Manipulation of Tissue Energy Metabolism in Meat-Producing Ruminants - Review -

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ABSTRACT : Skeletal muscle is of major economic importance since it is finally converted to meat for consumers. The increase in meat production with low costs of production may be achieved by optimizing muscle growth, whereas a high meat quality requires, among other factors, the optimization of intramuscular glycogen and fat stores. Thus, research in energy metabolism aims at controling muscle metabolism, but also liver and adipose tissue metabolism in order to optimize energy partitioning in favour of muscles. Liver is characterized by high anabolic and catabolic rates. Metabolic enzymes are regulated by nutrients through short-term regulation of their activities and long-term regulation of expression of their genes. Consequences of liver metabolic regulation on energy supply to muscles may affect protein deposition (and hence growth) as well as intramuscular energy stores. Adipose tissues are important body reserves of triglycerides, which result from the balance between lipogenesis and lipolysis. Both processes depend on the feeding level and on the nature of nutrients, which indirectly affect energy delivery to muscles. In muscles, the regulation of rate-limiting nutrient transporters, of metabolic enzyme activities and of ATP production, as well as the interactions between nutrients affect free energy availability for muscle growth and modify muscle metabolic characteristics which determine meat quality. The growth of tissues and organs, the number and the characteristics of muscle fibers depend, for a great part, on early events during the fetal life. They include variations in quantitative and qualitative nutrient supply to the fetus, and hence in maternal nutrition. During the postnatal life, muscle growth and characteristics are affected by the age and the genetic type of the animals, the feeding level and the diet composition. The latter determines the nature of available nutrients and the rate of nutrient delivery to tissues, thereby regulating metabolism. Physical activity at pasture also favours the orientation of muscle metabolism, towards the oxidative type. Consequently, breeding systems may be of a great importance during the postnatal life. Research is now directed towards the determination of individual tissue and organ energy requirements, a better knowledge of nutrient partitioning between and within organs and tissues. The discovery of new molecules (e. g. leptin), of new molecular mechanisms and of more powerful techniques (DNA chips) will help to achieve these objectives. The integration of the different levels of knowledge will finally allow scientists to formulate new types of diets adapted to sustain a production of high quality meat with lower costs of production. (*Asian-Aust. J. Anim. Sci. 2001. Vol. 14, No. 5 : 720-732*)

Key Words : Energy Metabolism, Tissue, Manipulation, Ruminants, Meat

INTRODUCTION

Meat consumption pattern differs greatly between countries. Indeed, in the 1990s, meat consumption ranged from 4 kg/head per year in India (on average 18 kg for Asia), to 78 kg/head per year for industrialized countries. However, the demand for meat in developing countries is increasing rapidly, especially in China (Gill, 1999). Therefore, the major objective of research in developing countries is to increase meat production with low costs of production. Meanwhile, in industrialized countries the meat industry, especially beef, faces major problems, which are the meat safety crisis and the unreliability of meat eating quality (for review, see Tarrant, 1998; Geay et al., 2001). Therefore, in developed countries nowadays, research programmes are mainly directed towards the improvement of meat quality rather than productivity. Generally, the first objective is thus to quantitatively satisfy the demand of consumers. This is what happened in Europe after the Second World War. Thereafter, the priority of research objectives switches from the improvement of productivity to the improvement of quality when the quantitative demand of consumers for meat is satisfied.

Generally speaking, animal production can be improved quantitatively through genetic selection, breeding systems, and nutrition. For instance, animals need appropriate nutrition to express their genetic potential. However, the effects of genetic, breeding and nutritional factors on meat quality are known to a limited extent and, thus, need to be studied. This raises the question of a possible antagonism between productivity and meat quality. For instance, the genetic selection in favour of rapid growth in turkeys led to an excessive glycolytic muscle metabolism to the detriment of some organoleptic meat qualities (for review, see Hocquette et al., 1998).

Ruminants have specific digestive and nutritional features: the microbial population of the rumen enables them to digest plants, and to take advantage of the plant cell walls and non-protein nitrogen in contrast to monogastric mammals. This specificity is also

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responsible for the generally lower efficiency of production observed in ruminants, as compared with monogastrics. This is the reason why the manipulation of the rumen ecosystem is the subject of active investigation to improve the production of meat products (for review, see Jouany et al., 2000). However, the manipulation of tissue metabolism may also support better performances as well as improved quality of animal products. Nowadays, the new challenge is to manipulate protein and energy metabolism of tissues in order to optimize the muscle metabolic characteristics which determine sensory properties of meat. In order to improve simultaneously average daily gain, body gain composition and muscle metabolism, a better knowledge of the partition of absorbed nutrients between organs (digestive tract, liver) and tissues (muscles and adipose tissues) (figure 1) as well as within muscles (i.e. between fibers and intramuscular adipocytes) (figure 2) is required.

The present paper describes recent data obtained in ruminants on the nutritional control of the partition of energy-yielding substrates between tissues and organs and within muscles, and the consequences on carcass and meat quality. It is complementary to other reviews focused on digestive and metabolic processes (Chilliard et al 1998a; Jouany et al., 2000) or focused on protein (Lobley, 1998) or energy (Hocquette et al 1998) metabolism in muscle of meat-producing animals. It is also complementary to recent reviews which deal with the control of muscle fiber ontogenesis (Picard et al., 2000) and the control of meat dietetic value by nutritional means (Wood et al., 1999; Geay et al., 2001). In the present paper, the expected consequences of the manipulation of energy metabolism on growth and muscle characteristics will first be summarised. Subsequently, selected and new aspects of the nutritional regulation of the major metabolic pathways will be described in the different organs and tissues during the prenatal and the postnatal growth periods.

OBJECTIVES OF THE MANIPULATION OF ENERGY METABOLISM IN MUSCLES AND OTHER TISSUES OR ORGANS

Muscle energy metabolism has to be controlled to optimize muscle biological functions, and metabolic characteristics related to meat quality. Indeed, the partition of energy substrates between oxidation (for ATP production) and deposition of glycogen or fat is of prime importance for muscle contractile activity, for thermogenesis and for muscle protein deposition to sustain muscle growth (for review, see Hocquette et al., 1998). However, the control of muscle energy metabolism also requires upstream control on (i) the partition of nutrients between the major tissues and organs (splanchnic tissues, adipose tissues, muscles) (figure 1) and (ii) the metabolic efficiency of these tissues or organs.

Optimizing energy stores in muscles with regards to meat quality

The quantities of glycogen and fat deposited intra-muscularly as well as the nature of the fatty acids deposited are major determinants of meat quality (Touraille, 1994).

Post-mortem muscle glycogen is converted to lactic acid through the glycolytic pathway, which determines the meat ultimate pH. The extent of the fall in *post-mortem* pH depends on glycogen content within muscles. The ultimate pH influences, in turn, many attributes of the meat, such as color, water-holding capacity, juiciness and tenderness (for review, see Touraille, 1994; figure 2). However, glycogen content of muscles *in vivo* partly depends on the exchanges of energy substrates (fat, carbohydrates) between liver, adipose tissues and muscles: any changes in hepatic or muscular glycogenolysis or in lipolysis of fat stores before slaughter affect the ultimate pH of the meat through changes in muscle glycogen content (Lister and Spencer, 1983).

The amount and the composition of fat stores within muscle tissues are also involved in organoleptic properties of the meat such as flavor, tenderness and juiciness (for reviews, see Touraille, 1994; Gandemer, 1999; figure 2), but also in its nutritional value (Wood et al., 1999). Generally speaking, the deposition of energy-yielding substrates (fat, carbohydrates) in intramuscular adipocytes in the form of TG will determine fat content and fatty acid composition of the meat. Intramuscular fat content varies according to muscle type, breed, age, sex and other animal factors. However, despite its great importance, very little is known about the development of intramuscular adipose tissue. By contrast, it is now recognised that the overall aroma of cooked meat results from an equilibrium between volatile products generated either by lipid oxidation or by the Maillard reaction between amino acids and reduced sugars. Consequently, flavour may be controlled by manipulating dietary fat composition or by adding natural antioxidants in the diet (for review, see Gandemer, 1999). The dietetic value of the meat depends on the ratio of polyunsaturated fatty acids (PUFA) to saturated fatty acids of lipids in the meat. It also depends on the nature on these PUFA (n-3 family, n-6 family, conjugated linoleic acid). These characteristics are mainly regulated by the type of diet distributed to ruminants (for review, see Geay et al., 2001).

Improving or maintaining high rates of protein deposition in muscles

Improving muscle characteristics related to meat quality should not be at the expense of muscle

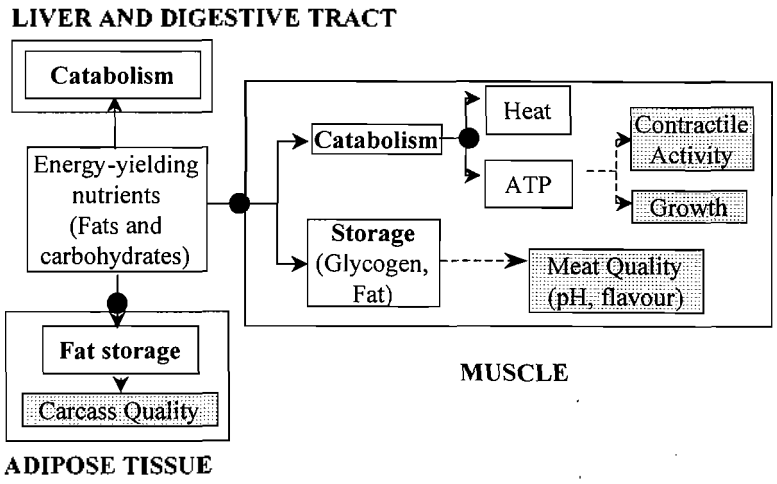
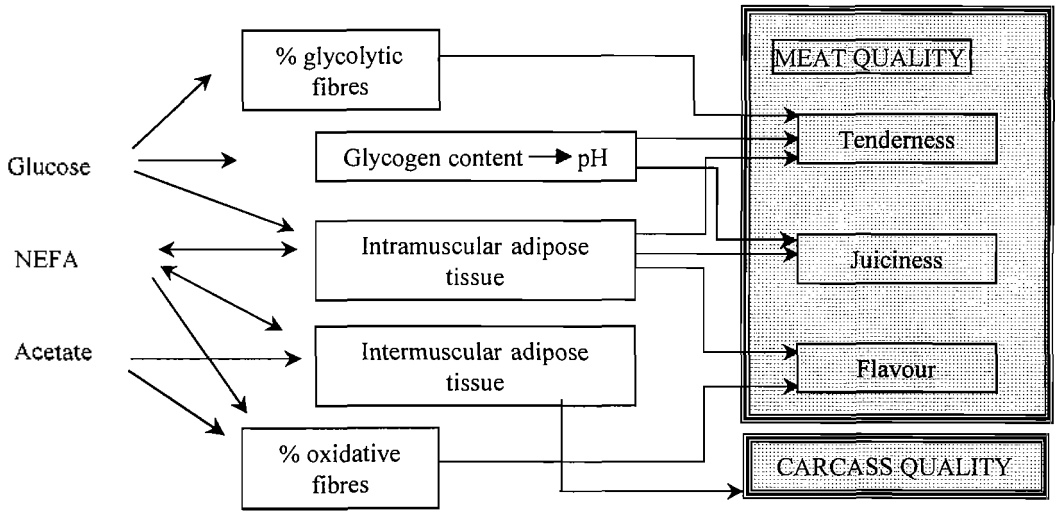


Figure 1. Nutrient partitioning between organs and tissues and within muscles. Energy-yielding nutrients may be taken up by organs and tissues to be either oxidized (liver, digestive tract, muscles) or stored as glycogen (liver, muscle) or as fat (adipose tissues, liver, muscles). The portal-drained viscera are, however, characterised by a high specific oxidative capacity compared to muscles. The control points of nutrient partitioning between adipose tissues and muscles, and within muscles between energy storage, heat loss and ATP production are subject of active investigation.



(adapted from Pethick and Dunshea, 1997 and Hocquette et al., 1998)

Figure 2. Relationships between muscle metabolic characteristics and quality traits of carcasses and meat. Glucose is a major energy-substrate for glycolytic fibers and the precursor of glycogen in fibers and of fatty acids in intramuscular adipocytes. Fats (long-chain fatty acids and acetate) are major energy-substrates for oxidative fibers and intermuscular adipocytes. Manipulation of the balance of energy-substrates may, therefore, alter the metabolic characteristics (metabolic properties of fibers, intramuscular contents of glycogen and fat) which affect meat quality traits.

growth. High rates of protein deposition in muscles remain an important objective. An increase in protein deposition may be achieved either by increasing protein synthesis and/or by decreasing protein degradation.

For both processes of protein synthesis and degradation, free energy is required. Consequently, any changes in energy supply to muscles, at a given amino acid supply, might alter protein deposition rate. For instance, metabolizable energy intake increases

protein synthesis rate in muscle to a larger extent than protein degradation rate (for review, see Lobley, 1992). Protein metabolism is also regulated by the nature of available energy-yielding substrates which may have direct or indirect modes of action via hormones. Such is the case with glucose, the protein sparing effect of which is partly mediated by insulin.

Conversely, any changes in protein turnover rate will incur specific and indirect energy requirements. For example, both protein synthesis and degradation rates are higher in slow-twitch oxidative than in glycolytic muscles, leading to higher energy requirements to meet similar rates of protein deposition (for review, see Hocquette et al., 1998).

Optimizing energy partitioning in favour of muscle tissue

Manipulation of muscle growth and characteristics cannot be achieved without applying a strategy that accounts for splanchnic tissue metabolism. Indeed, metabolic rates of the liver and of the portal-drained viscera (PDV) are up to 20 and 6 times higher, respectively, than that of the hind limb (composed approximately of two thirds of muscle). Thus, despite their lower mass relative to muscles, PDV and liver contribute for 17% and 13% to total energy expenditure versus 18% for muscles in preruminant calves. In weaned growing or adult ruminants, relative contributions are 16-29%, 17-31% and 18-20% for PVD, liver and muscles, respectively (for review, see Ortigues and Doreau, 1995; Bauchart et al., 1996; Chilliard et al., 1998a). Consequently, the metabolic fate of nutrients in the splanchnic tissues as well as their action on splanchnic hormonal secretion are of prime importance to control nutrient supply and use in peripheral tissues (figure 1).

Energy expenditure of splanchnic tissues is greatly influenced by nutrition. In ruminants, the increment in whole animal energy expenditure with increased intake originates mainly from the PDV (17-61%) and the liver (16-44%) rather than from the muscle mass (5-7%). 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 preruminants and to a lower extent in ruminants. On the other hand, metabolic rate of the liver is influenced by the balance among the supplied nutrients (for review, see Ortigues and Doreau, 1995; Bauchart et al., 1996).

Energy intake, food digestion, nutrient absorption and energy expenditure of splanchnic tissues determine energy supply to other tissues, especially muscles. Thus, the potential contribution of each nutrient to muscle oxidation differs greatly between preruminants and ruminants due to huge differences in the end-products of digestion (for review, see Hocquette and Bauchart, 1999). Splanchnic tissue metabolism also intervenes in the nature of the nutrients supplied to muscle. In ruminants, muscle acetate supply is influenced by acetate oxidation in other tissues as well as acetate production from fatty acids in the liver. Muscle glucose supply, on the other hand, depends on the hepatic metabolism of propionate and of the other gluconeogenic precursors. Integrative studies on the effects of nutrition and digestion on inter-organ and tissue exchanges are lacking.

NUTRITIONAL REGULATION OF ENERGY METABOLISM IN THE MAJOR ORGANS OR TISSUES

Whatever the species, tissue energy metabolism is regulated by food intake and composition, in other words by specific macro- or micro-nutrients including mineral supply. Conversely, fuel partitioning between oxidation and storage is thought to regulate food intake, at least in rats and humans (for review, see Friedman, 1998). In addition, leptin, a recently discovered hormone secreted by white adipocytes, is involved in the regulation of food intake by targeting satiety at the hypothalamic level in ruminants as in other species (for review, see Chilliard et al., 1998b).

The effects of undernutrition are 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 (NEFA) and ketone bodies at the expense of acetate and glucose) and by changes in the hormonal status (low thyroid hormone, insulin and IGF-I plasma levels, high GH, glucocorticoid and epinephrine plasma concentrations) (for review, see Chilliard et al., 1998a).

The qualitative effects of macro- and micro-nutrients are, however, 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. Only a few examples will be given in this section concerning the liver, muscles and adipose tissues only, although energy metabolism and gene expression in the digestive tract (for instance, the rumen) are also highly regulated by nutrients (for review, see Rémond et al., 1995; Jesse, 1998).

Liver

The liver plays a key metabolic role in converting the different metabolites. Liver is also characterized by a very intense metabolic rate with both elevated anabolic and catabolic activities. For instance, with respect to fat metabolism, the liver is able to synthetise fatty

acids and to 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) to muscle tissues. The liver metabolism is regulated by nutritional factors (the feeding level and the nature of the diet). Indeed, a higher food intake will increase liver energy expenditure, the hepatic gluconeogenic rate and will favour esterification of fatty acids at the expense of their oxidation. These changes will result from short-term mechanisms of regulation through the action of metabolites and by long-term mechanisms of regulation through changes in gene expression. The following examples aim to show how hepatic metabolism of fatty acids is regulated by these two types of biological mechanisms.

Regulation of enzyme activity by metabolites (allosteric effects): The enzyme called carnitine palmitoyltransferase I (CPT I) catalyzes the rate-limiting step of long-chain fatty acids (LCFA) transfer into mitochondria. It is, thus, involved in the control of LCFA oxidation and of ketone body production. CPT I activity is inhibited by malonyl-CoA, an intermediate in LCFA synthesis from acetyl-CoA. The intracellular concentration of malonyl-CoA and CPT I sensitivity to malonyl-CoA are both regulated, thereby controlling LCFA oxidation. The malonyl-CoA concentration is enhanced by a high rate of nutrient oxidation or by insulin which stimulates lipogenesis. However, the effects of the changes in malonyl-CoA concentration may be amplified by concomittant changes in the CPT I kinetic properties and/or in CPT I expression. Consequently, any changes in insulin secretion or in LCFA supply to the liver will modify the supply of ketone bodies to peripheral tissues and VLDL secretion by the liver. In addition, in the veal calf, a lower rate of LCFA oxidation than of LCFA esterification may induce fat accumulation within the liver as discussed below (for review, see Hocquette and Bauchart, 1999).

Propionate, which is absorbed in large quantities in ruminants, inhibits directly fatty acid oxidation and, indirectly, entry of LCFA into mitochondria. Indeed, CPT I may be 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 reduced food intake, 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 utilization of other gluconeogenic substrates such as lactate (for review, see Brockman, 1993) thus modifying the balance of nutrients supplied to the muscles.

Regulation of gene expression by macro- or micro-nutrients: Glucose and LCFA, the major nutrients in the preruminant calf, were shown to control gene expression in laboratory rodents (for reviews, see Clarke and Abraham, 1992; and Girard et al., 1994). The importance of this mechanism in preruminants or ruminants has not been assessed.

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, polyunsaturated fatty acids (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. But, the relative contribution of transcription vs. transcript stability as determinants of mRNA abundance varies for each transcript and is dependent on specific tissues (for reviews, see Clarke and Abraham, 1992; Girard et al., 1994).

In addition, an increased flux of weakly catabolized LCFA to the liver results in the activation of the peroxisome proliferator-activated receptors (PPARs) (Schoonjans et al., 1996a). The relative contribution of peroxisomes to total LCFA oxidation thus depends on physiological or nutritional conditions (for instance, fatty acid composition of the diet), and may partly determine acetate release by the liver. Another example relates to phytol metabolites (especially phytanic acid) derived from chlorophyll; they are present in the plasma of grass-fed ruminants and are able to activate the RXR-type nuclear receptor (Kitareewan et al 1996). As shown in rabbits, activated PPAR/RXR receptors modify the expression of specific genes involved in hepatic lipid metabolism: the gene expression of enzymes involved in LCFA catabolism and ketone body production are enhanced whereas enzymes involved in lipogenesis are decreased (Schoonjans et al., 1996a).

Adipose tissue

Adipose tissues are huge reserves of triglycerides, and hence of energy for the whole body. The importance of the energy stores results from a balance between lipogenesis and hydrolysis of triglycerides. The rate of both processes depend on feeding level and on the nature of dietary nutrients.

Regulation of adipose tissue metabolism by feeding level: The regulation of lipid metabolism in adipose tissue is greatly influenced by the feeding level: (i) LPL activity and lipogenesis rate (which control fat deposition) are affected by energy intake, but hormone-sensitive lipase activity and gene expression are less influenced by the level of nutrition according to Sprinkle et al. (1998) and Bonnet et al. (1998); (ii)

refeeding of underfed ewes or cows markedly increases, by pretranslational mechanisms, LPL activity (19-25 fold), and, to a lesser extent, fatty acid synthase activity (6-8 fold), but it has moderate effects on other lipogenic enzymes (Bonnet et al., 1998).

Leptin is also of prime importance in the regulation of metabolism. The factors which stimulate the synthesis/secretion of leptin include food intake, increased body fatness and insulin (for review, see Romsos, 1998). Indeed, leptin mRNA levels in adipose tissue of cows and ewes are decreased by undernutrition and then increased by refeeding as previously shown in laboratory rodents. Recent results in ewes indicate that leptin expression is also influenced by photoperiod (for review, see Chilliard et al., 1998b). Leptin inhibits food intake, reduces body weight and increases energy expenditure. Available data suggest a role for leptin in many tissues. An obvious objective of leptin research in livestock production would be the control of food intake to optimize body composition and to increase the efficiency of production (for review, see Romsos, 1998).

Regulation of adipose tissue metabolism by the nature of nutrients: The regulation of gene expression of lipogenic enzymes by glucose has been clearly demonstrated in adipose tissue of laboratory rodents. The signal metabolite could be glucose-6-phosphate rather than glucose itself (for review, see Ferré, 1999). This suggests that it may be possible to manipulate the intensity of the lipogenic pathway in adipose tissue by the nature of nutrients.

Some experiments suggested that it may be also the case in farm animals because the nature of available nutrients is highly regulated, for instance at weaning. Indeed, in the pig, carbohydrates provide approximately 17% and 55% of absorbed energy before and after weaning respectively. But ruminants are characterized by specific nutritional features related to the specificities of their digestion (low glucose availability and low post-prandial insulin secretion). Since solid feeds are digested as volatile fatty acids by rumen microorganisms, carbohydrates provide, indeed, approximately 18-26% of absorbed energy for preruminant calves (up to 40% in the case of veal calves) and less than 5% for ruminant calves.

First, the changes in nutrition which occur at weaning result in a drop of GLUT4 content per fat cell in bovines but a rise in pigs (for review, see Hocquette et al., 1998). Second, ATP citrate lyase, the key enzyme for lipogenesis from glucose, is usually low in ruminant adipose tissue, but it is increased in the sheep by exogenous glucose supply such as direct glucose infusion, or by diets with a high propensity to allow partial starch digestion in the small intestine (e.g. sorghum) although the rumen remains the major site of digestion. In other words, diets which promote starch digestion in the small intestine clearly increases ATP-citrate lyase activity and, thus, favour glucose as a lipogenic substrate in adipose tissues (for review, see Pethick and Dunshea, 1997).

Other enzymes such as lipoprotein lipase (LPL) are regulated by fatty acids through complex mechanisms which involve the activation of nuclear receptors such as PPARs in adipocytes (Schoonjans et al., 1996a, b; Grimaldi et al., 1999). Recent studies *in vivo* in the calf indicate that, for the same level of net energy intake, LPL activity is higher in adipose tissues with a fat-rich milk diet than with a low-fat forage diet. This suggests a direct regulation of LPL activity by the amount of dietary fat in ruminants as in monogastric mammals (Hocquette et al., 2001).

Generally, intramuscular and subcutaneous adipose tissues (figure 2) exhibit specific aspects of lipid metabolism unique to each tissue (Millet et al., 1991). More precisely, it seems that, unlike other adipocytes, intramuscular adipocytes (marbling depots) rely more on glucose and/or lactate as substrate for *de novo* lipogenesis than on acetate (Smith and Crouse, 1984). This suggests that it may be possible to manipulate intramuscular and external fat depots independently, in particular to increase fat within meat without increasing carcass fatness (for review, see Pethick and Dunshea, 1997). However, recent data in Hanwoo cattle adipose tissues do not support this conclusion (Lee et al., 2000a). Thus, a better knowledge of the regulation of glucose metabolism in adipocytes from different fat depots is first required.

Intramuscular adipocyte differentiation was thought to be related to the formation of marbling. It is well known, from studies in laboratory rodents, that fatty acids control adipocyte differentiation by acting through PPARs (for review, see Grimaldi et al., 1999 and Uauy et al., 2000), but this remains to be studied in farm animals. In Hanwoo cattle, retinoic acid inhibits the differentiation of adipocytes in a dose dependent manner, and intramuscular preadipocytes are less responsive to retinoic acid than other fatty tissues (Lee et al., 2000b). It thus suggests that the control of adipocyte differentiation may also be a mean to manipulate marbling independently of carcass fatness.

Muscle

Muscle tissues use carbohydrates and fatty acids as energy sources for the production of free energy (ATP). However, the interactions between carbohydrate and fatty acid metabolisms partly regulate muscle metabolism and, hence, energy expenditure.

Carbohydrate metabolism: Plasma arterial glucose is extracted by muscle through facilitative glucose transporters, mainly, the insulin-sensitive isoform, GLUT4. The rate-limiting role of glucose transport in

glucose homeostasis, glycogen deposition and glucose use as energy source was demonstrated by several *in vivo* and *in vitro* approaches. States of insulin resistance or of reduced potential of glucose use by muscles may impair growth (for review, see Bauchart et al., 1996 and Hocquette and Abe, 2000). 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).

First, chronic hyperglycemia is a well known cause of insulin resistance, as shown 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).

Second, increased muscle triglyceride content or a high proportion of saturated fats within muscles are inversely related to insulin action (for review, see Hocquette et al., 1998).

Third, 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).

Finally, other mechanisms linked to animal management or feeding strategy are thought to regulate glucose metabolism and insulin action: (i) leptin, the secretion of which is stimulated by food intake and body fatness, increases glucose uptake and, in some specific conditions, glycogen hind limb content in mice (Kamohara et al., 1997); (ii) plasma insulin levels increase with feeding frequency in sheep, but decrease with grazing in steers compared to control animals in a shed with similar growth rates; (iii) studies in many species including ruminants also indicate that the net appearance of glucose or propionate in the portal vein enhances muscle sensitivity to insulin (for review, see Hocquette et al., 1998). This indicates that the rate and the route of nutrient delivery may influence the action of insulin, possibly via the hepatic parasympathetic nerve.

Lipid metabolism: Muscle extraction rates of acetate (35-45%), ketone bodies (10-45%) and LCFA (20%) are much higher than that of glucose (4%) in ruminants. Different key enzymes or proteins have been identified as rate-limiting steps in uptake, intracellular transport (lipoprotein lipase, LPL; fatty acid binding protein, FABP) or catabolism (CPT I, enzymes of the Krebs cycle) of LCFA. Changes in energy demand or in nutrient supply induce intracellular variations in malonyl-CoA concentration and in the NADH/NAD^+ and acetyl-CoA/CoA ratios, thereby regulating partitioning of LCFA between anabolic (TG deposition) and catabolic (ATP production) pathways (for review, see Hocquette et al., 1998). Insulin also plays a major role in fat metabolism directing LCFA towards TG deposition in muscles. On the contrary, leptin directs LCFA towards oxidation and away from storage in rat muscles (Muoio et al., 1997).

Interactions between nutrients: 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 as shown in the bovine heart. But, 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 and Hocquette et al., 1998).

Free energy production: Following nutrient catabolism, protons accumulate between the two mitochondrial membranes by the action of the respiratory chain. Subsequently, ATP is generated from the energy of this proton gradient and transferred out of the mitochondria. The adenine nucleotide translocase (ANT) is considered as the rate-limiting step in this process. But, some protons may be lost due to the permeability of the inner mitochondrial membrane (proton leak). Proton leak may be due, at least in part, to direct transfer of protons into the mitochondrial matrix through uncoupling proteins (UCP) without any ATP synthesis. This results in a relative inefficiency of ATP production, and heat loss (figure 1). Mitochondrial proton leak is an important contributor of resting energy expenditure. Any changes in the regulation of proton leak and, thus, of oxidative phosphorylation may alter cellular energy expenditure, and hence, protein deposition. For instance, regulation of the expression of mitochondrial UCP may alter ATP production and play a significant role in energy expenditure (Freake, 1998). In addition, acyl-CoA esters derived from LCFA are potent inhibitors of ANT as shown in the bovine heart, thereby decreasing the relative ATP production (for review, see Faergeman and Knudsen, 1997).

NUTRITIONAL REGULATION OF ENERGY METABOLISM DURING GROWTH

Fetal life

Quantitatively, the potential for muscle growth is correlated with the number of muscle fibers. Qualitatively, specific meat properties (flavour, juiciness, tenderness, etc) depend partly on muscle characteristics and on their orientation towards a specific type of fibers (slow/fast; glycolytic/oxidative)

depending on the quality traits which need to be optimized (figure 2). Both processes (number and type of muscle fibers) are partly genetically determined. Muscle metabolism depends also on breeding factors during the postnatal growth (for review, see Geay et al., 2001). However, growth in utero also plays an important role depending on many factors including nutrient supply, and thus, maternal and fetal nutrition.

Early nutritional influences on placental and fetal growth: The fetus is dependent on mother food intake and on the transfer of oxygen and nutrients across the placenta. Any disturbance in this pathway, leading to substrate supply limitation, can modify early fetal development with possible long-term outcomes. For instance, it was shown that the average daily gain of lambs after birth was positively correlated with their birth weight (Villette and Theriez, 1981). Furthermore, there is a positive correlation between size at birth and placental weight because placenta development is essential for normal fetal development (Haesman et al., 1999). Numerous factors influence placental and fetal growth. Among them, maternal nutrition during pregnancy plays a key role, which may have long-term outcomes. Indeed, maternal undernutrition of ewes between 30 and 80 days of gestation results in a decrease in placental weight at 80 days, but in an increase in placental weight close to term (145 days) (Haesman et al., 1999). Undernutrition of ewes in the periconceptual period can also decrease fetal growth during gestation. Later, but very early in fetal life, malnutrition would impede cell division, organ growth and differentiation. Subsequently in prenatal life, it would lead to changes in metabolism, tissue composition and cell size. In addition, growth of brain and lungs is preserved at the expense of the liver and of skeletal muscles. Changes in the hormonal status are thought to be mediators of this nutritional adaptation since many of the putative endocrine regulators of cell differentiation and nutrient partitioning (hormones, growth factors) are highly nutritionally sensitive. Thus, maternal nutrient restriction between 28 and 77 days of gestation in sheep induces a decrease in maternal plasma thyroid hormone concentration at 77 days (Haesman et al., 1999). Furthermore, fetal undernutrition leads to insulin resistance and glucose intolerance after birth, thereby decreasing postnatal growth (for reviews, see Dauncey, 1997; Desai and Hales, 1997; Gluckman and Harding, 1997).

Most of the studies demonstrated that undernutrition of the fetuses occurs when their mothers are fed on low-protein or low-energy diets. By contrast, when rapidly growing pregnant young ewes are overnourished, nutrients are driven towards maternal tissue synthesis at the expense of placental growth, leading to fetal undernutrition (Wallace et al., 1997).

Nutritional programming of growth: Programming is a process whereby a stimulus or a metabolic attack, at a critical or sensitive period of fetal development, has lasting effects of lifelong significance. Nutritional programming has been demonstrated convincingly in a range of mammals. It is a concept widely accepted in both the fields of medical (Barker, 1997) and animal science (Heasman et al., 1999). Fetal undernutrition can be viewed as a long-term environmental adversity affecting fetal growth. Adaptation of the fetal metabolism could be considered as a response to this adversity. This adaptation has permanent effects leading to the concept of programming. The metabolism may be switched in a way adapted for malnutrition, but detrimental when nutrition is abundant (for review, see Desai and Hales, 1997). In addition to the effect of nutrient supply to the fetus, it has been suggested that the normal growth of the fetus also depends on the nature of nutrients. For instance, the fetus and the placenta are fully dependent on essential fatty acid supply, and particularly on long-chain polyunsaturated fatty acids in early life (Uauy et al., 2000).

Metabolic characteristics of the heart and skeletal muscles during foetal development: The metabolic differenciation of the bovine heart and skeletal muscle occurs mainly during the last third of fetal development. Furthermore, it is delayed in double-muscled cattle. However, the various enzyme activities or nutrient transporters which control muscle energy metabolism are differently regulated (for review, see Picard et al., 2000).

During fetal life, glucose and lactate account together for more than 75% of the fetal oxidative metabolism, regardless of the species. Therefore, it is speculated that the ontogenesis of the glucose-insulin-IGF I axis may be of great importance in the regulation of fetal growth (for review, see Gluckman, 1997). Recent studies in the bovine heart showed that the expression of the insulin and IGF I receptors decreases whereas the expression of the insulin-sensitive glucose transporter increases during the last third of gestation (Abe et al., 1999; Hocquette et al., 2000).

Postnatal life

High rates of protein deposition and, thus, of weight gain are characteristic features of young animals. But, these rates decline markedly with increasing age and this is associated with a decrease in insulin sensitivity and responsiveness of glucose use (for review, see Bauchart et al., 1996). In addition, at similar ages, energy metabolism is regulated by the absorption rate of nutrients, and consequently, by their rate of delivery to tissues and organs. Finally, tissue energy metabolism may be affected by rearing factors,

thereby modifying muscle metabolic characteristics involved in meat quality.

Quantitative regulation of metabolism and growth: Gerrits et al. (1997) developed a model integrating protein and energy metabolism in growing preruminant calves. In this model, muscle protein synthesis is dependent on the concentration of amino acids and of acetyl-CoA within the body which represent the availability of protein and energy sources, respectively. Thus, any increase in protein or in energy intake should result in higher protein deposition rates. In addition, increasing the dietary carbohydrate:fat ratio at equal protein and energy intakes induces a shift from fat to protein deposition. This is due, at least in part, to a high insulin secretion which stimulates protein deposition, but also, to a rise in the concentration of acetyl-CoA. Secondly, any increase in the amino acid oxidation rate decreases the size of the amino acid pool and results in lower protein synthesis and accretion rates. Conversely, any increase in the acetyl-CoA concentration may lead to an increase in fat deposition by *de novo* lipogenesis. Thus, the quantitative interaction between amino-acids and energy-yielding substrates is a key parameter for modeling growth. But, the representation of pools of other regulatory metabolites remains a concern for future models of metabolism.

In weaned ruminants, dietary protein and energy must also be supplied in a suitable ratio to sustain protein deposition, i.e. growth. This concept, however, is only meaningful when both endogenous and exogenous energy sources are considered (Chowdhury et al., 1997). The influence of the nutritional level on protein deposition may be of great importance since some diet restriction followed by refeeding during the growth period is commonly observed for grazing cattle. In growing finishing bovines or in dairy bovine breeds (i.e. for animals with a limited growth potential and with a high propensity to fatten), a restricted feeding strategy has the potential to reduce excess fat production and to increase carcass protein and water contents. Thus, increased feed efficiency may paradoxically occur as a result of changes in carcass composition and of reductions in maintenance energy expenditures (Murphy and Loerch, 1994). The hormonal status also changes during restriction and, thereafter, during compensatory growth, thereby affecting energy metabolism.

Regulation of metabolism by specific nutrients: Based on studies at the cellular or at the animal level, regulation of metabolism by specific nutrients is now a new frontier for nutrition scientists. In preruminants or weaned ruminants, the balance between carbohydrates and fats, or between forages or concentrates, respectively may affect energy expenditures and/or the fate of nutrients. But, more studies in livestock species are still needed to understand the biological processes underlying the regulation of metabolism by nutrients themselves as shown in the following examples.

Fatty liver may occur in the veal calf depending on nutritional factors, thereby affecting growth and health. Another important factor which may regulate hepatic TG metabolism is the nature of the dietary fatty acids such as PUFA or medium-chain fatty acids (MCFA). Compared to standard milk replacers for calves, PUFA-rich diets (soybean 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).

In weaned growing ruminants, efficiency of metabolizable energy utilization 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 utilization 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, and lower metabolic efficiency of VFA utilization. By contrast, possible changes in hepatic or muscular energy expenditure with diet composition have not been clearly noted (for review, see Ortigues and Visseiche, 1995).

Regulation of metabolism by the rate of nutrient delivery: Dietary carbodydrates, fat and protein 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. These different types of fuels may also affect the regulation of energy metabolism, especially in preruminants, such as in veal calves.

Generally, the coagulation of milk caseins in the abomasum of the calf results in the retention of dietary proteins and TG in an insoluble clot for several hours. This delays the absorption of amino acids and fatty acids. First, this alters the postprandial hormonal status, 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). Second, recent 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 ruminants, kinetics of nutrient absorption are less marked than in monogastrics, because of the buffering effect of the rumen. However it may be assumed that metabolic utilization of nutrients from diets of widely different rumen degradability still differ, similarly to preruminants.

Regulation of muscle metabolism by breeding factors: Muscle tissues are composed of fibers with different metabolic properties (oxidative, glycolytic, oxido-glycolytic) (figure 2). Their relative proportions depend on many physiological, genetic, hormonal and nutritional factors. For instance, a common situation in breeding growing cattle is a low food supply in winter when feed availability is low, and then ad libitum intake in spring when grass is growing. In that case, the animals increase their growth rate over that of unrestricted animals. Undernutrition results in a decrease in the glycolytic muscle metabolism, which is abolished during the refeeding period. An increase in feeding level usually induces a higher fat content in the carcass and in muscles. However, whereas carcass adipose tissue content is increased during compensatory growth, fat deposition in muscles is lower compared to control animals with a regular growth pattern (Hornick et al., 1998).

Body composition and fat intramuscular content result from the balance between energy intake and energy expenditure. It has been suggested that this balance may be affected by changes in muscle metabolic activity, and hence, by physical activity. It has been indeed well demonstrated that physical activity increases muscle oxidative metabolism as clearly shown in horses (Essen-Gustavsson and Lindholm, 1985). Recent data in humans have shown that muscle oxidative capacity may be influenced by overall daily physical activity rather than by intensive regular training (Morio et al., 2001). In other words, individuals who practice continuously moderate intensity activities in free-living conditions have a more oxidative muscle metabolism compared to sedentary individuals. When extrapolated to ruminants, it is tempting to speculate that grazing cattle may have a more oxidative muscle metabolism compared to indoor animals fed the same diet at the same level of energy intake. Indeed, when comparing bulls subjected to a higher spontaneous physical activity than tied ones, fibers are less glycolytic in muscles involved in movements for active animals (Jurie et al., 1998). Furthermore, in another experiment, it was shown that pasture (free animals in the fields) increased oxidative metabolism in oxidative muscles *(rectus abdominis)*, but reduced intramuscular fat content without any change in carcass fatness compared to animals fed indoors a maize-rich diet (Jurie et al., 2000). This may be due to a high catabolism of intramuscular fat by oxidative fibers. However, the respective effects of the diet (grass vs maize) and of physical activity in the fields need to be determined.

CONCLUSIONS AND PERSPECTIVES

Research on quantitative nutrition in growing ruminants is still needed to increase metabolic efficiency and growth rate and to optimize body composition, thereby to reduce the costs of production. To achieve this goal, the objective is always to predict accurately animal performance by an improved quantification of animal requirements and by a precise feed evaluation. However, as discussed in this paper, this needs, nowadays, a better knowledge of individual tissue and organ requirements and a better knowledge of nutrient fate within the major tissues and organs.

At the same time, muscle energy metabolism must be controlled to alter some specific muscle characteristics (fat and glycogen contents, fatty acid composition of fat, etc) related to meat quality (figure 2). These objectives require the clarification of the relative contributions of the different muscle metabolic characteristics to the final meat quality. This also implies that the more recent knowledge related to biological processes at the cellular level are integrated with classical data involving tissue or whole animal studies (for review, see Ortigues-Marty et al., 2001). In this paper, examples of cellular metabolism studies were given, indicating that wide possibilities remain to be explored on the influence of key enzyme or gene regulation on the control of metabolism at the whole body level.

The partitioning of energetic fuels among tissues and metabolic pathways serves to maintain a steady supply of energy to meet the tissue needs. Depending on nutritional level and diet composition, the splanchnic tissues have a profound quantitative and qualitative impact on the supply of nutrients to muscle. Therefore, in the future, nutritionists should be able to formulate diets to meet the specific nutritional requirements, on the one hand, of the gut and the liver and, on the other hand, of muscles taking into account transformation and recycling of nutrients by the splanchnic bed.

In addition, livestock science needs to utilize the emerging discoveries in other species. The regulation of metabolism by leptin, the regulation of gene expression or enzyme activity by macro- and micro-nutrients are among the recently discovered and exciting ideas. New concepts and techniques are now available to understand mechanisms that were impossible to adequately address a few years ago. For instance, the decipheration of an increasing number of genomes concomitantly with the development of new molecular techniques (the DNA chip technology) has open the way to an almost exhaustive analysis of gene expression in various nutritional and physiological conditions. This allowed a better understanding of the

basic molecular mechanisms which regulate energy metabolism at the tissue or the whole body levels. This also allows the discovery of new genes which might be important for the control of metabolism, growth, body composition and/or meat quality (for review, see Ortigues-Marty et al., 2001). The general objective in this field is to evaluate putative linkages between energy metabolism, its regulation and molecular markers (highly regulated genes). The next step will be the manipulation of these markers by various means, including nutrition, in order to improve metabolic efficiency and product quality.

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