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Review article

Facilitative glucose transporters in livestock species

Jean-François HOCQUETTE[a]*, Hiroyuki ABE[b]

[a] Unité de Recherches sur les Herbivores, INRA, Centre de Recherches de Clermont-Ferrand/Theix, 63122 Saint-Genès-Champanelle, France
[b] National Institute of Animal Industry, Tsukuba Norin-Danchi, PO Box 5, 305-0901, Japan

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Abstract — The study of facilitative glucose transporters (GLUT) requires carefully done immunological experiments and sensitive molecular biology approaches to identify the various mechanisms which control GLUT expression at the RNA and protein levels. The cloning of species-specific GLUT cDNAs showed that GLUT4 and GLUT1 diverge less among species than other GLUT isoforms. The key role of GLUT in glucose homeostasis has been demonstrated in livestock species. In vitro studies have suggested specific roles of GLUT1 and GLUT3 in avian cells. In vivo studies have demonstrated a regulation of GLUTs (especially of GLUT4) by nutritional and hormonal factors in pigs and cattle, in lactating cows and goats and throughout the foetal life in the placenta and tissues of lambs and calves. All these results suggest that any changes in GLUT expression and activity (such as GLUT4 in muscles) could modify nutrient partitioning and tissue metabolism, and hence, the qualities of animal products (milk, meat).

glucose transporter / pig / ruminant / poultry

Résumé — **Les transporteurs du glucose à diffusion facilitée chez les animaux de ferme.** L'étude des transporteurs du glucose à diffusion facilitée (GLUT) nécessite des techniques en immunologie ou en biologie moléculaire précises et sensibles pour étudier la régulation de leur expression au niveau ARNm ou protéique. Le clonage d'ADNc des différents GLUT a montré que GLUT4 et GLUT1 divergent moins entre espèces que les autres isoformes de GLUT. Le rôle important des GLUT dans le contrôle de l'homéostasie du glucose a été démontré chez les animaux de ferme. Des études in vitro ont suggéré un rôle spécifique de GLUT1 et de GLUT3 dans les cellules aviaires. Des études in vivo ont mis en évidence une régulation des GLUT (notamment GLUT4) par des facteurs nutritionnels ou hormonaux chez le porc et le bovin, chez la vache ou la chèvre en lactation, et tout au long de la vie fœtale dans le placenta et les tissus de l'agneau ou du veau. L'ensemble de ces résultats suggère que tout changement dans l'expression et l'activité des GLUT (tel que de GLUT4 dans les muscles) peut modifier la répartition des nutriments et le métabolisme tissulaire, et affecter ainsi la qualité des produits animaux (lait, viande).

transporteur du glucose / porc / ruminant / volaille

* Correspondence and reprints
E-mail: hocquet@clermont.inra.fr

1. INTRODUCTION

A major objective of research in Animal Science is to improve the production of meat or milk and to optimise the qualities of these animal products by the control of their biochemical characteristics. The major energy-yielding nutrients for tissues are carbohydrates and long-chain fatty acids in monogastric species, but, in ruminants, they are volatile fatty acids and ketone bodies. In all species, however, glucose is used by various tissues and organs for free energy (i.e. ATP) production. In addition, glucose may be converted either into glycogen or triacylglycerols which are subsequently stored within tissues (liver, adipose tissues, muscles) or into lactose which is subsequently incorporated into milk in the case of lactating females. Therefore, the basic biological mechanisms which control the partitioning of glucose between tissues and organs need to be better studied in order to improve the production and the qualities of meat and milk.

Among the biological mechanisms which control the fate of glucose, is glucose uptake by tissues, a process which is achieved by facilitative glucose transporters. These transporters can be divided into two families: insulin-sensitive (GLUT4) and non insulin-sensitive (GLUTs 1, 2, 3 and 5) glucose transporters in both monogastric (for review, see [34, 40]) and ruminant mammals (for review, see [2, 46]). These GLUT proteins exhibit sequence similarity but are encoded by distinct genes. Whereas GLUT1 and GLUT3 have a more generalised tissue distribution, GLUTs 2, 4 and 5 appear to have specialised physiological functions due to their specific tissue expression (for review, see [40]). The GLUT4 isoform is the subject of active investigation in laboratory rodents and humans because this transporter may be involved in the pathology of diabetes, body composition and obesity. By contrast, much less is known about glucose transporters in livestock species. This paper goes beyond the academic interest of increasing basic knowledge about glucose transporters in many species and aims at demonstrating that it can be important to assess the ability of tissues to take up glucose in meat or milk producing farm animals.

Thus, the present review focuses on recent data, demonstrating the key role of facilitative glucose transporters (especially GLUT4) in glucose homeostasis in livestock species with regards to energy metabolism and production of meat and milk. In the first part of this review, the general features of glucose metabolism will be described and compared among animal species. In the second part, the recent advances in GLUT characterization in livestock species will be described. In the two last parts, knowledge about the regulation of GLUT expression in animal models or in producing farm animals will be detailed.

2. GENERAL FEATURES OF GLUCOSE METABOLISM

2.1. Origin of glucose

Tissues rely on fuels (carbohydrates, lipids), which are transported within plasma to be taken up by tissues and organs according to their needs. In contrast to other nutrients [for instance, non-esterified fatty acids (NEFA) and triacylglycerols (TG)], blood glucose is maintained within tight limits in healthy animals. Glucose originates either from food, from hepatic neoglucogenesis or from mobilization of glycogen stored within the body.

The major end-products of digestion are glucose and fats (NEFA, TG) in adult monogastric species and also in milk-fed young animals (piglets, calves, lambs). By contrast, in weaned ruminants, microorganisms present in the rumen are capable of digesting fibrous material. This enables ruminants to eat and partly digest plant cellulose and hemicellulose. The principal products of

fermentation of dietary carbohydrates are short-chain fatty acids, mainly acetate, propionate and butyrate (for review, see [44]). As a consequence of the low dietary absorption of glucose, blood glucose level is slightly lower in weaned ruminants than in monogastric species, and ruminants have somewhat adapted the regulation of their glucose metabolism (for review, see [18]): for example, the major part of circulating glucose originates from hepatic neoglucogenesis from propionate, lactate, glycerol and amino acids, rather than food absorption.

In the intestine, the vectorial transport of hexoses from the lumen to the interstitial space is a two-step process: (i) uptake of glucose and galactose through the apical brush border is catalyzed by a Na+/D-glucose co-transporter (SGLT1), whereas uptake of fructose is catalysed by the GLUT5-fructose carrier, (ii) diffusion of glucose, galactose and fructose in the intestinal tissue in close proximity to blood capillaries is catalysed by GLUT2 and, in humans, also, by GLUT5 (for review, see [92]). Carbohydrates regulate the activity of SGLT1. This regulation occurs by changes in the expression of SGLT1 in response to the sugar content of the diet as shown in sheep (for review, see [86]). The key role of GLUT2 in intestinal glucose transport and metabolism was demonstrated in different species including the newborn pig [21].

Energy sources stored within the body are mainly glycogen and fats. The former is stored within hepatocytes or within muscle fibers. The latter is stored in the form of triacylglycerols within adipocytes located in various fatty tissues, for instance perirenal, omental, subcutaneous and also intermuscular and intramuscular adipose tissues. Glycogen is converted into glucose and triacylglycerols into fatty acids when energy is needed, for instance, upon physical activity, undernutrition, and high production of milk by dairy cows.

2.2. Fate of glucose

Uptake of individual nutrients by tissues depends on arterial nutrient supply (blood flow × nutrient plasma concentration) and on the fractional extraction rate of each nutrient, the latter being increased following insulin stimulation in the case of glucose.

Ruminants are characterized by higher plasma concentrations of volatile fatty acids and ketone bodies and by lower plasma concentrations of long-chain fatty acids than monogastrics due to the characteristic features of digestion in ruminants, but glucose arterial concentration remains high (3 to 7 mM) whatever the mammalian species ([54] and for review, see [14, 73, 75]). Birds, however, have a very high glycemia and lactatemia [87]. Consequently, in many species, potential energy supply from glucose is high. In other words, glucose is a major contributor in terms of blood energy supply to tissues.

The brain accounts for more than 10–15% of whole-glucose utilization in sheep. Glucose is the energy source for the brain, and the transport of this nutrient from blood to the brain is limited by the blood-brain barrier glucose transport system, which is the subject of active investigation in cattle (for review, see [46]).

Erythrocytes are known to consume a significant part of circulating glucose. However, bovine erythrocytes were previously known to lack sugar transport systems and sugar transport-related cytochalasin B binding sites (for review, see [46]). In fact, glucose transport into erythrocytes of sheep, cattle and horses is low, about one-third of that in dogs, humans and rats [8] and about 70% of that in pigs [9]. The minimal capacity of bovine erythrocytes to take up glucose may be explained by a very low expression of GLUT1 (at least 1/1 000 of that in human red blood cells) [55]. These results are in concordance with a lower rate of glycolysis in ruminant red blood cells than in red cells of humans and dogs [9]. Glucose

transport is also very low in avian red cells, which is due to a loss of GLUT3 during early development of these cells [57].

Skeletal muscle is also a major consumer of glucose in the body [75]. Glucose may be either oxidized or stored as glycogen. However, most of the glucose taken up by muscles is destined to be stored as glycogen (80% in sheep) [75]. The proportion of glucose which is potentially oxidized either directly or indirectly via glycogen contributes to 31–57% of muscle oxidation in sheep, 31–41% in humans and probably more in swine. This may be surprising since glucose extraction rates by muscles are consistently low compared to those of other nutrients. Indeed, glucose extraction rates by hindlimbs in the basal state (i.e. without any insulin stimulation) average 4% in ruminants and 9% in growing pigs whereas extraction rates for ketone bodies, volatile and long-chain fatty acids range from 10 to 45% (for review, see [52]).

In vivo adipose tissue accounts for approximately 25–40% of the glucose cleared in the pig [31]. On the contrary, adipose tissue in the ruminant represents only a minor fate of glucose disposal accounting for some 1% of total glucose utilization (for review, see [75]). As with muscles (as reflected by the hindlimb), sheep adipose tissue (as reflected by the tail fat pad) extracts about only 10% of the glucose presented to it (for review, see [18])

The low extraction rate of glucose by muscles and adipose tissues (4 to 10%) suggests a strong rate-limiting step for glucose uptake in vivo. Glucose transport rate was measured in incubated fibre strips of bovine muscle as previously described in humans [29]. This technique enabled us to conclude that, as in the rat muscle, hexokinase activity was higher than the glucose transport rate providing evidence that glucose transport is a rate-limiting step for glucose utilization by the bovine muscle in physiological conditions [45]. The rate-limiting role of glucose transport in glucose homeostasis and glycogen deposition within muscle cells has also been demonstrated by several in vivo or in vitro approaches (for review, see [46]) including transgenesis or knock-out experiments in laboratory rodents (for review, see [20]). However, some experiments in transgenic mice overexpressing glycogen synthase have indicated that glucose transport is not strictly rate-limiting for glycogen synthesis [62].

2.3. Regulation of glucose fate by insulin

Glucose is taken up into insulin sensitive tissues (muscle and adipose tissues) through facilitated diffusion by transmembrane glucose transporters, mainly the GLUT4 isoform [40]. The majority of GLUT4 is found inside the cell in the basal state, from where it can rapidly be translocated to the plasma membranes following stimulation either by insulin or exercise. This explains why the extraction rate of glucose increases from 2.6 to 9.6% following infusion of insulin in the hindlimb of growing cattle [78]. In addition, insulin stimulates not only glucose uptake, but also glucose oxidation and storage in muscles (synthesis of glycogen) and conversion of glucose into fats (lipogenesis) in the adipose tissue by increasing the activity of the key enzymes involved in these metabolic pathways. Consequently, insulin appears as the major regulator of glucose metabolism (for review, see [52]).

Studies in vivo on the whole body level have revealed that maximally insulin-stimulated glucose utilization rates are in the decreasing order: rats (20–35 $mg \cdot min^{-1}$ per kg body weight), humans and pigs (10 $mg \cdot min^{-1} \cdot kg^{-1}$), rabbits (7–8 $mg \cdot min^{-1} \cdot kg^{-1}$), and ruminants (2–5 $mg \cdot min^{-1} \cdot kg^{-1}$), leading to the idea that ruminants are less sensitive to insulin than other mammalian species, especially rats (for review, see [52]). This was confirmed by other in vivo studies with perfused muscles: insulin increases glucose uptake by the muscle tissue more

than 10-fold in rats [16] but less than 2-fold in sheep [24].

Moreover, in vitro studies using incubated muscle fiber strips showed that insulin stimulates glucose transport rate into muscles to a higher extent in humans (+123%) [29] and rats (+258%) than in calves (+82%) [45]. The ability of insulin to stimulate in vitro glucose transport rate in isolated adipocytes is also lower in pigs (+80%) [65], and sheep (+120–170%) [81] than in humans (+300%) [37] or in rats (+ approximately 500%) [80]. However, the effects of insulin on glucose uptake is age/body weight related, making comparison among species difficult. Nevertheless, it is clear that large differences exist between farm animals and rats relative to tissue response to insulin. Therefore, it is not unreasonable to speculate differences in the insulin-glucose transporter system among species.

3. CHARACTERIZATION OF GLUCOSE TRANSPORTERS IN LIVESTOCK SPECIES

3.1. Immunological studies

A direct approach to study glucose transporters is to detect the GLUT protein by Western blot analysis using available antibodies. However, many authors have considerable difficulties with this technique, whatever the animal species due to several practical problems. Firstly, some non-specific bands may be detected either with a non-immune serum [96], or even with polyclonal antibodies specifically raised against GLUTs [41, 49, 85]. Secondly, a confident detection of the GLUT proteins is made difficult because of the inconsistency of their electrophoretic behavior due to the heterogeneity of the protein glycosylation, as for GLUT1 [32, 61], GLUT3 [32] and GLUT4 [50, 96]. A protein doublet is even observed for GLUT1 [102] and GLUT4 in some circumstances [11] (for review, see [72]). Finally, it has been clearly demonstrated in cattle that adipose tissue, heart and skeletal muscle GLUT4 proteins are subjected to differential glycosylation, leading to a slightly higher molecular weight of the bovine GLUT4 protein in adipose tissue than in skeletal muscles [50].

The GLUT1 and GLUT3 proteins were detected by Western blot in the placenta and brain [26, 32, 61] of sheep and the GLUT1 protein in the mammary gland [102] and brain [32] of cattle. The intestinal fructose transporter (GLUT5) was characterized at the protein level in rabbits [70]. The GLUT2 protein was detected in the sheep liver [38], and was studied at the mRNA levels in bovine [101] and chicken liver [97].

A great deal of efforts have been made in studying the insulin-sensitive glucose transporter, GLUT4, which is thought to play a key role in glucose homestasis due to the regulation of its activity by insulin. A GLUT4-like protein was first detected in goat adipose tissue [94], bovine skeletal muscle [66] and ovine skeletal muscle [82] by Western blot analysis with an antibody against rat GLUT4. The GLUT4 protein was detected in all insulin-responsive tissues (heart, skeletal muscles, adipose tissues) from cattle and goats but not in other tissues (liver, intestine, brain, erythrocytes) [1, 45]. Thus, GLUT4 is the major glucose transporter in insulin-sensitive tissues as in other species. However, in ruminants, GLUT4 content seems to be higher in glycolytic than in oxidative muscles in contrast to the situation observed in rats [45]. In addition, GLUT4 content is higher in perirenal and omental adipose tissues than in subcutaneous adipose tissues in growing calves [47, 50]. This may be related to the lower metabolic activity of this latter tissue [51].

3.2. Cloning of GLUT cDNAs in livestock species

Besides cloning in laboratory rodents (rats, mice, guinea-pigs) and humans, partial or complete sequences of GLUT1 and

GLUT3 cDNAs were cloned in sheep [25] and chicken [96, 99]. GLUT1 cDNAs were also cloned from pigs, rabbits and cattle (Fig. 1). To our knowledge, when considering farm animals, GLUT2 cDNA was only cloned from chickens [97] and GLUT5 cDNA only from rabbits [70].

The recent cloning of GLUT4 probes in pigs [22, 58], sheep [15], and cattle [3, 49] will allow scientists to further understand the regulation of glucose transport in insulin-sensitive tissues of livestock animals. Only the bovine GLUT4 was completely sequenced. The full bovine GLUT4 cDNA is composed of 2 676 base pairs and encodes for a 509 amino acid protein. The deduced amino acid identities between bovine and rodent GLUT4 are greater than 90% while the amino acid identity between bovine GLUT1 and GLUT4 are rather lower (64%).

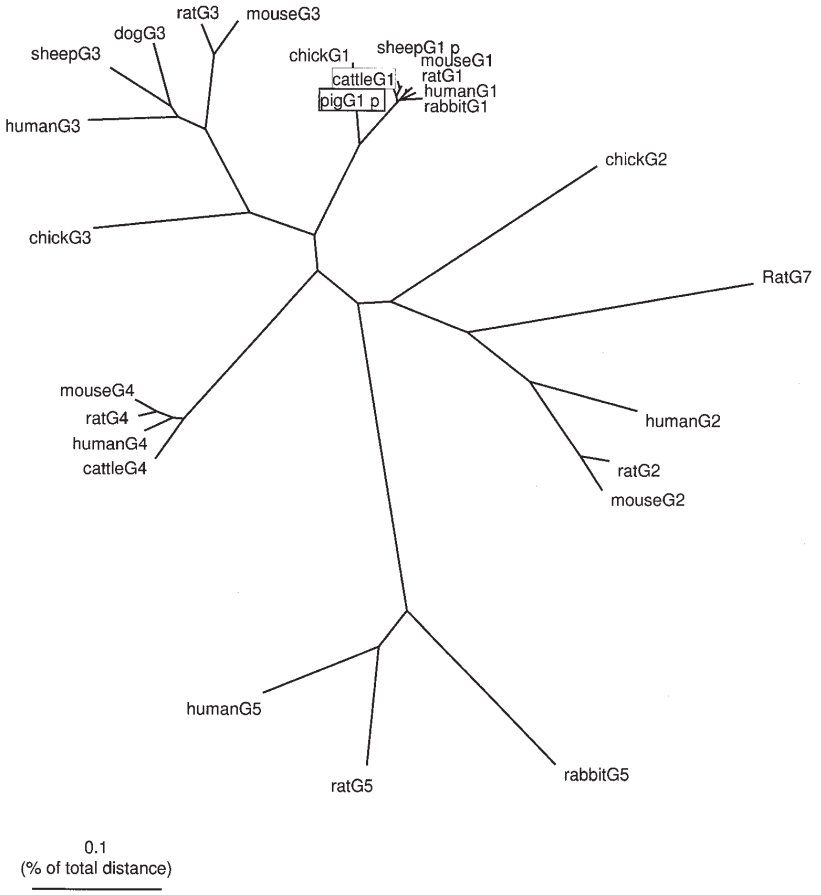

Figure 1. Unrooted phylogenic analysis of the 26 known vertebrate GLUT proteins using the pilup program. Each protein is designed by the common name of the animal followed by its isoform number (for instance, cattleG4 means cattle GLUT4). The sequences were extracted from GenBank 115.0 in December 1999. The accession numbers are as follows for full length sequences: X66031, Z22932, J03810, J03145, X15684, M37785, M20681, L39214, L35267, U17978, M75135, L07300, M60448, M13979, M22998, M21747, K03195, M20747, J045524, M23383, D26482, D13871, M55531, D63150. Partial sequences of pig GLUT1 (pigG1 p, X17058, 451 amino acids), and of sheep GLUT1 (sheepG1 p, U89029, 390 amino acids) were also added.

A unique amino acid conversion (Asn 508 to His) was found within the C-terminal region [4] which is considered to be important for GLUT4 translocation [23]. The GLUT4 C-terminal regions were also sequenced in other ruminants (sheep and goat) and pigs [4]. However, unlike in cattle, the unique conversion of Asn into His in position 508 was not found in these animals. Some other differences in the ruminants' GLUT4 protein itself or in insulin-related regulatory mechanisms are considered to explain the ruminants' relative insulin resistance.

The phylogenetic relationship of the 26 vertebrate GLUT proteins present in GenBank 115.0 in December 1999 shows that the first divergence separates the fructose transporter (GLUT5) from the others. The next divergence is the liver isoforms (GLUT2 and GLUT7) from the non-liver isoforms. GLUT4 is the next to diverge. The final divergence is GLUT1 from GLUT3. For GLUT2, GLUT1 and GLUT3, the chicken isoforms diverge before the mammalian GLUTs protein [96]. It is also noteworthy that GLUT4 and GLUT1 from the various species diverge less than other glucose transporter isoforms (Fig. 1).

3.3. Expression of GLUT genes in livestock species

A typical mRNA can be conveniently thought of as being divided into functional regions (5' or 3' untranslated regions (UTR), the coding region and the polyA tail). The 3'-UTR is thought to make a major contribution to the message stability (for review, see [68]). For instance, a 10 nucleotide cis-acting element of the bovine GLUT1 3'-UTR was shown to increase the GLUT1 mRNA half life by 228% [17]. Other results suggest differential GLUT1 mRNA binding to cytosolic and polysome proteins in the brain and peripheral tissues, which is consistent with the idea that GLUT1 gene expression is subject to regulation at the post-transcriptional level [95].

Most expression studies have been conducted so far by Northern blot analysis to achieve the following objectives: identifying the size of the GLUT transcripts, determining the tissue distribution of the GLUT expression and quantifying the levels of their mRNA in relationship with the GLUT protein levels in order to precise the major level or mechanism of regulation.

Northern blot hybridization was used to demonstrate the presence of a major transcript for GLUT4 at 2.7–2.8 kb in cattle [3, 49], pigs [30], rats and mice tissues. The larger size of the GLUT4 message in human tissues (3.5 kb) is thought to be due to differences in size of the 3' UTR (for review, see [72]). Unlike in sheep [25], the chicken GLUT3 isoform is expressed as two mRNAs of 1.7 and 3.2 kb [99], which may arise by alternative polyadenylation as is the case for the two GLUT3 mRNAs produced in human cells [60]. The message of the chicken GLUT1 is characterized by a larger size than that of mammalian GLUT1 (3.2 kb vs. 2.7 kb), which is probably due to a longer 3'-UTR [96].

As in other species, GLUT4 mRNA was detected in the heart, muscles and adipose tissue but not in non insulin-responsive tissues from cattle using either human [100] or bovine cDNA probes [3, 49]. Unlike human organs, the liver and kidney of lactating cows express a high GLUT5 mRNA level [100], the physiological role of this transporter still being a matter of conjoncture [70]. It is thought that GLUT5 participates in the uptake of glucose from the lumen of the small intestine and in the reabsorption of glucose in the kidney. Its physiological function, however, may differ among species [70] and remains unclear in the bovine liver.

Many authors have considerable difficulty in accurately measuring mRNA abundance by Northern blot using total RNA [30, 49], especially from adipose tissue [50]. To overcome this problem, some authors have developed a Northern blot procedure with poly A^+ RNA [30], and also a nuclease

protection assay that allows a more accurate quantification of low levels of GLUT4 mRNA as in pig tissues [22, 58].

From studies in laboratory rodents, it appears that changes in GLUT4 mRNA levels in skeletal muscles are of smaller magnitude than those in the adipose tissue and heart. Furthermore, larger changes are typically observed in red fibers compared to white muscle fibers, at least in laboratory rodents (for review, see [72]). Changes in mRNA levels result from both transcriptional regulation and post-transcriptional control. However, an appreciation of the contribution of mRNA stability to the regulation of gene expression is a rather more recent development. For instance, studies in cultured cells have demonstrated changes in GLUT1 mRNA half-life of 2–10 fold depending on the experimental models (for review, see [68]). Similarly, it has been demonstrated that chronic treatment of 3T3-L1 adipocytes with arachidonic results in a 50% decrease in the transcription rate of the GLUT4 gene, as well as a reduction in half-life from 8.0 h to 4.6 h [91]. In rats, the action of diabetes and benfluorex (a hypolipidemic and antihyperglycemic agent) clearly differs between red and white muscles [71]. Other studies in rats have also shown that the regulation of GLUT4 by thyroid hormones lies at the transcriptional level in red skeletal muscle, whereas in white muscles, it appears to operate via an alternative posttranscriptional mechanism [93]. Similar differences between muscle types have been suggested in bovine muscles [49].

To summarize, the GLUT protein expression may be controlled by various mechanisms including RNA and protein turnovers and translation efficiency. For GLUT4, the relative importance of these control mechanisms seems to differ between muscles (oxidative/glycolytic) [68, 93] or among species (monogastrics/ruminants) [49]. Therefore, a thorough investigation of the rates of glucose transporter synthesis and half-life is necessary in cattle.

4. REGULATION OF GLUT ACTIVITY AND EXPRESSION IN ANIMAL MODELS

4.1. In vitro regulation of GLUT activity and expression

4.1.1. Oncogenic transformation

Most transformed cells, including tumor cells, display increased rates of glucose metabolism compared to untransformed cells. This allowed the first cloning of GLUT1 from the HepG2 human hepatoma cell line, which was facilitated by its high level of expression. In rodents, the mechanisms whereby glucose transport is up-regulated by cell transformation are well understood. Indeed, stimulation of glucose transport involves an elevation in mRNA encoding the GLUT1 glucose transporter that is controlled at the levels of both transcription and mRNA stability, whereas GLUT3 expression is relatively unaffected. In contrast, the oncogene v-*src* or various mitogens were shown to increase GLUT3 mRNA level and GLUT3 transcription in chicken embryo fibroblasts rather than those of GLUT1. Therefore, the roles of GLUT1 and GLUT3 probably differ in avian and mammalian cells [96].

4.1.2. Cultured cells

Bovine cultured endothelial and smooth muscle cells are good models for studying the regulation of glucose transporters (GLUT1 and GLUT3), especially by hyperglycaemia, which is considered to be a common risk factor for the development of vascular complications in diabetes mellitus (for review, see [46]). For instance, it has been demonstrated using bovine cultured cells that metformin, an antidiabetic drug widely used to treat diabetic patients, affects glucose transport not only in insulin responsive tissues, but also in vascular cells [83]. In addition, hypoxia in cultured bovine retinal endothelial cells upregulates glucose

transport activity through an increase of GLUT1 expression. This observation may be important because retinal hypoxia often precedes proliferative diabetic retinopathy [90].

4.2. In vivo hormonal and nutritional regulation of GLUT activity and expression

4.2.1. Insulin

Studies in laboratory rodents have shown that hyperinsulinemia due to insulin infusion results in elevated GLUT4 protein levels in adipocytes, but the data in muscles are less clear (for review, see [68]). However, a 24-h euglycemic hyperinsulinemic clamp was found to be necessary in order to observe a significant increase in GLUT4 protein level in rat adipose tissue [77]. Thus, in both rats [77] and goats [12], a 6-h euglycemic hyperinsulinemic clamp did not change the level of GLUT4 protein in muscles and adipose tissues. Similarly, a 2-h clamp did not change GLUT4 expression in sheep muscles [38].

4.2.2. Growth hormone

Daily administration of growth hormone (GH) to growing animals can reduce adipose tissue growth by as much as 80% (for review, see [34]). The major underlying biological mechanism is a marked decrease in glucose transport and lipogenesis in adipose tissue with relatively no change in lipolysis. However, the reduction in fatty acid synthetase (FAS) gene expression (FAS being a key lipogenic enzyme) was of much greater magnitude than that of GLUT4 gene expression in pig adipose tissue following growth hormone treatment [30], although a 40% decrease in the GLUT4 protein was observed in some experiments [34]. It has thus been suggested that growth hormone affects the distribution of GLUT4 protein between plasma and intracellular membranes rather than total cell GLUT4 protein level [30].

In lactating cows, GH or GH-releasing factor does not affect mRNA levels of GLUT2, GLUT1 or GLUT5 in the liver or in the kidney [101]. In the mammary gland, GLUT1 protein level is unaffected by these hormonal treatments. On the contrary, GLUT4 mRNA levels is decreased by 44% in skeletal muscle as a result of GH treatment. A similar tendency has been suggested in omental fat. Providing consequences on GLUT4 protein levels, these results suggest that GH may increase glucose availability to the mammary gland during lactation by regulating GLUT4 expression in muscles and fatty tissues [102].

4.2.3. Nutrients

Postnatal development of GLUT4 was determined in the pig fed different energy intake levels [58]. RNase protection assays have revealed selective upregulation of porcine GLUT1 and GLUT4 by mild undernutrition: mRNA levels are elevated in *longissimus thoracis* and *rhomboideus*, but not in *diaphragma* or cardiac muscles in the growing pig. This demonstrates that GLUT expression is, at least in part, dependent on energy status.

Calves for veal production intensively fed with milk replacers develop insulin resistance, hyperglycemia and glycosuria [54]. These metabolic abnormalities are associated with inefficient glucose use as energy source, and low feed conversion and growth parameters (for review, see [14]). The insulin resistance of calves is exaggerated after milk consumption providing evidence for the involvement of nutritional factors [54]. Recent data suggest that lactose content in milk might be responsible for the development of the low insulin responsiveness [56]. The regulation of GLUT4 activity and expression by lactose are still unknown. However, other mechanistic studies in laboratory rodents indicate that a high glucose

entry rate induces an increase in the hexosamine pathway, thereby increasing intracellular glucosamine content which inhibits GLUT4 translocation following insulin stimulation [67].

Dietary γ-linolenic acid (GLA, 18:3(n-6)) is known to reduce body fat content and to increase fatty acid β-oxidation enzyme activities in the liver [89]. Dietary GLA tends to decrease GLUT4 expression in skeletal muscles and adipose tissues compared to control animals [59]. The mechanisms might be through PPARγ expression by GLA but these remain unknown.

5. REGULATION OF GLUT EXPRESSION IN FARM ANIMALS THROUGHOUT DEVELOPMENT, BREEDING AND PRODUCTION

5.1. Development

5.1.1. Gestation and foetal development

Before birth, glucose is the major fuel for both foetal energy metabolism and accretion, yet the foetus lacks the capacity for gluconeogenesis until late gestation and must thus rely on maternal glucose supply for growth and development. Glucose is transferred through the placenta by facilitated diffusion, but 30–50% of the glucose taken up by the placenta may be converted into lactate before being transferred to foetal circulation (for review, see [35]). Total glucose transporter concentrations in the sheep placenta increases 3.4-fold from mid- to late gestation [32]. Northern blot analysis in the placentas of pregnant ewes have demonstrated that GLUT1 and GLUT3 genes are characterized by distinct patterns of temporal expression during development: GLUT1 gene expression increases especially during the third quarter of gestation and tends either to decrease [25] or remains stable [32] towards term, whereas GLUT3 gene expression continues to increase throughout gestation [25, 32]. Consequently, in the sheep placenta, GLUT1 accounts for 86% of the total glucose transporter level at day 75 of gestation and 56% at day 140 [32]. Furthermore, placental GLUT1 concentrations are regulated by glycemia in the same manner in both rats and sheep. These changes may contribute to the regulation of maternoplacentofetal transport of glucose, thereby regulating placental and foetal growth [26].

In all foetal tissues examined so far, GLUT1 is expressed in relatively high concentrations compared with the adult in both rats [80], bovines [5, 19, 53] and ovines [27]. However, immunolocalisation experiments have indicated that bovine spermatozoa express GLUT1, GLUT2, GLUT3, GLUT5 and also low levels of GLUT4 [6]. GLUT1 expression was detected by RT-PCR in bovine oocytes and young embryos [63]. During gestation, GLUT1 expression tends to decline in the bovine heart [5] whereas it is the highest between 6 and 8 months of foetal development in bovine perirenal adipose tissue [53]. GLUT4 expression in the calf increases in both tissues during the last third of gestation [5], but it declines near term in the adipose tissue [53]. In late-gestation of the ovine fetus, foetal hyperglycemia or hypoglycemia causes time-dependent and tissue- and isoform-specific changes in foetal glucose transporter levels. For instance, in a case of excessive glucose, a downregulation of glucose transporter proteins protects the cell from glucose toxicity and prevents relative overgrowth. In contrast, limited glucose availability causes no major changes in GLUT protein levels [27]. Whether these foetal changes persist postnatally and alter the adult responses to changes in glycemia remains to be investigated.

5.1.2. Postnatal development and weaning

Glucose tolerance was shown to decrease with increasing age in calves (for review, see [14]) and lambs. This is not associated with any change in GLUT4 expression in

ovine muscles [38]. However, increased GLUT2 expression in the liver with age, as well as decreased GLUT2 expression with hyperinsulinemia in older lambs, is consistent with the development of insulin-resistance with age [38].

Extensive metabolic adaptations induced by profound changes in nutrition occur at weaning. In rats and pigs, weaning induces a shift from a fat-rich diet (milk) to a carbohydrate-rich diet leading to higher insulin blood levels in the postprandial state. By contrast, as calves develop from the non-ruminating to the ruminating state, carbohydrate (present in milk replacers and whole milk) provide 20–45% of the metabolizable energy intake for the preruminant calf or the veal calf and less than 5% for the weaned calf. In rats (for review, see [39]) and pigs [48], the nutritional changes which occur at weaning induce an increase in GLUT4 content in both skeletal muscles of the oxidative type and adipose tissues. By contrast, in the calf, GLUT4 content in the heart and skeletal muscles of the carcass does not change at weaning [50] and GLUT4 content in bovine adipose tissues decreases slightly (–39%) when the results are expressed on a per cell basis (i.e. per mg protein or per mg DNA) [50]. This difference in GLUT4 regulation between monogastric species and cattle may be associated with the large difference in the process of digestion and metabolism of nutrients.

5.2. Meat production

5.2.1. Growth rate

The efficiency with which ingested protein is used for growth in ruminants is lower with forage diets (high-fibre diets leading to a high proportion of acetate) than with concentrate diets (high-starch diets leading to a high production of propionate which is a glucose precursor). Recent data confirm the idea that glucose is efficient for muscle growth. Indeed, glucose transport rate was measured in incubated *rectus abdominis* muscle fibre strips from normal calves and double-muscled calves, the latter being characterised by a muscle hypertrophy of genetic origin. Basal and maximally insulin-stimulated glucose transport rates per g tissue wet weight are positively correlated with the weight of *rectus abdominis* muscle and growth parameters [76]. These results are in agreement with those in humans demonstrating that weight gain is positively correlated with glucose disposal at submaximally and maximally-stimulating insulin concentrations [88].

5.2.2. Meat quality

A fall in intramuscular pH due to glycogenolysis occurs after slaughter during conversion of muscles into meat. Ultimate pH is an important criterion of meat quality since it reflects the extent of post-mortem biological changes. In addition, it determines to some extent several meat quality traits such as colour, water-holding capacity, juiciness, and tenderness (for review, see [52]). In mammals, ultimate pH depends chiefly on muscle glycogen content at slaughter, until a threshold from which further increase in glycogen level does not affect meat pH [79]. Therefore, the regulation of muscle glucose metabolism (and thus, of glucose transporters) in meat-producing animals before slaughter might potentially affect meat quality (for review, see [52]).

In cattle, glycogen deficiency at slaughter results in dark-cutting because of a too high meat ultimate pH, thereby affecting meat quality. This problem is of commercial importance in major beef-producing countries [84]. Dark-cutting is considered to result primarily from glycogen mobilization in muscles by exposure of the animals to various forms of stress (mixed penning, transport, waiting before slaughter). Therefore, there is no relationship between GLUT4 content and glycogen levels in muscles due [36] to the major effects of stressed

factors. However, resynthesis of glycogen in the muscle of ruminants after chronic stress [69, 98] was shown to be lower than after post endurance exercise [42]. Glycogen repletion is linked, at least in part, to the activity of the glucose transport system, the rate-limiting step of glucose metabolism. From the available data in the literature, it is known that GLUT4 activity is enhanced after endurance exercise. In addition, glycogen repletion in monogastrics such as the pig is presumed to be much faster than in ruminants, which are less sensitive to the action of insulin through GLUT4 than monogastrics. The relationships between glycogen recovery and GLUT4 activity remain to be studied in farm animals.

5.3. Cold exposure and physical activity

Adaptative thermogenesis defined as a major component of energy expenditure, is regulated by environmental stimuli such as cold exposure. This process has been implicated in the regulation of body temperature, body weight, and metabolism. Thus, for meat-producing animals, it may have consequences on growth performances and muscle metabolic characteristics implicated in meat quality (for review, see [52]). In five-day-old piglets exposed to cold conditions, glucose uptake by skeletal muscles is increased immediately, whereas muscle mitochondria exhibit increased respiratory, oxidative and phosphorylative capacities after 48 h in the cold (for review, see [52]). These observations are consistent with those in rat skeletal muscle which demonstrated a 2–3 fold increase in GLUT4 mRNA levels between 6–24 h of cold exposure and then a decrease to 50% of the control value after 6 days in the cold [64].

Training alters the balance of fuel use during exercise: indeed, athletic or trained animals rely more on fat during exercise (for review, see [52]). Furthermore, in sheep, exercise training induces an increase in glycogen level in skeletal muscle, especially in muscles already containing a high amount of glycogen [74]. A similar response was found in the pig [33] and in other species (for review, see [43]). This may be due to an increased sensitivity of the muscle tissue to insulin by physical training as demonstrated in rodents and humans (for review, see [43]). In cattle, insulin level is lower with grazing, which also suggests an increase in insulin sensitivity with increased physical activity in the fields [7]. Furthermore, the development of solid food chewing in weaned calves concomitantly induces (i) a very high and almost constant contractile activity level of the masseter muscle in the cheek, and (ii) an increase in oxidative enzymes (e.g. ICDH) and in GLUT4 content only in this muscle [50]. All these observations are consistent with the fact that chronic contractile activity or exercise training likely increases GLUT4 protein content in the muscles, as it does in laboratory rodents (for review, see [68]).

Conversely, overexpression of GLUT4 in the muscle and fat of transgenic mice induced a 1.5-fold higher muscle glycogen level at rest, and a greater consumption of carbohydrate (up to 64% more) and less consumption of lipid (up to 40% less) during 30 min acute treadmill exercise [13]. All these observations underline the key role of GLUT4 expression in muscle energy metabolism during physical activity. Glucose is taken up by muscles passing, at least in part, through the glycogen pool before being oxidised.

5.4. Lactation

In vivo studies have shown that lactation in goats is associated with an impairment in the ability of insulin to maximally stimulate glucose utilisation [28]. This insulin resistance in goats originates from a post-receptor defect [10]. Indeed, lactation results in a 20 to 60% decrease in GLUT4 protein content in both crude membranes and homogenates from goat muscles, which is consistent with the 50% decrease in the

maximally stimulated-insulin response of whole body glucose utilisation [11]. This impairment in glucose disposal in skeletal muscles may spare glucose for the benefit of the mammary gland, a high-glucose consuming organ in lactating animals. The origin of the decrease in GLUT4 protein content in skeletal muscles from lactating goats is still unknown but could be related to a down-regulation of GLUT4 synthesis by growth hormone, the blood level of which increases in early-lactating animals.

6. CONCLUSION

Despite some technical difficulties in Western blot and Northern blot approaches, the GLUT family has been studied in farm animals as done some years before in laboratory rodents and humans. The general features of the GLUT protein are roughly the same in farm animals as in humans and laboratory rodents. However, some species-specific differences have been identified, such as, for instance, the low insulin response of glucose metabolism in ruminants, the low expression of GLUT1 in erythrocytes, the mechanisms of the regulation of GLUT expression (transcription, mRNA turnover or translation efficiency) and the respective roles of GLUT1 and GLUT3 in avian species.

The insulin-sensitive glucose transporter (GLUT4) appears to be a key-protein in the control of glucose uptake and metabolism in ruminants as in monogastric mammals. In all species, this transporter is involved in the control of glucose partitioning between tissues (muscles, adipose tissues, and indirectly, the mammary gland in lactating animals). Thus, it is thought to play an important role in the determination of body composition, which is a key parameter for producing animals. Indeed, meat producers are looking for an increased growth of muscles at the expense of adipose tissue, whereas, fat stores are of prime importance for the production of milk by lactating cows.

Glucose transporters remain to be studied in the ruminant liver which produces rather than uses glucose. Unlike other species, the bovine liver seems to express not only GLUT2 but also GLUT5. The physiological role of these transporters in the ruminant liver is still unknown.

Some research is also needed to better characterize some GLUT proteins in farm animals and their respective roles in some important physiological functions (glycogen level in muscles with regards to meat quality, physical activity, cold exposure).

For obvious reasons (facilities, size of samples...), primary cultures of bovine and avian cells (endothelial, vascular, retinal cells, transformed cells) have been shown to be interesting models for the study of the regulation of facilitative glucose transporters in relation to human diseases (cancer, diabetes-induced retinopathy and vascular complications). However, conclusions should be generalized with caution since some differences in the regulation of glucose transporters have been demonstrated among species. Farm animals are also good in vivo models to describe, for instance, the ontogenesis of GLUT expression during the foetal life.

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