CLA and 18:2 n-6 (Loor *et al.*, 2005). Some of the decrease in lipid secretion under high-concentrate diets could result from a propionate or glucose effect, which might stimulate insulin secretion and adipose tissue lipogenesis at the expense of mammary lipogenesis (the glucogenic theory). However, duodenal infusion of 1.2 kg/day glucose or its propionate equivalent only reduced lipid secretion by 5 to 8%. Propionate altered the milk fatty acid profile only slightly whereas glucose reduced short-chain fatty acids (C4 to C8) and, more markedly, C18-fatty acid secretion (Rigout *et al.*, 2003). As the two infusion treatments decreased the plasma acetate and β-OH-butyrate concentrations to the same extent, these changes cannot totally explain the different responses in milk fatty acid profile.

Several recent observations support the ancient '*trans*-fatty acid' theory to explain the milk fat depressing effects of both concentrate-rich (or starch-rich) diets and PUFA supplementations in the same paradigm (Figure 3). The changes in rumen biohydrogenations of dietary PUFA that occur when rumen pH decreases and/or when dietary PUFA concentration increases indeed result in increases of the concentrations of different *trans* isomers of 18:1 and 18:2 in milk, related to a shift of the ruminal production of *trans*-11 18:1 towards *trans*-10 18:1 (for a review, see Bauman and Griinari, 2003). These fatty acids, including *t*10,*c*12-CLA and *t*9,*c*11-CLA, are putative inhibitors of mammary lipogenic pathways (for a review, see Bernard *et al.*, 2007). Such a shift is marked when the diet is rich in starchy concentrates and/or in maize silage and is not observed when the basal diet is rich in hay (Roy *et al.*, 2006; Figure 3) or grass silage (Bell *et al.*, 2006), which favours the yield of c9,t11-CLA (the major CLA isomer in ruminants, which has putatively positive effects on health). This shift does not occur in the goat receiving a high concentrate diet supplemented with PUFA (Chilliard *et al.*, 2006), probably because ruminal fermentation is more stable in this species and/or because its mammary gland is less sensitive to the antilipogenic effect of t10,c12-CLA (Andrade and Schmidely, 2006). These different types of *trans*-fatty acids (18:1 and CLA) responses require further studies, since evaluation in rabbits showed that a 12-week intake of *trans*-10 18:1-rich butter changed the plasma lipoprotein profile (Bauchart *et al.*, 2007) and increased the occurrence of aortic lipid infiltration (Roy *et al.*, 2007), compared with *trans*-11 18:1 plus *c*9,*t*11-CLA-rich one.

Among diets not decreasing milk fat secretion, recent research has been aimed at decreasing saturated fatty acids and increasing *c*9,*t*11-CLA and/or 18:3 n-3 in order to match better with recommendations for human nutrition and health. This can be achieved mainly by increasing the proportion of good quality pasture and hay in ruminant diets (Ferlay *et al.*, 2006). Another strategy is to add plant oils or oilseeds to high forage diets (for a review, see Chilliard and Ferlay, 2004), although the putative side-effects on product quality (sensorial and nutritional aspects, including oxidative stability and effects of *trans*-11 18:1 intake on cardiovascular disease risk in humans) still require thorough investigation.

In conclusion, changes in feeding level and/or diet composition modify absorbed nutrients and, consequently, could change largely milk fat secretion and fatty acid composition, with putative modifications of the nutritional value of dairy products for consumers.

Conclusion

Research on quantitative nutrition in farm animals is still needed to increase metabolic efficiency and to optimise body composition, thereby reducing production costs. Research in animal nutrition is also of prime importance to

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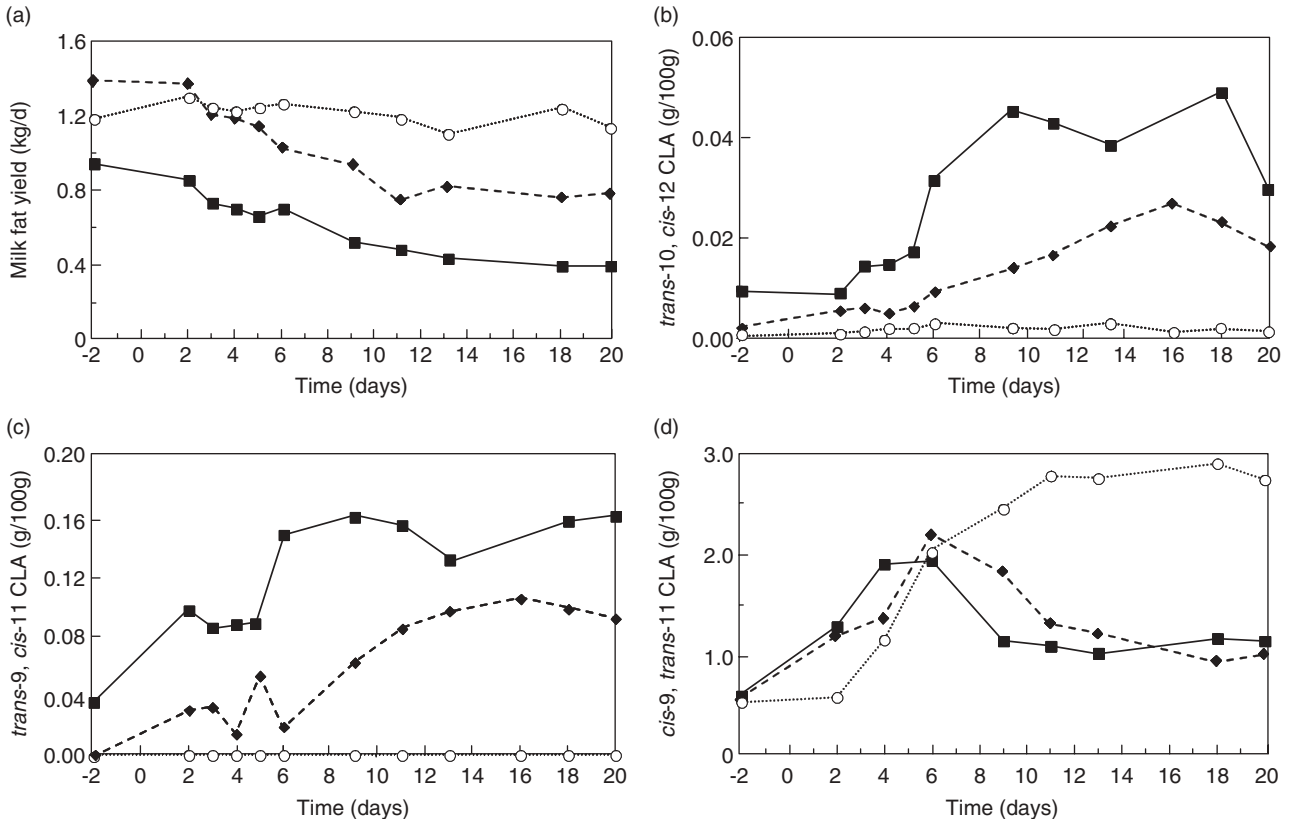

Figure 3 Effect of basal diet and plant oil supplementation on (a) milk fat yield, (b) milk fat *t*10,*c*12-CLA, (c) milk fat *t*9,*c*11-CLA and (d) milk fat *c*9,*t*11-CLA concentrations (g/100 g total fatty acids) for cows given either 'concentrate–sunflower oil' (unbroken line), 'maize silage–sunflower oil' (broken line) or 'hay–linseed oil' (dotted line) diets. Plant oils were included in the diet from day 0. Adapted from Roy et al. (2006).

ensure the production of meat and dairy products of the quality desired. Achieving these goals requires a better knowledge of individual tissue and organ requirements and a better knowledge of nutrient fate within the major tissues and organs of the body. Some major observations have, however, been highlighted in this review.

A major result of recent research is that the splanchnic tissues have a profound quantitative and qualitative impact on the supply of nutrients to other tissues and organs. Therefore, in the future, nutritionists should be able to formulate diets to meet specific nutritional requirements, on the one hand, of the gut and the liver and, on the other, of muscles and the mammary gland, taking into account transformation and recycling of nutrients by the splanchnic bed and adipose tissues. A second major conclusion is the demonstration that protein and energy metabolisms are regulated not only by food supply (namely the nutritional level) but also by the nature of nutrients (after absorption and digestion) and by nutrient delivery (which largely depends on the digestive process which differs according to nutrients). As a last major result, the examples of the nutritional regulation of metabolism given in this paper often indicate that mitochondria play a major role in mediating the action of nutrients: the more nutrients are catabolised for whatever reason associated with nutrition, the leaner the individuals are. Similarly, physical activity (which is known to increase the muscle oxidative capacity) favours the reduction of obesity and insulin resistance in human beings. This clearly emphasises the role of mitochondria in the regulation of nutrient fate within the body.

Despite some recent results, a wide range of possibilities remain to be explored with respect to the influence of nutrition on tissue and whole-body metabolism. In this context, livestock science needs to utilise the discoveries emerging from other species. Research in laboratory rodents and human beings have indeed demonstrated new and complex molecular mechanisms which contribute to explaining how and why nutrients and hormones regulate specific metabolic pathways. In addition, the wealth of information arising from genomics experiments (especially from metabolomics) offers considerable promise for characterising the complex links between nutrition of farm animals and product quality. Major advances have already been made in genomics but progress in the control of metabolism has been relatively slow so far despite great expectations. Scientific societies and networks have recently been organised to standardise procedures and methodologies with the ultimate aim of improving the reproducibility of genomic techniques. These initiatives should contribute to making genomics fully operative in animal science in the future. In addition, in the near future, the more recent knowledge related to biological processes

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at the cellular level will have to be integrated with classical data involving tissue or whole-animal studies to gain a broader view of metabolism.

References

Allen MS, Bradford BJ and Harvatine KJ 2005. The cow as a model to study food intake regulation. Annual Review of Nutrition 25, 523–547.

Andrade PVD and Schmidely P 2006. Effect of duodenal infusion of trans10,cis12-CLA on milk performance and milk fatty acid profile in dairy goats fed high or low concentrate diet in combination with rolled canola seed. Reproduction Nutrition Development 46, 31–48.

Attaix D, Combaret L, Pouch MN and Taillandier D 2001. Regulation of proteolysis. Current Opinion in Clinical Nutrition and Metabolic Care 4, 45–49.

Attaix D, Mosoni L, Dardevet D, Combaret L, Mirand PP and Grizard J 2005. Altered responses in skeletal muscle protein turnover during aging in anabolic and catabolic periods. The International Journal of Biochemistry and Cell Biology 37, 1962–1973.

Baker DH 2006. Comparative species utilization and toxicity of sulfur amino acids. The Journal of Nutrition 136, 1670S–1675S.

Balage M, Sinaud S, Prod'homme M, Dardevet D, Vary TC, Kimball SR, Jefferson LS and Grizard J 2001. Amino acids and insulin are both required to regulate assembly of the eIF4E. eIF4G complex in rat skeletal muscle. The American Journal of Physiology 281, E565–E574.

Ballard FJ, Filsell OH and Jarrett IG 1972. Effects of carbohydrate availability on lipogenesis in sheep. The Biochemical Journal 226, 193–200.

Bareille N, Faverdin P and Hay M 1997. Modification of feed intake response to a beta 2-agonist by bovine somatotropin in lactating or dry dairy cows. Journal of Dairy Science 80, 52–66.

Barnes DM, Calvert CC and Klasing KC 1995. Methionine deficiency decreases protein accretion and synthesis but not tRNA acylation in muscles of chicks. The Journal of Nutrition 125, 2623–2630.

Bauchart D, Ortigues I, Hocquette JF, Gruffat D and Durand D 1996. Energy and fat metabolism of the liver, the digestive tract and muscles: transport, processing, energy consumption, fixation by tissues. In Veal: Perspective to the year 2000 (ed. The French Federation of Veal Producers), pp. 255–290. Presse de Jouve, Le Mans, France.

Bauchart D, Roy A, Lorenz S, Chardigny JM, Ferlay A, Gruffat D, Sébédio JL, Chilliard Y and Durand D 2007. Butters varying in trans 18:1 and cis-9,trans-11 conjugated linoleic acid modify plasma lipoproteins in the hypercholesterolemic rabbit. Lipids 42, 123–133.

Bauman DE and Griinari JM 2003. Nutritional regulation of milk fat synthesis. Annual Review of Nutrition 23, 203–227.

Bechet D, Tassa A, Combaret L, Taillandier D and Attaix D 2005. Regulation of skeletal muscle proteolysis by amino acids. Journal of Renal Nutrition 15, 18–22.

Bell JA, Griinari JM and Kennelly JJ 2006. Effect of safflower oil, flaxseed oil, monensin, and vitamin e on concentration of conjugated linoleic acid in bovine milk fat. Journal of Dairy Science 89, 733–748.

Benatti P, Peluso G, Nicolai R and Calvani M 2004. Polyunsaturated fatty acids: biochemical, nutritional and epigenetic properties. Journal of the American College of Nutrition 23, 281–302.

Bennet WM, Connacher AA, Scrimgeour CM, Smith K and Rennie MJ 1989. Increase in anterior tibialis muscle protein synthesis in healthy man during mixed amino acid infusion: studies of incorporation of [1-13C]leucine. Clinical Science 76, 447–454.

Bermingham EN, Nozière P, Vernet J, Lapierre H, Léger S, Sauvant D, Ortigues-Marty I 2007. The relationships betwen intake and portal fluxes of energy metabolites in ruminants: a meta-analysis. Animal Feed Sciences Technologies (special issue Modelling), in press.

Bernard L, Leroux C and Chilliard Y 2007. Expression and nutritional regulation of lipogenic genes in the ruminant lactating mammry gland. Advances in Experimental Medicine and Biology, in press.

Berri C, Relandeau C, Le Bellego L and Picard M 2004. Effect of dietary lysine and stock density on broiler performance and breast meat quality. 2004 Joint Meeting of the American Dairy Science Association, American Society of Animal Science, Poultry Science Association, St Louis, USA; 2004/07/25-29. Journal of Animal Science 82 (Suppl 1).

Berri C, Debut M, Santé-Lhoutellier V, Arnould C, Boutten B, Sellier N, Baéza E, Jehl N, Jego Y, Duclos MJ and Le Bihan-Duval E 2005. Variations in chicken breast meat quality: implications of struggle and muscle glycogen content at death. The British Poultry Science 46, 572–579.

Boirie Y, Dangin M, Gachon P, Vasson MP, Maubois JL and Beaufrère B 1997. Slow and fast dietary proteins differently modulate postprandial protein accretion. Proceedings of the National Academy of Science USA 94, 14930–14935.

Bonnet M, Faulconnier Y, Hocquette JF, Bocquier F, Leroux C, Martin P and Chilliard Y 2004. Nutritional status induces divergent variations of GLUT4 protein content, but not lipoprotein lipase activity, between adipose tissues and muscles in adult cattle. The British Journal of Nutrition 92, 617–625.

Bonnet M, Faulconnier Y, Leroux C Jurie C, Cassar-Malek I, Bauchart D, Boulesteix P, Pethick D, Hocquette JF, Chilliard Y 2007. Glucose-6-phosphate dehydrogenase and leptin are related to marbling differences among Limousin and Angus or Japanese Black × Angus steers. Journal of Animal Science, in press. http://jas.fass.org/cgi/content/abstract/jas.2007-0062vl?ct (online).

Brockman RP 1993. Glucose and short-chain fatty acid metabolism. In Quantitative aspects of ruminant digestion and metabolism (ed. JM Forbes and J France), pp. 249–264. CAB International, Wallingford, UK.

Cassar-Malek I, Hocquette JF, Jurie C, Listrat A, Jailler R, Bauchart D, Briand Y and Picard B 2004. Muscle-specific metabolic, histochemical and biochemical responses to nutritionally induced discontinuous growth path. Animal Science 79, 49–59.

Cassar-Malek I, Bernard C, Jurie C, Barnola I, Gentès G, Dozias D, Micol D and Hocquette JF 2005. Pasture-based beef production systems may Influence muscle characteristics and gene expression. In Indicators of milk and beef quality (ed. JF Hocquette and S Gigli), EAAP publication no. 112, pp. 385–390. Wageningen Academic Publishers, Wageningen, The Netherlands.

Chartrin P, Bernadet MD, Guy G, Mourot J, Hocquette JF, Rideau N, Duclos MJ and Baéza E 2006. Does overfeeding enhance genotype effects on energy metabolism and lipid deposition in breast muscle of ducks? Comparative Biochemistry and Physiology 145, 413–418.

Chilliard Y 1993. Dietary fat and adipose tissue metabolism in ruminants, pigs, and rodents: a review. Journal of Dairy Science 76, 3897–3931.

Chilliard Y 1999. Metabolic adaptations and nutrient partitioning in the lactating animal. In Biology of Lactation (ed. J Martinet, LM Houdebine and HH Head), pp. 503–552. INRA, Paris, France.

Chilliard Y and Ottou JF 1995. Duodenal infusion of oil in midlactation cows. 7. Interaction with niacin on responses to glucose, insulin, and beta-agonist challenges. Journal of Dairy Science 78, 2452–2463.

Chilliard Y and Ferlay A 2004. Dietary lipids and forages interactions on cow and goat milk fatty acid composition and sensory properties. Reproduction Nutrition Development 44, 467–492.

Chilliard Y, Gagliostro G, Flechet J, Lefaivre J and Sebastian I 1991. Duodenal rapeseed oil infusion in early and midlactation cows. 5. Milk fatty acids and adipose tissue lipogenic activities. Journal of Dairy Science 74, 1844–1854.

Chilliard Y, Bocquier F and Doreau M 1998. Digestive and metabolic adaptations of ruminants to undernutrition, and consequences on reproduction. Reproduction Nutrition Development 38, 131–152.

Chilliard Y, Ferlay A, Faulconnier Y, Bonnet M, Rouel J and Bocquier F 2000. Adipose tissue metabolism and its role in adaptations to undernutrition in ruminants. The Proceedings of the Nutrition Society 59, 127–134.

Chilliard Y, Lerondelle C, Disenhaus C, Mouchet C and Paris A 2001. Recombinant growth hormone: Potential interest and risks of its use in bovine miilk production. In Biotechnology in Animal Husbandry (ed. R Renaville and A Burny), pp. 65–97. Kluwer Academic Publishing, Dordrecht, The Netherlands.

Chilliard Y, Ferlay A, Rouel J and Lamberet G 2003. A review of nutritional and physiological factors affecting goat milk lipid synthesis and lipolysis. Journal of Dairy Science 86, 1751–1770.

Chilliard Y, Delavaud C and Bonnet M 2005. Leptin expression in ruminants: nutritional and physiological regulations in relation with energy metabolism. Domestic Animal Endocrinology 29, 3–22.

Chilliard Y, Rouel J, Ferlay A, Bernard L, Gaborit P, Raynal-Ljutovac K, Lauret A and Leroux C 2006. Optimising goat's milk and cheese fatty acid composition. In Improving the fat content of foods (ed. C Williams and J Buttriss), pp. 281–312. Woodhead Publishing Limited, Cambridge, UK.

https://doi.org/10.1017/S1751731107000602 Published online by Cambridge University Press

Clarke SD and Abraham S 1992. Gene expression-nutrient control of pretranscriptional and posttranscriptional events. The FASEB Journal 6, 3146–3152.

Conway JM, Bier DM, Motil KJ, Burke JF and Young VR 1980. Whole-body lysine flux in young adult men: effects of reduced total protein and of lysine intake. The American Journal of Physiology 239, E192–E200.

Coulon JB and Rémond B 1991. Variations in milk output and milk protein content in response to the level of energy supply to the dairy cow: a review. Livestock Production Science 29, 31–47.

Coulon JB, Pradel P, Cochard T and Poutrel B 1998. Effect of extreme walking conditions for dairy cows on milk yield, chemical composition, and somatic cell count. Journal of Dairy Science 81, 994–1003.

Coulon JB, Dupont D, Pochet S, Pradel P and Duployer H 2001. Effect of genetic potential and level of feeding on milk protein composition. Journal of Dairy Research 68, 569–577.

Dann SG and Thomas G 2006. The amino acid sensitive TOR pathway from yeast to mammals. FEBS Letters 580, 2821–2829.

Drackley JK, Overton TR and Douglas GN 2001. Adaptations of glucose and long-chain fatty acid metabolism in liver of dairy cows during the periparturient period. Journal of Dairy Science 84, E100–E112.

Drackley JK, Donkin SS and Reynolds CK 2006. Major advances in fundamental dairy cattle nutrition. Journal of Dairy Science 89, 1324–1336.

Faergeman NJ and Knudsen J 1997. Role of long-chain fatty acyl-CoA esters in the regulation of metabolism and in cell signalling. The Biochemical Journal 323, 1–12.

Faulconnier Y, Bonnet M, Bocquier F, Leroux C and Chilliard Y 2001. Effects of photoperiod and feeding level on adipose tissue and muscle lipoprotein lipase activity and mRNA level in dry non-pregnant sheep. The British Journal of Nutrition 85, 299–306.

Ferlay A, Martin B, Pradel P, Coulon JB and Chilliard Y 2006. Influence of grass-based diets on milk fatty acid composition and milk lipolytic system in Tarentaise and Montbeliarde cow breeds. Journal of Dairy Science 89, 4026–4041.

Ferré P 1999. Regulation of gene expression by glucose. Proceedings of the Nutrition Society 58, 621–623.

Gagliostro G and Chilliard Y 1991. Duodenal rapeseed oil infusion in early and midlactation cows. 4. *In vivo* and *in vitro* adipose tissue lipolytic responses. Journal of Dairy Science 74, 1830–1843.

Garlick PJ and Grant I 1988. Amino acid infusion increases the sensitivity of muscle protein synthesis *in vivo* to insulin. Effect of branched-chain amino acids. The Biochemical Journal 254, 579–584.

Geay Y and Robelin J 1979. Variation of meat production capacity in cattle due to genotype and level of feeding. Genotype–nutrition interaction. Livestock Production Science 6, 263–276.

Girard J, Ferré P, Pégorier JP and Duée PH 1992. Adaptations of glucose and fatty acid metabolism during perinatal period and suckling-weaning transition. Physiological Reviews 72, 507–562.

Girard J, Perdereau D, Foufelle F, Prip-Buus C and Ferré P 1994. Regulation of lipogenic enzyme gene expression by nutrients and hormones. The FASEB Journal 8, 36–42.

Gondret F, Lebas F and Bonneau M 2000. Restricted feed intake during fattening reduces intramuscular lipid deposition without modifying muscle fiber characteristics in rabbits. The Journal of Nutrition 130, 228–233.

Gondret F, Hocquette JF and Herpin P 2004. Age-related relationships between muscle fat content and metabolic traits in growing rabbits. Reproduction Nutrition Development 44, 1–16.

Grizard J, Dardevet D, Papet I, Mosoni L, Patureau-Mirand P, Attaix D, Tauveron I, Bonin D and Arnal M 1995. Nutrient regulation of skeletal muscle protein metabolism in animals. The involvement of hormones and substrates. Nutrition Research Reviews 8, 67–91.

Grizard J, Picard B, Dardevet D, Balage M and Rochon C 1999. Regulation of muscle growth and development. In Protein metabolism and nutrition (ed. GE Lobley, A While and JC MAcRae), EAAP publication no. 96, pp. 177–201. Wageningen, The Netherlands.

Hamel FG, Fawcett J, Bennett RG and Duckworth WC 2004. Control of proteolysis: hormones nutrients and the changing role of the proteasome. Current Opinion in Clinical Nutrition and Metabolic Care 7, 255–258.

Havel PJ 2004. Update on adipocyte hormones: regulation of energy balance and carbohydrate/lipid metabolism. Diabetes 53(Suppl 1), S143–S151.

Hellerstein MK 2003. *In vivo* measurement of fluxes through metabolic pathways: the missing link in functional genomics and pharmaceutical research. Annual Review of Nutrition 23, 379–402.

Hocquette JF 2005. Where are we in genomics? Journal of Physiology and Pharmacology 56(Suppl 3), 37–70.

Hocquette JF and Bauchart D 1999. Intestinal absorption, blood transport and hepatic and muscle metabolism of fatty acids in preruminant and ruminant animals. Reproduction Nutrition Development 39, 27–48.

Hocquette JF and Abe H 2000. Facilitative glucose transporters in livestock species. Reproduction Nutrition Development 40, 517–533.

Hocquette JF, Castiglia-Delavaud C, Graulet B, Ferré P, Picard B and Vermorel M 1997. Weaning marginally affects glucose transporter (GLUT4) expression in muscles and adipose tissues in the calf. The British Journal of Nutrition 78, 251–271.

Hocquette JF, Jurie C, Bonnet M and Pethick DW 2005. Bovine intramuscular adipose tissue has a higher potential for fatty acid synthesis from glucose than subcutaneous adipose tissue. Proceedings of the 56th Annual Meeting of the European Association for Animal Production, Uppsala, 5–8 June, p. 248 (abstr.).

Hocquette JF, Ortigues-Marty I, Pethick DW, Herpin P and Fernandez X 1998. Nutritional and hormonal regulation of energy metabolism in skeletal muscles of meat-producing animals. Livestock Production Science 56, 115–143.

Hoppeler H and Martin F 2003. Plasticity of skeletal muscle mitochondria: structure and function. Medicine and Science in Sports and Exercise 25, 95–104.

Huang X, Eriksson KF, Vaag A, Lehtovirta M, Hansson M, Laurila E, Kanningen T, Thuesen-Olesen B, Kurucz I, Koranyi L and Groop L 1999. Insulin-regulated mitochondrial gene expression is associated with glucose flux in human skeletal muscle. Diabetes 48, 1508–1514.

Jurie C, Ortigues-Marty I, Picard B, Micol D and Hocquette JF 2006. The separate effects of the nature of diet and grazing mobility on metabolic potential of muscles from Charolais steers. Livestock Science 104, 182–192.

Khan A and Safdar M 2003. Role of diet, nutrients, spices and natural products in diabetes mellitus. Pakistan Journal of Nutrition 2, 1–12.

Kimball SR and Jefferson LS 2004. Molecular mechanisms though which amino acids mediate signaling though the mammalian target of rapamycin. Current Opinion in Clinical Nutrition and Metabolic Care 7, 39–44.

Kimball SR and Jefferson LS 2006. New functions for amino acids: effects on gene transcription and translation. The American Journal of Clinical Nutrition 83, 500S–507S.

Kimball SR, Farrell PA and Jefferson LS 2002. Invited review: role of insulin in translational control of protein synthesis in skeletal muscle by amino acids or exercise. Journal of Applied Physiology 93, 1168–1180.

Kino K and Okumura J 1986. The effect of single essential amino acid deprivation on chick growth and nitrogen and energy balances at *ad libitum*- and equalized-food intakes. Poultry Science 65, 1728–1735.

Leclercq B 1998. Specific effects of lysine on broiler production: comparison with threonine and valine. Poultry Science 77, 118–123.

Lobley GE 1991. Organ and tissue metabolism: present status and future trends. In Energy metabolism of farm animals (ed. C Wenk and M Boessinger), pp. 80–87. Institut für Nutztierwissenschaften, Zürich, Switzerland.

Lobley GE 1998. Nutritional and hormonal control of muscle and peripheral tissue metabolism in farm species. Livestock Production Science 56, 91–114.

Loor JJ, Ferlay A, Ollier A, Doreau M and Chilliard Y 2005. Relationship among trans and conjugated fatty acids and bovine milk fat yield due to dietary concentrate and linseed oil. Journal of Dairy Science 88, 726–740.

Loor JJ, Dann HM, Janovick Guretzky NA, Everts RE, Oliveira R, Green CA, Litherland NB, Rodriguez-Zas SL, Lewin HA and Drackley JK 2006. Plane of nutrition prepartum alters hepatic gene expression and function in dairy cows as assessed by longitudinal transcript and metabolic profiling. Physiological Genomics 27, 29–41.

Meijer AJ and Dubbelhuis P 2004. Amino acid signalling and the integration of metabolism. Biochemical and Biophysical Research Communications 313, 397–403.

Meredith CN, Wen ZM, Bier DM, Matthews DE and Young VR 1986. Lysine kinetics at graded lysine intakes in young men. The American Journal of Clinical Nutrition 43, 787–794.

https://doi.org/10.1017/S1751731107000602 Published online by Cambridge University Press

Muramatsu T 1990. Nutrition and whole-body protein turnover in the chicken in relation to mammalian species. Nutrition Research Reviews 3, 211–228.

Muramatsu T, Salter DN and Coates ME 1985. Protein turnover of breast muscle in germ-free and conventional chicks. The British Journal of Nutrition 54, 131–145.

Muramatsu T, Kato M, Tasaki I and Okumura J 1986. Enhanced whole-body protein synthesis by methionine and arginine supplementation in protein-starved chicks. The British Journal of Nutrition 55, 635–641.

Nieto R and Lobley GE 1999. Integration of protein metabolism within the whole body and between organs. In Protein metabolism and nutrition (ed. GE Lobley, A White and JC MacRae), EAAP publication no. 96, pp. 69–99. Wageningen, Netherlands.

O'Connor PM, Bush JA, Suryawan A, Nguyen HV and Davis TA 2003a. Insulin and amino acids independently stimulate skeletal muscle protein synthesis in neonatal pigs. The American Journal of Physiology 284, E110–E119.

O'Connor PM, Kimball SR, Suryawan A, Bush JA, Nguyen HV, Jefferson LS and Davis TA 2003b. Regulation of translation initiation by insulin and amino acids in skeletal muscle of neonatal pigs. The American Journal of Physiology 285, E40–E53.

Ollier S, Robert-Granié C, Bernard L, Chilliard Y and Leroux C 2007. Mammary transcriptome analysis of food-deprived lactating goats highlights genes involved in milk secretion and programmed cell death. The Journal of Nutrition 137, 560–567.

Ortigues I and Doreau M 1995. Responses of the splanchnic tissues of ruminants to changes in intake: absorption of digestion end products, tissue mass, metabolic activity and implications to whole animal energy metabolism. Annales de Zootechnie 44, 321–346.

Ortigues I and Visseiche AL 1995. Whole-body fuel selection in ruminants: nutrient supply and utilization by major tissues. The Proceedings of the Nutrition Society 54, 235–251.

Ortigues-Marty I, Hocquette JF, Bertrand G, Martineau C, Vermorel M and Toullec R 2003. The incorporation of solubilized wheat proteins in milk replacers for veal calves: effects on growth performance and muscle oxidative capacity. Reproduction Nutrition Development 43, 57–76.

Pearce J 1977. Some differences between avian and mammalian biochemistry. The International Journal of Biochemistry 8, 269–279.

Petersen KF, Dufour S, Befroy D, Garcia R and Shulman GI 2004. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. The New England Journal of Medicine 35, 664–671.

Pethick DW, Cummins L, Gardner GE, Jacobs RH, Knee BW, McDowell M, McIntyre BL, Tudor G, Walker PJ and Warner RD 2000. The regulation of glycogen level in the muscle of ruminants by nutrition. Proceedings of the New Zealand Society of Animal Production 60, 94–97.

Pethick DW, Harper GS and Oddy VH 2004. Growth, development and nutritional manipulation of marbling in cattle: a review. Australian Journal Agricultural Research 44, 705–715.

Piot C, Hocquette JF, Veerkamp JH, Durand D and Bauchart D 1999. Effects of dietary coconut oil on fatty acid oxidation capacity of the liver, the heart and skeletal muscles in the preruminant calf. The British Journal of Nutrition 82, 299–308.

Prod'homme M, Rieu I, Balage M, Dardevet D and Grizard J 2004. Insulin and amino acids both strongly participate to the regulation of protein metabolism. Current Opinion in Clinical Nutrition and Metabolic Care 7, 71–77.

Prod'homme M, Balage M, Debras E, Farges MC, Kimball S, Jefferson L and Grizard J 2005. Differential effects of insulin and dietary amino acids on muscle protein synthesis in adult and old rats. The Journal of Physiology 563, 235–248.

Proietto J, Filippis A, Nakhla C and Clark S 1999. Nutrient-induced insulin resistance. Molecular and Cellular Endocrinology 151, 143–149.

Proud CG 2006. Regulation of protein synthesis by insulin. Biochemical Society Transactions 34, 213–216.

Raben A, Mygind E and Astrup A 1998. Lower activity of oxidative key enzymes and smaller fiber areas in skeletal muscle of postobese women. The American Journal of Physiology 275, E487–E494.

Reeds PJ, Fjeld CR and Jahoor F 1994. Do the differences between the amino acid compositions of acute-phase and muscle proteins have a bearing on nitrogen loss in traumatic states? The Journal of Nutrition 124, 906–910.

Rigout S, Hurtaud C, Lemosquet S, Bach A and Rulquin H 2003. Lactational effect of propionic acid and duodenal glucose in cows. Journal of Dairy Science 86, 243–253.

Rimbert V, Boirie Y, Bedu M, Hocquette JF, Ritz P and Morio B 2004. Muscle fat oxidative capacity is not impaired by age but by physical inactivity: association with insulin sensitivity. The FASEB Journal 18, 737–739.

Roy A, Ferlay A, Shingfield KJ and Chilliard Y 2006. Examination of the persistency of milk fatty acid composition responses to plant oils in cows given different basal diets, with particular emphasis on trans-C18:1 fatty acids and isomers of conjugated linoleic acid. Animal Science 82, 479–492.

Roy A, Chardigny JM, Bauchart D, Ferlay A, Lorenz S, Durand D, Gruffat D, Faulconnier Y, Sébédio JL and Chilliard Y 2007. Butters rich either in *trans*-10-C18:1 or in trans-11-C18:1 plus cis-9 trans-11 CLA differentially affect plasma lipids and aortic fatty streak in experimental atherosclerosis in rabbits. Animal 1, 467–476.

Salter DN, Montgomery AI, Hudson A, Quelch DB and Elliot RJ 1990. Lysine requirements and whole-body protein turnover in growing pigs. The British Journal of Nutrition 63, 503–513.

Sauvant D, Soyeux Y and Chilliard Y 1983. Réflexions sur l'étiopathogénie des maladies de la nutrition. Bulletin Technique CRZV Theix INRA 53, 117–121.

Sell H, Dietze-Schroeder D and Eckel J 2006. The adipocyte-myocyte axis in insulin resistance. Trends in Endocrinology and Metabolism 17, 416–422.

Seve B, Reeds PJ, Fuller MF, Cadenhead A and Hay SM 1986. Protein synthesis and retention in some tissues of the young pig as influenced by dietary protein intake after early-weaning. Possible connection to the energy metabolism. Reproduction Nutrition Development 26, 849–861.

Sinaud S, Balage M, Bayle G, Dardevet D, Vary TC, Kimball SR, Jefferson LS and Grizard J 1999. Diazoxide-induced insulin deficiency greatly reduced muscle protein synthesis in rats: involvement of eIF4E. The American Journal of Physiology 276, E50–E61.

Smith SB and Crouse JD 1984. Relative contributions of acetate, lactate and glucose to lipogenesis in bovine intramuscular and subcutaneous adipose tissue. The Journal of Nutrition 114, 792–800.

Tesseraud S, Larbier M, Chagneau AM and Geraert PA 1992. Effect of dietary lysine on muscle protein turnover in growing chickens. Reproduction Nutrition Development 32, 163–171.

Tesseraud S, Grizard J, Debras E, Papet I, Bonnet Y, Bayle G and Champredon C 1993. Leucine metabolism in lactating and dry goats: effect of insulin and substrate availability. The American Journal of Physiology 265, E402–E413.

Tesseraud S, Peresson R, Lopes J and Chagneau AM 1996a. Dietary lysine deficiency greatly affects muscle and liver protein turnover in growing chickens. The British Journal of Nutrition 75, 853–865.

Tesseraud S, Maaa N, Peresson R and Chagneau AM 1996b. Relative responses of protein turnover in three different skeletal muscles to dietary lysine deficiency in chicks. British Poultry Science 37, 641–650.

Tesseraud S, Temim S, Le Bihan-Duval E and Chagneau AM 2001. Increased responsiveness to dietary lysine deficiency of *pectoralis major* muscle protein turnover in broilers selected on breast development. Journal of Animal Science 79, 927–933.

Tesseraud S, Abbas M, Duchene S, Bigot K, Vaudin P and Dupont J 2006. Mechanisms involved in the nutritional regulation of mRNA translation: features of avian model. Nutrition Research Reviews 19, 104–116.

Tesseraud S, Metayer S, Duchene S, Bigot K, Grizard J and Dupont J 2007. Regulation of protein metabolism by insulin: value of different approaches and animal models. Domestic Animal Endocrinology 33, 123–142.

Tremblay F, Jacques H and Marette A 2005. Modulation of insulin action by dietary proteins and amino acids: role of the mammalian target of rapamycin nutrient sensing pathway. Current Opinion in Clinical Nutrition and Metabolic Care 8, 457–462.

Um SH, D'Alessio D and Thomas G 2006. Nutrient overload, insulin resistance, and ribosomal protein S6 kinase 1, S6K1. Cell Metabolism 3, 393–402.

Unger RH 2005. Longevity lipotoxicity and leptin: the adipocyte defense against feasting and famine. Biochimie 87, 57–64.

Uyeda K and Repa JJ 2006. Carbohydrate response element binding protein ChREBP a transcription factor coupling hepatic glucose utilization and lipid synthesis. Cell Metabolism 4, 107–110.

https://doi.org/10.1017/S1751731107000602 Published online by Cambridge University Press

Van den Borne JJGC, Verstegen MWA, Alferink SJJ, Giebels RMM and Gerrits WJJ 2006a. Effects of feeding frequency and feeding level on nutrient utilization in heavy preruminant calve. Journal of Dairy Science 89, 3578–3586.

Van den Borne JJGC, Verstegen MWA, Alferink SJJ, Van Ass FHM and Gerrits WJJ 2006b. Synchronizing the availability of amino acids and glucose decreases fat retention in heavy preruminant calves. The Journal of Nutrition 136, 2181–2187.

Van den Borne JJ, Hocquette JF, Verstegen MW and Gerrits WJ 2007. Whole body and muscle energy metabolism in preruminant calves: effects of nutrient synchrony and physical activity. The British Journal of Nutrition 97, 667–675.

Virkamaki A, Daniels MC, Hamalainen S, Utriainen T, McClain D and Yki-Järvinen H 1997. Activation of the hexosamine pathway by glucosamine *in vivo* induces insulin resistance in multiple insulin sensitive tissues. Endocrinology 138, 2501–2507.

Volpi E, Lucidi P, Cruciani G, Monacchia F, Reboldi G, Brunetti P, Bolli GB and DeFeo P 1996. Contribution of amino acids and insulin to protein anabolism during meal absorption. Diabetes 45, 1245–1252.

Waterlow JC 1984. Protein turnover with special reference to man. Quarterly Journal of Experimental Physiology 69, 409–438.

Watt PW, Corbett ME and Rennie MJ 1992. Stimulation of protein synthesis in pig skeletal muscle by infusion of amino acids during constant insulin availability. The American Journal of Physiology 262, E453–E460.

Webel DM and Baker DH 1999. Cystine is the first limiting amino acid for utilization of endogenous amino acids in chicks fed a protein-free diet. Nutrition Research 19, 569–577.

Weickert MO and Pfeiffer AFH 2006. Signalling mechanisms linking hepatic glucose and lipid metabolism. Diabetologia 49, 1732–1741.

Wester TJ, Lobley GE, Birnie LM, Crompton LA, Brown S, Buchan V, Calder AG, Milne E and Lomax MA 2004. Effect of plasma insulin and branched-chain amino acids on skeletal muscle protein synthesis in fasted lambs. The British Journal of Nutrition 92, 401–409.

Yaman MA, Kita K and Okumura J 2000. Various macronutriments intakes additively stimulate protein synthesis in liver and muscle of food-deprived chicks. The Journal of Nutrition 130, 70–76.

Yang YP, Liang ZQ, Gu ZL and Qin ZH 2005. Molecular mechanism and regulation of autophagy. Acta Pharmacologica Sinica 26, 1421–1434.

Yoshizawa F, Nagasawa T, Nishizawa N and Funabiki R 1997. Protein synthesis and degradation change rapidly in response to food intake in muscle of food-deprived mice. The Journal of Nutrition 127, 1156–1159.

Yoshizawa F, Kimball SR, Vary TC and Jefferson LS 1998. Effect of dietary protein on translation initiation in rat skeletal muscle and liver. The American Journal of Physiology 275, E814–E820.

Zanusso J, Rémignon H, Guy G, Manse H and Babilé R 2003. The effects of overfeeding on myofibre characteristics and metabolical traits of the breast muscle in Muscovy ducks (*Caïrina moschata*). Reproduction Nutrition Development 43, 105–115.

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