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The Effect of Glucose and Glucose Transporter on Regulation of Lactation in Dairy Cow

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ABSTRACT

Glucose is universal and essential fuel of energy metabolism and in the synthesis pathways of all mammalian cells. Glucose is the one of the major precursors of lactose synthesis using glycolysis result in producing milk fat and protein. During the milk fat synthesis, lipoprotein lipase (LPL) and CD36 are required for glucose uptake. Various morecules such as acyl-CoA synthetase 1 (ACSL1) activity of acetyl-CoA synthetase 2 (ACSS2), ACACA, FASN AGPAT6, GPAM, LPIN1 are closely related with milk fat synthesis. Additionally, glucose plays a major role for synthesizing lactose. Activations of lactose synthesize enzymes such as membranebound enzyme, beta-1,4-galactosyl transferase (B4GALT), glucose-6-phosphate dehydrogenase (G6PD) are changed by concentration of glucose in blood resulting change of amount of lactose production. Glucose transporters are a wide group of membrane proteins that facilitate the transport of glucose over a plasma membrane. There are 2 types of glucose transporters which consisted facilitative glucose transporters (GLUT); and sodium-dependent transport, mediated by the Na^+/glucose cotransporters (SGLT). Among them, GLUT1, GLUT8, GLUT12, SGLT1, SGLT2 are main glucose transporters which involved in mammary gland development and milk synthesis. However, more studies are required for revealing clear mechanism and function of other unknown genes and transporters. Therefore, understanding of the mechanisms of glucose usage and its regulation in mammary gland is very essential for enhancing the glucose utilization in the mammary gland and improving dairy productivity and efficiency.

(Key words : Glucose, Lactose, Milk fat, Glucose transporter, Lactation)

INTRODUCTION

Glucose is un universal and essential fuel in energy metabolism and synthesis pathways of all mammalian cells (Cardenas *et al*., 1998). It is constantly and widely required at sufficient levels in the blood stream and used by glucolysis process. In lactating animals, glucose is the major precursor for lactose and is a substrate for the synthesis of milk proteins and fat in mammary secretory (alveolar) epithelial cells (MECs). However, mammary tissue is unable to synthesize glucose from other precursors due to its lack of glucose-6-phosphatase. Therefore, glucose in blood is the alternative supply for its glucose needs (Scott *et al*., 1976; Threadgold and Kuhn, 1979). The supply of glucose to mammary gland is a metabolic priority in lactating mammals resulting glucose uptake by the mammary gland can account for as much as 60~85% of the total glucose that enters the blood (Stacey *et al*., 1995; Kuhn *et al*., 1980).

Metabolites such as ATP and NADH are major factors of milk synthesis and have been studied intensively (Hurtaud *et al*., 2000). Xiao and Cant (2005) reported that 80% of intaked glucose in blood is utilized for producing milk fat, lactose and CO_2. Remained 20% of glucose is used for activating glucose receptors, enzymes and regulatory proteins (Xiao and Cant, 2005). However, there are still controversial opinions for utilizing of glucose. Rulquin *et al* (2004) reported that increase of glucose level in feed guarantee increase of milk production. In contrast, glucose only plays a basic role for primary metabolism (Al-Trad *et al*., 2009). These conflict opinions may due to lack of understanding for role of glucose in lactating metabolism. Therefore, this review is focus on role of glucose in lactation metabolism in molecular level and regulation of glucose transporter for glucose utilization.

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FUNCTION OF GLUCOSE IN MAMMARY GLAND DURING LACTATION

In lactating mammary gland, glucose is mainly used in the lactose synthesis, nicotinamide adenine dinucleotide phosphate (NADPH) generation, milk lipid synthesis, energy production, and nucleic acid and amino acid syntheses (Zhao, 2014). In lactose synthesis, firstly, glucose is irreversibly phosphorylated to glucose-6-phosphate (G6P) and consequently converted to UDP-galactose in the cytoplasm. These glucose and UDP-galactose are taken up by Golgi vesicles and used to synthesize lactose by the lactose synthase located in the Golgi membrane. Lactose synthase consists of two polypeptide subunits: α-lactalbumin (α-LA) and β1,4-galactosyltransferase (β4Gal-T1) (Ramakrishnan *et al*., 2001a), The mammary-specific α-LA changes the specificity of β4Gal-T1 from N-acetylglucosamine to glucose to produce lactose (Ramakrishnan *et al*., 2001b). Glucose-6-phosphate can also enter either the glycolysis pathway or the pentose phosphate shunt and converted to triose-phosphate and then to pyruvate during glycolysis.

In previous report, 75% of the glucose in lactating goats taken up by the mammary gland is used for lactose synthesis (Sasaki *et al*., 1978). Although level of glucose in blood is lower than normal range, glucose is fully utilized for lactating with priority manner and then remained glucose is used for other metabolism. Additionally, 8% of glucose is completely metabolized in the pentose phosphate shunt, which accounts for all CO_2 produced from glucose and provides at least 34% of the NADPH required for de novo fatty acid synthesis. Taken together, Approximately 80% of glucose in blood in lactating mammalians is utilized for producing lactose and milk lipid synthesis (Sunehag *et al*., 2002; Katz *et al*., 1974). Previous studies reported that 40% of glycerol and 59% of lactose are derived from glucose in cytoplasm in pigs (Linzell *et al*., 1969) and 98% of glucose and 68% of galactose in human lactose are derived from plasma glucose (Sunehag *et al*., 2002).

EFFECTS OF GLUCOSE ON MILK FAT SYNTHESIS BY REGULATING KEY GENES

Milk fat production by glucose is a very important aspect of dairy cow nutrition and has been studied for many decades (Zhao, 2014). However, very limited information is known for affection of glucose to milk fat synthesis in dairy cows. The synthesis of milk fat is regulated by multiple biological events such as transcription, translation, and protein turnover (Harvatine *et al*., 2009). Acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), diacyl glycerol acyl transferase (DGAT) and glycerol-3 phosphate acyl transferase (GPAT) are essential factors of milk fat synthesis(Bionaz and Loor, 2008; Bernard *et al*., 2008). Until recent study, many lipogenic genes are revealed that changed significantly at the lactation. For example, LPL and CD36 (mammary fatty acids uptake from the blood), intracellular fatty acids trafficking (FABP3), long-chain (ACSL1) and short-chain (ACSS2) are related in intracellular fatty acids activation, ACACA and FASN (*de novo* fatty acids synthesis), SCD (desaturation), AGPAT6 and GPAM (triacylglycerol synthesis), BTN1A1 and XDH (lipid droplet formation), BDH1 (ketone body utilization), and INSIG1 and PPARGC1A (transcription regulation) genes are closely involved in lipogenic metabolism (Bionaz and Loor, 2008; Gao *et al*., 2013) (Table 1). Recently, Liu *et al* (2013) found that while low (5 mmol/L) glucose increase mRNA of ACC, DGAT and GPAT. However, higher concentrations of glucose do not affect those of mRNA, while 20 mmlol/L glucose resulted in significant lower expression of FAS mRNA. The sterol regulatory element binding protein-1 (SREBP-1) is main transcription factor which controls expression of the genes encoding the enzymes for milk fat synthesis (Edwards *et al*., 2000), *in vitro* study revealed that SREBP-1 mRNA expression increased at low concentration of glucose and then decreased at 20 mmol/L. This result is may due to be a salvage response, which will increase the expression and activity of proteins required for nutrient acquisition (Hammerman and Fox, 2004).

In overall, high concentration of glucose environment tend to decrease expression of genes which involved synthesis and secretion of milk lipid and lactose as well as inhibit activity of lipoprotein lipase resulting decrease intramammary esterification process (Rigout *et al*., 2002). Additionally, glucose regulate translation of lipogenic enzymes which secreted from adipocyte, liver and pancreatic b-cells (Girard *et al*., 1997).

EFFECTS OF GLUCOSE ON MRNA EXPRESSION OF THE KEY GENES WHICH REGULATE LACTOSE SYNTHESIS

Glucose is the main precursor of lactose, and play an important role in lactose synthesis. Nevertheless, mechanism by which increased glucose usage affects lactose synthesis in bovine mammary epithelial cells

Table 1. Summary of the enzymes, genes and glucose transporters for regulating glucose in lactation process

Type	Major function		Reference
Enzymes			
Lipoprotein lipase (LPL)	Regulation of fatty acid and glucose uptake into tissues		(Bernard *et al*.,, 2008)
Membranebound enzyme	Synthesis of lactose		(Farrell *et al*., 2004)
Glucose-6-phosphate dehydrogenase (G6PD)	Regulation of pentose phosphate pathway of glucose		(Ramakrishnan *et al*., 2001b)
ATP, nicotinamide adenine dinucleotide phosphate (NADPH)	Metabolite of glucose metabolism and regulate milk production		(Hurtaud *et al*., 2000)
α-Lactalbumin (α-LA), β1,4-Galactosyltransferase (β4Gal-T1)	Synthesis of lactose		(Ramakrishnan *et al*., 2001a)
Acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), diacyl glycerol acyl transferase (DGAT), glycerol-3 phosphate acyl transferase (GPAT)	Regulation of milk fat synthesis		(Bernard *et al*.,, 2008)
Phosphofructokinase, hexokinase, pyruvate kinase (PK)	Regulation of metabolic pathway during glycolysis		(Renner *et al*.,, 1972)
Genes			
CD36	Regulation of fatty acid and glucose uptake into tissues		(Zhao, 2014)
FABP3	Trafficking of lipid acid into cytoplasm		(Bionaz and Loor, 2008)
Acyl-CoA synthetase 1 (ACSL1), acetyl-CoA synthetase 2 (ACSS2)	Produces energy for anabolic pathways		(Bionaz and Loor, 2008)
ACACA, FASN	Synthesis of *de novo* fatty acid		(Bionaz and Loor, 2008)
SCD, FADS1	Regulation of desaturation		(Bionaz and Loor, 2008)
AGPAT6, GPAM, LPIN1	Synthesis of triacylglycerol		(Bionaz and Loor, 2008)
BTN1A1, XDH	Regulation of lipid droplet formation		(Bionaz and Loor, 2008)
BDH1	Utilization of ketone body		(Bionaz and Loor, 2008)
INSIG1, PPARG, PPARGC1A	Regulation of mammary gland specific expression genes		(Bionaz and Loor, 2008)
Glucose transporter			
Name	Major sites of expression	Major function	Reference
GLUT1	Ubiquitous distribution in tissues and culture cells	Basal glucose uptake	(Mueckler *et al*., 1985)
GLUT2	Liver, islets, kidney, small intestine	High-capacity low-affinity transport	(Fukumoto *et al*., 1988)
GLUT3	Brain and nerve cells	Neuronal transport	(Kayano *et al*., 1988)
GLUT4	Muscle, fat, heart	Insulin-regulated transport in muscle and fat	(Fukumoto *et al*., 1989)
GLUT5	Intestine, kidney, testis	Transport of fructose	(Kayano *et al*., 1990)
GLUT6	Spleen, leukocytes, brain		(Doege *et al*., 2000a)
GLUT7	Small intestine, colon, testis	Transport of fructose	(Li *et al*., 2004)
GLUT8	Testis, blastocyst, brain, muscle, adipocytes	Fuel supply of mature spermatozoa	(Carayannopoulos *et al*., 2000)
GLUT9	Liver, kidney		(Phay *et al*., 2000)
GLUT10	Liver, pancreas		(McVie-Wylie *et al*., 2001)
GLUT11	Heart, muscle	Muscle-specific; fructose transporter	(Doege *et al*., 2001)
GLUT12	Heart, prostate, mammary gland		(Rogers *et al*., 2002)
HMIT	Brain	H^+/myo-inositol cotransporter	(Uldry *et al*., 2001)
SGLT1	Kidney, intestine	Glucose reabsorption in intestine and kidney	(Hediger *et al*., 1987)
SGLT2	Kidney	Los affinity and high selectivity for glucose	(Wells *et al*., 1992)

(BMEC) is still unclear. Farrell *et al*. reported that the membrane bound enzyme, beta-1,4-galactosyl transferase (B4GALT) and the milk protein α-lactoalbumin (LA) bind to form LS, which synthesizes lactose in the Golgi apparatus of mammary cells (Table 1) (Farrell *et al*., 2004). B4GALT is the unreplaceable enzyme known as transfer of galactose from uridine 59-diphospho-galactose to terminal N-acetylglucoseamine to form lactose (Ramakrishnan and Qasba 2001a). Compared with the low glucose treatment group, B4GALT mRNA was higher in the 5 and 10 mmol/L glucose treatments except in the 20 mmol/L treatment. However, unlike B4GALT mRNA, no significant changes of LA mRNA level were revealed for glucose (Mellenberger and Bauman 1974). The LS content was higher in BMEC incubated with high glucose than those incubated with low glucose. Based on past and present studies, increasing glucose availability may partly stimulates lactose synthesis by shifting the expression of B4GALT at transcriptional and post-transcriptional levels and then increase milk yield (Lemosquet *et al*., 2004).

FUNCTION OF GLUCOSE ON GLUCOSE METABOLISM

Glucose is main precursor for lactose synthesis in BMEC (Kleiber *et al*., 1955). However, metabolism of glycolysis and pentose phosphate pathway also plays an important role in glucose function (Abraham *et al*., 1954). Glycolysis is part of a major metabolic pathway for the catabolic conversing of glucose to energy. Phosphofructokinase, hexokinase, and PK are potential sites of control in the metabolic pathway. Especially, PK catalyzes the last event of glycolysis which makes formation of pyruvate and ATP (Table 1).

Renner *et al*. reported that the glucose concentration affect glucose metabolic pathways and relative flux through there pathways in liver cells (Renner *et al*., 1972). At low levels, glucose tends to be used by the cells for macro-molecular synthesis and oxidative processes. In case of higher than 1 mmol/L concentrations, glycolysis kicks out all excess glucose and converts to lactate. Process of generation of NADPH and pentose which called pentose phosphate pathway is an alternative to glycolysis. During this process, G6PD is the rate-controlling enzyme of this pathway (Rigout *et al*., 2002). This result revealed that increment of PK and G6PD activity induce elevation of glucose metabolism by glycolysis and pentose phosphate pathway when bovine mammary epithelial cell are exposed to elevated glucose concentrations.

GLUCOSE TRANSPOTERS

Glucose uptake in the mammary gland is very essential for milk production. There are 2 distinct processes of glucose transports which across the plasma membranes of mammalian cells. One is facilitative transport which mediated by a family of facilitative glucose transporters (GLUT) and the other is sodium-dependent transport which mediated by the Na^+/glucose cotransporters (SGLT).

There are 13 functional facilitative glucose transporter isoforms have been characterized and named as GLUT1-GLUT12 (based on the chronological order of publication) and H^+/myo-inositol cotransporter (HMIT). These transporters have similar structures which consist of 12 trans-membrane domains with both the amino and carboxy-terminals located in the cytoplasm, and an N-glycosylation site located on the first or ninth extracellular loop (Zhao and Keating, 2006). GLUT1 to GLUT5 have been extensively studied. GLUT1 has been ubiquitously detected in cells and tissues, including the mammary gland (Madon *et al*., 1990; Burant *et al*., 1991; Zhao *et al*., 1999). Because GLUT1 is densely existed in blood-tissue barrier (Cornford *et al*., 1994), GLUT1 is assumed to be the primary responsible transporter for basal glucose uptake. GLUT2 is closely related with the release of hepatic glucose, release of absorbed and reabsorbed glucose in the small intestine and kidney, and regulation of insulin secretion from β-cells. GLUT3 plays an important role as the neuronal glucose transporter. GLUT4 mediated insulin stimulated glucose uptake in skeletal muscle and adipose tissues (Holman and Sandoval, 2001). GLUT5 assume to participate in the uptake of dietary fructose from the lumen of the small intestine.

GLUT6 - 12 and HMIT are the relatively recently cloned functional glucose transporter. GLUT6 mRNA is mainly expressed in the spleen, brain and peripheral leukocytes (Doege *et al*., 2000a). However, more studies for activity of those transporters are still demandable. GLUT7 was cloned from human small intestinal tissue and was also found to be expressed in the colon, testis, and prostate (Li *et al*., 2004). GLUT7 transports both glucose and fructose with high affinity (Li *et al*., 2004). GLUT8 is founded that it is response to insulin-stimulated glucose uptake in the blastocyst. Therefore, GLUT8 is considered as another insulin-regulated glucose transporter (Carayannopoulos *et al*., 2000). Additionally, GLUT8 is involved in providing glucose for DNA synthesis in male germ cells because it is highly expressed in the male germ cells and its expression is strongly inhibited by estrogen treatment (Doege *et al*., 2000b).

GLUT9 is mainly founded in the kidney and liver (Phay *et al*., 2000). However, clear function of GLUT9 is still unclear. Expression of GLUT10 is highest in the liver and pancreas known as one of the genomic loci associated with non-insulin-dependent diabetes mellitus (McVie-Wylie *et al*., 2001). Although, strong expression of GLUT11 is observed in the heart and skeletal muscle, expression of GLUT11 is observed in various tissues. (Wu *et al*., 2002). GLUT12 which originally cloned from breast cancer cells also expressed in various tissues such as mammary glands, prostate, heart, skeletal muscle and brown adipose tissue. (Rogers *et al*., 2002). Lastly, predominant expression of HMIT in brain with specific transport activity for myoinositol is reported (Uldry *et al*., 2001) (Table 1).

MAJOR REGULATORY GLUCOSE TRANSPORTERS IN BOVINE MAMMARY GLAND

It is well reported that GLUT1, GLUT8, GLUT12, SGLT1 and SGLT2 are closely related with development of mammary gland, lactation and milk production efficiency. cDNA sequences of bovine glucose transporters have been reported fallowed as GLUT1 (GenBank accession #NM_174602), GLUT3 (NM_174603), GLUT4 (NM_174604), GLUT8 (AY208940), GLUT12 (AY514443), SGLT1 (AF508807), SGLT2 (AY208941), and SGLT5 (AY514442). In this sentence, mostly relevant glucose transports in the bovine mammary gland are briefly explained.

The GLUT1 mRNA is broadly expressed in lactating bovine cells. Especially, it is abundant in the kidney and mammary gland and rarely expressed in the omental fat and skeletal muscle. Generally, many growth stimuli such as growth hormone induce GLUT1 expression and sequentially lead energy increase and biosynthesis of dividing cells (Fladeby *et al*., 2003). Unlike other species, expression of bovine GLUT1 mRNA in adipo-tissue is dramatically changing during different period of lactation; very low expression in early lactation and strong expression in rate and lactation (Komatsu *et al*., 2005).

Expression of GLUT4 mRNA is mainly occurred in insulin-sensitive tissues such as the skeletal muscle, heart, and adipose tissue (Zhao *et al*., 1993; Abe *et al*., 1997) which may regulates glucose uptake in skeletal muscle and adipocyte (Watson *et al*., 2004; Watson and Pessin, 2006). Full-length of bovine GLUT8 cDNA is 2,073 bp and encodes 478-AA protein with a molecular weight of 51 kDa (Zhao *et al*., 2004). GLUT8 most strongly expressed in mammary tissue. However, it expressed in many other tissues such as lung, spleen, intestine epithelia, skeletal muscle, kidney and liver (Zhao *et al*., 2004).

Bovine GLUT12 is recently studied glucose transporter which consisted of 5 exons and 621AA with a molecular weight of 67 kDa. It is also expressed in various tissues, mostly abundant in spleen and skeletal muscle, intermediate levels in kidney, testes, and mammary gland, and lower levels in the liver, lungs, and intestine (Miller *et al*., 2005). Because of newly research of bovine GLUT12, not many information for function and regulation mechanism of bovine GLUT12 is existed.

Although Na^+/glucose cotransporters including SGLT-1 and SGLT2 were cloned more than couple of decades ago in human and mice, bovine SGLT1 and SGLT2 were recently cloned (Zhao *et al*., 2005a,b). Location of bovine SGLT1 gene is on chromosome 17 and consists of 15 exons with 47 kb size. The strongest expression of SGLT1 mRNA is observed in bovine intestinal tissues and comparably lower express in the bovine mammary gland (Zhao *et al*., 2005b). However, interestingly, expression of SGLT1 mRNA is strongly increased in the rumen and omasum of lactating cows. This phenomenon suggests that those tissues are involved with glucose absorption (Zhao *et al*., 1998). The bSGLT2 is located on chromosome 25 and consists of 14 exons with 9 kb size. SGLT2mRNA is mainly expressed in the bovine kidney and is comparably lower expressed in bovine mammary gland, liver, lung, spleen, intestine, and skeletal muscle (Zhao *et al*., 2005a). Although intensive studies for facilitative glucose transporters have been achieved during several decades, expression and physiological roles of Na^+/glucose transporters in the mammary gland and other tissues is still unclear.

CONCLUSION

Glucose uptake is major importance event for successful lactation in bovine mammary gland. Additionally, glucose metabolism regulates energy level, synthesis of milk fat and lactose production result in main affection of quality and amount of milk. Numbers of milk fat synthesis enzymes (ACC, FAS, DGAT and GPAT) and genes (SCD, FADS1, INSIG1, PPARG and PPARGC1A) are closely involved in lactation process. Glucose metabolic pathway is regulated by regulatory enzymes such as phosphofructokinase, hexokinase and pyruvate kinase and production of NADPH and pentose is controlled by G6PD. There are 2 families of glu-

cose transporters which selected facilitative transport, mediated by facilitative glucose transporters (GLUT1-GLUT12); and sodium-dependent transport, mediated by the Na^+/glucose cotransporters (SGLT1, SGLT2). Although, intensive studies for lactation have been conducted, more understanding for lactation with molecular level is required. Therefore, conscious understanding of mechanisms of glucose uptake and regulation pathway in the mammary gland will may enhance glucose utilization and improve milk productivity and efficiency in lactating cow.

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