Expressional Analysis of Glucose Transporter Isoforms in the Efferent Ductules of Male Sprague Dawley Rat during Postnatal Development

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ABSTRACT

A cell frequently utilizes glucose as a fuel of energy and a major substrate of lipid and protein syntheses. A regulation of glucose movement into and out of the cells is precisely controlled by cooperative works of passive and sodium-dependent active processes. At least 13 glucose cotransporter (*Slc2a*, GLUT) isoforms involve in passive movement of glucose in cells. The efferent ductules (EDs) play in a number of important functions for maintenance of male fertility. In the present study, using real-time PCR analysis, we determined gene expression of five *Slc2a* isoforms in the EDs. In addition, we compared expression levels of these *Slc2a* isoforms according to postnatal development ages, 1 week, 2 weeks, 1 month, and 3 months. Results from the current study showed that expression of *Slc2a1*, *Slc2a3*, and *Slc2a5* mRNAs reached the highest levels at 1 month of age, followed by a transient decrease at 3 months of age. In addition, the level of *Slc2a4* mRNA reminded at steady until 1 month of age and was significantly reduced at 3 months of age, whereas the highest level of *Slc2a* 8 mRNA was detected at 2 weeks of age. Data from the present study indicate a differential expression of various *Slc2a* isoforms in the ED according to postnatal ages. Thus, it is believed that glucose movement through the epithelial cells in the ED would be regulated by the coordinated manner among Slc2a isoforms expressed at a given age.

(Key words : Efferent ductules, Glucose transporter, Postnatal development, Male reproduction, Gene expression)

INTRODUCTION

The male reproductive tract is consisted of the testis and the excurrent duct, including the efferent ductules (EDs) and epididymis. The EDs are composed of a single layer of epithelial cells, which is surrounded by a thin layer of smooth muscle cells (Ilio and Hess, 1994). The epithelia of the EDs have two types of cells, nonciliated and ciliated cells (Ilio and Hess, 1994). The ciliated cells are characterized with long cilia protruding toward the lumen and numerous mitochondria near the base of cilia (Ilio and Hess, 1994). The nonciliated cells have typical features of reabsorbing cells, such as large quantities of endocytotic vesicles and lysosome in the apical cytoplasm (Hermo and Morales, 1984). As an embryonic analogue to the proximal tubules of the kidney (Hinton and Turner, 1988), the EDs share a number of morphological and physiological similarities with the proximal tubules (Hinton and Turner, 1988; Ilio and Hess, 1994). The EDs play a number of important functions for maintenance of male fertility, including reabsorption of a large amount of the testicular fluid secreted from the testis, secretion and/or absorption of ions and proteins, and movement of spermatozoa and the testicular fluid from the testis to the head of the epididymis (Ilio and Hess, 1994). Thus, it is no doubt that a vast energy would be required to regulate functions and maintain homeostasis of the EDs.

Most of mammalian cells utilize glucose as a major energy source in the form of ATP and an important substrate for biosyntheses of protein and lipid (Zhoa and Keating, 2007). Movement of glucose into and out of the cell is controlled by two major mechanisms, facilitative and sodium-dependent active glucose transport processes that are driven by the gradient of glucose concentration across the plasma membrane (Widdas, 1988). A few exceptions are the epithelial cells of small intestine and the proximal convoluted tubules of the kidney, at which glucose movement is occurred against its electrochemical gradient by a secondary active transport mechanism (Zhoa and Keating, 2007). Because blood glucose levels in mammals are maintained within a very narrow range by a number of homeostatic mechanisms (Zhoa and Keating, 2007), it is important for

the cells to regulate uptake of glucose from the interstitial fluid.

There are 13 members of passive and facilitative glucose transporters (*Slc2a*, GLUT) identified, *Slc2a1-13* (Zhoa and Keating, 2007). The sodium-dependent glucose transport is mediated by 6 members of Na$^+$/glucose cotransporters family (*Slc5A*, SGLT) (Wright and Turk, 2004). Even though GLUTs share structural homology and conserved DNA sequences, each GLUT is distinguishable in aspect with a type of and affinity to substrates and functional properties (Zhoa and Keating, 2007). In addition, certain *Slc2a*s have tissue-specific expression and specific cellular localization, indicating the presence of specialized functions of these GLUTs (Zhoa and Keating, 2007). For example, *Slc2a1* is ubiquitously distributed in most tissues, and *Slc2a2* is mainly found in the basolateral region of the kidney and intestinal absorptive epithelial cells (Kellett and Brot-Laroche, 2005). *Slc2a4* is particularly interested due to the main insulin-sensitive member of *Slc2a* family. With a relatively high affinity to glucose, *Slc2a4* is mostly expressed in adipose tissue and skeletal muscle (Kasahara and Kasahara, 1997). In the male reproductive tract, *Slc2a8* is predominantly expressed in the testes and is served to provide glucose as a fuel to mature spermatozoa (Zhao *et al.*, 2004). Other *Slc2a* isoforms present in the testis are *Slc2a5* and *Slc2a7*, which have a relatively high affinity to fructose (Burant *et al.*, 1992; Li *et al.*, 2004). Schűrmann *et al.* (2002) have demonstrated the localization of GLUT8 at the acrosomal region of mature spermatozoa within the seminiferous tubules and the epididymis. These researchers suggest that a number of *Slc2a* isoforms present in the male reproductive tract would involve in regulation of male fertility.

Up to date, no information is available for expression of *Slc2a* isoforms in the excurrent duct of the male reproductive tract. Thus, the aim of the present study was to determine gene expression of *Slc2a* isoforms in the ED of male rat. We further attempted to examine expression patterns of *Slc2a* isoforms in the ED at 4 different ages of postnatal development, 1 week, 2 weeks, 1 month, and 3 months of ages.

MATERIALS AND METHODS

Animals and Tissues Collection

Male Sprague Dawley rats were obtained from Samtako (Osan, S. Korea). For the present study, we used 4 different postnatal ages, two prepubertal groups (1 and 2 weeks of ages), one early pubertal group (1 month of age), and one adult group (3 months of age). Animals were housed under controlled temperature and humidity and given *ad libitum* food and water until reaching at proper ages. Male reproductive tissues were collected from experimental animals which were anesthetized by CO$_2$ stunning. The testes were separated from the rest of male reproductive tract, and epididymal fat covering the ED was rapidly removed in cold PBS buffer. The ED in an experimental group is pooled to obtain sufficient amount of total RNA. In the present study, we used 23 rats in total, 7 rats for 1 week, 6 rats for 2 weeks, 5 rats for 1 month, and 5 rats for 3 months of ages.

Total RNA Isolation and Real-Time Polymerase Chain Reaction Analysis

Total RNAs from pooled ED were isolated using easy-Blue total RNA extraction solution (iNtRON Biotechm Sungnam, S. Korea) and a polytron homogenizer (Fisher Scientific, Pittsburgh, USA). Collected RNA pellets were resuspended in RNA storage buffer (Ambion, Austin, USA) and stored in −80℃ freezer until further use for reverse-transcription (RT) reaction. UV spectrophotometer (Eppendorf, New York, USA) and agarose gel electrophoresis were utilized to determine the yield and the qualities of total RNAs, respectively. Complementary DNA (cDNA) was generated from 1 µl of total RNA in total volume of 20 µl with oligo-dT primer using ImProm-II^{TM} reverse transcription system (Promega, Madison, USA). The RT reaction was carried out at 25℃ for 5 min, at 42℃ for 1 hr, and 70℃ for 15 min. The real-time PCR was performed in a mixture of 1 µl of cDNA, 0.75 U of GoTaq polymerase (Promega, Madison, USA), 5 µl of 5x buffer, 0.2 mM of d-NTPs (Promega, Madison, USA), 2.5 µl of 3,000x SYBR Green (BMA, Rockland, USA), and 10 pmols of forward and reverse primers. A total volume of the mixture for real-time PCR was 25 µl. The PCR was carried out an initial step of pre-denaturation at 94℃ for 5 min, followed by denaturation at 94℃ for 30 sec, annealing at Tm for 30 sec, and extension at 72℃ for 30 sec of cycles. One cycle at 72℃ for 10 min was performed for the final extension of PCR. The sizes of PCR products were checked on 1.2% agarose gels under UV light. In the PCR analysis, we included *Gapdh* (glyceraldehyde-3-phosphate dehydrogenase) as an internal PCR control. Summary of primer information utilized for PCR analysis are present in Table 1.

Data Presentation and Statistical Analysis

A mean and a standard deviation for each experimental group were obtained from 3~5 repetition of the RT reaction and real-time PCR. The mRNA expression levels of *Slc2a* isoforms were compared with those of *Gapdh* and presented here as relative ratios between *Slc2a* isoform and *Gapdh*. Mean differences among 4 experimental age groups were compared using one-way ANOVA, followed by a post-hoc test, Tukey's test. Wh-

Table 1. Primer sequences and conditions for real-time PCR

Gene (GenBank access number)	Primer sequence	Expected PCR size (bps)	Tm (℃)
Slc2a1 (BC061873)	F : GCCTGAGACCAGTTGAAAGCAC (2188~2209) R : CTGCTTAGGTAAAGTTACAGGAG (2457~2479)	292	60
Slc2a3 (NM_017102.2)	F : AACAGAAAGGAGGAAGACCA (643~662) R : CGCAGCCGAGGGGAAGAACA (1253~1272)	630	58
Slc2a4 (NM_012751)	F : GTCATCAACGCCCCACAGAA (270~289) R : GAGAAGATGGCCACGGAGAGAG (385~406)	137	65
Slc2a5 (D13871)	F : TGGTGAATAACTTGGGCAGA (314~333) R : GAGAAGCCGATGAGGAGAAG (1069~1088)	775	60
Slc2a8 (AB033418)	F : TAACCTCACTTGACTGGGGG (1899~1918) R : CACTGAGACCAGGGAAGAGC (2092~2111)	213	60
Gapdh (X02231)	F : CCCCTGGCCAAGGTCATCCATGACAACTTT (540~569) R : GGCCATGAGGTCCACCACCCTGTTGCTGTA (1023~1052)	513	60

Slc2a1 : glucose transporter (GLUT) 1; Slc2a3 : GLUT3; Slc2a4 : GLUT4; Slc2a5 : GLUT5; Slc2a8 : GLUT8; and Gapdh : glyceraldehyde-3-phosphate dehydrogenase.
Numbers in parentheses of primer sequence indicate the positions of nucleotides in GenBank sequence.

en $p<0.05$, results were considered significant.

RESULTS

Differential Expression of Slc2a1 and Slc2a3 in the Efferent Ductules at Different Postnatal Ages

The expression of Slc2a1 and Slc2a3 mRNAs were detected in the EDs of rat during postnatal development (Fig. 1). A significant increase of Slc2a1 mRNA level was found at 2 weeks of age, compared with 1 week of age (Fig. 1A). The highest expression of Slc2a1 mRNA in the EDs was observed at 1 month of age, whereas the level of Slc2a1 mRNA at 3 months of age was not distinguishable with its at 1 week of age (Fig. 1A). Expression pattern of Slc2a3 in the EDs was similar with that of Slc2a1 (Fig. 1B). A level of Slc2a3 mRNA was significantly higher at 2 weeks of age than at 1 week of age (Fig. 1B). Moreover, a significant increase of Slc2a3 mRNA level was detected at 1 month of age, compared to that at 2 weeks of age (Fig. 1B). However, the level of Slc2a3 mRNA at 3 months of age was the lowest among experimental groups (Fig. 1B).
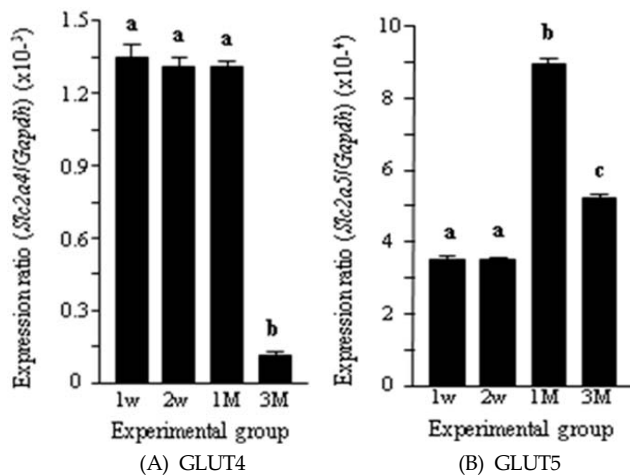
Expression Patterns of Slc2a4 and Slc2a5 in the Efferent Ductules of Rat during Postnatal Development

The presence of Slc2a4 and Slc2a5 transcripts in the EDs was also observed throughout postnatal period (Fig. 2). There was no significant difference on the level of Slc2a4 mRNA among early postnatal periods, 1 week, 2 weeks, and 1 month of ages (Fig. 2A). However, expre-
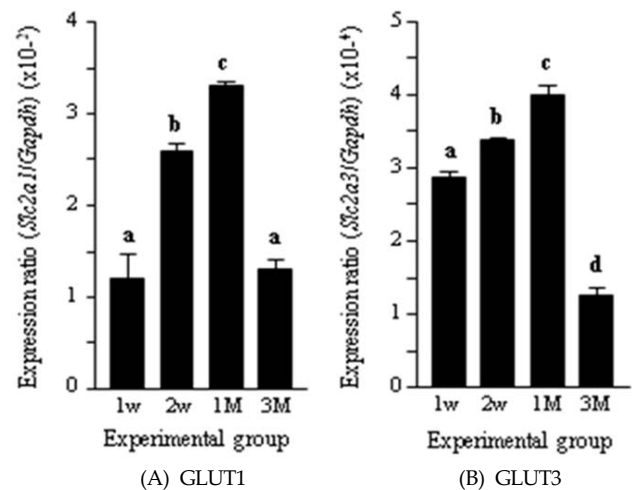

Fig. 1. Postnatal age-dependent expression of Slc2a1 (GLUT1) and Slc2a3 (GLUT3) genes in the efferent ductules. Abundance of Slc2a1 (A) or Slc2a3 (B) mRNA at different postnatal ages is shown here. Glyceraldehyde-3-phosphate dehydrogenase (Gapdh) was used as an internal control of real-time PCR analysis. Different letters indicate statistically significant at $p<0.05$. 1 w: 1 week of age, 2 w: 2 weeks of age, 1 M: 1 month of age, and 3 M: 3 months of age.

ssion of Slc2a4 in the EDs was significantly decreased at 3 months of age (Fig. 2A). Expression of Slc2a5 mRNA was significant increased at 1 month of age, compared with those at 1 week and 2 weeks of ages (Fig. 2B). The level of Slc2a5 mRNA in the EDs at 3 months of age was significantly lower than that at 1 month of age, but was clearly higher than those at 1 week and 2 weeks of ages (Fig. 2B).

Fig. 2. Expression patterns of *Slc2a4* (GLUT4) and *Slc2a5* (GLUT5) genes in the efferent ductules during postnatal development. Abundance of *Slc2a4* (A) or *Slc2a5* (B) mRNA is compared at different postnatal age here. Glyceraldehyde-3-phosphate dehydrogenase (*Gapdh*) was used as an internal control of real-time PCR analysis. Different letters indicate statistically significant at $p<0.05$. 1 w: 1 week of age, 2 w: 2 weeks of age, 1 M: 1 month of age, and 3 M: 3 months of age.
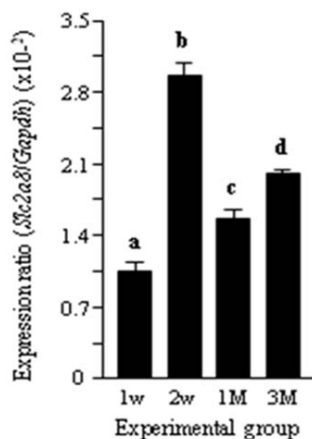
Fig. 3. Expressional change of *Slc2a8* (GLUT8) gene in the efferent ductules among different postnatal ages. Abundance of Slc2a8 mRNA at different postnatal ages is shown here. Glyceraldehyde-3-phosphate dehydrogenase (*Gapdh*) was used as an internal control of real-time PCR analysis. Different letters indicate statistically significant at $p<0.05$. 1 w: 1 week of age, 2 w: 2 weeks of age, 1 M: 1 month of age, and 3 M: 3 months of age.

Expression Pattern of *Slc2a8* in the Efferent Ductules during Postnatal Development

Expression pattern of *Slc2a8* in the EDs during postnatal development was somewhat different with those of other *Slc2a* isoforms (Fig. 3). The level of *Slc2a8* mRNA was significantly increased at 2 weeks of age, compared with that at 1 week of age (Fig. 3). However, expression of *Slc2a8* mRNA at 1 month of age was significantly lower than 2 weeks of age, but still significantly higher than 1 week of age (Fig. 3). A sig-

nificant increase of *Slc2a8* mRNA level was observed at 3 months of age, compared with that at 1 month of age (Fig. 3).

DISCUSSION

The present study shows gene expression of GLUT isoforms in the EDs of male reproductive tract, for the first time, to our knowledge. In addition, data from this research demonstrate differential expression of GLUT isoforms in the EDs according to postnatal ages. Moreover, the current study reveals that some of GLUT isoforms are expressed more predominantly than the others in the EDs.

The presence and localization of GLUT isoforms in the testis have been determined by a number of researches. The Sertoli cells in the testis possess GLUT1 (Carosa *et al.*, 2005; Galardo *et al.*, 2008; Riera *et al.*, 2002; Ulisse *et al.*, 1992), GLUT3 (Galardo *et al.*, 2008; ; Haber *et al.*, 1993), GLUT5 (Rand *et al.*, 1993), and GLUT8 (Carosa *et al.*, 2005; Gawlik *et al.*, 2008; Schürmann A *et al.*, 2002). Also, Chen *et al.* (2003) have shown the localization of GLUT8 in Leydig cells of the testis. In addition, others have found that GLUT8 is detected in germ cells and the acrosomal region of spermatozoa (Ibberson *et al.*, 2002; Schürmann A *et al.*, 2002). The present study revealed that the EDs possess 5 GLUT isoforms, including GLUT1, 3, 4, 5, and 8, at least. However, we can't rule out a possibility in which other GLUT isoforms would be present in the EDs. Also, because the fluid reabsorptive function of the EDs are tightly coupled with ion movement (Lee *et al.*, 2008), it is strongly possible that other types of glucose transporters, such as Na^+/glucose cotransporter family, other than GLUTs would exist in the EDs. Thus, a further study is required to determine expression of additional molecules relating to glucose movement through the epithelia of the EDs.

In designing the present study, we selected 4 different postnatal time-points. Active secretion of the testicular fluid in rat would not occur at 1 week of age, because the formation of Sertoli cell junction, an indicative of secretion of the testicular fluid, arises between 10 and 16 days of age (Gondos and Berndston, 1993; Nagano and Suzuki, 1976) and is completed around 20 days of age (Martin and Dierichs, 1983). Thus, it is likely that secretion of the testicular fluid becomes just prior to 2 weeks of age and active secretion of the fluid occurs around 1 month of age. At 3 months of age, a full secretion of the testicular fluid is expected. The present study showed that the highest levels of GLUT1, 3, and 5 mRNAs in the EDs were found at 1 month of age during postnatal development. These results imply that expression of GLUT1, 3, and 5 mRNAs

in the EDs would be stimulated by a factor(s) in the testicular fluid secreted during prepubertal period. Significant decreases of mRNA expression of these GLUT isoforms at 3 months of age suggest a possible inhibitory effect of gene expression by testicular factor(s) produced after puberty. In case of GLUT8, the mRNA abundance in the EDs reached the highest at 2 weeks of age in the present research. These observations indicate that gene expression of each GLUT isoform would be differentially regulated by various factors. Interestingly, mRNA level of GLUT4 during prepubertal age was not changed, but was significantly decreased at 3 months of age. Based on this result, it is speculated that gene expression of GLUT4 would not be controlled by the testicular factor(s) but might be regulated by a factor(s) in the testicular fluid and/or extra-testicular factor(s). In fact, expressional regulation of GLUT isoforms in the testis is regulated by a number of testicular and/or extra-testicular factors, including thyroid hormone (Carosa et al., 2005; Ulisse et al., 1992), follicle-stimulating hormone (Galardo et al., 2008), interleukin (Chen et al., 2003; Galardo et al., 2008), basic fibroblast growth factor (Galardo et al., 2008), and human chorionic gonadotropin (Chen et al., 2003). In addition, estrogen and testosterone involve in regulation of GLUT expression in the testis (Doege et al., 2000; Nualart et al., 2009). Therefore, it is reasonable to consider that gene expression of GLUT isoforms in the EDs would be regulated by differential testicular and/or non-testicular factor(s) influencing on the development and function of the EDs at different postnatal ages.

The GLUTs play a number of important functions in various tissues, including basal glucose uptake, transport of fructose, insulin-regulated transport of glucose in muscle and fat, and fuel supply of mature spermatozoa (Zhao and Keating, 2007). These functions of GLUTs are dependent on their localization in the cells and specificity to substrates (Zhao and Keating, 2007). In the testis of male reproductive tract, GLUT8 is involved in supply of fuel for motility and mitochondrial potential of spermatozoa (Gawlik et al., 2008) and differentiation of spermatocytes (Ibberson et al., 2002). The EDs are a metabolically active tissue which would require utilization of high energy. In addition, reabsorption of the testicular fluid in the EDs is regulated by a number of transporters coupled with organic and inorganic matters (Lee et al., 2008). Thus, it is speculated that GLUTs present in the EDs would participate in establishment of glucose gradient between inside and outside of the lumen of the EDs, so that active and/or passive fluid movement through the epithelia of the EDs occurs. Moreover, it would not be surprised that the EDs utilize itself a high amount of glucose as metabolic energy to maintain a variety of functions, such as movement of cilia and endocytosis and secretion of proteins. Detail physiological function and localization

of GLUTs in the EDs should be examined in future researches.

In conclusion, the present study has demonstrated differential expression of a number of GLUT isoforms in the EDs of male reproductive tract during postnatal development. Results from the present research also suggest a possible role of GLUTs influencing on functions of the EDs at different postnatal ages.

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