

Original Review Article

An overview of solute carrier family (facilitated glucose transporter) genes and their role in bovine mammary gland functioning

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Abstract

Milk yield greatly depends on mammary lactose synthesis due to its osmoregulatory property for mammary uptake of water. A large amount of glucose is required by lactating dairy cows as the main precursor for lactose synthesis. Solute carriers (glucose transporters) in the bovine mammary gland play a key role in the transport of glucose and therefore milk synthesis. Different sugar transporters have their own specific characteristics which indicates that uptake of glucose into mammary cells is complex. Their specific characteristics further determine their expression levels in individual cells or tissues and thus provide a high degree of specificity in the control of glucose uptake under different physiological conditions. In this review we report the role of major solute carriers in functioning of mammary gland and their expression. These solute carriers are highly regulated with different mechanisms. Studies are further needed to address their physiological functions in mammary gland. The major focus should be on proper utilization of glucose in the bovine mammary gland which is of major importance for successful lactating period in the dairy cow.

Keywords: Solute carrier/glucose transporter, Mammary gland, livestock

1. Introduction

Glucose is the main source of energy in eukaryotic organisms and plays a critical role in maintaining cellular homeostasis and different metabolic functions. Every mammalian cell is dependent on the continuous supply of glucose, for generating ATP molecules which is the primary source of energy. Through various studies, glucose has acquired a role as a signalling molecule to control glucose and energy homeostasis. Glucose can regulate gene transcription, enzyme activity, hormone secretion, and the activity of gluco-regulatory neurons. Glucose is a ubiquitous fuel which is used as an energy source in most organisms for synthesis of several important substances such as starch, cellulose and glycogen. A general view is that glucose, the obligate precursor molecule for synthesis of lactose, is the main determinant of milk volume through osmosis (Kuhn, 1978; Holt, 1983; Neville and Picciano, 1997). However, the mammary gland itself cannot synthesize glucose from other precursors because of the lack of glucose-6-phosphatase (Scott *et al* 1976; Threadgold and Kuhn, 1979). It has also been suggested that rate of lactose synthesis serves as a major factor influencing milk volume (Neville *et al* 1983; Cant *et al* 2002). Therefore, the mammary gland is dependent on the blood supply for its glucose needs. Indeed, mammary gland uptake can account for as much as 60 to 85% of the total glucose that enters the blood (Bisker *et al* 1974). In mammary gland

glucose uptake show a linear or positive correlation with Lactose synthesis and milk yield in the mammary gland in dairy animals (Kronfeld, 1982; Hurtaud *et al* 2000; Kim *et al* 2001; Cant *et al* 2002). Glucose uptake in the mammary gland increases dramatically to meet the requirement of milk synthesis. In a lactating cow, 72 g of glucose is required to produce 1 kg of milk (Kronfeld, 1982). Therefore, in a cow producing 40 kg of milk per day, the mammary gland is required to take up about 3 kg of glucose daily. The increased glucose demand in the mammary gland for lactation is accomplished by increased glucose transporter expression in this tissue from pregnancy to early lactation.

Studies have documented that for milk synthesis during lactation, glucose uptake by the mammary epithelial cells (MEC) is an important step (Threadgold *et al* 1982; Threadgold and Kuhn, 1984; Wilde and Kuhn, 1981). Also in different mammalian cells, glucose transport into the mammary epithelial cells is specific, saturable, Na⁺-independent, and inhibitable by cytochalasin-B or phloretin in the guinea pig, rat, mouse, and cow (Amato and Loizzi, 1979; Threadgold *et al* 1982; Prosser, 1988; Delaquis *et al* 1993; Xiao and Cant, 2003; Xiao *et al* 2004). Thus milk yield is directly related to the glucose uptake by the MECs. During lactation, glucose is predominantly transported across plasma membrane of MECs by passive transport due to establishment of glucose concentration gradient: 3.0 to 3.5 mM in plasma to 0.1 to 0.3 mM within the cell (Faulkner *et al* 1981). This report has led to the belief that transport of glucose across the plasma membrane of epithelial cells may only be a

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passive process of facilitated diffusion (Delaquis *et al* 1993). These processes involve the transfer of glucose across plasma membranes and this occurs via integral transport proteins (Zhao and Keating, 2007). For glucose transport across mammary tissues, multiple glucose transporter isoforms have been detected, including *GLUT1*, 8, and 12. Depending upon the tissue/cell types, however glucose transport across the plasma membranes is carried out by two different processes. First is facilitative transport that is mediated by a family of facilitative glucose transporters (*GLUT*; Mueckler, 1994; Joost & Thorens, 2001) and another is sodium dependent transport that is mediated by the Na⁺/glucose co-transporters (*SGLT*; Wright, 2001) Both these transporter categories comprises of two structurally and functionally distinct groups having distinct transporter function in different cells and tissues. In dairy animals, ATP-binding cassette (ABC) transporters superfamily and solute carriers or glucose transporters (*SLC/GLUT*) are the two major types of transporter superfamily that have been mostly involved in active transport of milk constituents. While ABC transporters play an important role in regulating cellular cholesterol homeostasis and transfer of wide variety of substrate across cellular membrane, solute carriers are involved in glucose uptake. At the time of onset of lactation, glucose uptake in the mammary gland increases dramatically and expression of these transporters has been correlated with the milk synthesis. In the mammalian cells, glucose transport across the plasma membranes is carried out by two different processes. First is facilitative transport that is mediated by a family of solute carriers/glucose transporters (*SLC2A1/GLUT*) and another is sodium dependent transport that is mediated by the Na⁺/glucose co-transporters (*SGLT*) (table 1). Facilitative diffusion of glucose across plasma membrane is mediated by a family of glucose transporters. A number of glucose transporter genes (*GLUT1*(*SLC2A1*), *GLUT3*(*SLC2A3*), *GLUT4*(*SLC2A4*), *GLUT5*(*SLC2A5*), *GLUT8*(*SLC2A8*), and *GLUT12*(*SLC2A12*) responsible for basal glucose uptake along with sodium dependent *SGLT1* and *SGLT2* were found to be expressed in the bovine lactating mammary gland at different levels (Zhao *et al* 2007). Expressions of these transporters are known to be under transcriptional regulation and nuclear orphan receptors. In the present review, our main focus is to describe the role of those glucose transporters which play an important role in functioning of mammary gland.

2. Facilitative Glucose Transporters

2.1 Characteristics and Functions of GLUT Genes

Facilitative glucose transporters (*GLUTs*) are responsible for passively transporting monosaccharides across the plasma membrane. In recent years, number of glucose transporters have been identified (Wood and Trayhurn, 2003). Most *GLUT* proteins catalyze the facilitative (energy-independent) bidirectional transfer of their substrates across membranes, and they may exhibit either symmetric or asymmetric transport kinetics. *GLUTs* are proteins of ~500 amino acids and are predicted to possess

12 transmembrane-spanning alpha helices and a single N-linked oligosaccharide. Most of these proteins are known to be structurally conserved and related (Zhao and Keating, 2007). Sequence comparisons of all 13 family members show that the sequences are more conserved in the putative transmembrane regions and more divergent in the loops between the TM and in the C- and N-terminal regions. Schematic representation of *GLUT* family of proteins is presented in fig. 2. The *GLUT* family members comprises of 13 members at present which can be grouped into three different subclasses based on their sequence similarities(fig. 1); Class I,II and III (fig 1; Thorens and Mueckler, 2010; Joost *et al* 2002). These three subclasses of sugar transporters have been defined on the basis of sequence homology and structural similarity; Class I (*GLUTs* 1–4) are glucose transporters; Class II (*GLUTs* 5, 7, 9 and 11) are fructose transporters; and Class III (*GLUTs* 6, 8, 10, 12 and *HMIT1*) are structurally atypical members of the *GLUT* family, which are poorly defined at present (Bryant *et al* 2002).

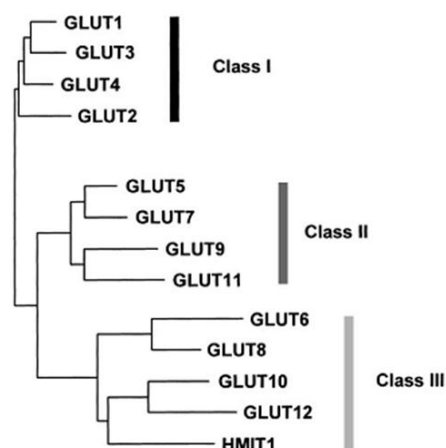


Fig. 1: Classification of *GLUT* family members (Joost *et al* 2002)

These solute carriers vary in tissue distribution, kinetic characteristics (Michaelis constant, K_m) and substrate specificities, implying that each transporter plays a distinct role in tissue glucose utilization and maintenance of body glucose homeostasis. For instance, whereas the human and rodent *GLUT1* have a K_m of 6.9 to 17 mM for d-glucose (Gould *et al* 1991; Burant and Bell, 1992; Nishimura *et al* 1993), hepatocyte *GLUT* (*GLUT2*) has a 2 to 10-fold higher K_m and a higher V_{max} to allow glucose efflux following gluconeogenesis (Gould *et al* 1991; Burant and Bell, 1992; Colville *et al* 1993). *GLUT3* and *GLUT4*, with lower K_m values, mediate the uptake of glucose by the brain and the insulin-regulated glucose uptake by skeletal muscle, respectively (Burant and Bell, 1992; Colville *et al* 1993; Nishimura *et al* 1993).

Glucose transporter 5 has a high affinity for fructose, with a poor ability to transport glucose (Corpe *et al* 2002). Therefore almost all of the *GLUT* and *SGLT* proteins have been shown to transport glucose but with different kinetics and efficiencies for glucose and hexose transport. These differences reveal that each transporter isoform plays a

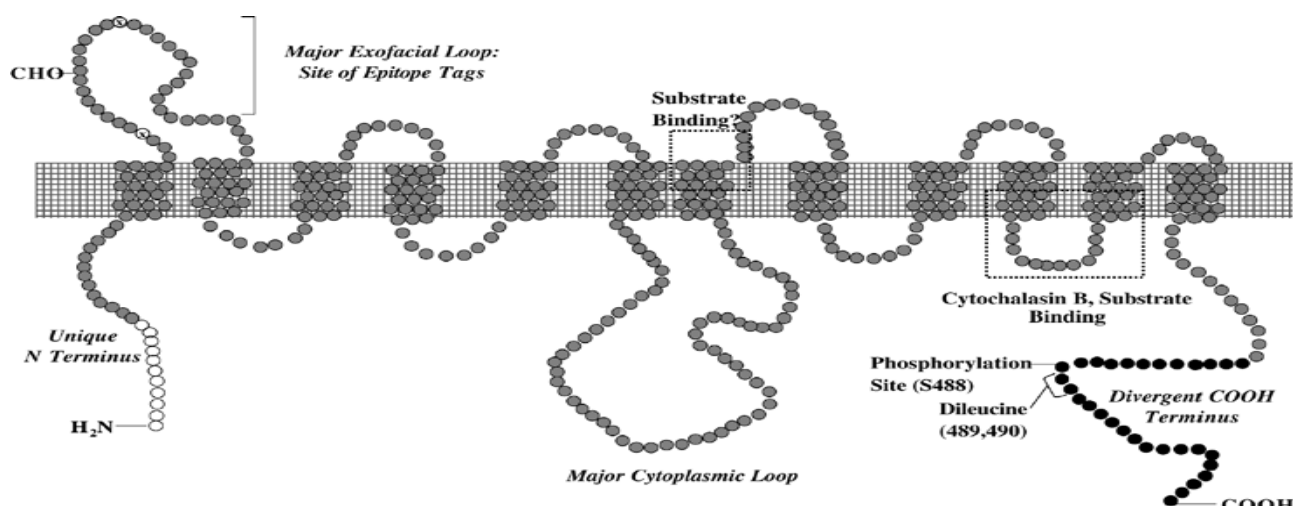


Fig. 2: Schematic representation of the GLUT family of proteins (Bryant *et al* 2002).

specific role in glucose uptake in various tissues and in glucose homeostasis. The tissue wise distribution and function of different transporters are summarized in

table 1. The characteristics of different facilitative glucose transporters and their role is reviewed here under.

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

¹aa- amino acids. (Feng-Qi Zhao et al. 2007, Functional properties and genomics of glucose transporters)

Protein	Major isoform (aa) ¹	Proposed function	Major sites of expression
Facilitative glucose transporters (<i>GLUT/SLC2A1</i>)			
<i>GLUT1</i>	492	Basal glucose uptake; transport across blood tissue barriers	Ubiquitous distribution in tissues and culture cells
<i>GLUT2</i>	524	High-capacity low-affinity transport	Liver, islets, kidney, small intestine
<i>GLUT3</i>	496	Neuronal transport	Brain and nerves cells
<i>GLUT4</i>	509	Insulin-regulated transport in muscle and fat	Muscle, fat, heart
<i>GLUT5</i>	501	Transport of fructose	Intestine, kidney, testis
<i>GLUT6</i>	507		Spleen, leukocytes, brain
<i>GLUT7</i>	524	Transport of fructose	Small intestine, colon, testis
<i>GLUT8</i>	477	Fuel supply of mature spermatozoa; Insulin-responsive transport in blastocyst	Testis, blastocyst, brain, muscle, adipocytes
<i>GLUT9</i>	511/540		Liver, kidney
<i>GLUT10</i>	541		Liver, pancreas
<i>GLUT11</i>	496	Muscle-specific; fructose transporter	Heart, muscle
<i>GLUT12</i>	617		Heart, prostate, mammary gland
HMIT	618/629	H ⁺ /myo-inositol co-transporter	Brain
Na ⁺ /glucose cotransporters (<i>SGLT</i>)			
<i>SGLT1</i>	664	Glucose reabsorption in intestine and kidney	Kidney, intestine
<i>SGLT2</i>	672	Low affinity and high selectivity for glucose	Kidney
<i>SGLT3</i>	660	Glucose activated Na ⁺ channel	Small intestine, skeletal muscle

2.2 Glucose transporter1 (*GLUT1/SLC2A1*) gene

One of the major glucose transporter, *GLUT1* falls into Class I family of glucose transporters and has been ubiquitously detected in cells and tissues, including the mammary gland (Madonet *et al* 1990; Burant *et al* 1991; Zhao *et al* 1999). The deduced protein sequence of *GLUT1* is composed of nearly 488-492 amino acids across various mammalian species with a molecular weight of approximately 54 kDa. It is the most conserved isoform and exhibits approximately 74-98 % sequence identity among these species (Thorens and Mueckler, 2010). The most divergent region is in the putative loop 1 where the glycosylation site is located. There is a unique proline-rich sequence in this region. In addition, the C-terminal tail is most variable with the exception of the last 7 amino acids in fish. This solute carrier is the major *GLUT* isoform expressed in the bovine mammary gland and its expression is developmentally regulated (Zhao *et al* 1993; Zhao and Keating, 2007). From 40 d before parturition to 7 d postcalving, *GLUT1* expression in the bovine mammary gland increases more than 100-fold (Zhao and Keating, 2007; Finucane *et al* 2008). This dramatic increase in *GLUT1(SLC2A1)* expression may be responsible for supplying the mammary gland with increased glucose needed during lactation. *bGLUT1* transport activity was inhibited by mannose and galactose, but not fructose, indicating that *bGLUT1* may also be able to transport mannose and galactose and provides functional insight into the transport properties of *bGLUT1* in taking up glucose across mammary epithelial cells for milk synthesis. Its role has also been reported in other species such as rats. Presence of *GLUT1* and *GLUT4* in the rat mammary gland before conception have been shown (Burnolet *et al* 1990 and Camps *et al* 1994). However, the expression of *GLUT4* decreases progressively during pregnancy and becomes undetectable during lactation, whereas the levels of *GLUT1* increase during pregnancy and peak during lactation. *GLUT12* targets the apical membrane (Macheda *et al* 2003). Madon *et al.* (1990) have used quantitative western blotting and cytochalasin-B binding studies to demonstrate that *GLUT1* represents the major glucose transporter species in plasma membranes and about half of the glucose transporters in the golgi membranes of lactating rat mammary epithelial cells.

2.3 Glucose Transporter 4 (*GLUT4/SLC2A4*)gene

GLUT4 is another glucose transporter which has been extensively studied in human and rodents because of its key role in the regulation of glucose homeostasis by insulin. *GLUT4* belongs to Class I family and comprises of 509-510 amino acid protein with a molecular weight of approximately 55 kDa in human, bovine, rat and mouse. In these species it is highly conservative with 91- 96% sequence identity. *GLUT4* was also identified as the main glucose transporter and undergoes a rapid translocation from the intracellular location to the cell surface, resulting in a dramatic increase in cellular glucose transport activity (Gonzalez and McGraw 2006). *GLUT4*, which is expressed primarily in muscle and fat cells, is found in a

complex intracellular tubulo-vesicular network that is connected to the endosomal-trans-Golgi network (TGN) system. The addition of insulin, or exercise in the case of muscle cells, causes *GLUT4* to shift from its intracellular location to the plasma membrane. *GLUT4* has been widely studied due to its role as the main insulin-sensitive member of this family and thus its role in diabetes. Its expression is highest in the insulin sensitive tissues including brown and white adipose tissue and skeletal and cardiac muscle (Zhao and Keating, 2007). In addition, *GLUT4* mRNA expression in bovine adipose tissue and skeletal muscle does not seem to vary with the stage of lactation (Komatsu *et al.*, 2005). Although bovine *GLUT4* is highly homologous with the *GLUT4* of other species, there was a unique amino acid conversion in the C-terminal region of *GLUT4*: that is, the 25 amino acid sequence in the C terminal region is identical in human, rat, and mouse, but one amino acid (Asn 508) is replaced by His in the bovine. In fetal bovine perirenal adipose tissue, *GLUT4* protein levels markedly increase during fetal development, reach maximal expression at 6 to 8 months of age, and sharply decrease thereafter, with a simultaneous increase in the *GLUT1* protein level (Hocquette *et al* 2006). In the lactating cow, *GLUT4* expression in the skeletal muscle and omental fat is dramatically reduced by administering GH and GH-releasing factor (GHRF), consistent with the regulation of nutrient partitioning by these hormones to shift more glucose from these tissues to the mammary gland for the purpose of increased milk synthesis (Zhao *et al* 1996b). In addition, this glucose transporter has also been extensively studied in humans and rodents because of its key role in the regulation of glucose homeostasis by insulin. Its expression is highest in insulin sensitive tissues including brown and white adipose tissue and skeletal and cardiac muscle similar to humans (Zhao *et al* 1993; Abe *et al* 1997) which tells about the role in insulin regulation of glucose uptake in these tissues. These studies showed that *GLUT4* plays an important role in glucose utilization by various tissues.

2.4 Glucose Transporter 8 (*GLUT8/SLC2A8*)gene

GLUT8(SLC2A), is the third major solute carrier. It is a member of Class III family, whose members are distinguished by the presence of a putative glycosylation site on loop 9 rather than on loop 1. In human, *GLUT8* is highly expressed in testis, consistent with a possible role in glucose supply to mature spermatozoa (Schurmann *et al.*, 2002). It is highly homologous to *GLUT8* of other mammals and exhibits all motifs that are presumably required for sugar transport activity. Several studies have shown *GLUT8* abundance in bovine testes, at intermediate levels in bovine lung, kidney, spleen, intestine and skeletal muscle, and at lower levels in bovine liver, consistent with the distribution reported for human, rat and mouse *GLUT8* (Ibberson *et al* 2000, Doege *et al* 2000, Schurmann *et al* 2002). Zhao *et al* (2004) further supported these findings when they found that *GLUT8* mRNA is expressed at high level in a bovine testes, at moderate level in lactating bovine mammary gland along with other tissues such as

kidney, lung, spleen, intestine epithelia, skeletal muscle, and at lower level in liver. The expression of *GLUT8*(*SLC2A8*) in human testes is fully suppressed by a high dose of estrogen. The expression of *GLUT8* has been shown to depend on gonadotropin secretion in human testes and to be regulated by insulin in the blastocyst. Evidences are there to suggest that *GLUT8* expression is gonadotropin-dependent and its mRNA is present in testes of adult and pubertal rats, but not in prepubertal rats (Doerge *et al* 2000).

GLUT8 mRNA expression in the mammary gland may be specifically regulated stimulated by the mammogenic and lactogenic hormones, progesterone and prolactin. The regulation of *GLUT8* is not well understood. Except for the response of *GLUT8* expression to estrogen in male testes, hormonal regulation of *GLUT8* is unclear. Although the sugar transport activity of bovine *GLUT8* has not been tested, expression of rat *GLUT8* protein in *Xenopus* oocytes revealed a high affinity glucose transport activity that could be specifically inhibited by fructose (Ibberson *et al* 2000). As mentioned above, insulin stimulates *GLUT8* translocation in blastocysts (Caryannopoulos *et al* 2000), but not in fat cells (Lisinski *et al* 2001) and neuroblasts (Verhey *et al* 1994). There is some evidence indicating that glucose itself may influence the location and expression of *GLUT8*. Glucose challenge resulted in translocation from an intracellular compartment to the ER in rat hippocampal cells (Piroli *et al* 2002), however, it is not clear whether this effect occurs due to insulin or by glucose itself. Differentiated 3T3-L1 adipocytes cells when starved resulted in reduced relative *GLUT8* mRNA levels, which could be restored by addition of glucose or galactose (Scheepers *et al* 2001). The developmental regulation of *GLUT8* expression in the mammary gland reported by Zhao *et al* (2004) strongly suggests that *GLUT8* is regulated by lactogenic hormones and it may play a role in glucose uptake in the lactating mammary gland.

2.5 Glucose Transporter 12 (*GLUT12/SLC2A12*)

GLUT12 belongs to the Class III family and contains a number of similar features to *GLUT4* such as dileucine motifs at the both the N- and C- termini in similar locations to the *GLUT4* FQQI and LL internalization motifs in human (Rogers *et al.*, 2002). The gene spans 36 kb (Miller *et al* 2005) and is transcribed to a 2,423-bp full-length mature mRNA, predicted to encode a protein of 621a.a. with a molecular weight of 67 kDa (Miller *et al* 2005). *GLUT12* was originally cloned from the human breast cancer cell line, MCF-7 (Rogers *et al.*, 2002). Subsequently, its expression was found to be stronger in ductal cell carcinoma in situ cells than in benign ducts of breast cancer tissues (Rogers *et al.*, 2003). This has indicated its possible role in glucose uptake in breast cancer tissue. Rogers *et al.* (2002) reported that *GLUT12* expression appears to be restricted to insulin-sensitive skeletal muscle, heart and fat and is, thus, postulated to be another insulin-responsive glucose transporter in normal human adult tissues. It is ubiquitously expressed in bovine tissues, being most abundant in the spleen and skeletal

muscle, at intermediate levels in the kidney, testes, and mammary gland, and at lower levels in the liver, lungs, and intestine (Miller *et al.*, 2005) which is different from the insulin-sensitive tissue-restricted expression of *GLUT12* in the human (Rogers *et al.*, 2002).

2.6 Other glucose transporters: *GLUT2*(*SLC2A2*), *GLUT3*(*SLC2A3*) and *GLUT5*(*SLC2A5*)

GLUT2, *GLUT3* (Class I) and *GLUT5* (Class II) are some other transporters which do not express significantly in mammary gland. *GLUT2* protein is present in human breast tissue (Brown and Wahl, 1993) but not found to be expressed in the bovine and rat mammary gland (Burnol *et al* 1990; Madon *et al* 1990; Zhao *et al* 1993). Neither *GLUT3* nor *GLUT5* is expressed in human or rat mammary tissues (Brown and Wahl, 1993; Camps *et al* 1994). Very low levels of human *GLUT3* and *GLUT5* mRNA transcripts were found during northern blotting in bovine mammary gland (Zhao *et al* 1993). Till date, no reports of these three *GLUTs* have been found to play any role in bovine mammary glands. It is thus essential to generate information about SNPs/variations and expression kinetics of these glucose transporters.

3. Na⁺/glucose co-transporters (*SGLT*)

3.1 *SGLT1*(*SLC5A1*) and *SGLT2*(*SLC5A2*)

GLUTs/SLC2As were presumed to be solely responsible for the uptake of glucose in various tissues, however secondary active transporters were lately found which can move a specific nutrient substrate against its concentration gradient in an energy requiring transport process. Although *SGLT1* and *SGLT2* were cloned more than a decade ago and has been well characterized in human and rodent species, bovine *SGLT1* and *SGLT2* were recently cloned (Zhao *et al* 2005a,b). The bovine genome contains a single copy of each gene. In bovine, *SGLT1* gene is located on chromosome 17 and consists of at least 15 exons extending over at least 47 kb. The *bSGLT2* is located on chromosome 25 and consists of 14 exons that span only 9 kb. Interestingly, *SGLT1* mRNA is strongly expressed in the rumen and omasum of lactating cows, suggesting that these tissues may be involved in glucose absorption (Zhao *et al* 1998). The expression of the Na⁺/glucose cotransporter *SGLT1* was earlier detected in the lactating bovine mammary gland (Zhao *et al* 1998 and 1999). Expression of *SGLT1* mRNA is most abundant in bovine intestinal tissues, at intermediate levels in the bovine kidney, at lower levels in the bovine mammary gland, liver, and lungs, and not detectable in the bovine spleen, skeletal muscle, and testes (Zhao *et al* 2005b). As in other species, the *SGLT2* mRNA is predominantly expressed in the bovine kidney as a 2.3-kb transcript, and is expressed at lower levels in the bovine mammary gland, liver, lung, spleen, intestine, and skeletal muscle as a 3.0-kb transcript (Zhao *et al* 2005a). Also they have found that expression and developmental regulation of bovine *SGLT2*

in the mammary gland may have a physiological role in milk synthesis.

4. Single Nucleotide Polymorphism in *GLUTs/SLCs*

Genetic variation like single nucleotide polymorphisms (SNP) can greatly influence gene expression and functions of proteins. This minor variation in the DNA sequence may influence the development of certain diseases or the response to pathogens, drugs, or other agents. Recently, apart from variations in coding region, focus has also been oriented towards studying the variations in flanking regions of coding sequence (CDS), mainly in promoter region of genes that regulate their transcriptional rate and thus determine the amount of transcripts (Malewski *et al* 1998; Szymanowska *et al* 2004a; Szymanowska *et al* 2004b). Since variation (SNP, deletion/insertion) in the gene promoter may be located within the potential transcriptional factor binding sites or cis-regulatory sequence, they can modulate (increase/ decrease) the efficiency of the transcription of structural gene and thus, influence gene expression and milk traits. The regulatory sequences may be located within the core transcriptional unit, or proximal promoter or distal regulatory elements and thus mutation in these regions might have more lasting effects by altering the protein gene regulation.

Association of genetic polymorphism within the 5'-flanking or coding regions of glucose transporters with differential glucose uptake has also been reported in several studies (Ng *et al* 2002, Grabellus *et al* 2010). Some of the polymorphic studies have been done on glucose transporter genes in humans and shown to be associated with diabetes, cancer etc. for eg. SNPs of the *GLUT1* gene, which is located on chromosome 1p35-p31.3, have been shown to be associated with the risk of diabetic nephropathy (Hodgkinson *et al* 2001; Ng *et al* 2002), vascular calcifications (Rufino *et al* 2008), and renal carcinoma (Page *et al* 2005). *Xba*I G>T SNP of *GLUT1* gene is associated with an increased ¹⁸F-FDG uptake and a more advanced tumor grade or growth in breast cancer (Grabellus *et al* 2010). In humans, *GLUT12* is expressed in prostate cancer and breast cancer (Rogers *et al* 2003), whereas it is absent in normal prostate and expressed at very low levels in normal breast tissue (Chandler *et al* 2003). Glucose transporter-1 (*GLUT1*) deficiency syndrome is an autosomal dominant haplo-insufficiency disorder, leading to a reduced glucose transport into the brain (Seidner *et al* 1998). It is highly expressed in the endothelial cells of erythrocytes and the blood-brain barrier and is exclusively responsible for glucose transport into the brain (Vannucci *et al* 1997; Barros *et al* 2007). *GLUT1/SLC2A1* deficiency syndrome was first described in 1991 by De Vivo *et al.* (1991). Glucose transporter-1 deficiency syndrome is caused by mutations in the *SLC2A1* gene in humans and results in impaired glucose transport into the brain which causes mental retardation, and epilepsy in some cases (Leen *et al* 2010). It can be diagnosed by a low concentration of glucose in the spinal fluid. It can also be diagnosed by testing of glucose transport in red blood cells. Genetic testing for the *SLC2A1* gene confirms this syndrome in

about 70% of cases. The Ketogenic Diet (high-fat, low-carbohydrate, moderate protein diet) is the treatment of choice for *GLUT1(SLC2A1)*.

Evidence of any polymorphic studies are negligible in solute transporters in livestock which could work as marker for glucose utilization or its regulation during lactation in livestock species. Very recently a project has been sanctioned by USDA to Dr. Zhao F Q, University of Vermont, Burlington entitled, "Single Nucleotide Polymorphisms of Glucose Transporters as Breed Selection Markers for Milk Productivity in Dairy Cattle". The project has been undertaken mainly keeping in mind that will potentially help to develop the SNPs of these solute carriers as breed selection markers and that may have a direct impact in dairy breeding program for improving milk productivity and efficiency. More number of such studies needs to be encouraged and carried out for development of selective markers to find out the reasons for truncated lactation length and also which can result in developing a breeding policy in selecting animals to improve livestock productivity. Similar studies have to be carried out in livestock to find the SNPs related to diseases caused due to mutation in various solute carriers.

5. Conclusion and future perspective

Different solute carriers possess specific characteristics which indicates that uptake of glucose into mammary cells is complex. Their specific characteristics further determine their expression levels in individual cells or tissues and thus provides a high degree of specificity in the control of glucose uptake under different physiological conditions. The major focus should be on proper utilization of glucose in the bovine mammary gland which is of major importance for successful lactating period in the dairy cow. Uptill now *GLUT1/SLC2A1* has been thought to be only major transporter for uptake of glucose in mammary epithelial cells. But recent studies have found the role of *GLUT/SLC2A* 4, 8, 12 and *SGLT1* and *SGLT2* in glucose transport in mammary gland. A number of studies have been done in relation to differential expression of some of these transporters genes during lactation and dry period in livestock species (Farke *et al* 2008; Mani *et al* 2009; Mani *et al* 2010). In contrast, no information is available about the expression kinetics of major glucose transporters in Indian native cow. Further, unlike exotic cattle (Holstein Frisian and Jersey), characteristics of important transporter genes are poorly understood in native cattle of India. Any information pertaining to genes associated with milk production will always be of great interest for our native cattle breeds. Further studies are required to study the expression pattern of major transporter genes to understand their physiological functions during different lactation stages so as to take advantage of their role in milk production. The studies have to be done keeping in mind the complex nature of these transporters, their stage specific (lactation stages) expression and regulation. Also animals are needed to be screened for the analysis of single nucleotide polymorphism in different solute carrier genes which may affect their structural or functional ability. At last, thorough knowledge of their structure,

mechanism and regulation is required for glucose uptake in the mammary gland so as to increase milk production in livestock which will have a good impact on the dairy industry.

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