University of Massachusetts Medical School

GRADUATE SCHOOL OF BIOMEDICAL SCIENCES

BIOCHEMISTRY AND MOLECULAR PHARMACOLOGY

Ph.D. THESIS DEFENSE

KENNETH LLOYD

MENTOR: Anthony Carruthers, PhD
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LRB 816

"Understanding Human Erythrocyte Glucose Transporter (GLUT1) Mediated Glucose Transport Phenomena Through Structural Analysis"

GLUT1-mediated, facilitated sugar transport is proposed to be an example of transport by a carrier that alternately presents exofacial (e2) and endofacial (e1) substrate binding sites. This hypothesis is incompatible with observations of co-existent exo- and endofacial ligand binding sites, transport allostery, and e1 ligand (e.g. cytochalasin B) induced GLUT1 sugar occlusion. The fixed-site carrier model proposes co-existent, interacting e2 and e1 ligand binding sites but involves sugar translocation by geminate exchange through internal cavities. Demonstrations of membrane-resident dimeric and tetrameric GLUT1 and of e2, e1 and occluded GLUT conformations in GLUT crystals of monodisperse, detergent-solubilized proteins suggest a third model. Here, GLUT1 is an alternating access carrier but the transporter complex is a dimer of GLUT1 dimers, in which subunit interactions produce two e2 and two e1 conformers at any instant. The crystallographic structures in different conformations can be utilized to further understand the transport cycle, ligand binding behavior and complex kinetics observed in GLUT1. Specifically, the GLUT1 crystal structure and homology models based upon related major facilitator superfamily proteins were used in this study, to understand inhibitor binding, ligand binding induced GLUT1 transport allostery and the existence of helix packing/oligomerization motifs and glycine induced flexibility. These studies suggest that GLUT1 functions as an oligomeric allosteric carrier where cis-allostery is an intramolecular behavior and trans-allostery is an intermolecular behavior. Additionally, mutations of a dynamic glycine affect the turnover of the transporter while mutations to helix packing motifs affect affinity.

Mentor(s)

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