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Review

Solute carriers as drug targets: Current use, clinical trials and prospective ☆

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Transporters in health and disease (SLC series)

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ABSTRACT

Solute carriers (SLCs) comprise a large family of membrane transporters responsible for the transmembrane transport of a wide variety of substrates such as inorganic ions, amino acids, neurotransmitters and sugars. Despite being the largest family of membrane transport proteins, SLCs have been relatively under-utilized as therapeutic drug targets by approved drugs. In this paper, we aim to catalogue therapeutic SLCs utilized by approved drugs or currently in clinical trials. By mining information on clinical trials from the Centerwatch.com "drugs in clinical trials database" we were able to identify potentially novel SLC drug targets currently under development. We also searched the literature for SLCs that have been discussed as future therapeutic drug targets. We find SLCs to be utilized as therapeutic targets in treatment of a wide variety of diseases and disorders, such as major depression, ADHD, osteoporosis and hypertension. Drugs targeting SLCs for treatment of diabetes, constipation and hypercholesterolaemia are currently in clinical trials. SLC drug targets have also been explored in clinical trials for cardioprotection after an ischemic event. SLCs are of particular interest as targets in antineoplastic treatment and for the targeted transport of cytotoxic drugs into tumors, e.g. via the glucose transporters GLUT1-5 and SGLT1-3.

Contents

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1. Introduction

Solute carriers (SLCs) comprise the largest family of membrane transport proteins in the human organism. Phylogenetic studies have identified at least 384 unique protein sequences forming 52 distinct SLC families (Fredriksson et al., 2008; Hoglund et al., 2011). SLCs regulate the transport of several substrates such as inorganic ions, nucleotides, amino acids, neurotransmitters, sugars, purines, fatty acids and drug molecules across biological membranes (Hediger et al., 2004). Despite the large number of genes encoding solute carriers, and their important range of functions, only 12 unique SLCs were found to currently be utilized as therapeutic drug targets in a recent estimate of the number of molecular drug targets encoded by the human genome (Rask-Andersen et al., 2011). These targets are heavily exploited as 63 FDA approved agents have been reported to mediate their therapeutic action via these SLCs, most commonly in treatment of hypertension. This can be compared to G protein-coupled receptors (GPCRs), a gene family of roughly the same size, when discounting olfactory GPCRs. In total 82 GPCRs were identified as therapeutic targets for 357 unique drugs (Rask-Andersen et al., 2011). SLCs constitute important pathways for drug absorption from the intestinal lumen and transport across cell membranes. Designing drugs to utilize these transporters is a possible venue for improving bioavailability. The rational design of drugs targeting specific SLCs for transport, also enables cell type-specific drug delivery, e.g. in delivery of antineoplastic agents into tumor cells (Nakanishi and Tamai, 2011). SLCs are also utilized as drug targets in themselves, e.g. the inhibition of SLC12 family ion transporters which are targeted by diuretics, or the specific inhibition of SLC6 family monoamine transporters by SSRIs and SNRIs which has greatly improved the treatment of a broad range of psychiatric disorders enabling the move from less selective, and side effect-prone, tricyclic compounds. The abnormal function of SLCs, due to mutations or genetic variants, has also been implicated as underlying factors in a large number of human diseases. As an example, querying the OMIM database (online Mendelian inheritance in man) for "solute carriers" returns allelic variants in 82 genes linked to a wide variety of disease phenotypes such as autism, diabetes, cancer, psychiatric disorders and neurodevelopmental disorders (http://www.ncbi.nlm.nih.gov/omim).

Here we aim to review solute carriers as drug targets with a focus on presenting previously unexploited SLCs currently being discussed and explored in clinical trials. Data on clinical trials was retrieved from the "drugs in clinical trials database" at Centerwatch.com, a privately funded database focusing on clinical trials involving pharmacological intervention. Information on clinical trials is publically available through clinicaltrials.gov, a public database cataloguing clinical trials currently in progress. This database was developed by the national institute of health (NIH), the National Library of Medicine (NLM) and the food and drug administration (FDA). At present (October 2011), it contains information on more than 100,000 clinical trials being conducted all over the world. This information has been parsed by Centerwatch.com to produce the "drugs in clinical trials"-database (DCTdb). DCTdb contains information on about 4000 clinical trials utilizing a pharmaceutical intervention. This information was kindly provided to us by Centerwatch.com. Each entry was analyzed manually to identify the molecular target of each agent. Through this process we were able to identify trials involving drugs mediating their therapeutic effect specifically via SLCs. Out of about 3797 compounds currently in clinical trials, 74 agents were identified to target 12 different SLCs for their therapeutic effect. Out of these, 11 compounds were identified as targeting and mediating their therapeutic effect via two novel SLC-targets (Table 1), i.e. targets not previously exploited by approved drugs (Table 1) (Fig. 1). We also conducted literature searches to identify prospective SLCs being discussed as potential drug targets as well as to identify potential new indications for SLCs already utilized.

2. SLC drug targets in treatment of CNS-disorders

2.1. SLC6 monoamine transporters

SLC6 is the most exploited family among solute carriers with about 42 drugs currently approved by the FDA (Rask-Andersen et al., 2011). All but one of these drugs target the monoamine transporters SLC6A2, SLC6A3 and SLC6A4. Tiagabine, an anticonvulsant, targets the sodium- and chloride dependent GABA transporter 1 (GAT1, SLC6A1). About 60 clinical trials are also currently in progress for drugs specifically targeting SLC6 family members, most commonly for analgesia, psychiatric disorders and ADHD. SLC6 interacting drugs with new indications are also being developed e.g. for migraine and cluster headaches, as well as cognitive dysfunction in multiple sclerosis patients. Infusion of metamphetamine, which interacts with