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SLC1 family of amino acid transporters in GtoPdb v.2025.3

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Abstract

The SLC1 family of sodium dependent transporters includes the plasma membrane located glutamate transporters and the neutral amino acid transporters ASCT1 and ASCT2 [3, 54, 40, 41, 9].

Contents

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Database links

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References

1. Abram M, Jakubiec M, Reeb K, Cheng MH, Gedschold R, Rapacz A, Mogilski S, Socała K, Nieoczym D and Szafarz M *et al.*. (2022) Discovery of (*R*)-*N*-Benzyl-2-(2,5-dioxopyrrolidin-1-yl)propanamide [**(*R*)-AS-1**], a Novel Orally Bioavailable EAAT2 Modulator with Drug-like Properties and Potent Antiseizure Activity *In Vivo*. *J Med Chem* **65**: 11703-11725 [PMID:35984707]
2. Alexander SPH, Kelly E, Mathie A, Peters JA, Veale EL, Armstrong JF, Faccenda E, Harding SD, Pawson AJ and Sharman JL *et al.*. (2019) THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: Transporters. *Br J Pharmacol* **176 Suppl 1**: S397-S493 [PMID:31710713]
3. Amara SG and Arriza JL. (1993) Neurotransmitter transporters: three distinct gene families. *Curr Opin Neurobiol* **3**: 337-44 [PMID:8103691]
4. Apricò K, Beart PM, Crawford D and O'Shea RD. (2004) Binding and transport of [3H](2S,4R)- 4-methylglutamate, a new ligand for glutamate transporters, demonstrate labeling of EAAT1 in cultured murine astrocytes. *J Neurosci Res* **75**: 751-9 [PMID:14994336]
5. Apricò K, Beart PM, Crawford D and O'shea RD. (2007) Comparison of [(3)H]-(2S,4R)-4-methylglutamate and [(3)H]D-aspartate as ligands for binding and autoradiographic analyses of glutamate transporters. *Neurochem Int* **51**: 507-16 [PMID:17590480]
6. Apricó K, Beart PM, Lawrence AJ, Crawford D and O'Shea RD. (2001) [(3)H](2S,4R)-4-Methylglutamate: a novel ligand for the characterization of glutamate transporters. *J Neurochem* **77**: 1218-25 [PMID:11389172]
7. Arriza JL, Kavanaugh MP, Fairman WA, Wu YN, Murdoch GH, North RA and Amara SG. (1993) Cloning and expression of a human neutral amino acid transporter with structural similarity to the glutamate transporter gene family. *J Biol Chem* **268**: 15329-32 [PMID:8101838]
8. Bailey CG, Ryan RM, Thoeng AD, Ng C, King K, Vanslambrouck JM, Auray-Blais C, Vandenberg RJ, Bröer S and Rasko JE. (2011) Loss-of-function mutations in the glutamate transporter SLC1A1 cause human dicarboxylic aminoaciduria. *J Clin Invest* **121**: 446-53 [PMID:21123949]
9. Beart PM and O'Shea RD. (2007) Transporters for L-glutamate: an update on their molecular pharmacology and pathological involvement. *Br J Pharmacol* **150**: 5-17 [PMID:17088867]
10. Boudker O, Ryan RM, Yernool D, Shimamoto K and Gouaux E. (2007) Coupling substrate and ion binding to extracellular gate of a sodium-dependent aspartate transporter. *Nature* **445**: 387-93 [PMID:17230192]
11. Bröer A, Brookes N, Ganapathy V, Dimmer KS, Wagner CA, Lang F and Bröer S. (1999) The astroglial ASCT2 amino acid transporter as a mediator of glutamine efflux. *J Neurochem* **73**: 2184-94 [PMID:10537079]
12. Bröer A, Wagner C, Lang F and Bröer S. (2000) Neutral amino acid transporter ASCT2 displays substrate-induced Na+ exchange and a substrate-gated anion conductance. *Biochem J* **346 Pt 3**: 705-10 [PMID:10698697]
13. Buneman P, Christie G, Davies JA, Dimitrellou R, Harding SD, Pawson AJ, Sharman JL and Wu Y. (2020) Why data citation isn't working, and what to do about it *Database* **2020** [PMID:32367113]
14. Colleoni S, Jensen AA, Landucci E, Fumagalli E, Conti P, Pinto A, De Amici M, Pellegrini-Giampietro DE, De Micheli C and Mennini T *et al.*. (2008) Neuroprotective effects of the novel glutamate transporter inhibitor (-)-3-hydroxy-4,5,6,6a-tetrahydro-3aH-pyrrolo[3,4-d]-isoxazole-4-carboxylic acid, which preferentially inhibits reverse transport (glutamate release) compared with glutamate reuptake. *J Pharmacol Exp Ther* **326**: 646-56 [PMID:18451317]
15. Colton CK, Kong Q, Lai L, Zhu MX, Seyb KI, Cuny GD, Xian J, Glicksman MA and Lin CL. (2010) Identification of translational activators of glial glutamate transporter EAAT2 through cell-based high-throughput screening: an approach to prevent excitotoxicity. *J Biomol Screen* **15**: 653-62 [PMID:20508255]
16. Coon and TR *et al.*. (2004) Abstract Viewer/Itinerary Planner, Program No. 168.10. Society for Neuroscience:
17. Dunlop J. (2006) Glutamate-based therapeutic approaches: targeting the glutamate transport system. *Curr Opin Pharmacol* **6**: 103-7 [PMID:16368269]
18. Dunlop J and Butera JA. (2006) Ligands targeting the excitatory amino acid transporters (EAATs). *Curr Top Med Chem* **6**: 1897-906 [PMID:17017964]
19. Dunlop J, Eliasof S, Stack G, McIlvain HB, Greenfield A, Kowal D, Petroski R and Carrick T. (2003) WAY-855 (3-amino-tricyclo[2.2.1.02.6]heptane-1,3-dicarboxylic acid): a novel, EAAT2-preferring, nonsubstrate inhibitor of high-affinity glutamate uptake. *Br J Pharmacol* **140**: 839-46 [PMID:14517179]
20. Dunlop J, McIlvain HB, Carrick TA, Jow B, Lu Q, Kowal D, Lin S, Greenfield A, Grosanu C and Fan K *et al.*. (2005) Characterization of novel aryl-ether, biaryl, and fluorene aspartic acid and diaminopropionic acid analogs as potent inhibitors of the high-affinity glutamate transporter EAAT2. *Mol Pharmacol* **68**: 974-82 [PMID:16014807]
21. Eliasof S, McIlvain HB, Petroski RE, Foster AC and Dunlop J. (2001) Pharmacological characterization of threo-3-methylglutamic acid with excitatory amino acid transporters in native and recombinant systems. *J Neurochem* **77**: 550-7 [PMID:11299317]

22. Esslinger CS, Agarwal S, Gerdes J, Wilson PA, Davis ES, Awes AN, O'Brien E, Mavencamp T, Koch HP and Poulsen DJ *et al*.. (2005) The substituted aspartate analogue L-beta-threo-benzyl-aspartate preferentially inhibits the neuronal excitatory amino acid transporter EAAT3. *Neuropharmacology* **49**: 850-61 [PMID:16183084]
23. Esslinger CS, Cybulski KA and Rhoderick JF. (2005) Ngamma-aryl glutamine analogues as probes of the ASCT2 neutral amino acid transporter binding site. *Bioorg Med Chem* **13**: 1111-8 [PMID:15670919]
24. Fontana AC, de Oliveira Beleboni R, Wojewodzic MW, Ferreira Dos Santos W, Coutinho-Netto J, Grutle NJ, Watts SD, Danbolt NC and Amara SG. (2007) Enhancing glutamate transport: mechanism of action of Parawixin1, a neuroprotective compound from Parawixia bistriata spider venom. *Mol Pharmacol* **72**: 1228-37 [PMID:17646426]
25. Fontana AC, Guizzo R, de Oliveira Beleboni R, Meirelles E Silva AR, Coimbra NC, Amara SG, dos Santos WF and Coutinho-Netto J. (2003) Purification of a neuroprotective component of Parawixia bistriata spider venom that enhances glutamate uptake. *Br J Pharmacol* **139**: 1297-309 [PMID:12890709]
26. Gameiro A, Braams S, Rauen T and Grewer C. (2011) The discovery of slowness: low-capacity transport and slow anion channel gating by the glutamate transporter EAAT5. *Biophys J* **100**: 2623-32 [PMID:21641307]
27. Ganel R, Ho T, Maragakis NJ, Jackson M, Steiner JP and Rothstein JD. (2006) Selective up-regulation of the glial Na+-dependent glutamate transporter GLT1 by a neuroimmunophilin ligand results in neuroprotection. *Neurobiol Dis* **21**: 556-67 [PMID:16274998]
28. Garaeva AA, Oostergetel GT, Gati C, Guskov A, Paulino C and Slotboom DJ. (2018) Cryo-EM structure of the human neutral amino acid transporter ASCT2. *Nat Struct Mol Biol* **25**: 515-521 [PMID:29872227]
29. Gebhardt FM, Mitrovic AD, Gilbert DF, Vandenberg RJ, Lynch JW and Dodd PR. (2010) Exon-skipping splice variants of excitatory amino acid transporter-2 (EAAT2) form heteromeric complexes with full-length EAAT2. *J Biol Chem* **285**: 31313-24 [PMID:20688910]
30. Gendreau S, Voswinkel S, Torres-Salazar D, Lang N, Heidtmann H, Detro-Dassen S, Schmalzing G, Hidalgo P and Fahlke C. (2004) A trimeric quaternary structure is conserved in bacterial and human glutamate transporters. *J Biol Chem* **279**: 39505-12 [PMID:15265858]
31. Goursaud S, Focant MC, Berger JV, Nizet Y, Maloteaux JM and Hermans E. (2011) The VPAC2 agonist peptide histidine isoleucine (PHI) up-regulates glutamate transport in the corpus callosum of a rat model of amyotrophic lateral sclerosis (hSOD1G93A) by inhibiting caspase-3 mediated inactivation of GLT-1a. *FASEB J* **25**: 3674-86 [PMID:21730107]
32. Grewer C, Balani P, Weidenfeller C, Bartusel T, Tao Z and Rauen T. (2005) Individual subunits of the glutamate transporter EAAC1 homotrimer function independently of each other. *Biochemistry* **44**: 11913-23 [PMID:16128593]
33. Grewer C and Grabsch E. (2004) New inhibitors for the neutral amino acid transporter ASCT2 reveal its Na+-dependent anion leak. *J Physiol (Lond.)* **557**: 747-59 [PMID:15107471]
34. Grewer C and Rauen T. (2005) Electrogenic glutamate transporters in the CNS: molecular mechanism, pre-steady-state kinetics, and their impact on synaptic signaling. *J Membr Biol* **203**: 1-20 [PMID:15834685]
35. Grunewald M and Kanner BI. (2000) The accessibility of a novel reentrant loop of the glutamate transporter GLT-1 is restricted by its substrate. *J Biol Chem* **275**: 9684-9 [PMID:10734120]
36. Hassanein M, Qian J, Hoeksema MD, Wang J, Jacobovitz M, Ji X, Harris FT, Harris BK, Boyd KL and Chen H *et al*.. (2015) Targeting SLC1a5-mediated glutamine dependence in non-small cell lung cancer. *Int J Cancer* **137**: 1587-97 [PMID:25821004]
37. Huang S, Ryan RM and Vandenberg RJ. (2009) The role of cation binding in determining substrate selectivity of glutamate transporters. *J Biol Chem* **284**: 4510-5 [PMID:19074430]
38. Jensen AA, Erichsen MN, Nielsen CW, Stensbøl TB, Kehler J and Bunch L. (2009) Discovery of the first selective inhibitor of excitatory amino acid transporter subtype 1. *J Med Chem* **52**: 912-5 [PMID:19161278]
39. Jiang J and Amara SG. (2011) New views of glutamate transporter structure and function: advances and challenges. *Neuropharmacology* **60**: 172-81 [PMID:20708631]
40. Kanai Y and Hediger MA. (2003) The glutamate and neutral amino acid transporter family: physiological and pharmacological implications. *Eur J Pharmacol* **479**: 237-47 [PMID:14612154]
41. Kanai Y and Hediger MA. (2004) The glutamate/neutral amino acid transporter family SLC1: molecular, physiological and pharmacological aspects. *Pflugers Arch* **447**: 469-79 [PMID:14530974]
42. Kim K, Lee SG, Kegelman TP, Su ZZ, Das SK, Dash R, Dasgupta S, Barral PM, Hedvat M and Diaz P *et al*.. (2011) Role of excitatory amino acid transporter-2 (EAAT2) and glutamate in neurodegeneration: opportunities for developing novel therapeutics. *J Cell Physiol* **226**: 2484-93 [PMID:21792905]
43. Koch HP, Brown RL and Larsson HP. (2007) The glutamate-activated anion conductance in excitatory amino acid transporters is gated independently by the individual subunits. *J Neurosci*

27: 2943-7 [PMID:17360917]
44. Koch HP, Kavanaugh MP, Esslinger CS, Zerangue N, Humphrey JM, Amara SG, Chamberlin AR and Bridges RJ. (1999) Differentiation of substrate and nonsubstrate inhibitors of the high-affinity, sodium-dependent glutamate transporters. *Mol Pharmacol* **56**: 1095-104 [PMID:10570036]
45. Lau CL, O'Shea RD, Broberg BV, Bischof L and Beart PM. (2011) The Rho kinase inhibitor Fasudil up-regulates astrocytic glutamate transport subsequent to actin remodelling in murine cultured astrocytes. *Br J Pharmacol* **163**: 533-45 [PMID:21309758]
46. Leary GP, Stone EF, Holley DC and Kavanaugh MP. (2007) The glutamate and chloride permeation pathways are colocalized in individual neuronal glutamate transporter subunits. *J Neurosci* **27**: 2938-42 [PMID:17360916]
47. Lee A and Pow DV. (2010) Astrocytes: Glutamate transport and alternate splicing of transporters. *Int J Biochem Cell Biol* **42**: 1901-6 [PMID:20883814]
48. Lee SG, Su ZZ, Emdad L, Gupta P, Sarkar D, Borjabad A, Volsky DJ and Fisher PB. (2008) Mechanism of ceftriaxone induction of excitatory amino acid transporter-2 expression and glutamate uptake in primary human astrocytes. *J Biol Chem* **283**: 13116-23 [PMID:18326497]
49. Levy LM, Warr O and Attwell D. (1998) Stoichiometry of the glial glutamate transporter GLT-1 expressed inducibly in a Chinese hamster ovary cell line selected for low endogenous Na+-dependent glutamate uptake. *J Neurosci* **18**: 9620-8 [PMID:9822723]
50. Lopes C, Pereira C and Medeiros R. (2021) ASCT2 and LAT1 Contribution to the Hallmarks of Cancer: From a Molecular Perspective to Clinical Translation. *Cancers (Basel)* **13** [PMID:33429909]
51. Machtens JP, Kovermann P and Fahlke C. (2011) Substrate-dependent gating of anion channels associated with excitatory amino acid transporter 4. *J Biol Chem* **286**: 23780-8 [PMID:21572047]
52. Nothmann D, Leinenweber A, Torres-Salazar D, Kovermann P, Hotzy J, Gameiro A, Grewer C and Fahlke C. (2011) Hetero-oligomerization of neuronal glutamate transporters. *J Biol Chem* **286**: 3935-43 [PMID:21127051]
53. Oppedisano F, Galluccio M and Indiveri C. (2010) Inactivation by Hg2+ and methylmercury of the glutamine/amino acid transporter (ASCT2) reconstituted in liposomes: Prediction of the involvement of a CXXC motif by homology modelling. *Biochem Pharmacol* **80**: 1266-73 [PMID:20599776]
54. Palacín M, Estévez R, Bertran J and Zorzano A. (1998) Molecular biology of mammalian plasma membrane amino acid transporters. *Physiol Rev* **78**: 969-1054 [PMID:9790568]
55. Pinilla-Tenas J, Barber A and Lostao MP. (2003) Transport of proline and hydroxyproline by the neutral amino-acid exchanger ASCT1. *J Membr Biol* **195**: 27-32 [PMID:14502423]
56. Qin L, Cheng X, Wang S, Gong G, Su H, Huang H, Chen T, Damdinjav D, Dorjsuren B and Li Z *et al.*. (2024) Discovery of Novel Aminobutanoic Acid-Based ASCT2 Inhibitors for the Treatment of Non-Small-Cell Lung Cancer. *J Med Chem* **67**: 988-1007 [PMID:38217503]
57. Reyes N, Ginter C and Boudker O. (2009) Transport mechanism of a bacterial homologue of glutamate transporters. *Nature* **462**: 880-5 [PMID:19924125]
58. Romera C, Hurtado O, Mallolas J, Pereira MP, Morales JR, Romera A, Serena J, Vivancos J, Nombela F and Lorenzo P *et al.*. (2007) Ischemic preconditioning reveals that GLT1/EAAT2 glutamate transporter is a novel PPARgamma target gene involved in neuroprotection. *J Cereb Blood Flow Metab* **27**: 1327-38 [PMID:17213861]
59. Rose EM, Koo JC, Antflick JE, Ahmed SM, Angers S and Hampson DR. (2009) Glutamate transporter coupling to Na,K-ATPase. *J Neurosci* **29**: 8143-55 [PMID:19553454]
60. Rothstein JD, Patel S, Regan MR, Haenggeli C, Huang YH, Bergles DE, Jin L, Dykes Hoberg M, Vidensky S and Chung DS *et al.*. (2005) Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. *Nature* **433**: 73-7 [PMID:15635412]
61. Ryan RM and Mindell JA. (2007) The uncoupled chloride conductance of a bacterial glutamate transporter homolog. *Nat Struct Mol Biol* **14**: 365-71 [PMID:17435767]
62. Ryan RM, Mitrovic AD and Vandenberg RJ. (2004) The chloride permeation pathway of a glutamate transporter and its proximity to the glutamate translocation pathway. *J Biol Chem* **279**: 20742-51 [PMID:14982939]
63. Shigeri Y, Shimamoto K, Yasuda-Kamatani Y, Seal RP, Yumoto N, Nakajima T and Amara SG. (2001) Effects of threo-beta-hydroxyaspartate derivatives on excitatory amino acid transporters (EAAT4 and EAAT5). *J Neurochem* **79**: 297-302 [PMID:11677257]
64. Shimamoto K, Lebrun B, Yasuda-Kamatani Y, Sakaitani M, Shigeri Y, Yumoto N and Nakajima T. (1998) DL-threo-beta-benzyloxyaspartate, a potent blocker of excitatory amino acid transporters. *Mol Pharmacol* **53**: 195-201 [PMID:9463476]
65. Shimamoto K, Otsubo Y, Shigeri Y, Yasuda-Kamatani Y, Satoh M, Kaneko S and Nakagawa T. (2007) Characterization of the tritium-labeled analog of L-threo-beta-benzyloxyaspartate binding to glutamate transporters. *Mol Pharmacol* **71**: 294-302 [PMID:17047096]
66. Shimamoto K, Shigeri Y, Yasuda-Kamatani Y, Lebrun B, Yumoto N and Nakajima T. (2000)

Syntheses of optically pure beta-hydroxyaspartate derivatives as glutamate transporter blockers. *Bioorg Med Chem Lett* **10**: 2407-10 [PMID:11078189]
67. Tamarappoo BK, McDonald KK and Kilberg MS. (1996) Expressed human hippocampal ASCT1 amino acid transporter exhibits a pH-dependent change in substrate specificity. *Biochim Biophys Acta* **1279**: 131-6 [PMID:8603078]
68. Torres-Salazar D and Fahlke C. (2007) Neuronal glutamate transporters vary in substrate transport rate but not in unitary anion channel conductance. *J Biol Chem* **282**: 34719-26 [PMID:17908688]
69. Utsunomiya-Tate N, Endou H and Kanai Y. (1996) Cloning and functional characterization of a system ASC-like Na+-dependent neutral amino acid transporter. *J Biol Chem* **271**: 14883-90 [PMID:8662767]
70. Vandenberg RJ, Ju P, Aubrey KR, Ryan RM and Mitrovic AD. (2004) Allosteric modulation of neurotransmitter transporters at excitatory synapses. *Eur J Pharm Sci* **23**: 1-11 [PMID:15324920]
71. Vandenberg RJ, Mitrovic AD, Chebib M, Balcar VJ and Johnston GA. (1997) Contrasting modes of action of methylglutamate derivatives on the excitatory amino acid transporters, EAAT1 and EAAT2. *Mol Pharmacol* **51**: 809-15 [PMID:9145919]
72. Veruki ML, Mørkve SH and Hartveit E. (2006) Activation of a presynaptic glutamate transporter regulates synaptic transmission through electrical signaling. *Nat Neurosci* **9**: 1388-96 [PMID:17041592]
73. Yernool D, Boudker O, Jin Y and Gouaux E. (2004) Structure of a glutamate transporter homologue from Pyrococcus horikoshii. *Nature* **431**: 811-8 [PMID:15483603]
74. Zerangue N and Kavanaugh MP. (1996) Flux coupling in a neuronal glutamate transporter. *Nature* **383**: 634-7 [PMID:8857541]
75. Zerangue N and Kavanaugh MP. (1996) Interaction of L-cysteine with a human excitatory amino acid transporter. *J Physiol (Lond.)* **493 (Pt 2)**: 419-23 [PMID:8782106]
76. Zerangue N and Kavanaugh MP. (1996) ASCT-1 is a neutral amino acid exchanger with chloride channel activity. *J Biol Chem* **271**: 27991-4 [PMID:8910405]
77. Zhou LM, Gu ZQ, Costa AM, Yamada KA, Mansson PE, Giordano T, Skolnick P and Jones KA. (1997) (2S,4R)-4-methylglutamic acid (SYM 2081): a selective, high-affinity ligand for kainate receptors. *J Pharmacol Exp Ther* **280**: 422-7 [PMID:8996224]
78. Zou S, Pita-Almenar JD and Eskin A. (2011) Regulation of glutamate transporter GLT-1 by MAGI-1. *J Neurochem* **117**: 833-40 [PMID:21426345]