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Glucose transporters in cattle - a review*

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Glucose is the major energy source for the animal cells. It is important substrate for protein and lipid synthesis. This sugar is absorbed into the cells from body fluids *via* glucose transporters – structurally related trans-membrane proteins. There are two types of glucose transport - passive and active. The facilitative-glucose-transporter family of proteins (solute co-transporters GLUT, encoded by *SLC2A* genes) participates in energy-independent process of glucose transport. The Na^+/ glucose co-transporter family proteins SGLT (solute carriers, encoded by *SLC5A* genes) mediate the Na^+-linked transport of glucose against the electrochemical gradient. In this review, we describe genomic structure and function of the bovine glucose transporters. Intra-species comparative analyses o the amino acid identities of glucose transporter proteins is also described, as well as the information on the nucleotide sequence polymorphisms in the bovine glucose transporter genes.

KEY WORDS: cattle / glucose transporters / intra-species comparison

Introduction

Glucose, a monosaccharide is an important carbohydrate substrate for both protein and lipid synthesis. It derives directly from hydrolysis of ingested disaccharides and polysaccharides or is synthesized from other substrates in animals' organs, mostly in liver. Cells use glucose as a primary source of energy and as a metabolic intermediate. Glucose may be converted either into glycogen or triacylglycerols which are

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subsequently stored within tissues or, in the mammary gland, into lactose. Glucose is a ubiquitous fuel in biology. It is used as an energy source in most organisms, from bacteria to humans. Through glycolysis and later in the reactions of the citric acid cycle, glucose is oxidized to eventually form CO_2 and water, yielding energy sources, mostly in the form of ATP, and reducing power in the form of NADPH, through the pentose phosphate.

The insulin actions, hormonal changes and other mechanisms, regulate the concentration of glucose in the blood. A high-fasting blood sugar level is an indication of pre-diabetic and diabetic conditions. Glucose is a primary source of energy for the brain, and transport of this nutrient from blood to the brain is limited by the blood-brain barrier glucose transport system [Takata *et al.* 1990]. Regulation of glucose transport in response to environmental signals is complex and varies according to cell type and to the external stimuli.

Skeletal muscle is a major consumer of glucose in the body. In the muscle tissue, glucose may be either oxidized or stored as glycogen. Adipose tissue in ruminants represents only a minor target for glucose disposal accounting for some 1% total glucose utilization.

Glucose is a principal precursor of lactose, the major milk carbohydrate. The mammary gland itself cannot synthesize glucose from other precursors because of the lack of glucose-6-phosphatase enzyme [Threadgold and Kuhn 1979]. Therefore, the mammary gland is totally dependent on the blood supply for its glucose needs; during lactation it utilizes 60-85% of the total glucose that enters blood. In lactating cow, 72 g of glucose is required to produce 1 kg of milk [Kronfeld 1982]. The increased glucose demand for lactation is accomplished by increased glucose transporter expression in mammary gland tissues from pregnancy to early lactation [Zhao and Keating 2007].

Glucose transport across the plasma membranes of mammalian cells is carried out by two distinct processes employing the passive, facilitative, energy-independent glucose transporters GLUT, encoded by *SLC2A* genes, and the active sodium-dependent and energy-dependent glucose transporters SGLT, encoded by *SLC5A* genes. Moreover, the facilitative glucose transporters can be divided into two families: insulin-sensitive (GLUT4) and insulin non-sensitive (GLUTs: 1, 2, 3 and 5) [Mueckler 1994]. Each glucose transporter plays specific role in cellular metabolism, which is determined by its tissue and substrate-specificity and expression in different physiological states [Thorens 1996].

Most of the studies of the structure and function of glucose transporters and their genes were carried out with humans or laboratory animals – mice and rats. There are relatively little studies carried out of the bovine glucose transporters and the genes encoding these proteins.

In this review, we describe genomic structure, protein structure and function of the bovine glucose transporters as well as their intra-species comparative analyses with the pairwise basic local alignment search tool (BLAST, (http://blast.ncbi.nlm.nih.gov/Blast.cgi).) used for analysis the amino acid identities of glucose transporter proteins.

In addition, the information is given on the nucleotide sequence polymorphisms in the bovine glucose transporter genes as well as some basic information about regulation of these genes in ruminants. This information could be useful for further studies of glucose transporter genes as molecular markers of production and functional traits in farm animals.

Facilitative-glucose-transporters (GLUT)

The family of facilitative energy-independent glucose transporters GLUTs (solute carriers; gene symbol *SLC2A*) consists of proteins which utilize the diffusion gradient of glucose (and other sugars) across the cell plasma membrane in the energy-independent process. They exhibit different substrate specificities and tissue expression profiles [Wood and Trayhurn 2003]. These transporters are structurally conserved and related, consisting of 12 trans-membrane domains with both amino and carboxy-terminals located in the cytoplasm (Fig. 1), and N-glycosylation sites located on either

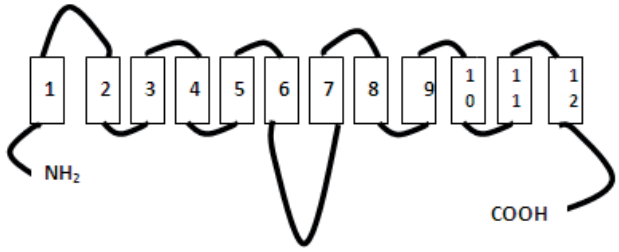

Fig. 1. Schematic membrane topology of GLUTs.

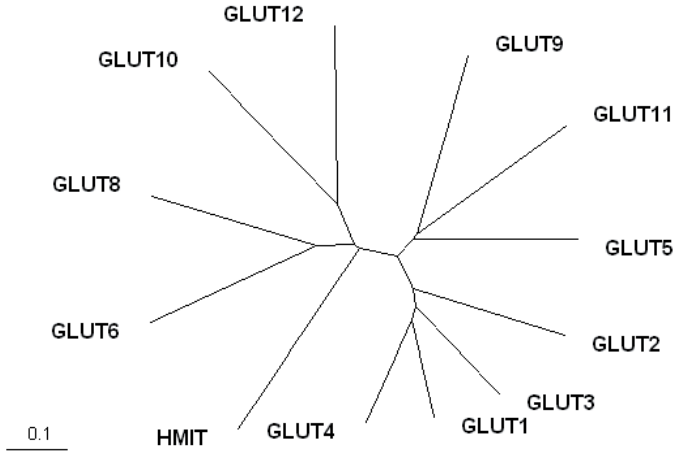

Fig. 2. Unrooted phylogenetic tree of the 12 bovine members of the GLUT family transporters (generated with the use of phylogeny program - http://www.ebi.ac.uk/ Tools/phylogeny/ clustalw2_phylogeny/).

the first or ninth extracellular loop. In humans there have been found 13 functional facilitative glucose transporters, described as GLUT1 – 12 and H^+/myo-inositol cotransporter (HMIT) [Joost and Thorens 2001]. Also in the cattle, 13 analogous GLUT proteins and *SLC2A* genes, as well the *SLC2A13* gene encoding HMIT protein, have been identified. Some properties of 11 bovine GLUTs and HMIT are presented in Tables 1 and 2. The GLUT family of sugar transports is divided into three classes. Class 1 includes GLUT1, GLUT4, GLUT3, and GLUT2 which are 65, 66 and 54% identical in bovine. Class II is comprised of GLUT9, GLUT11 and GLUT5 (fructose transporter), which are 56% and 43% identical. Class III is composed of GLUT6, GLUT8, GLUT10, GLUT12 and HMIT, with their amino acid sequences identical in 43, 63, 26 and 29%, respectively. All of them have a characteristic glycosylation site on loop 9. The phylogenetic tree of 12 members of the bovine SLC2A family of glucose transporters is shown in Figure 2.

Table 1. Summary of the properties of facilitative glucose transporter and Na^+Glucose co-transporter family members

Protein	Gene	Crmosome location	Exon No.	Gene length (bp)	Major isoform (a.a.)	Accession No.	
						gene	protein
			Facilitative glucose transporters (GLUT)				
GLUT1	SLC2A1	Chr3.89 29407 .. 56560	10	28203	492	AC_000160	NP_777027
GLUT2	SLC2A2	Chr.1 97220100..97250239	11	30140	510	AC_000158	NP_001096692
GLUT3	SLC2A3	Chr5.100 676448 .. 686746	11	12880	494	AC_000162	NP_777028
GLUT4	SLC2A4	Chr.19 27616613..27622203	11	5591	509	AC_000176	NP_777029
GLUT5	SLC2A5	Chr16.31 657532 .. 684346	7	21094	501	AC_000171	NP_001094512
GLUT6	SLC2A6	Chr11.76 606514 .. 613176	10	7250	507	AC_000168	NP_001073725
GLUT8	SLC2A8	Chr11.71 1239522 .. 1247990	10	9032	478	AC_000168	NP_963286
GLUT9	SLC2A9	Chr.6 109907497..110067530	15	160034	409	AC_000163	XP_002688502
GLUT10	SLC2A10	Chr13.47 2677325 .. 2689744	5	11862	536	AC_000170	NP_001179368
GLUT11	SLC2A11	Chr17.51 332722 .. 348113	13	15113	496	AC_000174	NP_001180026
GLUT12	SLC2A12	Chr9.84 417402 .. 486519	5	32203	621	AC_000166	NP_001011683
HMIT	SLC2A13	Chr5.45 1917303 .. 2436656	10	497285	648	AC_000162	NP_001179892
			Na^+/glucose cotransporters (SGLT)				
SGLT1	SLC5A1	Chr17.48 60171 .. 108186	15	49509	664	AC_000174	NP_777031
SGLT2	SLC5A2	Chr25.38 490906 .. 500658	14	9751	673	AC_000182	NP_976236
SGLT4	SLC5A9	Chr.3. 98566749..98587443	18	20695	705	AC_000160	NP_001192865
SGLT5	SLC5A10	Chr19.22 256007 .. 311032	15	55077	597	AC_000176	NP_001001442
SMIT2	SLC5A11	Chr25.30 1417602 .. 1463879	17	57028	674	AC_000182	NP_001029832
SMCT2	SLC5A12	Chr15.57 1635870 .. 1686094	15	51295	617	AC_000172	NP_001094529

Table 2. The glucose transporter (GLUT) family of facilitative sugar and Na^+/Glucose cotransporter family members, functional characteristics

Protein	Main tissue localization	Functional characteristics
GLUT1	Brain, mammary gland, kidney, omental fat, skeletal muscle, bovine follicle, bovine ovary, and corpus luteum	Basal glucose transport across blood tissue barriers
GLUT2	Liver, islets, small intestine, kidney and jejunal region	Glucose (low affinity)
GLUT3	Brain, bovine ovary, follicles and corpus luteum	Glucose (high affinity)
GLUT4	Heart, muscle, brain and adipose tissue	Transport of glucose in all insulin-responsive tissues
GLUT5	Small intestine, testes, kidney, muscle, brain and adipose tissue	Fructose (high affinity), glucose (low affinity)
GLUT6	Spleen, peripheral leucocytes and brain	not detemined
GLUT8	Testes, mammary gland, kidney, intestine epithelia, skeletal muscle, blastocyst and liver	Insulin-responsive transport in blastocyst
GLUT9	Kidney and liver	not detemined
GLUT10	Liver and pancreas	not detemined
GLUT11	Heart, muscle (short form) liver, lung, trachea and brain (long form)	Glucose (low affinity), transport of fructose (long form)
GLUT12	Spleen, skeletal muscle, kidney, testes, mammary gland, liver, lung and intestine	Insulin-dependent glucose uptake in mammary gland
HMIT	Brain	H^+ /myo-inositol transporter
SGLT1	Intestine and kidney	Glucose (high affinity)
SGLT2	Kidney, mammary gland	May play a role in milk synthesis
SGLT4	not determined	not detemined
SGLT5	Small intestine, brain, kidney, liver and lung	not detemined
SMIT2	n.d.	Sodium/myo-inositol cotransporter 2
SMCT2	Kidney, small intestine and skeletal muscle	Sodium-coupled monocarboxylate transporter2 (low affinity)

GLUT1

GLUT1 is the insulin-independent glucose transporter. The bovine *SLC2A1* gene encoding GLUT1 protein is composed of 10 exons and localizes to the bovine chromosome 3 (BTA3). Its sequence is available in the GenBank database under Acc. No. AC_000160. In the GenBank SNP database are recorded 45 SNPs (single nucleotide polymorphisms) for *SLC2A1* gene: 41 in introns, one in 5'-untranslated region, and 3 in exons. The full-length of the bovine GLUT1 transcript has 2,533 nucleotides (nt). The GLUT1 protein consists of 492 amino acids (a.a), with a predicted molecular weight of 54 kDa [Zhao *et al*. 1996]. GLUT1 was detected with different molecular weights in lactating mammary gland and in dry stages, probably due to differential posttranslational modifications. In a pair wise basic local alignment search tool (BLAST) analysis the amino acid identities relative to GLUT1 varies from 54% for GLUT2 to 31% for GLUT12 and 29% for HMIT (Suppl. Fig. S1).The deduced amino acid sequence of bovine GLUT1 (Acc. No. NP_777027) is 99% identical to that of ovine, 97% with human, 97% with mouse, 97% with rat, 97% with dog, and 88% with chicken (Suppl. Fig. S2).

In bovine GLUT1 the unique proline-rich sequence was found between the putative first two transmembrane domains, near to the N-glycosylation site, at Asn^{45} [Boado and Pardridge, 1990]. As learned from the topology model, bovine GLUT1 has modified a.a. residues - phosphothreonine Thr^{234} between 6 and 7 transmembrane domains and phosphoserine Ser^{490} in the cytoplasmic domain (Fig. 3).

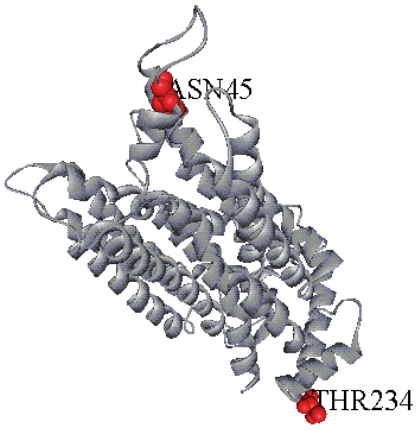

Fig. 3. Structure of GLUT1 – red balls represent N-glycosylated Asn^{45} and phosphorylated Thr^{234} amino acids, and grey ribbon shows secondary structure of GLUT1 protein (on the basis of sequence available in GenBank, Acc. No. NP_777027, generated with the use of ViwerLite 4.2 program).

In the bovine, the GLUT1 has been detected in the mammary gland, kidney, omental fat and skeletal muscle [Zhao *et al.* 1999], in fetal tissues [Hocquette *et al.* 2006], follicle and corpus luteum [Nishimoto *et al.* 2006]. The expression level of GLUT1 in bovine ovary was comparable to its expression in brain. In bovine cortical arteries, GLUT1 was shown to be responsible for basal glucose transport [Nishizaki and Matsuoka 1998].

GLUT2

The bovine *SLC2A2* gene encoding GLUT2 protein is composed of 11 exons and localizes to the chromosome 1 (BTA1). Its sequence is available in the GenBank database under Acc. No. AC_000158. In the GenBank SNP database are recorded 216 SNPs for *SLC2A2* gene: 202 in introns, 1 in 5'-untranslated region, 3 in exons, and 10 in 3'-untranslated region. The full-length bovine GLUT2 transcript has 2,707 nt; GLUT2 protein contains 510 a.a. with a predicted molecular weight of 56 kDa. The deduced amino acid sequence of bovine GLUT2 (NP_001096692) is 97, 90, 81, 81, 80 and 62% identical to that of ovine, porcine, human, mouse, rat and chicken, respectively. (Suppl. Fig. S3). With the topology model, bovine GLUT2 has N-glycosylation site at Asn^{62} between transmembrane domains 2 and 3 (Fig. 4).

In cattle, the low affinity glucose transporter GLUT2 was shown to be involved in the regulation of insulin secretion from β-cells, in the release of hepatic glucose, in the release of absorbed and reabsorbed glucose in the small intestine jejunal region, and kidney [Zhao *et al.* 1993, 1998, Liao *et al.* 2010].

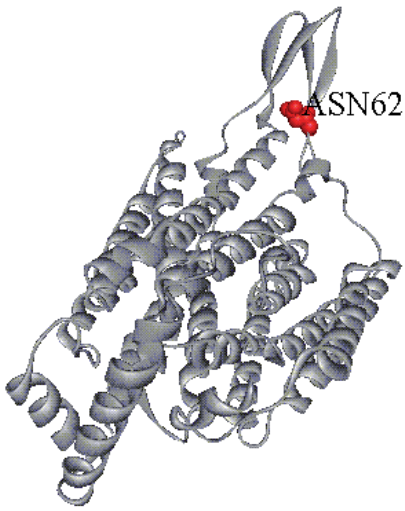

Fig. 4. Structure of GLUT2 – red balls represent N-glycosylated Asn^{62} amino acid, grey ribbon shows secondary structure of GLUT2 protein (on the basis of sequence available in GenBank - acc. No. NP_001096692, generated with the use of ViwerLite 4.2 program).

GLUT3

The bovine *SLC2A3* gene, coding for the GLUT3 protein, is composed of 11 exons and localizes to the chromosome 5 (BTA5). Its sequence is available in the GenBank database under Acc. No. NP_777028. In the GenBank SNP database 26 SNPs for *SLC2A3* gene are recorded: 17 in introns, 1 in 5'-untranslated region, 1 in exon, and 7 in 3'-untranslated region. The full-length bovine GLUT3 transcript has 4,066 nt; it encodes the 494-a.a. protein, with the predicted molecular weight of 56 kDa. The deduced amino acid sequence of bovine GLUT3 (NP_777028) is 99, 99, 90, 86, 83, 83 and 75% identical, respectively, with that of ovine, caprine, dog, human, mouse, rat and chicken (Suppl. Fig. S4). As shown in the topology model (Fig. 5),

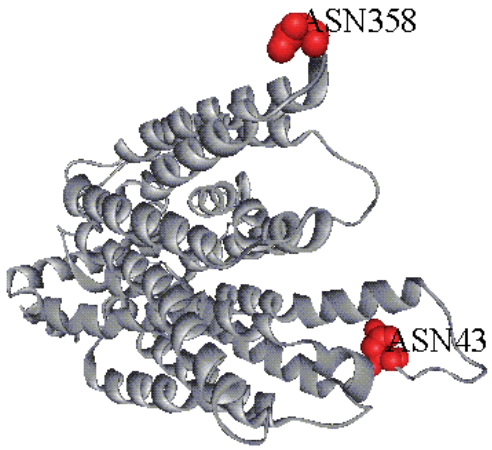

Fig. 5. Structure of GLUT3 – red balls represent N-glycosylated Asn^{43} and Asn^{358} amino acids, grey ribbon shows secondary structure of GLUT3 protein (on the basis of sequence NP_777028, available in GenBank, generated with the use of ViwerLite 4.2 program).

bovine GLUT3 has two N-glycosylation sites, between transmembrane domains 1 and 2 (Asn^{43}) and transmembrane domains 9 and 10 (Asn^{358}), and another modified a.a. residue - phosphoserine Ser^{485} in the cytoplasmic domain (not shown).

GLUT3 is a high affinity transporter; it is a major brain neuronal glucose transporter. The mRNA encoding GLUT3 was detected in bovine follicles and corpus luteum. The expression level of GLUT3 in bovine ovary was shown comparable to that in brain [Nishimoto *et al.* 2006].

GLUT4

GLUT4 is an insulin-responsive glucose transporter. The bovine GLUT4-encoding *SLC2A4* gene is composed of 11 exons and localizes to the chromosome 19 (BTA19). Its sequence is available in the GenBank database under Acc. No. AC_000176. In the GenBank SNP database are recorded 5 SNPs for *SLC2A4* gene, all of them located in introns. The full-length bovine GLUT4 transcript has 1,543 nt; the protein contains 509 a.a., with a predicted molecular weight of 55 kDa [Abe *et al.* 1997]. Western blot analyses showed the difference in the GLUT4 molecular weight between skeletal muscle (48 kDa) and adipose tissue (53-55 kDa), probably due to different post-translation modifications, such as glycosylation [Zhao *et al.* 1993]. The deduced amino acid sequence of the bovine GLUT4 (NP_777029) is 93, 93, 93, 93 and 93% identical, respectively, with that of human, pig, dog, mouse and rat GLUT4 (Suppl. Fig. S5). In the bovine GLUT4 there is an N-linked glycosylation site at Asn^{57}, highly conserved with human GLUT4, located between putative transmembrane domains 1 and 2 (Fig. 6). The nucleotide sequence of mRNA coding for the 38 a.a. of the terminal domain of insulin-responsive glucose transporter GLUT4 has 91-97% identity with that in sheep, goat and pig. There was found one amino acid conversion

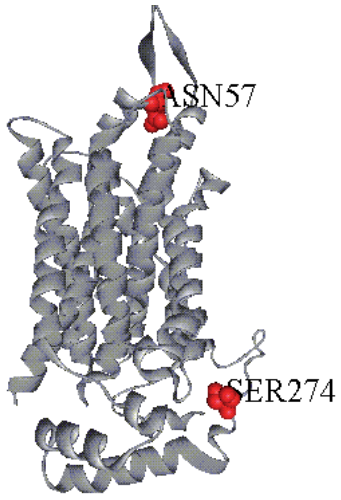

Fig. 6. Structure of GLUT4 – red balls represent N-glycosylated Asn^{57} and phosphorylated Ser^{274} amino acids; grey ribbon shows secondary structure of GLUT4 protein (on the basis of sequence NP_777029 available in GenBank, generated with the use of ViwerLite 4.2 program).

Asn^{508} to His in the C-terminal domain between these species [Abe *et al.* 1997, 1998]. With the topology model, bovine GLUT4 is shown to have the modified a.a. residues between 6 and 7 transmembrane domains - phosphoserine Ser^{274}, and in cytoplasmic domain - phosphoserine Ser^{488} (not shown).

The GLUT4 protein is insulin-sensitive glucose transporter and was first detected in goat adipose tissue [Trayhurn *et al.* 1993] and bovine skeletal muscle [Mandarino *et al.* 1994]. In cattle, GLUT4 was detected in all insulin-responsive tissues: skeletal muscle, heart and adipose tissues [Zhao *et al.* 1993, Abe *et al.* 1997]. The GLUT4 protein levels are significantly higher in oxidative than in glycolytic muscles [Hocquette *et al.* 1995, Duhlmeier *et al.* 2005]. GLUT4 content is higher in perirenal and omental adipose tissues than in subcutaneous adipose tissues in growing calves [Hocquette *et al.* 1996, 2006]. The mRNA encoding GLUT4 was detected in bovine follicles and corpus luteum, the expression level of GLUT4 in bovine ovary was much lower than in muscle and adipose tissue [Nishimoto *et al.* 2006]. The insulin-dependent glucose transporter GLUT4 recycles between the muscle cell membrane and an intracellular tubulo-vesicular pool. In hyperglycemic states, insulin is secreted from endocrine pancreas and stimulates myocyte glucose uptake by increasing the translocation of intracellular GLUT4 vesicles into the plasma membrane [Kahn 1996, Duhlmeier *et al.* 2005].

GLUT5

The bovine GLUT5 gene *SLC2A5* is composed of 7 exons and localize to the chromosome 16 (BTA16). Its sequence is available in the GenBank database under Acc. No AC_000171. In the GenBank SNP database are recorded 20 SNPs in *SLC2A5* gene introns. The bovine GLUT5 mRNA is 2,140 nt long, and the protein contains 501 a.a. with molecular weight of 55 kDa. The deduced amino acid sequence of bovine GLUT5 (NP_001094512) is 98, 80, 78 and 78% identical to that of ovine, human, mouse and rat, respectively (Suppl. Figure S6). There is N-linked glycosylation site at Asn^{51} located between putative first two transmembrane domains of GLUT5.

The GLUT5 has higher affinity for fructose than glucose and it is localized in the apical brush border membranes of the small intestine and is also expressed in testes, kidney, muscle, brain and adipose tissue [Davidson *et al.* 1992].

GLUT6

The bovine GLUT6 gene (symbol *SLC2A6*) is composed of 10 exons and localize to the chromosome 11 (BTA11). Its sequence is available in the GenBank database under Acc. No. AC_000168. In the GenBank SNP database are recorded 29 SNPs for *SLC2A6* gene: 21 in introns, 7 in exons, and 1 in 3'-untranslated region. The full-length bovine GLUT6 transcript has 2,112 nt; the protein contains 507 a.a. with molecular weight of 54 kDa. The deduced amino acid sequence of bovine GLUT6

(NP_001073725) is 88, 80 and 78% identical to that of human, mouse and rat, respectively (Suppl. Fig. S7). GLUT6 mRNA is expressed in the spleen, peripheral leukocytes and brain [Doege *et al.* 2000a].

GLUT8

The bovine GLUT8 gene (symbol *SLC2A8*) is composed of 10 exons and localizes to the chromosome 11 (BTA11). Its sequence is available in the GenBank database under Acc No. AC_000168. Thirty three SNPs were identified in the bovine *SLC2A8* gene: 7 in exons and 26 in introns.

The bovine GLUT8 mRNA is 2,073 nt long; the encoded protein contains 478 a.a. with a predicted molecular weight of 51 kDa [Zhao *et al.* 2004]. The deduced bovine GLUT8 a.a. sequence (Acc. No. NP_963286) is 26 and 24% identical to bovine GLUT1 and GLUT4, respectively. It is also 89, 88, 84, 83 and 58% identical to that of human, dog, rat, mouse and chicken GLUT8, respectively (Suppl. Fig. S8). The bovine GLUT8 has an N-linked glycosylation site on loop 9 and putative di-leucine internalization motif. The exoplasmic loop between transmembrane 9 and 10 is longer in GLUT8 (30 *vs.* 9 a.a.), and has a glycosylation site that is not present in GLUT1. The sequence of bovine GLUT8 contains several sugar transporter signatures, characteristic for GLUT family. The sugar transport protein signatures 1 are located between a.a. 87 and 104 (GGwlLDrAGRKlslvlcA) in loop 2 and between a.a. 310 and 327 (AAliMDrAGRRllltlsG) in loop 8. The sugar transport protein signature 2 (LtGLacGiaslvapvYisEiaypevR) is located between a.a. 129 and 154 in transmembrane domain 4 and loop 4 (Fig. 7). Other motifs found in GLUT8 are: PETPR in loop 6, QQLSGVN in helix 7, GWGPIPW in helix 10 and PETKG in C-terminal tail [Doege *et al*. 2000b, Joost and Thorens, 2001]. Bovine GLUT8 also contains an N-terminal di-leucine motif that has been shown to direct the protein to intracellular storage compartments [Uldry *et al.* 2001].

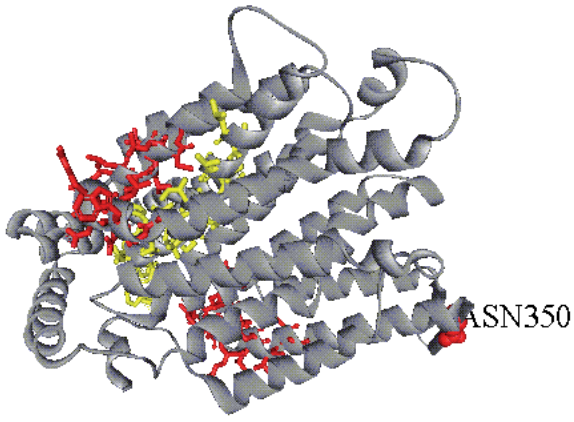

Fig. 7. Structure of GLUT8 – red balls represent N-glycosylated Asn^{350} amino acid; red sticks and yellow sticks show sugar transport protein signature 1 and 2, respectively; grey ribbon shows secondary structure of protein (on the basis of sequence No. NP_963286 available in GenBank, generated with the use of ViwerLite 4.2 program).

The bovine GLUT8 transcript is predominantly expressed in testes, mammary gland, kidney, lung, spleen, intestine epithelia, skeletal muscle and liver [Zhao *et al.* 2004]. The expression pattern of GLUT8 mRNA is comparable to that of GLUT1 [Zhao and Keating, 2007]. GLUT 8 expression in mammary gland may be tissue-specifically regulated and stimulated by the mammogenic and lactogenic hormones - progesterone and prolactin [Zhao *et al.* 2004]. Zhao *et al.* [2004] have shown, that the rapid increase of GLUT8 expression in the mammary gland and rise of blood estrogen levels during lactation indicate that GLUT8 expression is not suppressed by estrogen in the mammary tissues. Insulin stimulates GLUT8 translocation in blastocyst but not in fat cells and neuroblasts.

GLUT9

The bovine GLUT9 gene (symbol *SLC2A9*) is composed of 15 exons and localize to the chromosome 6 (BTA6). Its sequence is available in the GenBank database under Acc. No AC_000163. Six SNPs were identified in the bovine *SLC2A9* gene (encoding GLUT9), three located in exons and three in introns, which were significantly associated in with milk traits in German brown cattle [Seefried 2008].

For the bovine GLUT9 six different transcripts were detected, the longest mRNA has 2,515 nt and the shortest – 1,646 nt; protein contains 409 a.a. The deduced amino acid sequence of bovine GLUT9 (XP_002688502) is 86, 84, 84 and 83% identical to that of dog, human, rat and mouse, respectively (Suppl. Fig. S9). GLUT9 have been detected in kidney and liver [Phay *et al.* 2000].

GLUT10

The bovine GLUT10 gene (symbol *SLC2A10*) is composed of 5 exons and localize to the chromosome 13 (BTA13). Its sequence is available in the GenBank database under Acc. No. AC_000170. In the GenBank SNP database are recorded 24 SNPs for *SLC2A10* gene: 17 in exons, 6 in 3'-untranslated region and 1 in 5'-untranslated region. The bovine GLUT5 transcript is 2,257 nt long, and protein contains 536 a.a. with molecular weight of 56 kDa. The deduced amino acid sequence of bovine GLUT10 (Acc. No. NP_001179368) is 82, 76 and 75% identical to that of human, rat and mouse, respectively (Suppl. Fig. S10). GLUT10 is expressed in the liver and pancreas [McVie-Wylie *et al.* 2001].

GLUT11

The bovine GLUT11 gene (symbol *SLC2A11*) is composed of 13 exons and localize to the chromosome 17 (BTA17). Its sequence is available in the GenBank database under Acc. No. AC_000174. In the GenBank SNP database are recorded 17 SNPs for

SLC2A11 gene: 6 in exons and 11 in 3'- untranslated region. The bovine GLUT11 transcript is 2,178 nt long; protein contains 496 a.a. and has molecular weight of 53 kDa. The deduced amino acid sequence of bovine GLUT11 a.a. (NP_001180026) is 83% identical to that of human (Suppl. Fig. S11).

There have been described two splice variants of GLUT11 transcript and protein, formed through the skipping of exon 2, which results in long 503 a.a. and short 493 a.a. forms. The short form is expressed in heart and skeletal muscle [Doege *et al.* 2001]; the long form is detected in liver, lung, trachea and brain [Wu *et al.* 2002].

GLUT12

The bovine GLUT12 gene (symbol *SLC2A12*) is composed of 5 exons and localizes to the chromosome 9 (BTA9). Its sequence is available in the GenBank database under Acc. No. AC_000166. In the GenBank SNP database were identified 31 SNPs in *SLC2A12* gene introns.

The bovine GLUT12 mRNA is 2,423 nt long; protein contains 621 a.a. with a predicted molecular weight of 67 kDa [Miller *et al.* 2005]. The deduced bovine GLUT12 a.a. sequence (Acc. No. NP_001011683) is 88, 83 and 82% identical to that of human, rat and mouse, respectively (Suppl. Fig. S12). With the topology model, bovine GLUT12 has few N-glycosylation sites, between transmembrane domains 5 and 6 (Asn^{195}) and transmembrane domains 9 and 10 (Asn^{375}). The major structural differences unique to bovine GLUT12 are longer loop between the putative transmembrane domains TM 9 and 10 and longer N-and C-termini [Miller *et al.* 2005]. The large loop 9 contains glycosylation sites Asn^{387}, Asn^{400} and Asn^{405} (Fig. 8). The sequence of bovine GLUT12 has several characteristically conserved sugar transporter family signatures. The sugar transport proteins signature 1 (GGVLIDrYGRRaaiilsS) is located between a.a. 101 and 118, GRK/R in loop 2, GR in loop 3, E··RG in loop 4, PXXPR in loop 6, GXGPXXW in helix 10 and PETKG in C-terminal tail [Joost and Thorens 2001].

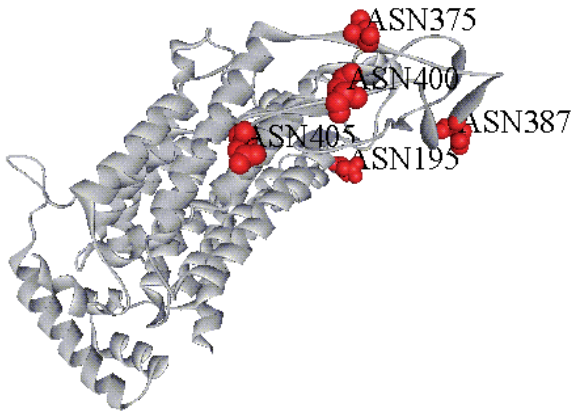

Fig. 8. Structure of GLUT12 – red balls represent N-glycosylated Asn^{195}, Asn^{375}, Asn^{387} Asn^{400} and Asn^{405} amino acids; grey ribbon shows secondary structure of GLUT12 protein (on the basis of sequence NP_001011683 available in GenBank, generated with the use of ViwerLite 4.2 program).

GLUT12 mRNA is expressed in the spleen, skeletal muscle, kidney, testes, mammary gland, liver, lungs, and intestine [Miller *et al.* 2005]. The mRNA of GLUT12 level in the mammary gland of lactating cows is lower than that in non-lactating. The increment of GLUT12 expression in non-lactating mammary gland indicates its possible role in regulating insulin-dependent glucose uptake and development of the mammary secretory epithelium [Komatsu *et al.* 2007].

HMIT

The bovine HMIT gene (symbol *SLC2A13*) proton myo-inositol cotransporter is composed of 10 exons and localize to the chromosome 5 (BTA5). Its sequence is available in the GenBank database under Acc. No. AC_000162. In the GenBank SNP database are recorded 5 SNPs in the exons of *SLC2A13* gene. The bovine HMIT transcript is 1,947 nt long; protein contains 648 a.a. with molecular weight of 70,5 kDa. The deduced amino acid sequence of bovine HMIT (Acc. No. NP_001179892) is 97, 89 and 89% identical to human, mouse) and rat HMIT (Suppl. Fig. S13). HMIT is expressed mostly in brain [Uldry *et al*. 2001].

Na+/GLUCOSE COTRANSPORTERS SGLT

The Na+/glucose cotransporter family (gene symbol *SLC5A*, protein symbol SGLT), consists of low-affinity glucose transporters. SGLT is a family of solute-linked carriers that contain sodium-coupled transporters for several nutrients. The Na^+-electrochemical gradient provided by the Na^+-K^+ ATPase pump is utilized to transport substrates into cells against its concentration gradient. The cotransported substrates are sugars, inositol, proline, pantothenate, iodide, urea and other undetermined solutes. This family contains 12 genes (SLC5A1-SLC5A12) coding for 12 SGLT proteins. Six most commonly expressed SGLT family transporters and their genes are presented in Tables 1 and 2. The nutrients that are transported *via* SGLT proteins include glucose (SGLT1, 2, 4 and 5) [Hediger *et al.* 1989, Wells *et al.* 1992], myo-inositol (SMIT1 and 2; sodium-dependent myo-inositol transporters 1 and 2) [Berry *et al.* 1996, Roll *et al.* 2002], iodide (SLC5A5/NIS Na^+/iodide cotransporter) [Smanik *et al.* 1996], biotin and pantothenate (SLC5A6/SMVT sodium-coupled multivitamin transporter) [Wang *et al.* 1999], choline (SLC5A7/CHT1 choline transporter) [Apparsundaram *et al.* 2001] and short chain fatty acids/lactate/nicotinate (transporters SLC5A8, 12/SMCT1,2 sodium-coupled monocarboxylate transporter) [Ganapathy *et al.* 2005].

These proteins are mainly located in the brush-border membranes of intestinal epithelial cells in the small intestine and in the proximal tubules of the kidney [Wright and Turk, 2004]. SGLT transporters contain several characteristic and conserved sodium solute symporter family signatures and have 14 transmembrane domains (Fig. 9). The first cotransporter proteins, Na^+/glucose and Na^+/proline cotransporters, were identified in the rabbit intestinal brush border [Peerce and Wright, 1985]. In a pair

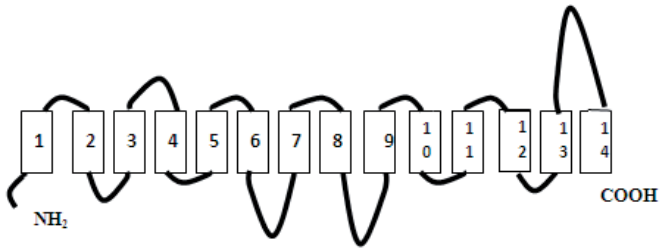

Fig. 9. Schematic membrane topology of SGLTs.

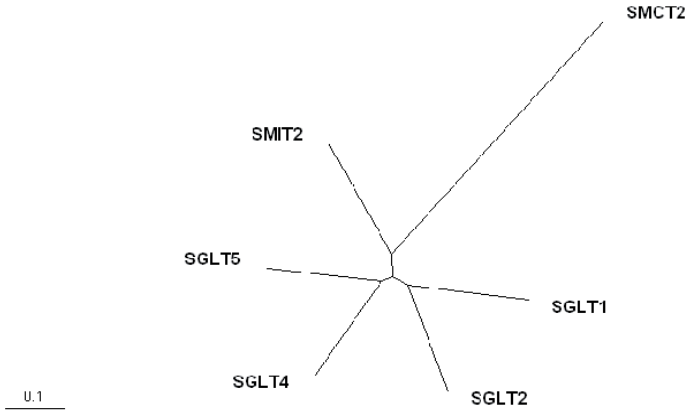

Fig. 10. Unrooted phylogenetic tree of the 6 bovine members of SGLT family cotransporters (generated with the use of phylogeny program - http://www.ebi.ac.uk/Tools/phylogeny/ clustalw2_phylogeny/).

wise basic local alignment search tool (BLAST) analysis the amino acid identities relative to SGLT1 (encoded with *SLC5A1* gene) are 60% for SGLT2, 55% for SGLT4, 57% for SGLT5, 51% for SMIT2 and 24% for SMCT2 (Suppl. Fig. S14). Unrooted phylogenetic tree of 6 bovine members of the of SGLT family transporters is shown in Figure 10.

SGLT1

The bovine SGLT1 gene (symbol *SLC5A1*) is composed of 15 exons and localizes to the chromosome 17 (BTA17). Its sequence is available in the GenBank database under Acc. No. AC_000174. In the GenBank SNP database were deposited 400 SNPs of the bovine *SLC5A1* gene: 1 in 3'-untranslated region, 385 in introns, and 14 in exons. Bovine SGLT1 transcript length is 2,248 nt; protein contains 664 a.a. with molecular weight of 73 kDa [Zhao *et al.* 2005]. Amino acid sequence of SGLT1 protein is 58% identical to SGLT2. The deduced amino acid sequence of bovine SGLT1 (Acc. No. NP_777031) is 98, 89, 89, 88, 87 and 86% identical to that of ovine, swine, dog, mouse, rat and human, respectively (Suppl. Fig. S15).

Glucose transporter SGLT1 is responsible for the high-affinity, conservative uptake of most monosaccharides (glucose and galactose), except fructose. SGLT1 mRNA was shown most abundant in bovine intestinal tissues, in the jejunal region [Liao *et al.* 2010], intermediate in kidney, low in mammary gland, liver, lungs, and not detectable in spleen, skeletal muscle and testes [Zhao *et al.* 2005]. In bovine cortical arteries SGLT1 plays the role of a molecular sensor for copying with stress such as hypoglycaemia [Nishizaki and Matsuoka 1998].

SGLT2

The bovine SGLT2 gene (symbol *SLC5A2*) is composed of 14 exons and localizes to the chromosome 25 (BTA25). Its sequence is available in the GenBank database under Acc. No. AC_000182. In the GenBank SNP database are recorded 33 SNPs of the bovine *SLC5A2* gene: 6 in 3'-untranslated region, 26 in introns, and 1 in an exon.

The full-length bovine SGLT2 transcript has 2,261 nt; protein contains 673 a.a. with a predicted molecular weight of 73 kDa [Zhao *et al.* 2005]. The deduced bovine SGLT2 a.a. sequence (Acc. No. NP_976236) is 58% and 48% identical to bovine SGLT1 and SGLT5, respectively. It is 92%, 92%, 91% and 91% identical to dog, human, mouse and rat SGLT2 sequence, respectively (Suppl. Fig. S16). The major differences are in the last loop region between the putative transmembrane domains 13 and 14 and in the N-terminal region. There are several signatures in the SGLT2 protein. The sodium solute symporter family signature 1 (GwnIyasVIALLGItmiYTvtGGLaA) is located between a.a. 171 and 196 and the sodium solute symporter family signature 2 (ALfvpRvnekGAfwGLIGGIL) – between a.a. 474 and 494 (Fig. 11) – Zhao *et al.* [2005].

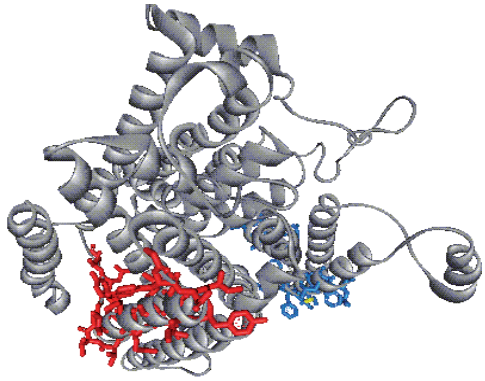

Fig. 11. Secondary structure of SGLT2 protein – red sticks and blue sticks represent sodium solute symporter protein family signature 1 and signature 2, respectively; grey ribbon shows secondary structure of SGLT2 protein (on the basis of sequence NP_976236 available in GenBank, generated with the use of ViwerLite 4.2 program).

The SGLT2 is predominantly expressed in bovine kidney and its mRNA is at lower levels in mammary gland, liver, lung, spleen, intestine, and skeletal muscle [Zhao *et al.* 2005]. Expression of SGLT2 mRNA in bovine mammary gland increases more than 10-fold from late pregnancy to early lactation, similar to SGLT1. This indicates that SGLT2 may play a role in milk synthesis in the lactating mammary gland.

SGLT4

The bovine SGLT4 gene (symbol *SLC5A9*) is composed of 18 exons and localizes to the chromosome 3 (BTA3). Its sequence is available in the GenBank database under Acc. No. AC_000160. The full-length bovine SGLT4 transcript has 2,418 nt, although 3 other transcripts were detected in bovine tissues: 4,147 nt (X1), 3,119 nt (X2) and 4,150 nt (X3); the protein contains 705 a.a. The deduced bovine SGLT4 a.a. sequence (Acc. No. NP_001192865) is 86, 85 and 80% identical to that of human, rat and mouse (Suppl. Fig. S17). SGLT4 is widely expressed in the body.

SGLT5

The bovine SGLT5 gene (symbol *SLC5A10*) is composed of 15 exons and localizes to the chromosome 19 (BTA19). Its sequence is available in the GenBank database under Acc. No. AC_000176. In the GenBank SNP database are recorded 174 SNPs of the bovine *SLC5A10* gene: 167 in introns, 7 in exons. The bovine SGLT5 transcript is 2,042 nt long; the protein contains 597 a.a. with a predicted molecular weight of 64.7 kDa. The deduced bovine SGLT5 a.a. sequence (Acc. No. NP_001001442) is 86%, 85% and 84% identical to that of human, mouse and rat, respectively (Suppl. Fig. S18). With the topology model, bovine SGLT5 has two N-glycosylation sites in extracellular domain (Asn^{5}) and in transmembrane domains 2 and 3 (Asn^{97}), and three modified residue in transmembrane domain 4 - phosphoserine Ser^{142}, phosphoserine Ser^{142} and phosphothreonine Thr^{142}. SGLT5 is expressed in small intestine, brain, kidney, liver and lung in human.

SMIT2

The bovine SMIT2 gene (symbol *SLC5A11*) sodium/myo-inositol cotransporter 2 is composed of 17 exons and localizes to the chromosome 25 (BTA25). Its sequence is available in the GenBank database under Acc. No. AC_000182. In the GenBank SNP database are recorded 332 SNPs of the bovine *SLC5A11* gene: 318 in introns, 11 in exons, 2 in 5'-untranslated region, and 1 in 3'-untranslated region.

The full-length bovine SMIT2 transcript has 2,277 nt; protein contains 674 a.a. with a predicted protein molecular weight of 73,9 kDa. The deduced bovine SMIT2 a.a. sequence (Acc. No. NP_001029832) is 95, 88, 84 and 84% identical to that of caprine, human, mouse and rat (Suppl. Fig. S19).

SMCT2

The bovine SMCT2 gene (symbol *SLC5A12*) sodium-coupled monocarboxylate transporter 2 is composed of 15 exons and localizes to the chromosome 15 (BTA15).

Its sequence is available in the GenBank database under Acc. No. AC_000172. In the GenBank SNP database are recorded 105 SNPs of the bovine *SLC5A12* gene: 103 in introns, 1 in exon, and 1 in 5'-untranslated region. The bovine SMCT2 transcript is 2,924 nt long; protein contains 617 a.a. with a predicted molecular weight of 67.4 kDa. The deduced bovine SMCT2 a.a. sequence (Acc. No. NP_001094529) is 90%, 83% and 80% identical to the sequence of human, rat and mouse SMCT2, respectively (Suppl. Fig. S20). The SMCT2 protein is highly hydrophobic with 13 putative transmembrane domains (instead of 14 domains typical for other SGLTs) with N-terminus at the exoplasmic side of membrane and C-terminus the cytoplasmic side of membrane. With the topology model, bovine SMCT2 has two N-glycosylation sites, between transmembrane domains 6 and 7 (Asn^{219}) and in transmembrane domains 12 and 13 (Asn^{480}).

The SMCT2 is expressed predominantly in the cortical portion of the kidney, at lower level in in small intestine, skeletal muscle and it is a low-affinity transporter [Srinivas *et al.* 2005].

Conclusion and perspectives

There are two types of glucose transporters: passive, facilitative glucose transporters GLUT (encoded by *SLC2* genes) and active Na^+/glucose cotransporters SGLT (gene symbol *SLC5*), which participate in the Na^+-linked transport process against electrochemical gradient. Both types of glucose transporters are expressed in cattle. Their protein and genomic sequences are highly related among ruminants, the sequence identity being in the range of 91 to 99% between different ruminant species, and in the range 75 to 99% with that of other mammals. Multiple glucose transporter proteins are present in bovine cells and all bovine tissues express more than one of these transporters in order to efficiently obtain sufficient glucose from the extracellular fluid for cell metabolism. Each glucose transporter has different transport regulatory properties and plays specific roles in maintenance of whole body glucose homeostasis.

Due to their function genes encoding glucose transporters are considered possible candidate markers for production traits of farm animals, including cattle. Genetic variation - nucleotide sequence polymorphisms of *SLC2A* and *SLC5A* genes like SNPs, InDels or STRs can influence gene expression or functions of glucose transporter proteins. This, in turn, can decrease or increase glucose supply for animals' tissues and organs, such as muscles and mammary gland and thus greatly influence milk or meat yield or quality.

In humans it was shown that DNA sequence variations in glucose transporter genes may influence the development of certain diseases, like diabetes or cancer [Ng *et al.* 2002; Grabellus *et al.* 2010]. Association of genetic polymorphism of glucose transporters with differential glucose uptake has also been reported in several studies [Mueckler *et al*. 1994, Ng *et al.* 2002, Grabellus *et al.* 2010]. Glucose transporter-1

(GLUT1) deficiency is leading to a reduced glucose transport into the brain [Seidner *et al.* 1998]. It is highly expressed in the endothelial cells and in the blood-brain barrier and is exclusively responsible for glucose transport into the brain [Vannucci *et al.* 1997, Barros *et al.* 2007]. Glucose transporter-1 deficiency syndrome is caused by mutations in the *SLC2A*1 gene in humans and results in impaired glucose transport into the brain which causes mental retardation, and epilepsy. It can be diagnosed by a low concentration of glucose in the spinal fluid and by testing of glucose transport in red blood cells. Genetic testing for the *SLC2A*1 gene confirms this syndrome.

Very little studies have been carried out of polymorphism of glucose transporter genes in livestock. Although in the GenBank SNP database hundreds of single nucleotide substitutions (SNPs) in bovine glucose transporter genes are recorded, mostly derived from next generation sequencing (NGS) studies, they have not been validated with other methods and their association with production or functional traits was not studied. Seefried [2008] in his doctoral thesis has analyzed polymorphisms in different candidate genes for milk production traits in three cattle breeds. In his study, six polymorphic markers were identified in the *SLC2A9* gene (encoding GLUT9) which were significantly associated in with milk traits (milk yield, fat content, protein content) in German brown cattle. Three of the significantly associated markers were located in a translated region (exons) and three have an intronic position. Recently, a project has been established at the University of Vermont, Burlington entitled, ''Single Nucleotide Polymorphisms of Glucose Transporters as Breed Selection Markers for Milk Productivity in Dairy Cattle'', but the results have not been published yet.

Apart from variations in coding regions of genes, focus has also been oriented towards studying the variations in regulatory regions, mainly in promoter regions which regulate a gene transcriptional rate and thus determine the amount of transcripts [Adamowicz *et al.* 2006, Martin *et al.* 2002, Szymanowska *et al.* 2004, Szreder *et al.* 2008]. Such variations (SNPs, deletion/insertions) in the gene promoter may be located within the potential transcriptional factor binding sites or cis-regulatory sequences; they can modulate (increase or decrease) the efficiency of the transcription and influence gene expression levels. Similarly, nucleotide sequence variations in 3'-UTR regions could influence binding of the regulatory micro RNA molecules, and thus influencing stability of target mRNAs and expression of the encoded proteins (Chekulaeva and Filipowicz, 2009). Nucleotide sequence polymorphisms in the regulatory regions can influence expression levels of glucose transporter genes, and thus influence glucose transport efficiency. However, up to now, very little is known about the regulation of glucose transporter genes in cattle, and more generally, in ruminants. In the sheep, the *SGLT1* gene promoter was shown to contain a 16-bp element that binds members of the Sp1 family of transcription factors that enhance basal expression. Also in the sheep, it was shown that SGLT1 promoter contains HNF-1 binding site that appears to be involved in the increase of intestinal *SGLT1* gene expression in response to dietary glucose. HNF-1 and two GC boxes are critical for basal expression. **[**Martin *et al.* 2000]. Recently, in our laboratory at IGAB PAS in Jastrzębiec, a project have been

carried out aiming at discovering functional polymorphisms in the bovine glucose transporter genes. SNP and InDel polymorphisms were identified in *SLC2A* and *SGLT* genes, some of them located in in the regulatory sequences – promoter and 3'-UTR regions. The effect of these mutations on the expression levels of glucose transporter genes has been experimentally confirmed. The results will be published soon.

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