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Transporting Your Way Across the BBB and Around the CNS

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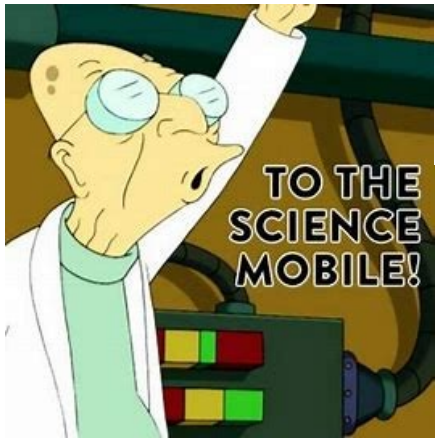
Santa Clara, CA
January 27, 2026

Outline

- Transporters: the basics
- Transporters: a few fun facts
- The blood brain barrier (BBB)
- Transporters at the BBB
- The central nervous system (CNS)
- CNS transporters
- Drugs targeting CNS transporters
- Something very new with Q and q
- Wrap-up



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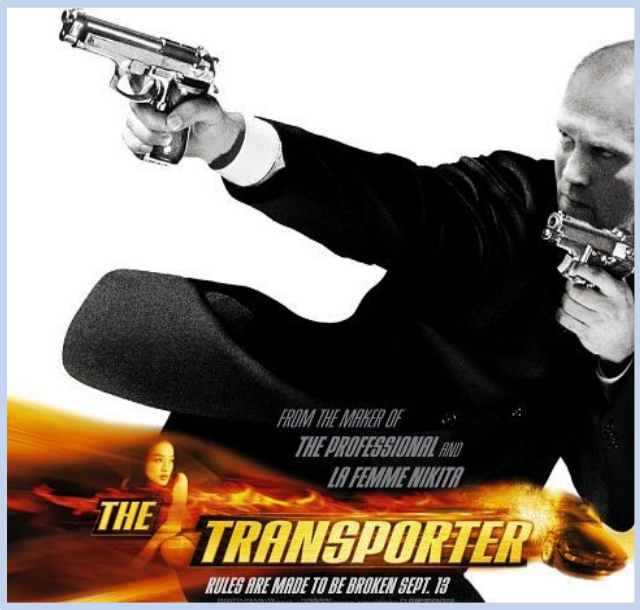
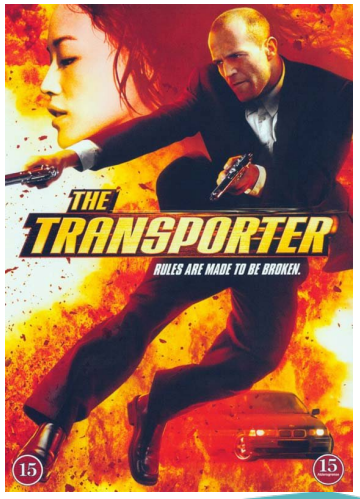
What is a Transporter?





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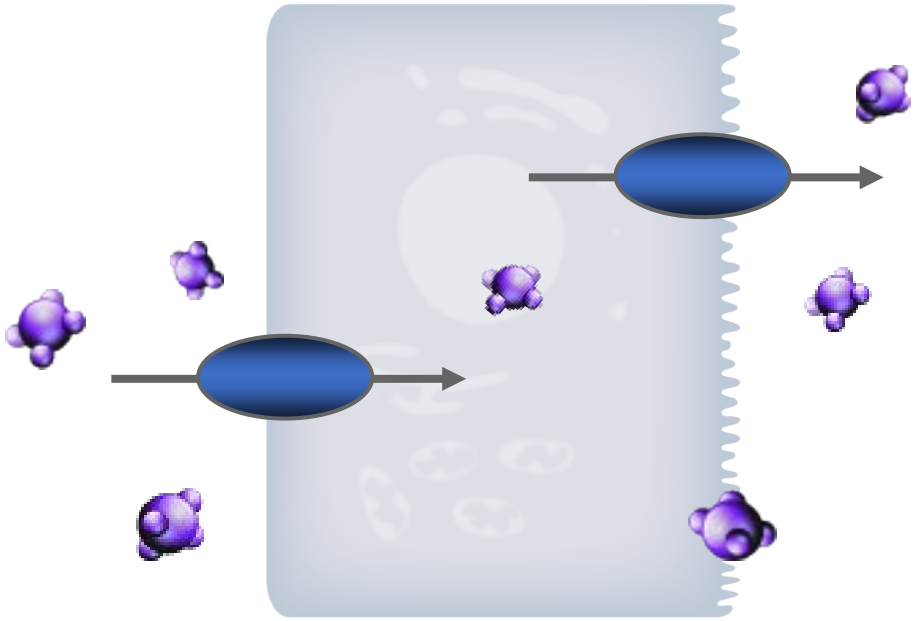
What is a Transporter and What Do They Do?

- Transporters are membrane proteins responsible for moving molecules into and out of cells



- Drugs
- Nutrients
- Ions
- Signaling molecules
- Cellular waste
- Environmental Toxins

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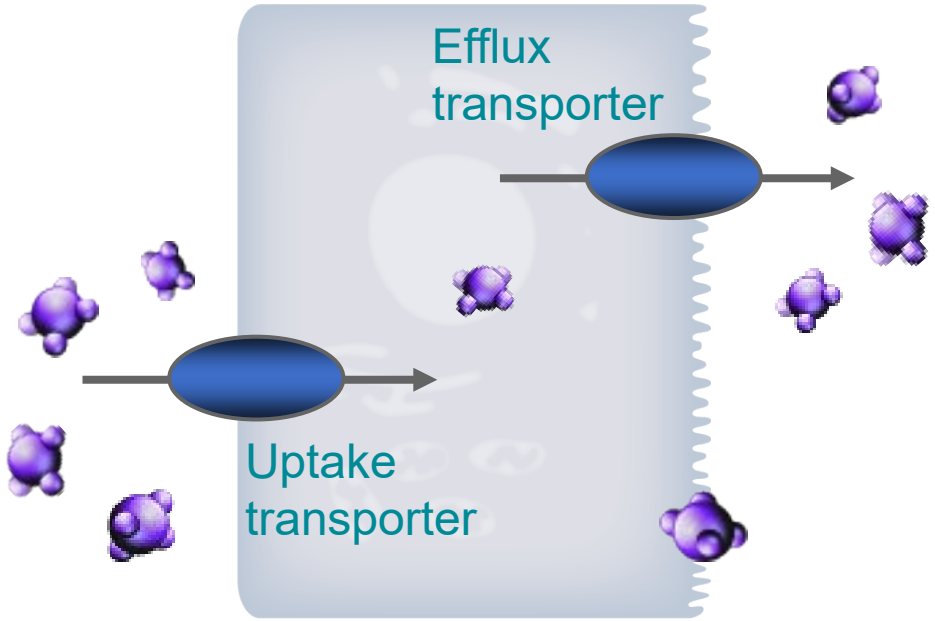
Uptake and Efflux Transporters

Uptake transporters are responsible for moving molecules into cells



Efflux transporters are responsible for moving molecules out of cells

→ Any type of cells – intestine, kidney, liver, brain, etc.

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How Many Transporters?

- Humans have hundreds of known transporters expressed throughout the body
- These transporters are grouped into two broad families:
  - SLC (solute carrier family of proteins)
    - >400 transporters, 66 families
    - Example: SLC22A6 = OAT1
  - ABC (ATP-binding cassette transporters)
    - 49 transporters, 7 families
    - Example: ABCB1 = P-gp (P-glycoprotein)

Typically uptake transporters

Typically efflux transporters

http://nutrigene.4t.com/humanabc.htm
http://www.genenames.org/genefamilies/SLC

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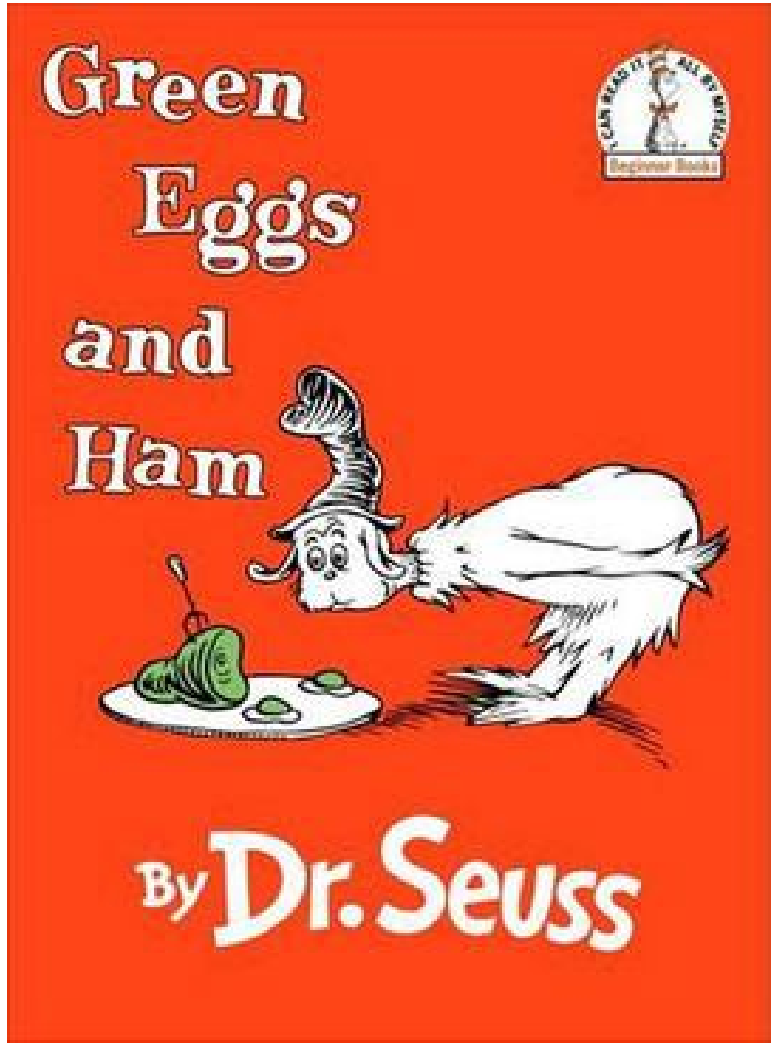
Transporters: A Few Fun Facts

An Early Influence

I do not like green eggs and ham.

I do not like them, Sam-I-Am.



By https://www.amazon.com/Green-Eggs-Ham-Beginner-Books/dp/0394900162
Fair use, https://en.wikipedia.org/w/index.php?curid=52155598

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White Tigers and the SLC45A2 Transporter

- A SNP in SLC45A2 is causative of the Bengal white tiger phenotype

"Tiger, Tiger, Burning Bright, Just One Gene to Make It White"
-National Geographic, May 2013

The genetic basis of white tigers.**Xu X**, Dong GX, Hu XS, Miao L, Zhang XL, Zhang DL, Yang HD, Zhang TY, Zou ZT, Zhang TT, Zhuang Y, Bhak J, Cho YS, Dai WT, Jiang TJ, Xie C, Li R, Luo SJ.**Curr Biol**. 2013 Jun 3;23(11):1031-5. doi: 10.1016/j.cub.2013.04.054. Epub 2013 May 23.PMID: 23707431 **Free article.**

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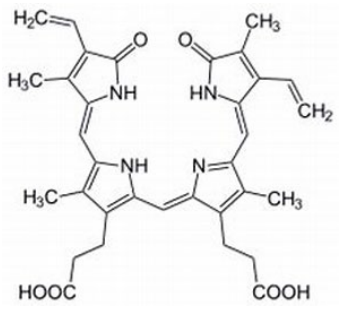
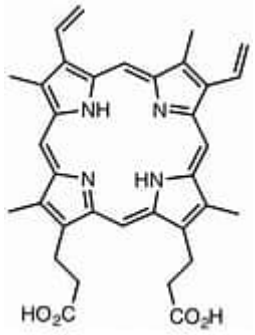
Eggshell Colors

Eggshell colors are determined by the pigments that are secreted when eggs develop in uterus of a hen. Pigment protoporphyrin is derived from blood hemoglobin and contributes to brown eggshell coloration. By contrast, blue eggs have billiverdin or oocyanin pigment in their shells.



biliverdin



protoporphyrin

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Blue Eggs: The Result of OATP1B3 Expression

No OATP1B3 single nucleotide polymorphisms were found to be linked with blue egg phenotype, however the sequences that came from blue-egg laying hens had a 4.3kb endogenous retrovirus sequence insertion upstream of the SLCO1B3 gene, which caused OATP1B3 to be expressed in the uterus.

An EAV-HP insertion in 5' Flanking region of SLCO1B3 causes blue eggshell in the chicken.**Wang Z**, **Qu L**, Yao J, Yang X, Li G, Zhang Y, Li J, Wang X, Bai J, Xu G, Deng X, Yang N, Wu C.PLoS Genet. 2013;9(1):e1003183. doi: 10.1371/journal.pgen.1003183. Epub 2013 Jan 24.PMID: 23359636 **Free PMC article.**

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Blue Eggs, Green Eggs

If chickens that lay blue eggs are crossbred with chicken that lay brown eggs, the result will be chickens that lay green eggs.

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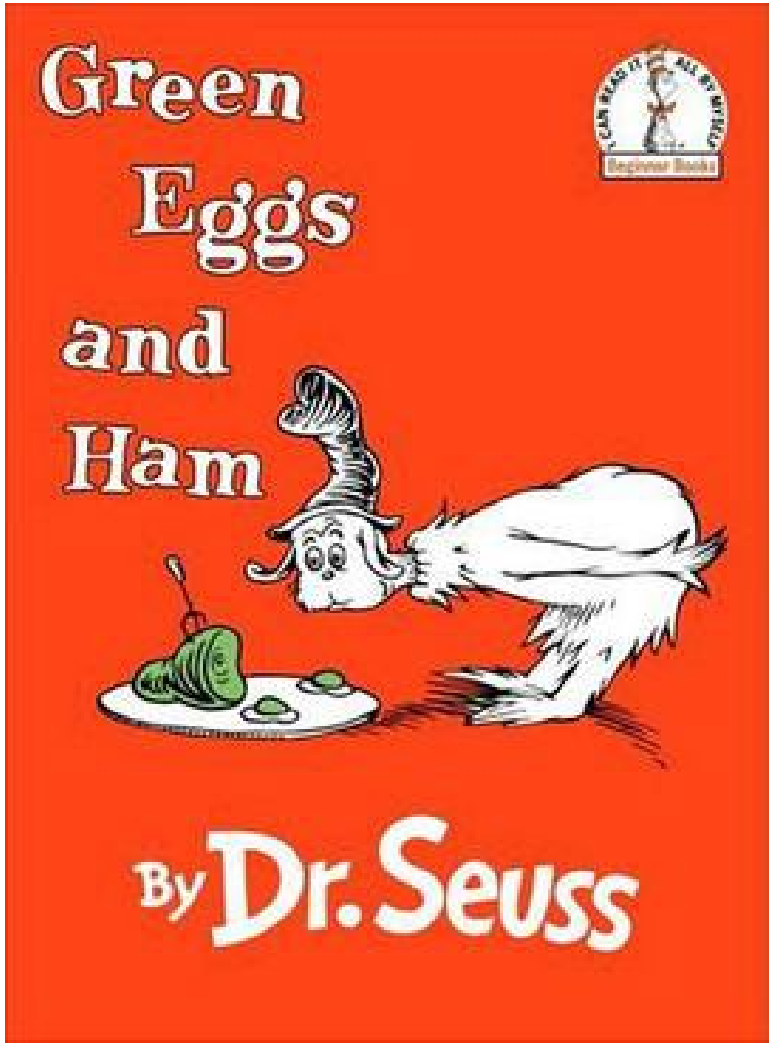
Green Eggs… are Due to Transporters!

I do so like green eggs and ham.

Thank you.

Thank you, Sam-I-Am

Thank you, Theodor Geisel, aka Dr. Suess!



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Transporters and ADME

Transporters Control ADME Properties of Drugs

- Transporters can have clinically relevant effects on the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs by controlling the absorption, distribution, metabolism, and elimination (ADME) of those drugs.
  - Absorption: Intestinal transporters can be responsible for drug absorption
  - Distribution: Expressed throughout body, transporters modulate the access (of both drugs and endogenous molecules) to various sites in the body
  - Metabolism: While not metabolic enzymes, transporters can deliver parent drugs into hepatocytes and can efflux metabolites into the bile
  - Elimination: Transporters can determine drug elimination, moving drugs and metabolites into bile or urine.

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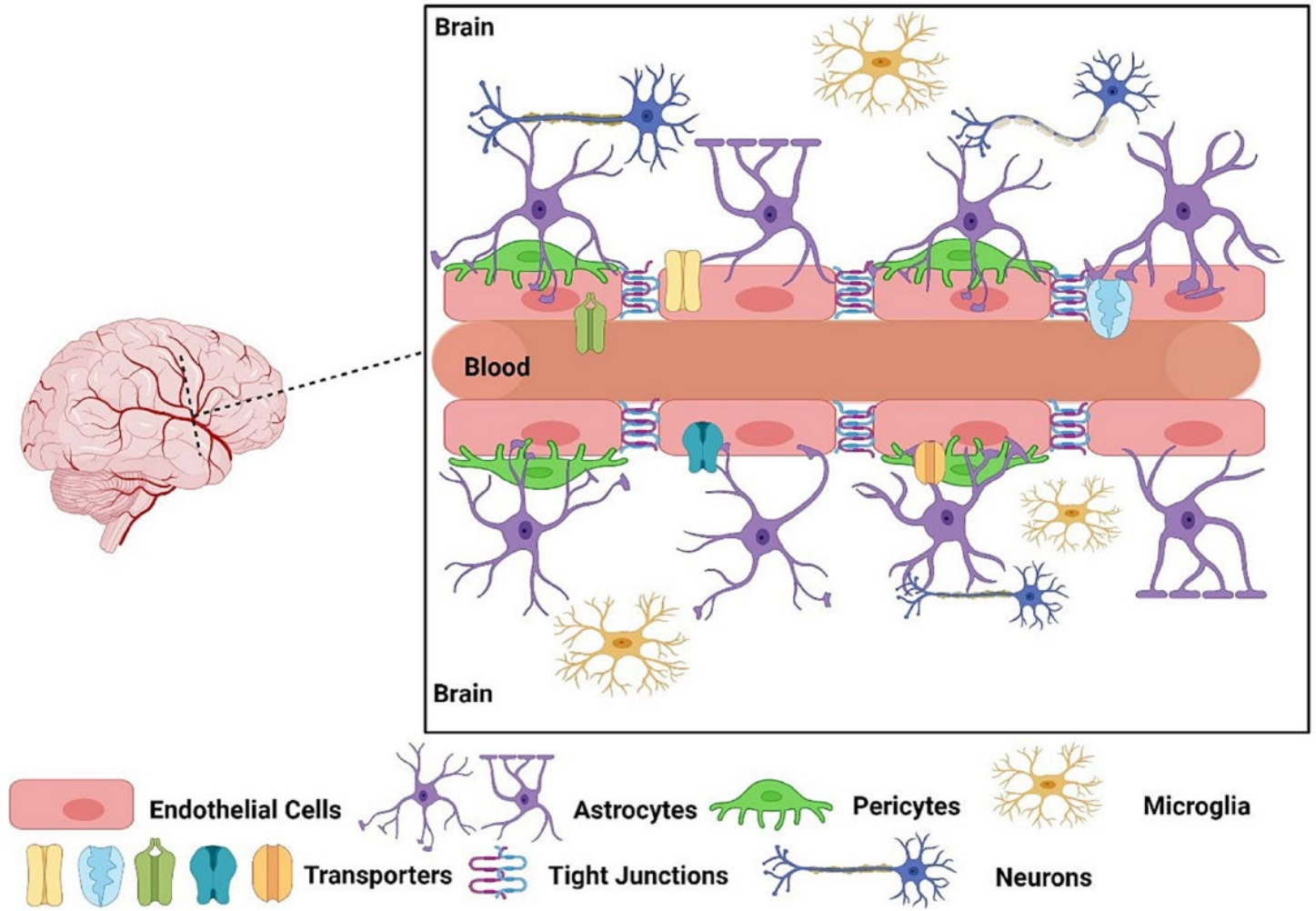
The Blood Brain Barrier (BBB)

The Blood Brain Barrier

- Endothelial cells of capillary walls connected by tight junctions plus a variety of other cells restricts entry of nearly all molecules.
- But... Some molecules need to get in (nutrients) or out (waste).
- Transporters are key.



Blood-brain barrier transporters: An overview of function, dysfunction in Alzheimer's disease and strategies for treatment.
Chaves JCS, Dando SJ, White AR, Oikari LE.Biochim Biophys Acta Mol Basis Dis. 2024 Feb;1870(2):166967. doi: 10.1016/j.bbadis.2023.166967. Epub 2023 Nov 24.PMID: 38008230 **Free article.** Review

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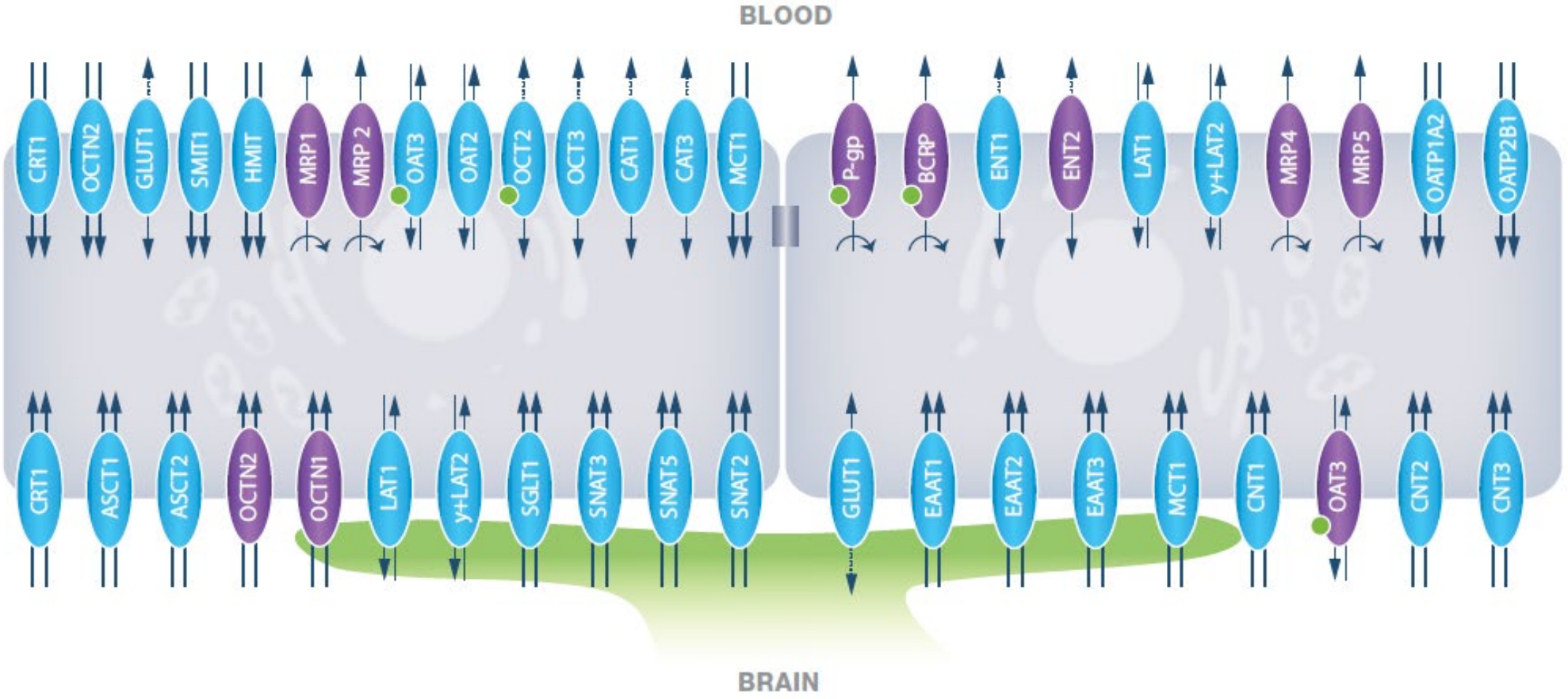
Many Transporters Involved at the Blood Brain Barrier



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Efflux Transporters at the BBB

- In addition to all of the physical barriers, there are several efflux transporters at the BBB that work to prevent the uptake of drugs.

  - P-gp (ABCB1)
  - BCRP (ABCG2)
  - MRP1 (ABCC1)
  - MRP2 (ABCC2)
  - MRP4 (ABCC4)
  - MRP5 (ABCC5)

  These efflux transporters are all well expressed at the BBB, and act to prevent the uptake of drugs.

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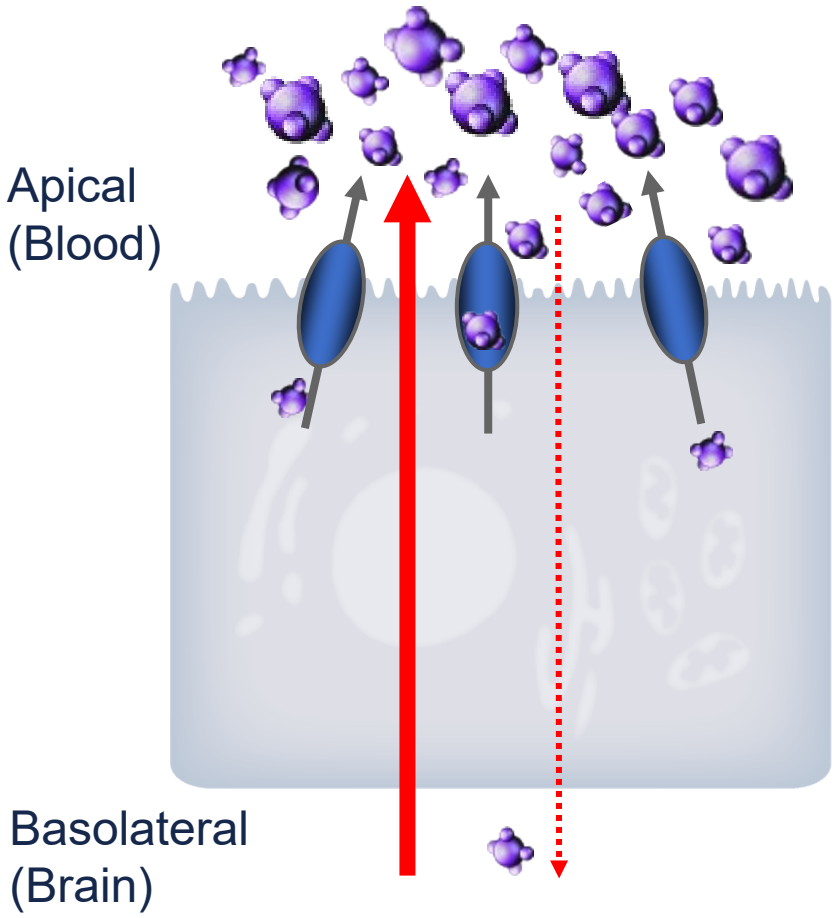
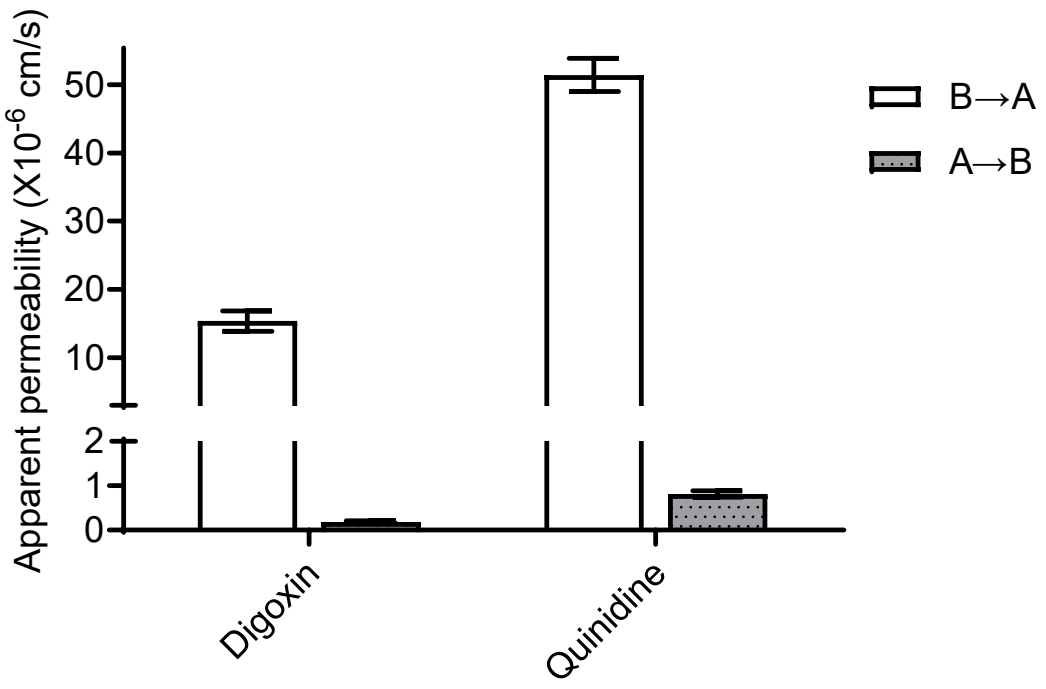
P-gp: An Incredibly Efficient Efflux Transporter





100-fold higher B->A transport than A->B transport in a MDCK-MDR1 cell monolayer

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  - MRP5 (ABCC5)

  These efflux transporters are all well expressed at the BBB, and act to prevent the uptake of drugs.

- Each of these efflux transporters can recognize many drugs (100s or 1000s), and very efficiently pump it out of cells back into the blood.

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Transporter Specificity? Human P-gp is known to transport hundreds of different drugs, including...

Aliskiren (Tekturna®)	Empagliflozin (Jardiance®)	Lovastatin (Mevacor®)	Saquinavir (Invirase®)
Ambrisentan (Letairis®)	Erythromycin (E.E.S®, Ery-tab®)	Maraviroc (Selzentry®)	Saxagliptin (Onglyza®)
Apixaban (Eliquis®)	Estradiol (Climara®, Estrace®, etc.)	Methylprednisolone (Solu-Medrol®)	Silodosin (Rapaflo®)
Atorvastatin (Lipitor®)	Etoposide (Toposar®)	Methotrexate	Simvastatin (Zocor®)
Boceprevir (Victrelis®)	Everolimus (Afinitor®)	Morphine (MS Contin®, etc.)	Sirolimus (Rapamune®)
Bromocriptine (Cycloset®, Parlodel®)	Ezetimibe (Zetia®)	Nelfinavir (Viracept®)	Sitagliptin (Januvia®)
Carbamazepine (Tegretol®)	Fexofenadine (Allegra®)	Nilotinib (Tasigna®)	Sofosbuvir (Sovaldi®)
Carvedilol (Coreg®)	Fluvastatin (Lescol®)	Ombitasvir (Viekira Pak™)	Tacrolimus (Prograf®)
Cimetidine (Tagamet®)	Fosamprenavir (Lexiva®)	Paclitaxel (Taxol®)	Ticagrelor (Brilinta®)
Colchicine (Colcrys®)	Imatinib (Gleevec®)	Paliperidone (Invega®)	Telaprevir (Incivek®)
Cyclosporine (Neoral®)	Indacaterol (Arcapta®)	Paritaprevir (Viekira Pak™)	Tetracycline
Dabigatran (Pradaxa®)	Indinavir (Crixivan®)	Phenytoin (Dilantin®)	Tipranavir (Aptivus®)
Dapagliflozin (Farxiga®)	Itraconazole (Sporanox®)	Posaconazole (Noxafil®)	Tolvaptan (Samsca®)
Dasabuvir (Viekira Pak™)	Ivermectin (Stromectol®)	Pravastatin (Pravachol®)	Topotecan (Hycamtin®)
Dexamethasone (Decadron®)	Lapatinib (Tykerb®)	Prazosin (Minipress®)	Umeclidinium (Anoro Ellipta®)
Digoxin (Lanoxin®)	Ledipasvir (Harvoni™)	Quinidine	Vecuronium
Diltiazem (Cardizem®, Cartia®, etc)	Levomilnacipran (Fetzima®)	Ranitidine (Zantac®)	Verapamil (Calan®,Covera-HS®, etc.)
Domperidone	Linagliptin (Tradjenta®)	Ranolazine (Ranexa®)	Vilanterol (Anoro Ellipta®)
Doxorubicin (Adriamycin®)	Loperamide (Imodium®)	Ritonavir (Norvir®)	Vinblastine
Edoxaban (Savaysa®)	Losartan (Cozaar®)	Rivaroxaban (Xarelto®)	Vincristine (Vincasar®)

https://examine.com/glossary/p-glycoprotein-substrates/
http://www.straighthealthcare.com/p-glycoprotein.html

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Efflux Transporters at the BBB

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  These efflux transporters are all well expressed at the BBB, and act to prevent the uptake of drugs.
- Each of these efflux transporters can recognize many drugs (100s or 1000s), and very efficiently pump it out of cells back into the blood.
- Many drugs are substrates of multiple efflux transporters – even if one is inhibited, the other can usually nearly completely prevent drug uptake

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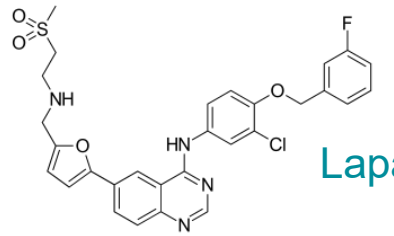
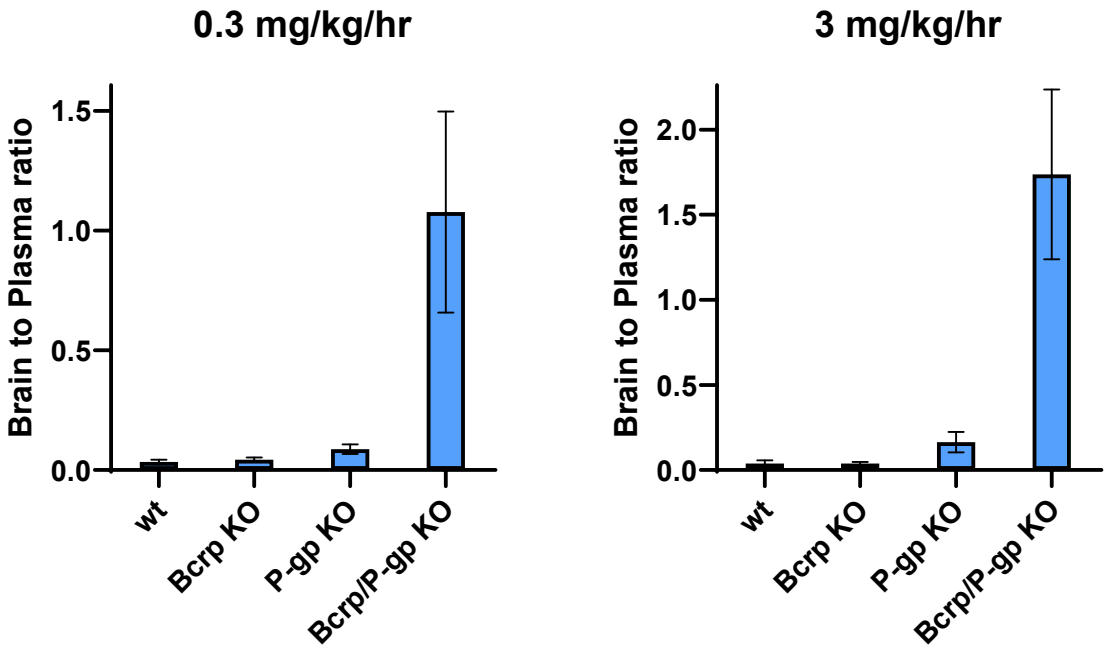
Example - Lapatinib



- A tyrosine kinase inhibitor used in treating breast cancers.
- Substrate of both P-gp and BCRP
- Very low brain to plasma ratio
- Small effects in Bcrp or P-gp knockout mice
- >40-fold increase in brain uptake in Bcrp/Pgp double knockout mice



An unexpected synergist role of P-glycoprotein and breast cancer resistance protein on the central nervous system penetration of the tyrosine kinase inhibitor **lapatinib** (N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine; GW572016).Polli JW, Olson KL, Chism JP, John-Williams LS, Yeager RL, Woodard SM, Otto V, Castellino S, Demby VE.Drug Metab Dispos. 2009 Feb;37(2):439-42. doi: 10.1124/dmd.108.024646. Epub 2008 Dec 4.PMID: 19056914

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Can We Improve Drug Uptake into the Brain by Inhibiting P-gp?

Drug name	MOA	Phase	Adverse effects	Outcomes	References
First generation					
Verapamil	Calciumchannel blocker	phase II	Hypotension, cardiotoxicity	No clinical benefit	(11, 12)
Second generation					
Dexverapamil	calcium channel blocker	Phase II	Cardiotoxicity	ORR 9%, DCR 19% (18)	(18)
S9788	p-gp inhibitor	Phase I	arrhythmia	Further development limited by severe arrythmia	(20)
PSC-833	p-gp inhibitor	Phase III	NS	No benefit seen in phase III trials	(21–29)
Third generation					
Zosuquidar	p-gp inhibitor	Phase III	neurotoxicity	No clinical benefit seen in solid and hematological cancers	(31–37)
Elacridar	p-gp inhibitor	Phase I	neutropenia	Demonstrated increase in bioavailability of accompanying chemotherapy drug (oral topotecan, oral paclitaxel)	(38–44)
Tariquidar	p-gp inhibitor	Phase II	NS	Modest ORR in pretreated patients (5–10% in most trials) Demonstrated potential for development as radiotracer coupled with radioactive [11C] labeling	(45–53)

MOA, mechanism of action; ORR, Objective response rate; DCR, disease control rate (combination of response rate and stable disease rates); NS, Not significant.

Clinical Perspective of FDA Approved Drugs With P-Glycoprotein Inhibition Activities for Potential Cancer Therapeutics.Lai JI, Tseng YJ, Chen MH, Huang CF, Chang PM.Front Oncol. 2020 Nov 16;10:561936. doi: 10.3389/fonc.2020.561936. eCollection 2020.PMID: 33312947 **Free PMC article.** Review.

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Can We Improve Drug Uptake into the Brain by Inhibiting P-gp?

- Probably not
- Several P-gp inhibitors have been developed and tested in clinical trials
- Most have failed due to either inhibitor toxicity or enhanced penetration/accumulation of the drugs into non-CNS tissues.
- P-gp is expressed throughout the body (intestine, renal proximal tubules, bile canaliculi, etc.), and inhibition can lead to greater systemic exposure – and in turn, dose limiting toxicity or off-target effects

Transport Mechanisms at the Blood-Brain Barrier and in Cellular Compartments of the Neurovascular Unit: Focus on CNS Delivery of Small Molecule Drugs. Ronaldson PT, Davis TP.Pharmaceutics. 2022 Jul 20;14(7):1501. doi: 10.3390/pharmaceutics14071501.PMID: 35890396 **Free PMC article.** Review.

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Can We Improve Drug Uptake into the Brain using the Lipinski "Rule of 5"?

- Optimize passive permeability using molecules that are:
  - MW < 500
  - Have cLogP values between 1.5 – 2.5
  - Polar surface areas < 90 $Å^2$
  - Fewer than 5 hydrogen bond donors, fewer than 10 hydrogen bond acceptors
  - Are primarily uncharged at physiological pH

- Maybe... But such molecules are very non-selective, cannot control delivery into brain tissue.

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What Can We Do to Get Molecules into the Brain?

- One approach could be to design molecules that are not substrates of efflux transporters like P-gp (or at least are weaker substrates)

Can we find an example of similar molecules with differing P-gp activity?

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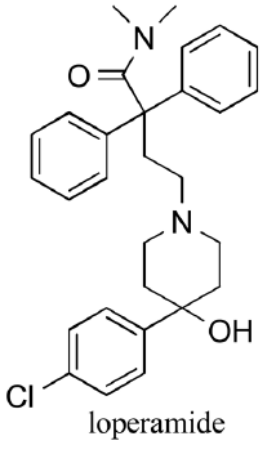
What Can We Do to Get Molecules into the Brain?

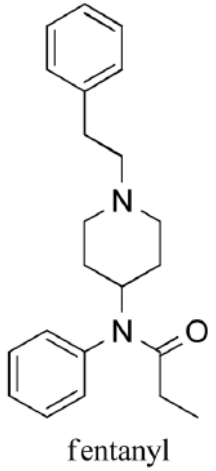
- Opioids – Similar molecules with differing P-gp activities



loperamide

Very strong P-gp substrate

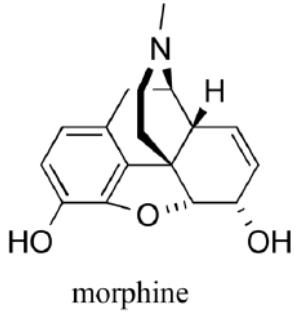
Very low brain uptake



fentanyl

Very weak or non-P-gp substrate

High brain uptake



morphine

Weak P-gp substrate

While loperamide and fentanyl are both opioids, P-gp activity limits loperamide absorption from the intestine and prevents brain uptake.

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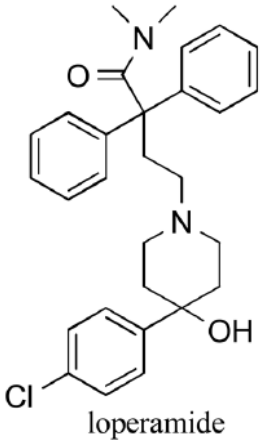
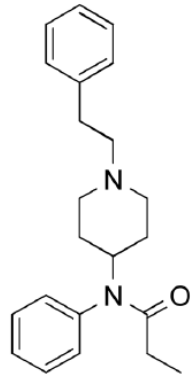
Loperamide & P-gp

- P-gp limits both oral bioavailability of loperamide and brain penetration

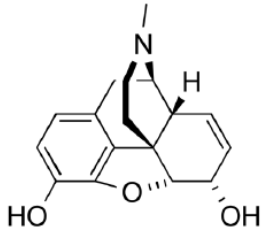
	Oral	Brain uptake		
Opioid	Bioavailability	wt mice	KO mice	KO/wt
Morphine	30%	1.04 ± 0.03	1.29 ± 0.08	1.24 ± 0.08
Fentanyl	33%	184 ± 24	228 ± 9	1.24 ± 0.17
Loperamide	0.3%	9.86 ± 1.73	103 ± 6	10.4 ± 1.9



loperamide



fentanyl



morphine

When loperamide was administered to P-gp KO mice:

- Loperamide accumulated in the brain
- Mice exhibited opioid-mediated CNS effects.

Opioid analgesics and P-glycoprotein efflux transporters: a potential systems-level contribution to analgesic tolerance.Mercer SL, Coop A.Curr Top Med Chem. 2011;11(9):1157-64. doi: 10.2174/156802611795371288.PMID: 21050174 **Free PMC article.** Review.

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Another Approach: Using Uptake Transporters to Improve Drug Uptake into the Brain

- Many CNS drug targets are receptors/transporters that recognize relatively small, polar molecules (serotonin, dopamine, glutamate, etc.)
- These are not “Lipinski rule of 5” type compounds.
- Numerous SLC uptake transporters are also expressed at the BBB and may provide a way to transport drugs into the brain.
- These transporters include members from the OATP, OAT, OCT, OCTN, NT, and MCT families, as well as amino acid transporters like LAT1.
- A few examples....

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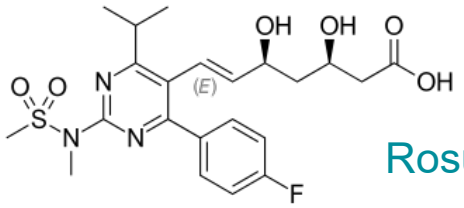
OATP Transporters



Rosuvastatin

- Oatp1a4 (rat) and OATP1A2 & OATP2B1 (human) are amongst the most highly expressed uptake transporters at the BBB.
- OATP substrates that exhibit pharmacological/physiological effects in the brain include statins, prostaglandin E_2, dehydroepiandrosterone sulfate (DHEAS), and estradiol-17β-D-glucuronide.
- Neuroprotective effects of statins have been observed in preclinical studies, and stroke patients given statins showed a 4.6-fold decrease in death rates, 8.67-fold lower risk of early neurological deterioration, and decrease in mean infarction volume.

Statin treatment withdrawal in ischemic stroke: a controlled randomized study.Blanco M, Nombela F, Castellanos M, Rodriguez-Yáñez M, García-Gil M, Leira R, Lizasoain I, Serena J, Vivancos J, Moro MA, Dávalos A, Castillo J.Neurology. 2007 Aug 28;69(9):904-10. doi: 10.1212/01.wnl.0000269789.09277.47.PMID: 17724294 Clinical Trial.

Role of Transporters in Central Nervous System Drug Delivery and Blood-Brain Barrier Protection: Relevance to Treatment of Stroke.Brzica H, Abdullahi W, Ibbotson K, Ronaldson PT.J Cent Nerv Syst Dis. 2017 Apr 6;9:1179573517693802. doi: 10.1177/1179573517693802. eCollection 2017.PMID: 28469523 **Free PMC article.** Review.

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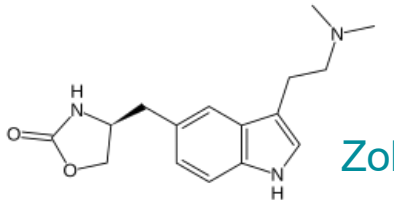
OATP Transporters & Triptans



Zolmitriptan

- Triptans (almotriptan, naratriptan, sumatriptan, zolmitriptan, etc.) are used to treat migraine and cluster headaches, using OATP1A2 to cross the BBB.
- Interestingly, triptans do not cross the BBB in rodents – they are not substrates for Oatp1a4. No differences in brain accumulation were seen between wt and Oapt1a4 KO mice.
- In OATP1A2 knock-in mice, zolmitriptan levels in the CNS were 1.6-fold higher than wt controls, confirming that zolmitriptan is a substrate for human OATP1A2 but not rodent Oatp1a4.

Transport Mechanisms at the Blood-Brain Barrier and in Cellular Compartments of the Neurovascular Unit: Focus on CNS Delivery of Small Molecule Drugs.Ronaldson PT, Davis TP.Pharmaceutics. 2022 Jul 20;14(7):1501. doi: 10.3390/pharmaceutics14071501.PMID: 35890396 **Free PMC article.** Review.

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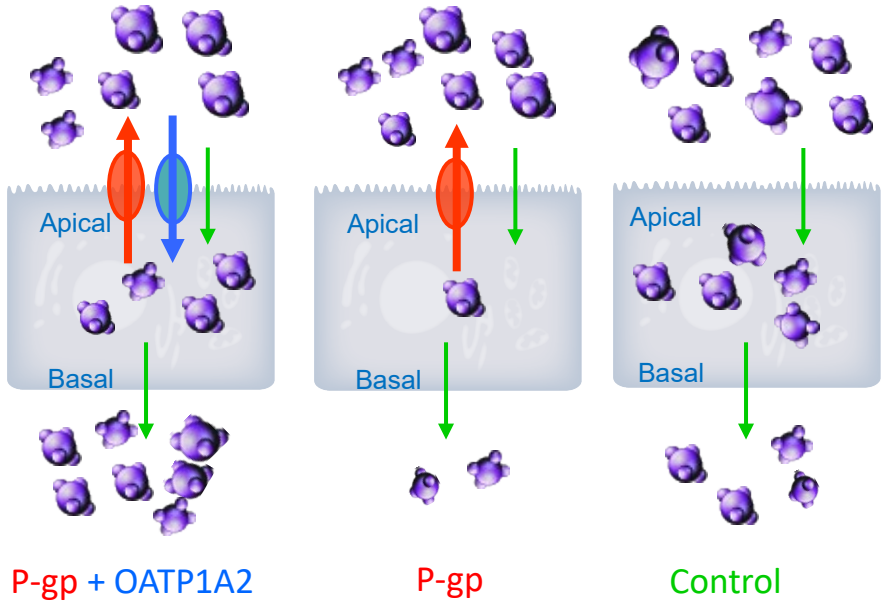
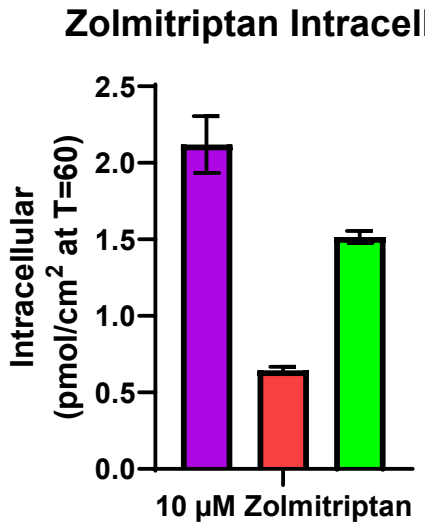
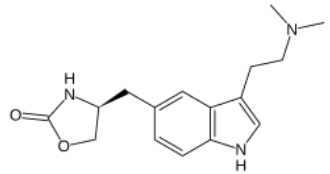
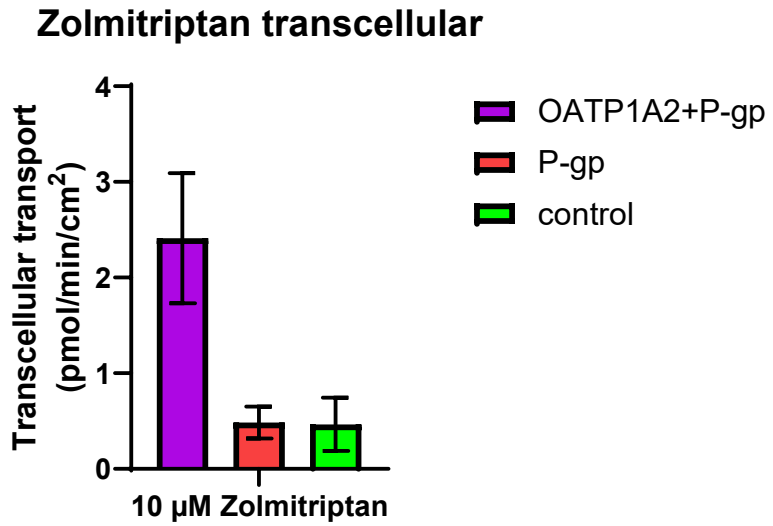
OATP1A2 Uptake Can Overcome P-gp Efflux









- Triptans such as Zolmitriptan are P-gp substrates
- OATP1A2 can offset luminal efflux by P-gp and help drugs such as triptans cross the BBB

Ngo et al., Poster P195, ISSX 2025

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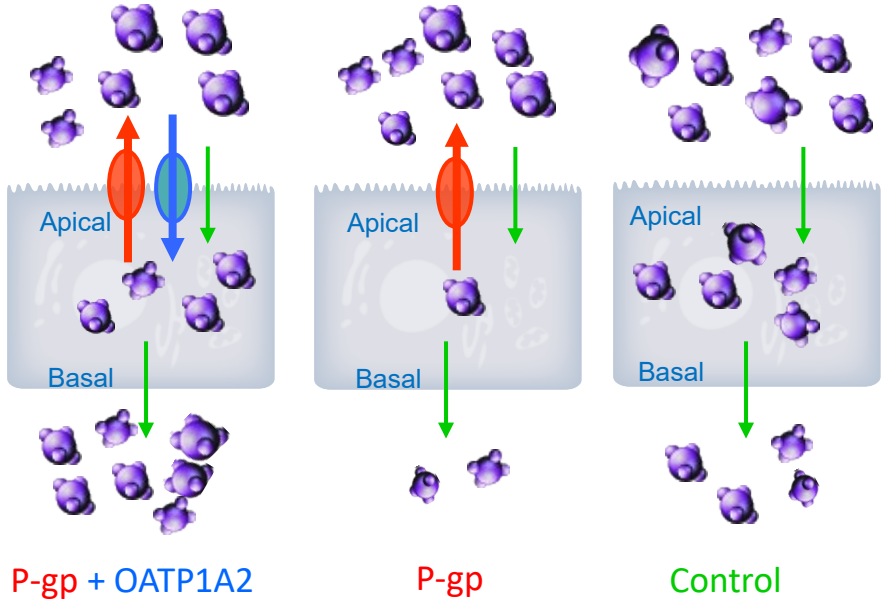
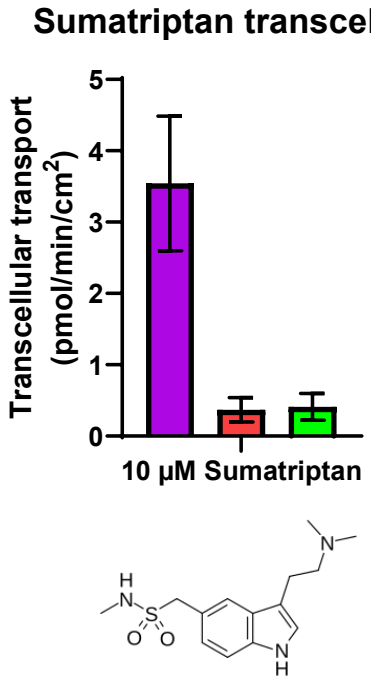
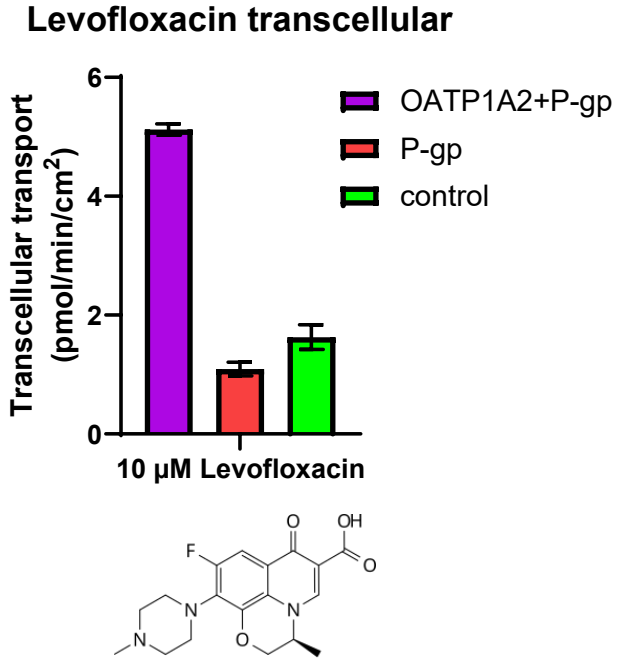
OATP1A2 Uptake Can Overcome P-gp Efflux







- Triptans such as Sumatriptan are P-gp substrates
- OATP1A2 can offset luminal efflux by P-gp and help drugs such as triptans cross the BBB

Ngo et al., Poster P195, ISSX 2025

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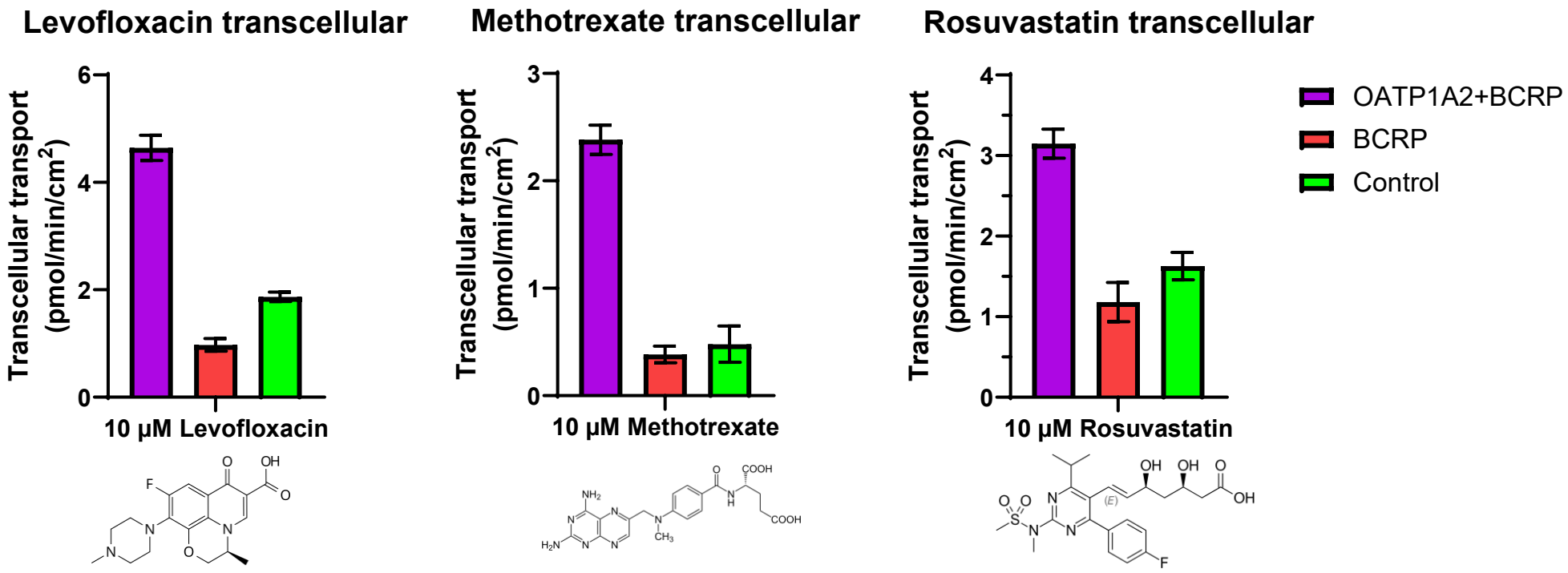
OATP1A2 Uptake Can Overcome BCRP Efflux



- OATP1A2 can offset luminal efflux by BCRP and help drugs such as statins cross the BBB

Ngo et al., Poster P195, ISSX 2025

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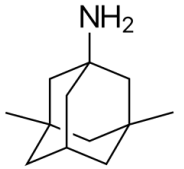
OCTs



Memantine

- OCT1, OCT2, and OCT3 offer another BBB target.
- Memantine uses the OCTs to cross the BBB
- Memantine functions as an antagonist of the N-methyl-D-aspartate (NMDA) receptor and is used to attenuate excessive glutamate release in stroke victims. Memantine is also used to slow the progression of Alzheimer's disease and for treatment of cognitive impairment and memory loss.

Stroke → Decreased oxygen & glucose → Increased calcium influx → Increased glutamate release → Excitotoxicity → Neuronal injury, death

Transport Mechanisms at the Blood-Brain Barrier and in Cellular Compartments of the Neurovascular Unit: Focus on CNS Delivery of Small Molecule Drugs.
Ronaldson PT, Davis TP.Pharmaceutics. 2022 Jul 20;14(7):1501. doi: 10.3390/pharmaceutics14071501.PMID: 35890396 **Free PMC article.** Review.

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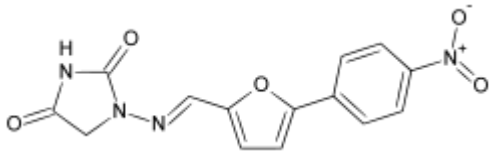
OAT2/OAT3



Dantrolene

- Dantrolene is used to treat spasticity after strokes or in patients with cerebral palsy or multiple sclerosis.
- Dantrolene also appears to be neuroprotective, reducing excitotoxicity, apoptosis, and neuroinflammation in neurodegenerative diseases.
- Substrate of OAT2 and OAT3, allowing it to cross the BBB.

•Organic Anion Transporter 2: An Enigmatic Human Solute Carrier.Shen H, Lai Y, Rodrigues AD.Drug Metab Dispos. 2017 Feb;45(2):228-236. doi: 10.1124/dmd.116.072264. Epub 2016 Nov 21.PMID: 27872146 Review.

Counter-flow suggests transport of dantrolene and 5-OH dantrolene by the organic anion transporters 2 (OAT2) and 3 (OAT3).Burckhardt BC, Henjakovic M, Hagos Y, Burckhardt G.Pflugers Arch. 2016 Nov;468(11-12):1909-1918. doi: 10.1007/s00424-016-1894-6. Epub 2016 Nov 3.PMID: 27812757

Approaches to Optimizing Dantrolene Neuroprotection for the Treatment of Alzheimer's Disease.Abou MB, Sun L, Wei H.Curr Alzheimer Res. 2020;17(4):324-328. doi: 10.2174/1567205017666200522204722.PMID: 32442084 **Free PMC article.** Review.

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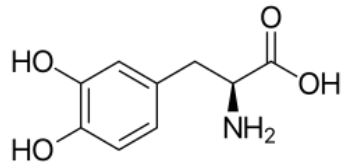
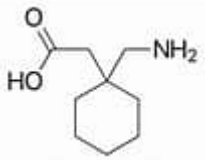
LAT1

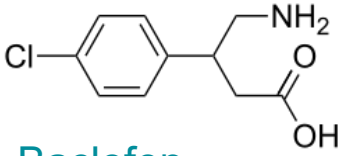
- Mediates the transport of various drugs and prodrugs across the BBB, including levodopa, gabapentin, baclofen, melphalan
- Drug substrates are used for a number of conditions, from Parkinson's to epilepsy to spasticity to neuropathic pain to cancer
- Broad substrate specificity and high expression on both sides of the BBB (luminal and abluminal) make LAT1 an attractive target for brain-targeted drugs



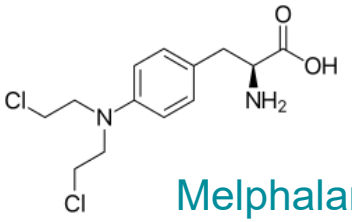
Levodopa



Gabapentin



Baclofen



Melphalan

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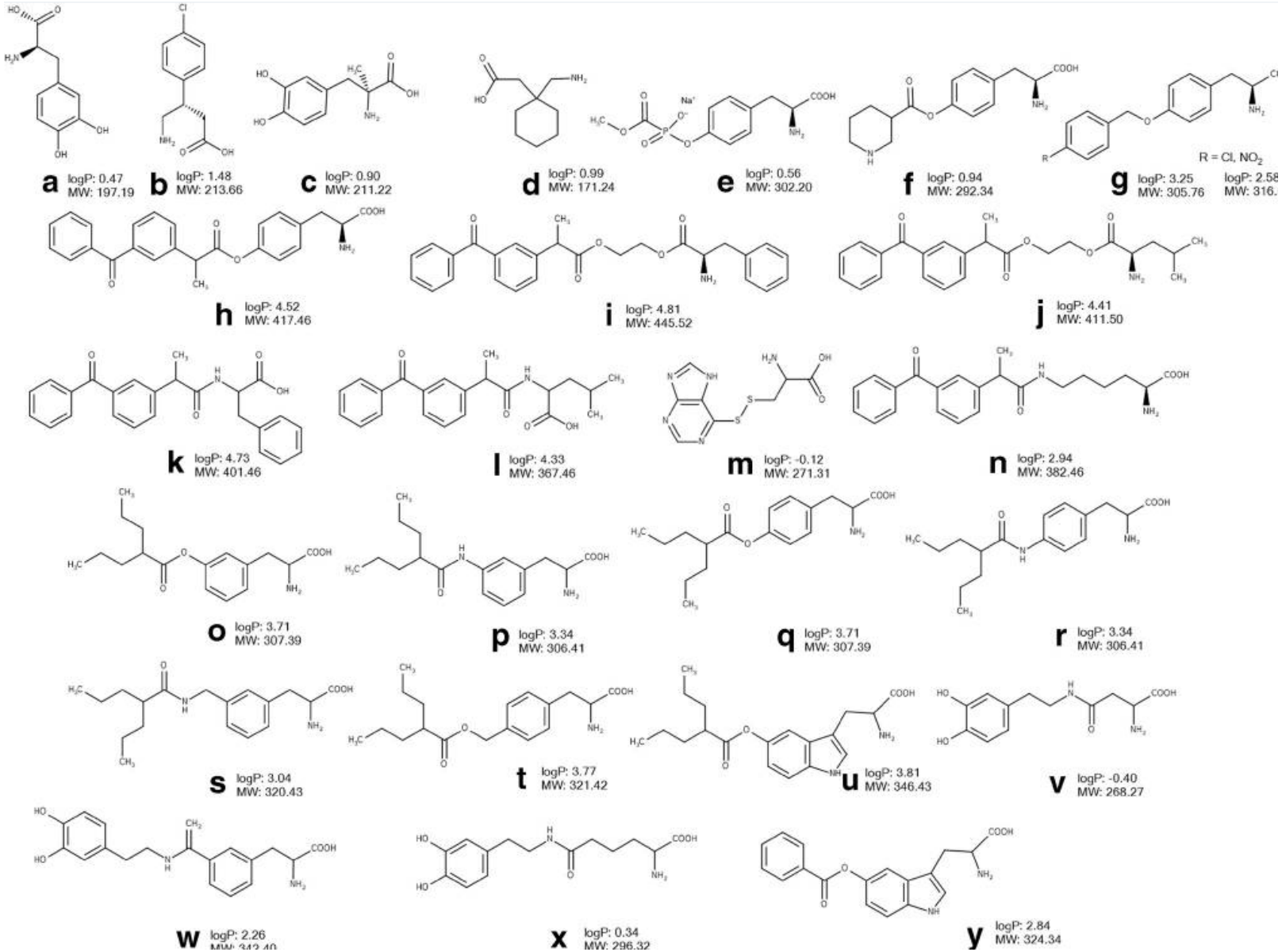
Using LAT1

- Subset of CNS drugs and derivatives designed to utilize LAT1



L-Type amino acid transporter 1 as a target for drug delivery.Puris E, Gynther M, Auriola S, Huttunen KM.Pharm Res. 2020 May 6;37(5):88. doi: 10.1007/s11095-020-02826-8.PMID: 32377929 **Free PMC article.** Review.

Additional Transporters Expressed at the BBB

- EAAT1, EAAT2, EAAT3 – abluminal, primarily remove glutamate from brain
- ASCT1, ASCT2 – transports small neutral amino acids (L- and D-), involved in neurotransmitter homeostasis
- BGT1 – transports betaine and GABA, potential target for epilepsy and excitotoxicity
- CAT1, CAT3 – cationic amino acid transporters, involved in NMDA receptor activation and mTOR regulation
- SNAT1, SNAT2 – neutral amino acids (glutamine)
- ENT1, ENT2, ENT4 (PMAT) – nucleosides, monoamine neurotransmitters
- xCT – Cystine/glutamate transporter, involved in excitatory signaling
- OCTN1, OCTN2 – cationic substates

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BBB Transporters - Summary

- Numerous uptake transporters are expressed at the BBB and may be useful in getting drugs into the brain
- Active transport can overcome efflux by P-gp and other efflux transporters and allow passage into the brain, at least for some drugs

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Moving from the BBB into the CNS

Neurotransmitter Transporters in the CNS

- Serotonin transporter (SERT)
- Dopamine transporter (DAT)
- Norepinephrine transporter (NET)

- GABA transporters (GATs)
- Glutamate transporters (EAATs, VGLUTs)
- Glycine transporters (GlyTs)

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SERT (SLC6A4)

Serotonin
(5-hydroxytryptamine)

- The serotonin transporter is a monoamine transporter
- Responsible for serotonin reuptake (from the synaptic cleft back to the presynaptic neuron)
- Dysregulation of SERT impacts mood and emotional stability

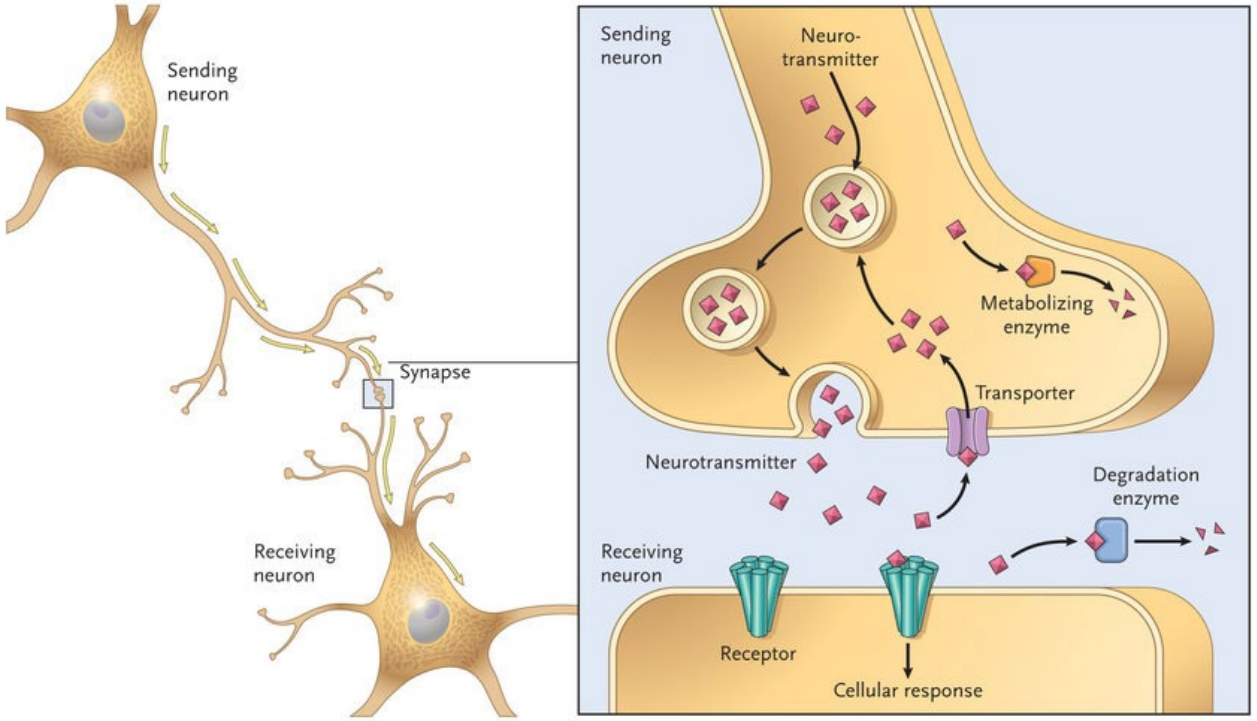

Figure from: https://www.researchgate.net/publication/352268822_Opiate_Addiction_and_its_Confounding_Crisis

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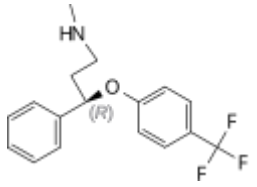
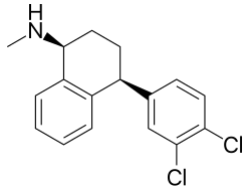
SSRIs (Serotonin Reuptake Inhibitors)

Serotonin
(5-hydroxytryptamine)

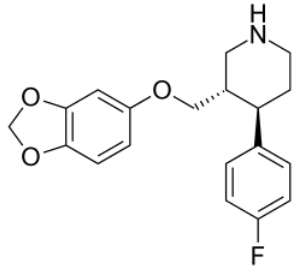
- Inhibition of SERT will prolong serotonin signaling
- Used for treatment of depression, anxiety, panic disorder, PTSD, and OCD
- Examples include fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), citalopram (Celexa), escitalopram (Lexapro), fluvoxamine (Luvox)



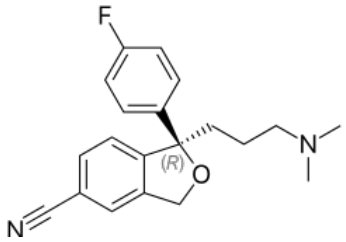
Fluoxetine



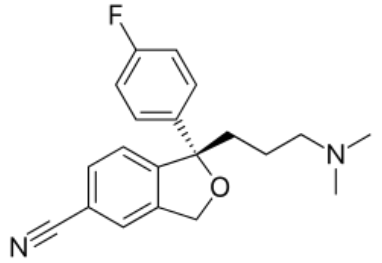
Sertraline



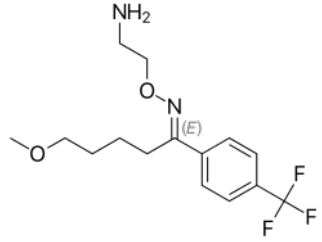
Paroxetine



Citalopram



Escitalopram



Fluvoxamine

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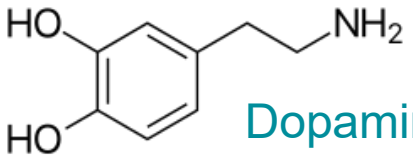
DAT (SLC6A3)



Dopamine

- The dopamine transporter is another monoamine transporter
- Responsible for dopamine reuptake (from the synaptic cleft back into cytosol)
- Dopamine is essential for reward and pleasure pathways.
- Dysregulation of DAT can lead to disorders like ADHD, bipolar disorder, depression, eating disorders, addiction disorders, and Parkinson's disease
- Drugs that target DAT can function as substrates, inhibitors, dopamine releasers, or allosteric modulators

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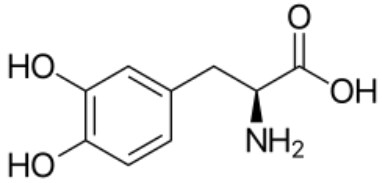
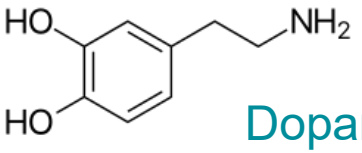
Levodopa (L-dopa)

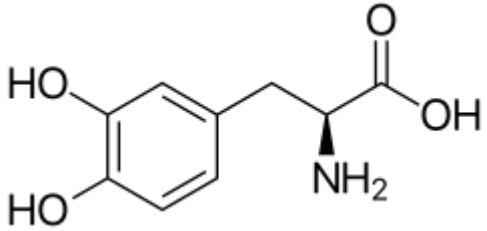


Levodopa

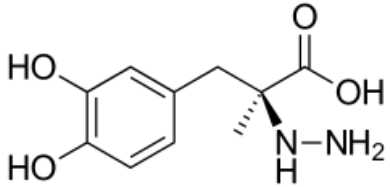


Dopamine

- A dopaminergic medication used to treat Parkinson's and some other conditions.
- A prodrug of dopamine, capable of crossing the blood brain barrier (dopamine cannot).
- Generally administered with carbidopa to inhibit peripheral decarboxylase activity.
- Increases concentrations of dopamine in the synaptic cleft.



Levodopa



Carbidopa

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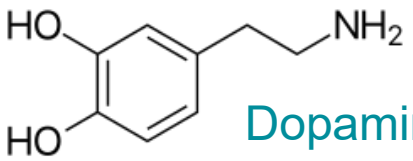
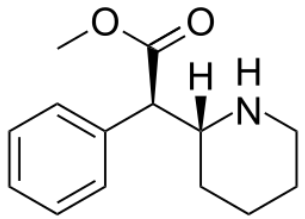
DRIs (Dopamine Reuptake Inhibitors)



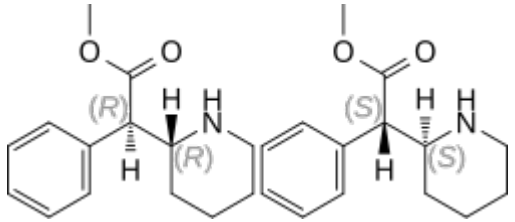
Dopamine

- Inhibition of DAT increases extracellular dopamine concentrations and dopaminergic neurotransmission
- Used for treatment of ADHD, narcolepsy, binge eating disorders, depression, smoking cessation
- Can have a high abuse potential
- Examples include bupropion (Wellbutrin), dexmethylphenidate, methylphenidate (Ritalin), amineptine

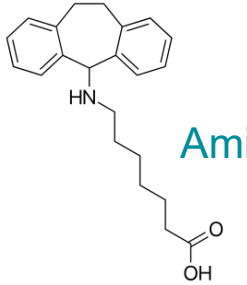
Bupropion



Dexmethylphenidate



Methylphenidate



Amineptine

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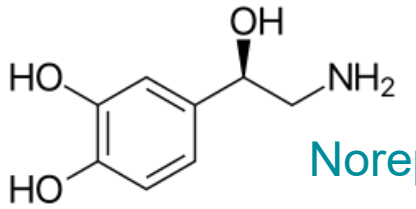
NET (SLC6A2)



Norepinephrine

- The norepinephrine transporter is another monoamine transporter, responsible for norepinephrine reuptake
- Norepinephrine regulates attention and response actions.
- Dysregulation of NET can lead to disorders like ADHD and psychiatric disorders.

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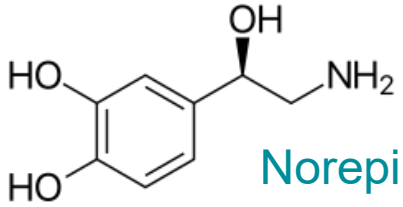
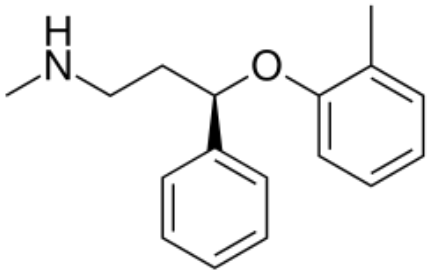
Drugs that Selectively Target NET (NRIs)

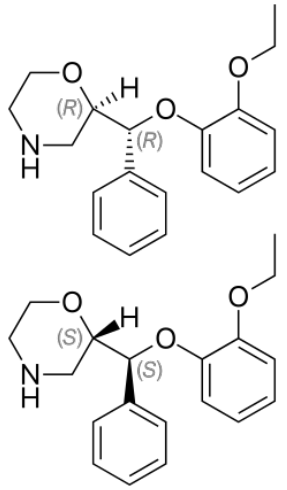


Norepinephrine

- Atomoxetine (Strattera): Primarily used to treat ADHD, selectively inhibits NET, increasing norepinephrine availability without affecting other monoamine transporters
- Reboxetine: Selective NET inhibitor, used in the treatment of depression (not approved in the US)



Atomoxetine



Reboxetine

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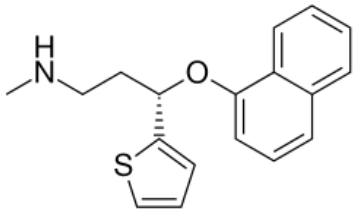
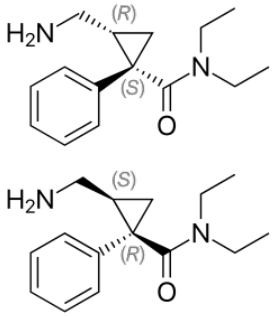
SNRIs (Serotonin-Norepinephrine Reuptake Inhibitors)

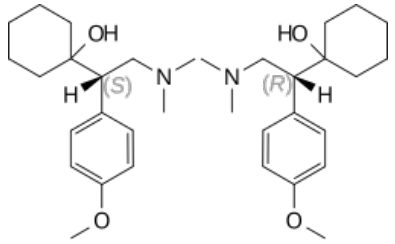
- Block both SERT and NET
- Duloxetine (Cymbalta): Used for depression, anxiety, pain (fibromyalgia).
- Milnacipran: Used for fibromyalgia, depression
- Venlafaxine (Effexor): Used for depression, anxiety, panic disorder, PTSD



Duloxetine



Milnacipran



Venlafaxine

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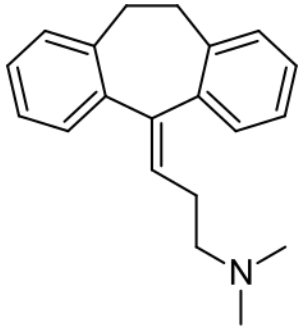
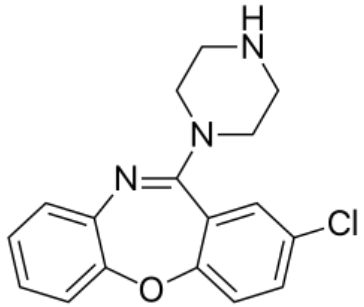
TCAs (Tricyclic Antidepressants)

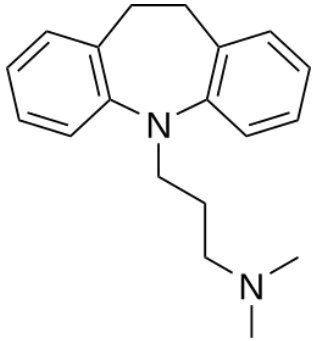
- Inhibit SERT and other transporters (NET)
- Used primarily for treatment of depression, also used for insomnia, migraine, and OCD
- Examples include Amitriptyline, Amoxapine, Imipramine



Amitriptyline



Amoxapine



Imipramine

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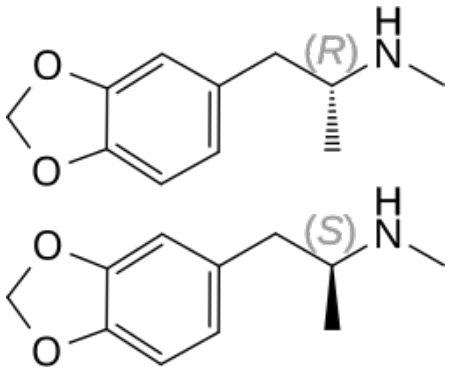
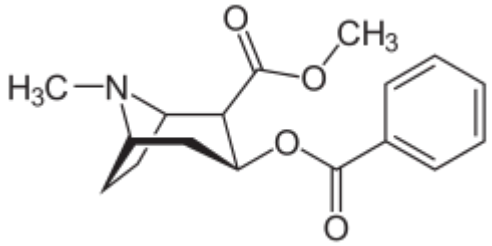
Other Drugs that Inhibit SERT, DAT, NET

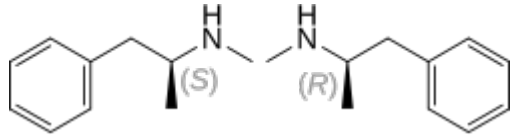
- MDMA (ecstasy) binds to SERT and triggers a massive release of serotonin, leading to psychoactive and empathogenic effects
- Cocaine binds to SERT, DAT, and NET and blocks reuptake, leading to rapid, massive increases in extracellular dopamine – stimulant with high abuse potential
- Ketamine, phencyclidine (PCP): DRIs
- Methamphetamine inhibits SERT (FDA approved for ADHD treatment)



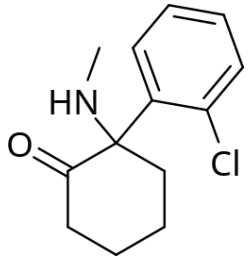
MDMA
(3,4-Methylenedioxymethamphetamine)



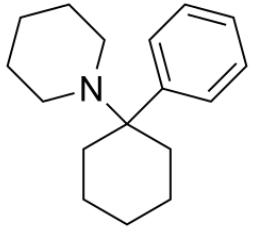
Cocaine



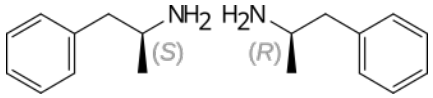
Methamphetamine



Ketamine



Phencyclidine



Amphetamine

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CNS Transporters - Summary

- Monoamine transporters (SERT, DAT, NET) are targets for a wide variety of neurological disorders, psychiatric disorders, and neurodegenerative diseases.
- Excitatory and inhibitory neurotransmission transporters (EAATs, GATs, GlyTs) could also be drug targets for neurodegenerative diseases, epilepsy, and others.
- Developing effective CNS medications requires solving two challenges simultaneously... Optimizing target specificity while still being able to cross the BBB.

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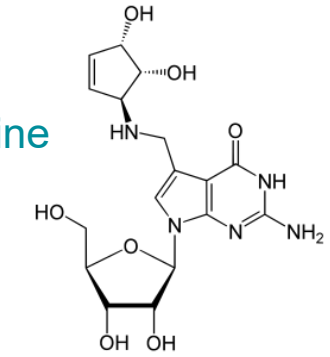
ELEVATING SCIENCE®

Something Very New: Q and q

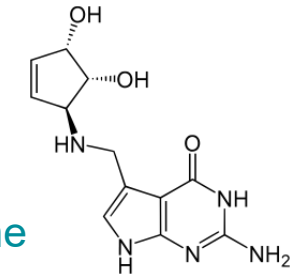
Something Very New

Queuosine



- Queuosine (Q) is found in the Wobble position of the anticodon of tRNAs specific for Asn, Asp, His, and Tyr in all eukaryotes – but is only produced by bacteria.
- Queuine (q) deficiency impairs aromatic amino acid hydroxylase enzymes, leading to deficiencies in serotonin, dopamine, norepinephrine, and melatonin – and may be a cause of diseases linked to these neurotransmitters.
- Q/q is essential for brain function, stress response, and possibly cancer prevention.

Queuine



Queuine: A Bacterial Nucleobase Shaping Translation in Eukaryotes.Ehrenhofer-Murray AE.J Mol Biol. 2025 Aug 15;437(16):168985. doi: 10.1016/j.jmb.2025.168985. Epub 2025 Feb 15.PMID: 39956693 **Free article.** Review.

Meet the psychobiome.Pennisi E.Science. 2020 May 8;368(6491):570-573. doi: 10.1126/science.368.6491.570.PMID: 32381701

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How Do Queuine/Queuosine Get Into the Brain?

- SLC35F2 has been identified as the sole transporter responsible for both queuine (K_m = 67 nM) and queuosine (K_m = 174 nM) uptake.
- SLC35F2 is selective for Q/q, and is not a general transporter for other nucleosides or nucleobases.

The oncogene SLC35F2 is a high-specificity transporter for the micronutrients queuine and queuosine.Burtnyak L, Yuan Y, Stojek E, Pan X, Gunaratne L, Silveira d'Almeida G, Fergus C, Martinelli M, J Reed C, Fernandez J, Patel BI, Marquez I, Ehrenhofer-Murray AE, Swairjo MA, Alfonzo JD, Green BD, Kelly VP, de Crécy-Lagard V.Proc Natl Acad Sci U S A. 2025 Jun 24;122(25):e2425364122. doi: 10.1073/pnas.2425364122. Epub 2025 Jun 17.PMID: 40526720

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SLC35F2

- Deficiencies in Q/q may be associated with various neurological issues due to deficiencies in serotonin, dopamine, norepinephrine, etc.
- But SLC35F2 has also been described as an oncogene, with overexpression correlated with a variety of cancers, and with poor prognosis.
- Further characterizing and finding drugs to modulate the activity of the SLC35F2 transporter could provide treatments for any number of diseases.

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Wrap-up

- Transporters are key determinants in how drugs can either gain entry or be excluded from the brain.
- At least in some cases, uptake transporters can overcome efflux transporters, allowing drugs to cross the BBB.
- CNS transporters are attractive targets to treat numerous neurological and neurodegenerative diseases.

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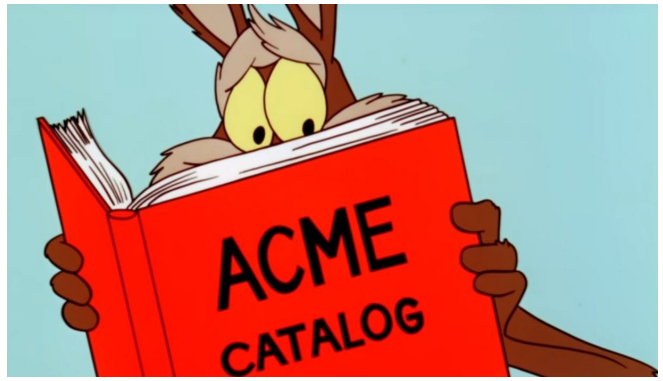
BBB/CNS Transporters



- We have assays available for many BBB transporters:
  - OATP1A2, OATP2B1, LAT1, MCT1, OCTN1, OCTN2, OCT2, OCT3, OAT2, OAT3, CNT1, CNT2, CNT3, ENT1, ENT2, CAT1, CAT3, ASCT2
  - BCRP, P-gp, MRP1, MRP2, MRP4
- We have assays available for many CNS transporters:
  - EAAT1, EAAT2, EAAT3, GlyT1, GlyT2, asc1, xCT, ASCT2, ATB0+
  - SERT, DAT, NET, GAT1, GAT2, GAT3, CAT1, CAT2, CAT3,
  - ChT, CRT1, CT1, BGT, ProT, SBAT1, DMT, AGC1, CTL1
  - ENT1, ENT2, ENT4, CNT1, CNT2, CNT3
  - SNAT1, SNAT2, OCT2, OCT3
- If we don't have the transporter assay available, our technology allows us to develop it quickly most of the time

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Transporters… Discover more!

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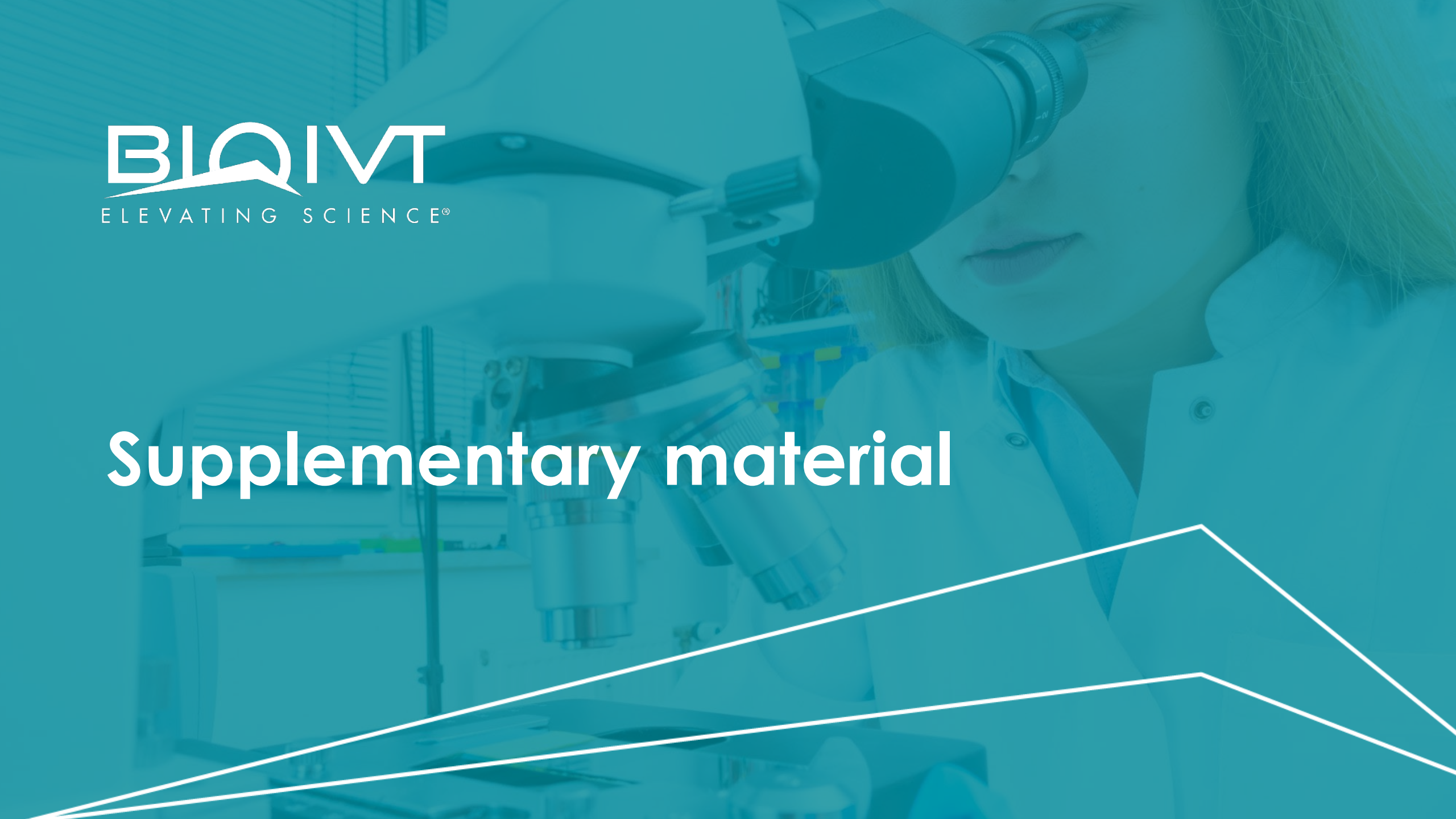
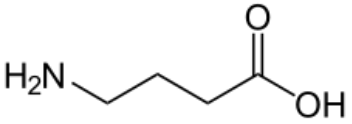


Supplementary material

GABA Transporters: GAT1, GAT2, GAT3, BGT1



GABA

- GABA transporters (SLC6 family) help to regulate inhibitory neurotransmission in the brain.
- Reabsorb GABA from the synaptic cleft into the cytoplasm.

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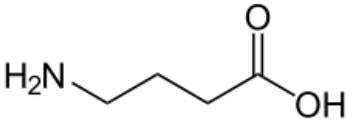
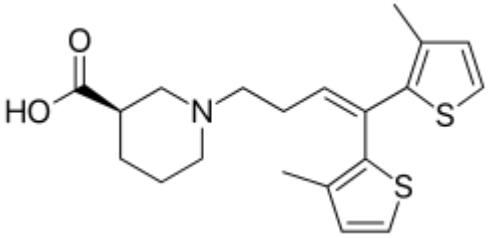
Drugs that Target GABA Transporters

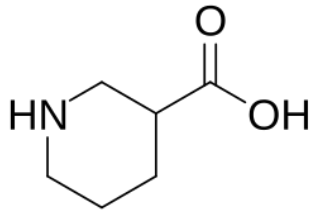


GABA

- Tiagabine (Gabitril): Anticonvulsant medication, used to treat epilepsy. Off label, used for treatment of anxiety and panic disorder.
- Nipecotic acid: Not used clinically (poor BBB penetration) but is used in research.



Tiagabine



Nipecotic acid

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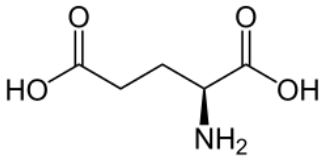
Glutamate Transporters: EAATs, VGLUTs



Glutamate

- Glutamate is the most abundant excitatory neurotransmitter in the CNS.
- Excitatory amino acid transporters (EAATs, SLC1A family) remove glutamate from the synaptic cleft by reuptake into glial cells and neurons.
- Vesicular glutamate transporters (VGLUTs, SLC17A family) move glutamate from the cytoplasm into synaptic vesicles.

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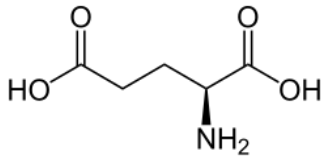
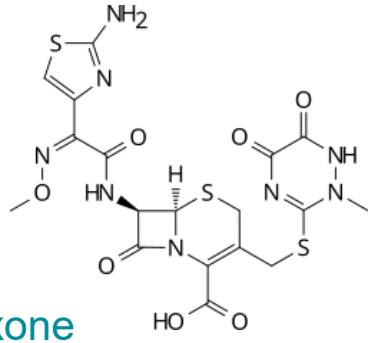
Drugs that Target Glutamate Transporters

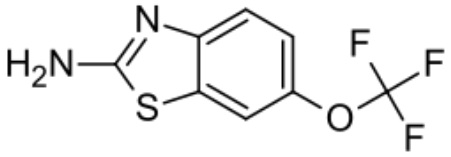


Glutamate

- Ceftriaxone (Rocephin): A beta-lactam antibiotic that also upregulates EAAT2 expression. May have potential to mitigate excitotoxic damage by reducing extracellular glutamate levels.
- Riluzole: Used as a treatment for ALS, it appears to stimulate glutamate clearance from the synapse.



Ceftriaxone



Riluzole

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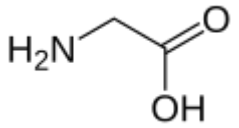
Glycine Transporters: GlyT1, GlyT2



Glycine

- Glycine is another inhibitory neurotransmitter in the CNS.
- The GlyTs mediate the reuptake of glycine from the synaptic cleft back into the presynaptic neurons.

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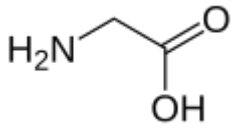
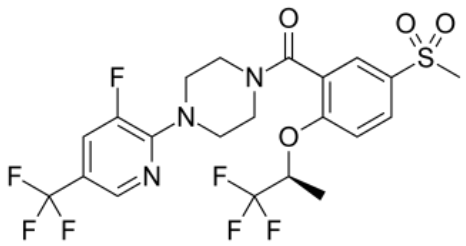
Drugs that Target Glycine Transporters

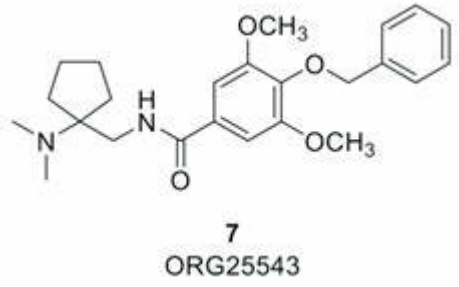


Glycine

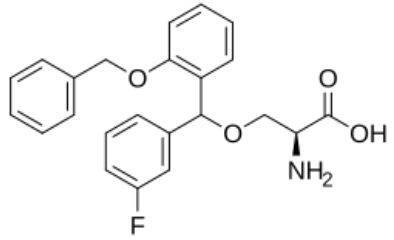
- Bitopertin: GlyT1 inhibitor, was in clinical trials for treatment of schizophrenia.
- ORG25543, ALX1393: Selective GlyT2 inhibitors, non-opioid analgesics with potential use in neuropathic pain



Bitopertin



ORG25543



ALX1393

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