



Recent developments in ligands and chemical probes targeting solute carrier transporters

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Abstract

Solute carrier (SLC) membrane transporters remain a largely unexploited target class, despite their central roles in cell identity and metabolism. This gap is reflected in the lack of high-quality chemical ligands or probes and in the small number of compounds that have progressed toward clinical development. In this review, we discuss recent advancements in SLC ligand discovery as well as new candidates that have been added to the investigational toolkit, with a particular focus on first-in-class ligands and the cognate discovery strategies. The availability of new probes expands the opportunity to elucidate the functions of SLCs and their relevance in physiology and explores any future potential of SLC druggability.

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Ligand discovery, Solute carrier (SLC) transporters, Small-molecule probes, First-in-class ligands, Drug discovery, PET tracers, Cancer, Modulators of neurotransmission.

Introduction

With more than 440 classified members organized in 65 families, solute carrier (SLC) proteins are the largest

group of transmembrane transporters and the second largest group of membrane proteins [1]. They regulate the translocation of diverse chemical matter across cellular membranes and play an essential role in cell metabolism and cellular identity [2]. Furthermore, some SLCs are involved in the translocation of small-molecule drugs and can influence their pharmacodynamics and pharmacokinetics [3]. Given the key roles of SLCs in the chemical homeostasis of cells, alterations in their expression, localization, or function are linked to a variety of diseases, including rare genetic diseases, diabetes, and cancer [4,5].

Our understanding of SLCs is highly skewed toward a limited number of established subfamilies, whereas the rest remain less intensively studied [6]. Historically, the drug development efforts for SLC-targeting small molecules have been limited compared with other target classes of similar relevance [6–8]. Nevertheless, a growing interest in the pharmacological potential of SLCs led to the approval of 10 drugs targeting SLCs in the last decade, with SLC5 glucose transporters receiving particular attention [9].

It has been previously hypothesized that the availability of tools, especially chemical probes, is key to enhance research efforts into specific target classes [10–12]. In our opinion, the development of small molecules targeting SLCs can create interesting opportunities to both move SLC targets toward the clinic and provide important conduit tools to characterize SLC function. To better understand developments in this target class, we summarize in this review the recent literature reporting new compounds targeting SLCs. We focused on articles published in the last 2 years featuring two categories of compounds: (1) modulators of SLCs: new molecules that directly influence SLC function; and (2) tracers, probes, and modified compounds: compounds exploiting the SLC transport mechanism to achieve specific physiological effects. Importantly, the pharmacology of SLCs and their relevance as drug targets have been reviewed recently in studies by Wang et al., Zhang et al., and Schumann et al. [4,5,13] and will not be detailed in this review.

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