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STRUCTURAL STUDIES ON SLC6A15 NEUTRAL AMINO ACID TRANSPORTER

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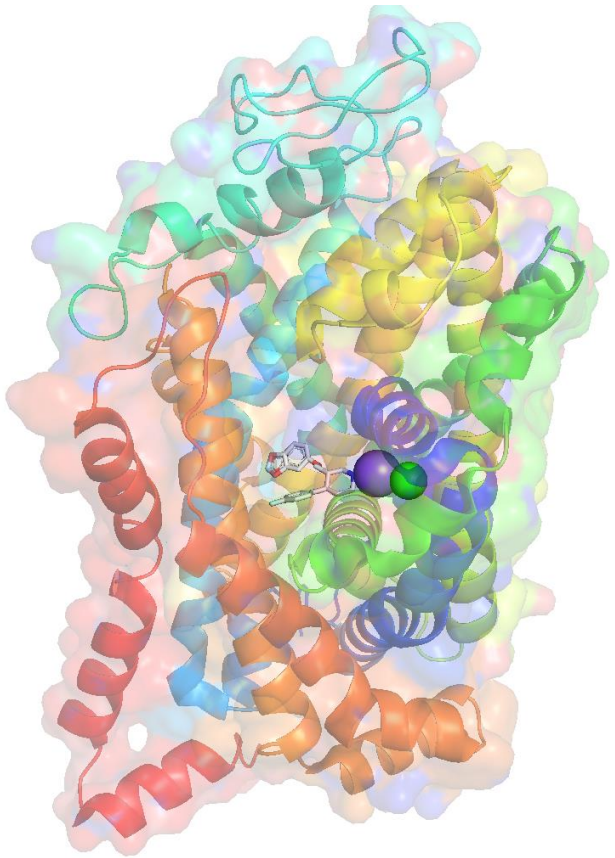
Structural studies on SLC6A15 neutral amino acid transporter



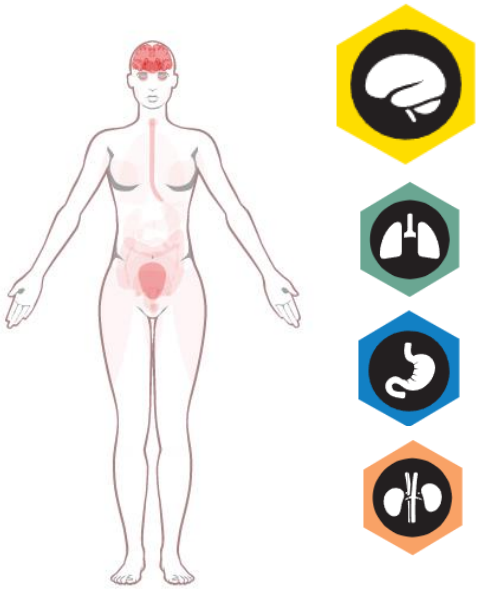
Abstract:
Transporters from the SLC6 family play many important physiological functions. They are responsible for transport of neurotransmitters, osmolytes or energy substrates thus they participate in the nerve signaling and maintaining cellular and organism homeostasis. Depending on the sequence identity SLC6 family is divided into 4 groups: monoamine transporters, GABA transporters, amino acid transporters group I, and transporters for amino acids group II named also orphan transporters (OTs). OTs include 6 proteins, products of genes SLC6A15-SLCA620, whose 3D structures still remain unsolved (with one exception - SLC6A19).Their primary physiological function is supplying cells with nutritional neutral amino acids throughout sodium coupled symport. SLC6A15 (alias B(0)AT2) is mainly expressed in central nervous system. It allows for the transport of proline, branched-chain amino acids or methionine from extracellular compartment to the cell. Studies showed evidence that impaired functioning of SLC6A15 can be associated with major depressive disorder, behavioral changes or obesity. Since significance of SLC6A15 in the course of mentioned illnesses was proved we conducted preliminary *in silico* investigation to construct spatial structure of mentioned transporter using homology modeling. Further, we made an attempt to provide principles of substrate selectivity and functioning of the transporter. Using solved structures of the transporters for serotonin, dopamine, leucine (SERT, DAT, LeuT) and SLC6A19 we generated reliable models of SLC6A15 and performed docking studies. Obtained results showed significant role of hydrophobic pocket and non-helical fragments of TM6 and TM1 for binding of substrates.

Keywords: SLC6; Amino acid transporters group II, SLC6A15, molecular modeling, homology models

SLC6A15 (B(0)AT1) FUNCTIONS

Introduction

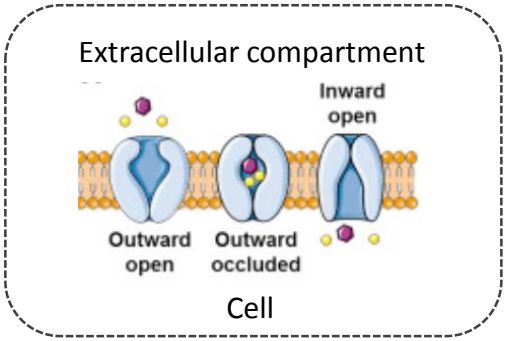
SLC6A15 OCCURENCE



Brain:

- Cortex
- Cerebellum
- Brain stem

https://www.proteinatlas.org/ENSG00000072041-SLC6A15/tissue



Transport of amino acids:

- Proline
- Valine
- Leucine
- Isoleucine
- Methionine

Role in patogenesis:

- Depresive disorders
- Mood changes

10.1016/j.bpj.2015.02.010

SCL6A15 STRUCTURE

SLC6A15

- 3D structure remains unknown
- Shares 50% amino acid sequence identity with SLC6A19 (B(0)AT1) and 40% with SLC6A3 (Dopamine transporter (DAT))
- SLC6A15 is built of 730 amino acids
- Contains highly conserved regions with other SLC6 members, responsible for transport mechanism

Aim of study

- Construction of reliable 3D structural models of **SCL6A15**
- Indication of the principles of substrate selectivity and functioning of the transporter

Methods: generating models

Experimentally solved 3D Structures of known SCL6A15 homologues as templates for homology modelling

RCSB PDB PROTEIN DATA BANK

Serotonin transporter

Leucine transporter

Dopamine transportes

SLC6A19

Selection of templates & sequences alignment (target-template)

SWISS-MODEL
HOMOLOGY MODELLING OF PROTEIN STRUCTURES AND COMPLEXES

Modeller

Homology modelling

Generation of set of models

SLC6A15 models

Evaluation of models (mathematical assesment & visual inspection)

Chosen SLC6A15 models

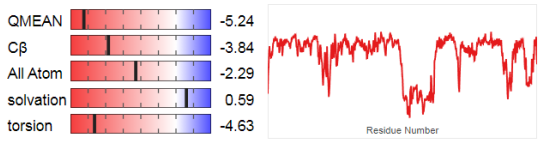
Results and discussion: obtained models

3D models of SCL6A15:

- SCL6A15 shares well preserved transmembrane domains with the SCL6 family: TM1, TM3, TM6, TM8, T10
- Significant elongation of extracellular loop EL4 hinder modeling of SCL6A15 – EL4 requires to be refined
- Key residues responsible for transport mechanism and substrate interaction are well conserved what allows for reliable representation of ligand interactions with SCL6A15

Assessment of model built on SLC6A3 dopamine transporter (4xp1.A)

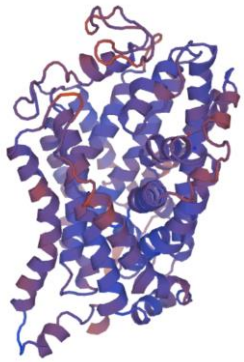
Model #14	File	Built with	Oligo-State	Ligands	GMQE	QMEAN
	PDB	ProMod3 3.2.0	monomer	None	0.52	-5.24

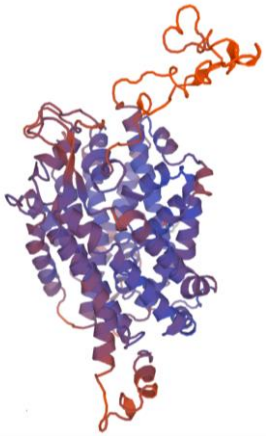


Template	Seq Identity	Oligo-state	QSQE	Found by	Method	Resolution	Seq Similarity	Range	Coverage	Description
4xp4.1.A	40.26	monomer	0.00	HHblits	X-ray	2.80Å	0.41	59 - 668	0.72	Dopamine transporter

Template 4xp1.A

SCL6A15



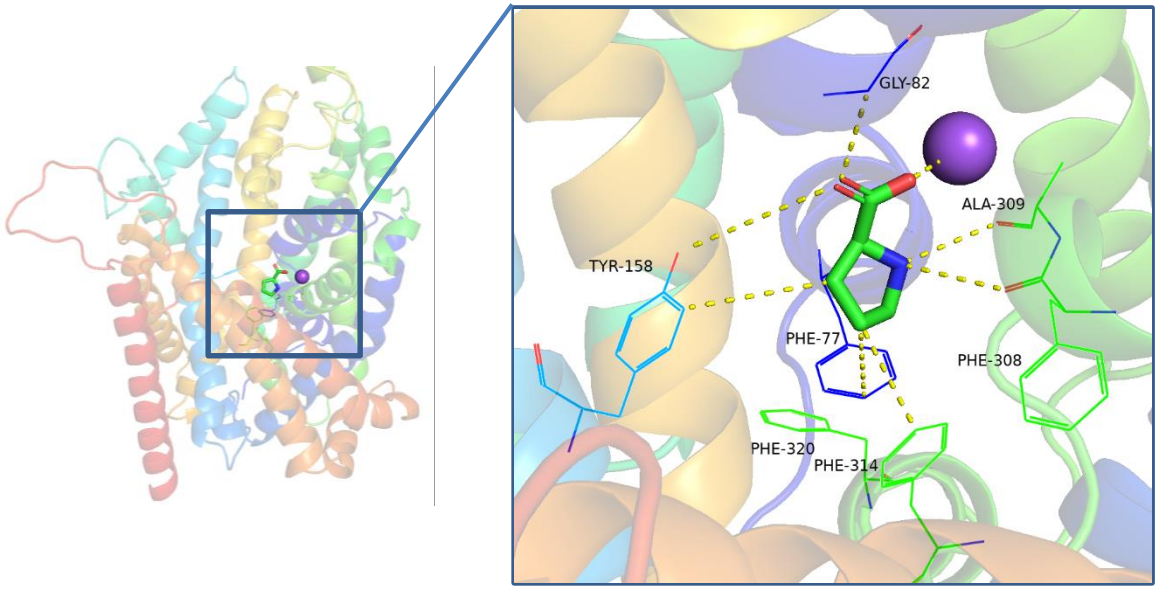


Results and discussion: docking of amino acids

Chosen SLC6A15 models → Docking of amino acids (SCHRÖDINGER.) → Evaluation of Bidning modes

Results of molecular docking of substrates to the SLC6A15 models

Docking of proline to the model built on leucine transporter template:



Docking of amino acids:

- Preffered amino acids with **hydrophobic side chains**

Proline binding mode:

- Optimal geometry of aliphatic ring of substrate allows for interactions with hydrophobic subpocket what explain its selectivity

Conclusions

- Well conserved transmembrane domains and substrate binding sites allow for obtaining reliable models of **SCL6A15**
- Our results are contribution into better understanding of molecular functioning of **SCL6** family members
- Obtained models can be useful tool for discover novel inhibitors of **SCL6A15**