Molecular Aspects of Medicine 34 (2013) 121–138

Contents lists available at SciVerse ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

Review

The SLC2 (GLUT) family of membrane transporters ☆

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Guest Editor Matthias A. Hediger
Transporters in health and disease (SLC series)

ARTICLE INFO

Article history:
Received 6 March 2012
Accepted 3 July 2012

Keywords:
SLC2
GLUT
Membrane transport
Glucose transporters
Glucose homeostasis

ABSTRACT

GLUT proteins are encoded by the SLC2 genes and are members of the major facilitator superfamily of membrane transporters. Fourteen GLUT proteins are expressed in the human and they are categorized into three classes based on sequence similarity. All GLUTs appear to transport hexoses or polyols when expressed ectopically, but the primary physiological substrates for several of the GLUTs remain uncertain. GLUTs 1–5 are the most thoroughly studied and all have well established roles as glucose and/or fructose transporters in various tissues and cell types. The GLUT proteins are comprised of ~500 amino acid residues, possess a single N-linked oligosaccharide, and have 12 membrane-spanning domains. In this review we briefly describe the major characteristics of the 14 GLUT family members.

Contents

☆ Publication in part sponsored by the Swiss National Science Foundation through the National Center of Competence in Research (NCCR) TransCure, University of Bern, Switzerland; Director Matthias A. Hediger; Web: http://www.transcure.ch.

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http://dx.doi.org/10.1016/j.mam.2012.07.001

1. Introduction

The transport of monosaccharides, polyols, and other small carbon compounds across the membranes of eukaryotic cells is mediated by members of the GLUT family of integral membrane proteins that are encoded by the SLC2 genes and are members of the major facilitator superfamily (MFS) (see Table 1) (reviewed in Augustin, 2010; Joost et al., 2002; Thorens and Mueckler, 2010; Uldry and Thorens, 2004). The 14 human GLUT proteins possess various substrate specificities and are involved in the transport of several hexoses in addition to myo-inositol (Uldry et al., 2001), urate (Bibert et al., 2009; Matsuo et al., 2008; So and Thorens, 2010), glucosamine (Maher and Harrison, 1990), and ascorbate (Lee et al., 2010). All of the members of the GLUT family are facilitative transporters with the exception of HMIT, which is a H+/myo-inositol symporter (Uldry et al., 2001). It is highly likely that the major substrates for several GLUT proteins have not yet been identified.

The 14 GLUT proteins are comprised of ~500 amino acid residues and can be categorized into three classes based on sequence similarity: Class 1 (GLUTs 1–4, 14); Class 2 (GLUTs 5, 7, 9, and 11); and Class 3 (GLUTs 6, 8, 10, 12, and HMIT). All GLUT proteins appear to possess 12 transmembrane segments, a single site of N-linked glycosylation, a relatively large, central, cytoplasmic linker domain, and exhibit topologies with both their N and C termini positioned in the cytoplasm (Mueckler et al., 1985). The Class 1 and 2 GLUT proteins are structurally distinguishable from the Class 3 proteins by virtue of the location of their sites of N-linked glycosylation, which reside in the first exofacial linker domains of the Class 1 and 2 GLUTs and in the fifth exofacial linker domains of the Class 3 proteins.

One or more GLUT proteins are expressed in virtually every cell type of the human body. Eleven of the 14 members of the GLUT family are capable of transporting glucose under experimental conditions, although in several cases the principal physiologic substrates for the proteins have not been definitively identified (Thorens and Mueckler, 2010). The physiological explanation for the redundancy of proteins that transport glucose is most likely the critical nature of this sugar as a circulating fuel in humans and the consequent need for multiple glucose transporters with different kinetic and regulatory properties that are expressed in a cell-type specific fashion.

2. GLUT1

2.1. Transport kinetics

GLUT1, encoded by the *SLC2A1* gene, was one of the first membrane transporters to be purified (Baldwin and Lienhard, 1989; Kasahara and Hinkle, 1977) and cloned (Birnbaum et al., 1986; Mueckler et al., 1985) and is likely one of the most extensively studied of all membrane transport systems. The kinetics of glucose transport via GLUT1 have been explored since radioisotopic substrates became readily available in the early 1950s (reviewed in Carruthers et al., 2009; Lowe and Walmsley, 1986). Two prominent characteristics of glucose transport have been observed in human erythrocytes. Firstly, the apparent affinity (the K_m or half-saturation concentration) for transport is, under certain experimental conditions, higher at the outward substrate-binding site than at the cytoplasmic binding site, and secondly, transport occurs at a faster rate when substrate is present on the trans side of the membrane (the side of the membrane to which transport is being measured) as compared to zero trans conditions where substrate is present only in the aqueous compartment from which transport is being measured. The latter phenomenon is called trans or exchange acceleration and suggests that a conformational change involving the unloaded transporter is rate limiting for net transport to occur. Many investigators believe that most of the available kinetic and biophysical data are consistent with an alternating conformation mechanism for glucose transport whereby mutually exclusive substrate binding sites are sequentially exposed to either the exoplasm or the cytoplasm (Gorga and Lienhard, 1981; Lowe and Walmsley, 1989; Wheeler and Whelan, 1988) (see Fig. 1). However, the kinetics of glucose transport as measured in the erythrocyte are complex and some experimental observations are not consistent with a simple asymmetric carrier type model (Cloherty et al., 1996). This has led to the proposal of alternative mechanisms, including fixed-site models in which multiple binding sites are simultaneously accessible from both sides of the membrane (Carruthers et al., 2009). It has been argued that asymmetric transporter distribution under equilibrium conditions with the standard carrier model violates energy conservation laws (Naftalin, 2008).

However, abandonment of the carrier model for glucose transport is premature, in large part because of experimental difficulties associated with accurately measuring the kinetics of transport in erythrocytes. Questions concerning the validity of the alternately conformation model are based almost entirely on steady-state kinetic experiments. Glucose transporters are present at a very high concentration in the erythrocyte membrane (up to 10% of total integral membrane protein) (Gorga and Lienhard, 1982), and thus the rate of transport is extremely high. True initial rates of transport are at best difficult to measure using traditional methods, and the vast bulk of experimental findings that appear to contradict the alternating conformation