

Supporting Information

**Competition Between Li^+ and Na^+ in Sodium Transporters and Receptors: Which Na^+ -
Binding Sites are “Therapeutic” Li^+ Targets?**

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Table S1. PDB entries of the transporter and receptor structures with Na⁺.^a

PDB ID	Protein	Resolution (Å)	CATH code	Other PDB structures with sodium
2A65	Leucine transporter LeuT	1.65	N/A	2Q6H, 2Q72, 2QB4, 2QEI, 3F3A, 3F3C, 3F3D, 3F3E, 3F48, 3F4I, 3F4J, 3GJC, 3GJD, 3GWU, 3GWV, 3GWW, 3MPN, 3MPQ, 3QS4, 3QS5, 3QS6, 3TT1, 3TT3, 3TU0, 3USG, 3USI, 3USJ, 3USK, 3USL, 3USM, 3USO, 3USP, 4FXZ, 4FY0, 4HMK, 4HOD, 4MM4, 5JAE, 5JAF, 5JAG
3KBC	Aspartate transporter GltPh	3.51	1.10.38 60.10	2NWX, 3KBC, 3V8F, 3V8G, 4IZM, 4OYF, 4X2S, 5CFY
4XP1	Dopamine transporter DAT	2.89	N/A	4M48, 4XNX, 4XP1, 4XP4, 4XP5, 4XP6, 4XP9, 4XPA, 4XPB, 4XPF, 4XPG, 4XPH, 4XPT
5E9S	Glutamate transporter GltTk	2.80	N/A	N/A
5I71	Serotonin transporter SERT	3.15	N/A	5I6X, 5I71, 5I73, 5I75, 6AWN, 6AWO, 6AWP, 6AWQ
5LM4	Glutamate transporter GLAST1/EAAT	3.10	N/A	5LLM, 5LLU, 5LM4
3C32	Glutamate receptor kainate GluK1 (GluR5)	1.72	3.40.19 0.10	N/A
3G3F	Glutamate receptor kainate GluK2 (GluR6)	1.38	3.40.19 0.10	2XXR, 2XXT, 2XXU, 3G3F, 3G3G, 3G3H, 3G3I, 3G3J, 3G3K, 3OM1, 4BDL, 4BDN, 4BDO, 4BDQ, 4BDR
3S9E	Glutamate receptor kainate GluK3 (GluR7)	1.60	3.40.19 0.10	N/A
3OM1	Glutamate receptor kainate GluK5 (KA2)	1.68	3.40.50 .2300	N/A
3VW7	GPCR receptor Protease-activated PAR1	2.20	1.20.10 70.10 1.10.53 0.40	N/A

4BVN	GPCR receptor Adrenergic b1AR	2.10	1.20.10 70.10	2VT4, 2Y00, 2Y02, 2Y03, 2Y04, 2YCW, 2YCY, 3ZPQ, 3ZPR, 4AMJ, 4BVN, 5A8E
4EIY	GPCR receptor Adenosine A2AAR	1.80	1.20.10 70.10 1.20.12 0.10	N/A
4LDE	GPCR receptor Adrenergic b2AR	2.79	1.10.53 0.40 1.20.10 70.10	4LDE, 4LDL, 4LDO, 4QKX
4N6H	GPCR receptor Opioid d-OR	1.80	1.20.12 0.10 1.20.10 70.10	4N6H, 4RWD
5NDD	GPCR receptor Protease- activated PAR2	2.80	N/A	5NDD, 5NDZ

Table S2. Relative % SASA and hydrogen bonds (HBs) made by the Na⁺-coordinating residues in the representative PDB structures.

Na ⁺ -binding residues	% SASA	# of HB (as an acceptor)	# of HB (as a donor)	HB-partner residues
Leucine transporter LeuT <u>2A65</u>				
Na1:				
Ala22	0.41	—	1	Met18 ^{MM}
Asn27	0	1	1	Gly24 ^{MS} Gly24 ^{MM}
Thr254	0	—	2	Glu290 ^{SS} Gln250 ^{MM}
Asn286	0	1	2	Glu287 ^{SS} Ala282 ^{MM} Glu290 ^{MM}
Leu (substrate)	0	2	2	Gly26 ^{MM} Tyr108 SM Phe253 ^{MM} Ser256 ^{MS}
Na2:				
Gly20	0	—	1	Leu16 ^{MM}
Val23	3.17	—	1	Ala19 ^{MM}
Ala351	0	—	1	Leu347 ^{MM}
Thr354	0	1	2	Phe350 SM Phe350 ^{MM} H ₂ O ^{HM}
Ser355	0	2	2	Asn21 SM Gly352 ^{MM} Ala358 ^{MM} Ile359 ^{MM}
Aspartate transporter GltPh <u>3KBC</u>				
Na1:				
Gly306	0	—	1	Thr302 ^{MM}
Asn310	1.2	1	—	Thr92 ^{SS}
Asn401	0	1	2	Gly313 ^{MS} Arg397 ^{MM} Asp500 SM
Asp405	3.0	3	1	Val402 ^{MM} Gly408 ^{MM} Thr409 ^{MM} Thr409 SM
Na2:				
Thr308	47.5	—	2	Leu305 SM Leu305 ^{MM}
Ser349	0.3	—	3	Ala345 ^{MM} Ala345 SM Val346 SM
Ile350	16.8	—	1	Val346 ^{MM}
Thr352	1.3	—	2	Ala348 ^{MM} Ala348 SM
Dopamine transporter DAT <u>4XP1</u>				
Na1:				
Ala44	0	—	1	Val40 ^{MM}
Asn49	0.1	1	2	Asp46 ^{MS} Ser356 ^{SS} Asp46 ^{MM}
Ser320	1	—	1	Gln316 ^{MM}
Asn352	0.7	1	2	Thr348 ^{MM} Ser349 ^{MM} Ser356 ^{MM}
Na2:				
Gly42	0.5	—	1	Leu38 ^{MM}
Val45	0.9	—	1	Ile41 ^{MM}
Leu417	0.5	—	2	Met413 ^{MM} Leu414 ^{MM}
Asp420	0	3	—	Thr268 ^{SS} Gly424 ^{MM} H ₂ O ^{HM}

Ser421	0	1	2	Phe43 SM Asp46 ^{SS} Gly425 ^{MM}
Glutamate transporter GltTk <u>5E9S</u>				
Na1:				
Gly309	0	1	1	Asn313 ^{MM} Thr305 ^{MM}
Asn313	0	—	3	Asn313 SM (intraresidue HB) Gly309 ^{MM} Asp409 ^{SS}
Asn405	0	2	1	Gly316 ^{MS} Thr317 ^{MS} Thr317 ^{SS}
Asp409	1.8	3	1	Asp409 ^{SS} Thr413 ^{MM} Thr413 SM Val406 ^{MM}
Na2:				
Thr311	0.3	—	1	Leu308 ^{MM}
Ser352	0.1	—	4	Ala348 ^{MM} Ala348 SM Val349 SM Met314 SM
Ile353	7.1	—	1	Val349 ^{MM}
Thr355	0	—	2	Ala351 ^{MM} Ala356 SM
Na3:				
Tyr91	1.2	—	2	Thr305 SM Ile87 ^{MM}
Thr94	1.2	2	3	Tyr90 SM Asp315 ^{SS} Tyr90 ^{MM} Ala98 ^{MM} Gln244 SM
Ser95	2.6	2	—	Ala98 ^{MM} Val99 ^{MM}
Asn313	0	—	3	Gly309 ^{MM} Asn313 SM (intraresidue HB) Asp409 ^{SS}
Asp315	0	4	—	Leu319 ^{MM} Thr94 ^{SS} Gln244 ^{SS} Tyr249 ^{SS}
Serotonin transporter SERT <u>5I7I</u>				
Na1:				
Ala96	0.9	—	1	Val92 ^{MM}
Asn101	1	—	3	Asn368 SM Ser372 ^{SS} Asp98 ^{MS}
Ser336	4.7	1	1	Gln332 ^{MM} Asn368 ^{SS}
Asn368	6.7	3	2	Asn101 SM Ser372 ^{MM} Ser372 SM Ser336 ^{SS} Thr364 ^{MM}
Na2:				
Gly94	2.4	—	1	Leu90 ^{MM}
Val97	3.8	—	1	Ile93 ^{MM}
Leu434	0.7	—	2	Met430 ^{MM} Leu431 ^{MM}
Asp437	3	2	1	Thr284 ^{SS} Asp437 ^{MS} (intraresidue HB) Ala441 ^{MM}
Ser438	0	1	1	Tyr95 SM Gly442 ^{MM}
Glutamate transporter GLAST1/EAAT <u>5LM4</u>				
Thr376	7	—	—	—
Ser417	0	—	2	Met379 SM Ala413 ^{MM}
Ala420	1.9	—	1	Ala416 ^{MM}
Ile418	34.9	—	1	Thr414 ^{MM}
Glutamate receptor Kainate GluR5 (K1) <u>3C32</u>				
Glu96	0	2	1	Thr92 ^{MM} Phe101 ^{MS} Lys103 ^{SS}
Ile99	0	—	1	Arg95 ^{MM}
Asp100	0	5	1	Gly223 ^{MS} 3H ₂ O ^{HS} 2Thr220 ^{MM}

Glutamate receptor Kainate GluR6 (K2) <u>3G3F</u>				
Glu97	0	3	1	Thr93 ^{MM} Lys104 ^{SS} Arg228 ^{SS} H ₂ O ^{HS}
Ile100	0	—	1	Arg96 ^{MM}
Asp101	0	5	1	Gly224 ^{MS} Arg228 ^{SS} 2H ₂ O ^{HS} Thr221 ^{MM} Thr221 ^{MM}
Glutamate receptor Kainate K5 (KA2) <u>3OM1</u>				
Phe162	0	—	1	Leu158 ^{MM}
Ser165	5.3	1	—	Glu167 ^{MS}
Glu167	15.6	1	1	Ser165 ^{MS} H ₂ O ^{HS}
Glutamate receptor Kainate GluR7 (K3) <u>3S9E (chain B)</u>				
Na1:				
Ser24	24.9	1	—	H ₂ O ^{HM}
Arg26	54.9	—	2	Asp32 ^{SS} H ₂ O ^{SH}
Na2:				
Asn5	80.7	2	—	2H ₂ O ^{HS}
Ser52	31.3	1	1	Ser7 ^{SS} Leu8 ^{MM}
GPCR receptor Protease-activated PAR1 <u>3VW7</u>				
Ser189	2.3	1	3	Asn185 ^{MM} Asn185 SM Asn185 ^{SS} Met193 ^{MM}
Asp148	0.4	2	1	Leu144 ^{MM} Val152 ^{MM} Asn185 ^{SS}
Asp367	1.7	3	1	Ser363 ^{MM} Ile370 ^{MM} Tyr371 ^{MM} H ₂ O ^{HS}
GPCR receptor Adrenergic b1AR <u>4BVN</u>				
Na1:				
Cys198	20	—	1	Asp195 ^{MM}
Cys192	6.1	1	1	Asp195 ^{MM} Gln188 ^{MM}
Asp195	42.4	2	2	Lys191 ^{MM} Cys192 ^{MM} Cys198 ^{MM} Gly197 ^{MS}
Na2:				
Asp87	0	5	1	Leu83 ^{MM} Gly91 ^{MM} Ser336 ^{SS} 3H ₂ O ^{HS}
Ser128	0.2	1	2	Cys124 ^{MM} Cys124 SM Leu132 ^{MM}
GPCR receptor Adenosine A2AAR <u>4E1Y</u>				
Asp52	0	4	—	Ser281 ^{SS} 3H ₂ O ^{HS}
Ser91	0	—	1	Leu87 SM
GPCR receptor Adrenergic b2AR <u>4LDE</u>				
Asn1103	5.8	1	2	Glu1188 ^{MS} H ₂ O ^{MH} Glu1107 ^{MM}
Glu1187	28	1	1	Asn1183 ^{MM} Thr1189 ^{SS}
Cys1184	2.9	—	1	Glu1180 ^{MM}
Cys1190	8.4	—	—	—
GPCR receptor Opioid d-OR <u>4N6H</u>				
Asp95	0	6	1	Ser311 ^{SS} Asn314 ^{SS} 2H ₂ O ^{HS} Thr99 ^{MM} Thr99 SM Leu91 ^{MM}
Ser135	0	1	2	Asn131 ^{MM} Asn131 SM Leu139 ^{MM}
Asn131	1.1	2	3	Ile127 ^{MM} Ser135 ^{MM} Ser135 SM 2H ₂ O ^{SH}

GPCR receptor Protease-activated PAR2 <u>5NDD</u>				
Asp121	0.4	2	1	Leu117 ^{MM} Ser124 ^{MM} Val125 ^{MM}
Asp340	0	3	1	Asn336 ^{MM} Val343 ^{MM} Tyr344 ^{MM} H ₂ O ^{HS}
Ser162	0	1	2	Asn158 ^{MM} Asn158 SM Leu166 ^{MM}
Asn336	0.6	2	2	Ser333 ^{MM} Ser333 SM Ile339 ^{MM} Asp340 ^{MM}