MedNut Mail

The How, When, Where, Which and Why of pharmacotnutrition

Organic Anion Transporting Polypeptides (OATPs) and pharmaconutrition

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Editorial

Role and function

Organic Anion Transporting Proteins (OATPs) are influx transporters ie transport substrates from blood into organs and cells. OATPs can transport compounds that are relatively large and have a high degree of albumin binding under physiological conditions; they also mediate xenobiotic uptake.

In conjunction with the Organic Anion Transporters (OATs), the OATPs are important in hepatobiliary transport, renal secretion, intestinal absorption, and brain penetration of various compounds.

OATP inducers - increase OATP activity; currently none have been identified.

OATP inhibitors - slow or stop the rate of activity and transport.

OATP modulators - are compounds that interact with the OATPs to either enhance or reduce their activity.

OATP substrates – are compounds the OATPs transport; can also be inhibitors.

OATP Isoforms

There are 11 known isoforms of which -

- OATP1B1 + OATP1B3 have been studied extensively,
- OATP1A2 + OATP2B1 have limited data,
- the other 7 polypeptides are not well defined.

Summary of nutrition-related findings for the 11 known isoforms -

OATP1A2	
Role	• delivers thyroid hormones to the kidney, across the BBB, and excretion via the liver, • essential to all-trans-retinol uptake by retinal pigment epithelial cells, • has either a direct or indirect role in bile salt transport.
Location	all major organs including intestines, liver, kidney, lung, bile duct, retina, placenta, prostate, testes, brain and Blood Brain Barrier.
Substrates	retinoids, T4, T3, thyroxine, epicatechin gallate.

Inhibitors	include flavonoids, Ginkgo flavonoids, apigenin, kaempferol, quercetin, fruit juice, naringin (in grapefruit, orange juice), hesperidin, grapefruit compounds (at commonly consumed volumes), apple juice, tea leaf extract and catechins (epigallocatechin gallate), green tea flavonoid (epicatechin gallate), pomelo juice.
OATP1B1	**Included in drug discovery processes to minimise drug-drug interactions**
Role	monophasic (one binding site) and biphasic (two binding sites) capabilities.
Location	basolateral surface of hepatocytes (liver), kidney, intestine, blood-brain barrier, placenta, however there are many claims that this transporter is liver-specific transporter under normal physiological conditions.
Substrate	T4, T3, vitamin D3-glucuronide.
Inhibitors	include - naringenin, naringin, quercetin, daidzein (soy bean, soy products), genistein (lima bean, soy bean and products), glycyrrhizin (liquorice), caffeine, epigallocatechin gallate, epicatechin gallate, Silybin A + silybin B (Silybum marianum flavonoids), clementine and mandarin juice (nobiletin, sinensetin, and tangeretin). Ingestion of high amounts of polymethoxyflavones such as nobiletin, sinensetin, and tangeretin, may increase the risk of interactions with OATP1B1 xenobiotic substrates.
OATP1B3	**Included in drug discovery processes to minimise drug-drug interactions**
Location	basolateral surface of hepatocytes (liver), kidney, intestine, placenta, and the blood-brain barrier, however there are many claims that this transporter is liver-specific transporter under normal physiological conditions.
Substrate	eicosanoids, T3, T4, vitamin D3-glucuronide, vitamin D3-sulfate.

Inhibitors	include - various flavonoids from ginkgo (apigenin, kaempferol, quercetin), grapefruit (naringenin, naringin, rutin), daidzein (soy bean, soy products), genistein (lima bean, soy bean and products), glycyrrhizin (liquorice), caffeine, clementine and mandarin juice (nobiletin, sinensetin, and tangeretin). Ingestion of high amounts of polymethoxyflavones such as nobiletin, sinensetin, and tangeretin, may increase the risk of interactions with OATP1B3 xenobiotic substrates.
OATP1C1	
Role	specific, highly active Thyroid Hormone transporter.
Location	blood-brain barrier and in the testes.
Substrate	thyroid hormones.
OATP2A1	
OATP2B1	
Role	expression is regulated by thyroid hormones. transport activity is pH-dependent with enhanced activity at acidic conditions.
Location	multiple organs including heart, liver (hepatocytes), intestine (luminal membrane of enterocytes), kidney, blood-brain barrier, skeletal muscle, eye, lung, pancreas, spleen, testes, placenta, and ovary.
Substrate	quercetin, T3, T4, rT3, vitamin D3-sulfate.

Inhibitors	food inhibitors include grapefruit (naringenin, naringin, rutin), orange (hesperidin, sinensetin, didymin, narirutin), apple, (phloridzin, phloretin) ginkgo (apigenin, kaempferol, quercetin), daidzein (soy bean, soy products), genistein (lima bean, soy bean and products), glycyrrhizin (liquorice), caffeine, tea leaf extract, epicatechin gallate, epigallocatechin gallate, black cohosh extract, Echinacea extract, Milk thistle (Silybum marianum flavonoids). *in vitro* food inhibitors include - Apigenin (marjoram, parsley, Chinese cabbage, ginkgo), kaempferol (capers, cumin, caraway, dill, common pea, tarragon, cabbage—Brassica oleracea var., garden cress, ginkgo), quercetin (onion, Chinese cabbage, capers, black elderberry, ginkgo). A mixture of phloridzin, phloretin, hesperidin, and quercetin at the concentrations present in apple juice could significantly inhibit OATP2B1.
OATP3A1	
Role	maintain stable retinoid signalling. Note - disruption of retinoid signalling may be an opportunity for male fertility management (male contraception).
Location	Testes.
Substrate	retinoids.
OATP4A1	
OATP4C1	
Location	kidney specific.
Substrate	thyroid hormone (tri-iodothyronine).
OATP5A1	
Role	a determinant of cell shape, differentiation and motility.
Location	foetal brain, prostate, skeletal muscle and thymus.
OATP6A1	

Transporter deficiencies

OATP deficiencies can be long term or short term, and are likely due to -

1. **Inherited metabolic disorders** – such as Pachydermoperiostosis – a mutation in OATP2A1 that results in increased PGE2 (arachidonic acid derived prostaglandin E2) levels and decreased PGE3 (eicosanoic acid derived prostaglandin E3) ie eicosapentanoic acid and docosahexanoic acid levels;
2. **Polymorphisms (variants)** – variations of a specific DNA sequence that can involve either a single nucleotide (aka single-nucleotide polymorphism, or SNP), or a longer DNA sequence; examples include –
    a. OATP1A2 - associated with a range of polymorphisms, and is involved in the neurodegenerative disease supranuclear palsy;
    b. OATP1B1 - expression of the polymorphism (rs4149056) increases the risk for statin-induced myopathy which affects 10–20% European and Middle Eastern populations and 10–15% East Asian populations;
    c. OATP1B1 and OATP1B3 – polymorphisms increase liver inefficiency in bilirubin uptake resulting in serum accumulation and jaundice;
3. **Environmental** – likely to manifest at any age and is dependent upon the environmental insult; identified inhibitors include –

    a. fruit juices - grapefruit, Seville orange, lemon, apple, mulberry;

    b. vitamin D deficiency – decreases OATP1B1/2B1 expression in the liver;

    c. eicosanoid deficiency (eicosapentanoic acid, docosahexanoic acid) – decreases OATP2A1, and thus alters the composition of membrane lipids which can then alter transporter conformation such as partial misfolding or modifications;

    d. *in vitro* - Apigenin (marjoram, parsley, Chinese cabbage, ginkgo), kaempferol (capers, cumin, caraway, dill, common pea, tarragon, cabbage—Brassica oleracea var., garden cress, ginkgo), and quercetin (onion, Chinese cabbage, capers, black elderberry, ginkgo).

    There is speculation that even micromolar concentrations of naringin may confer an inhibitory effect on OATP1A2.

    e. others include – T4, T3, rT3.

It seems to me that we really do need to know which nutrients and foodstuffs are OATP substrates and inhibitors, whether their intakes are dose-dependent, and

duration of their effect on the transporters so we can determine the best time to administer therapeutic interventions to compensate for inadequate nutrient uptake.

What actions will you initiate when you see someone whose prescribed medicines are transported by an OATP will you –

- clarify adequacy of dietary intake of retinoids, eicosanoids and vitamin D, request blood tests, and then compare findings?
- if there is disagreement between oral intake and blood test results, will you question altered expression of one or more OATPs?
- clarify thyroid function?
- recommend nutrient interventions be administered at different times from the prescribed medicines?

Conclusions

Our knowledge about the extent OATPs impact our nutrient uptake and transport is very limited, primarily because there has been a reasonable level of investigation into only two of the eleven known isoforms. From the limited evidence we do have, altered availability of any of the OATPs can have significant health impacts.

Case study

Medical History with Nutritional Aspect

Amputation	☐	Constipation	☐	Dysphagia	☐	MND	☐
Anaemia	☐	CVA	☐	Enteral Feed	☐	MS	☐
Arthritis	☐	CVD	☐	Falls	☐	Osteoporosis	☐
Cancer	☐	Dementia	☐	Fracture	☐	PD	☐
CCF	☐	Dentures	☐	Frailty	☐	Pressure Area	☐
Chest Infection	☐	Depression	☑	Gout	☐	Renal	☐
COAD	☐	DM Type 1	☐	Hypertension	☐	Ulcer	☐
Confusion	☐	DM Type 2	☐	Incontinent	☐	UTI	☐

Food Allergies: Chronic Regional Pain,

Other: unusual neurological nasty

Biochemistry with Pharmaconutrition Consequences

No recent relevant results available.

Medications That May Adversely Affect Nutritional Status

Drug	Vits + Mins	bpp	>90%	N/V	C/D	Wt	App	Tst	Thir	Sal	Drlg	d m	Dys	BSL
Cholecalciferol	(1/day)	☐	☐					☐				☐	☐	☐
Clonazepam		☐	☐	NV	C	↕	↕	☐		↑		☐	☑	☐
Clonidine	carnitine	☐	☐	NV	C		↓	☐				☑	☐	☑
Duloxetine		☐	☐	NV				☐				☑	☐	☐
Esomeprazole	(40 mg/day) B1, B12, Ca, Fe,	☑	☐	NV	CD	↑		☑				☑	☐	☐
Folic Acid		☑	☐					☐				☐	☐	☐
Frusemide	(160 mg/day) Ca, Cl, K, Mg, Na	☑	☐	NV	CD		↓	☐				☑	☐	☑
Lactulose		☐	☐	NV	D		↓	☐				☐	☐	☑
Levetiracetam	D	☐	☐	NV	D	↑	↑	☐				☑	☐	☐
Lorazepam		☑	☐	NV			↕	☐		↑		☑	☐	☐
Methadone		☑	☐	NV	C			☐				☑	☐	☐
Metoprolol		☐	☐	NV	CD	↑		☑				☑	☐	☑
Paracetamol		☐	☐	NV	CD			☐				☐	☐	☐
Pregabalin		☐	☐	NV	CD	↓	↑	☑		↑		☑	☑	☐
SENOKOT		☐	☐		D			☐				☐	☐	☐
		▩	☐					▩				▩	▩	▩

Extra drug: Mg (2/day), B6 (12.5 mg x 2/wk), B1(100 mg/day)

Transporter-mediated interactions and nutrients

Transporter	OCT1		OCT2		OCT3		THTR2		OCTN1		MATE1		MATE2	
Nutrients - Sub	B1, choline, carnitine		B1, choline, creatinine		B1		B1, B6		carnitine		B1, creatinine		B1, carnitine, creatinine, NMN	
Nutrients - Inh														
Location	intestines, liver		kidney		intestines, liver, kidney		Intestines, breast, adipose tissue, placenta		Intestines, kidney		Liver, kidney		kidney	
DRUG	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**
Clonazepam		Y												
Clonidine		Y			Y							Y		Y
Duloxetine				Y										
Esomeprazole		Y												
Lorazepam		Y												
Methadone				Y										
Metoprolol				Y										
Sub – substrate, Inh – inhibitor, B1 – thiamine, B2 – riboflavin, B3 – nicacin, B5 – pantothenic acid, B6 – pyridoxine, B7 – biotin, B9 – folic acid, B12 – cobalamin, NMN – N-methylnicotinamide														

Comments – medication and nutrition impacts only

I called this person Mr AYM which stands for “Angry Young Man” as he had every right to be angry as it seems there was significant room for improvement in his overall management – especially during his hospitalisations.

I have not named Mr AYM’s yukky neurological nasty as it is sufficiently unusual that there is a risk that he may be identified.

Data summary

Biochemistry

No recent relevant biochemistry available – “old” blood test results indicate -

- ? high B6 - path lab report indicates this can be understated in the presence of anaemia. Sustained high pyridoxine intake is associated with increased risk of irreversible peripheral neuropathy. Given current result advisable to consider a trial of reducing frequency of dose to second-daily or weekly or even a "pyridoxine holiday" for 3 months
- high folate - evidence indicates elevated folate levels diminish cognitive

function therefore advisable to review current intervention and consider either a "folate holiday" for 6 months or a reduced frequency of intervention such as weekly.

Glycaemia

Currently prescribed 6 medications that alter glycaemia.

Pharmaconutrition

Currently prescribed 12 medications that include nausea and vomiting as side effects.

Currently prescribed 9 medications that include diarrhoea and dry mouth as side effects.

Currently prescribed 8 medications that include constipation as a side effect.

Currently prescribed 7 medications that include altered appetite as a side effect.

Currently prescribed 6 medications that include hypokalaemia as a side effect.

Currently prescribed 4 medications that include tremor and sweating as side effects.

Currently prescribed 3 medications that include hyponatraemia and altered salivation as side effects.

Calcium and vitamin D interventions recommended whilst clonazepam prescribed – currently only prescribed a vitamin D intervention.

Clonidine inhibits carnitine and choline uptake.

Esomeprazole decreases B12, vitamin C, magnesium, zinc, and iron absorption, may decrease calcium absorption, and decreases thiamine availability.

Frusemide increases urinary excretion of calcium, magnesium, potassium, sodium and thiamine.

Chronic use of lactulose and Senokot may promote excessive loss of water and electrolytes, especially potassium, and their regular monitoring recommended.

Levetiracetam may decrease vitamin D availability.

Dietary levels of caffeine intake in conjunction with paracetamol inhibit antinocieception.

Concurrent ingestion of paracetamol and iron resulted increased rate of iron absorption and decreased extent of drug absorption; the authors advise drug and iron to be administered at different times from each other.

Pregabalin may decrease folate availability.

Currently prescribed vitamin D (1 tab/day). Vitamin D tabs typically provide 25 mcg vitamin D per tab (25 mcg vitamin D is equivalent to 1000 IU vitamin D). Vitamin D is associated with conferring neurological protection. Advisable to clarify vitamin D

status and if still low then review current management strategy.

Currently prescribed the daily double ie two drugs that compromise magnesium status - being frusemide and esomeprazole. Magnesium deficiency manifests as confusion, disorientation, personality changes, loss of appetite, depression, muscle cramps, tingling, numbness, hypertension, cardiac dysrhythmia, seizures. Cellular magnesium status is unknown whilst magnesium levels within acceptable range however if magnesium levels are low then typically indicates significant cellular depletion and intervention recommended. Currently prescribed 2 x Magmin that provide about 74.8 mg elemental magnesium. Last blood test indicated low/marginal magnesium levels; men require 420 mg elemental magnesium/day. Since Mr AYM has an unusual neurological nasty, and is prescribed two drugs that decrease magnesium availability, advisable to consider a magnesium intervention that provides about 300 mg elemental magnesium per day. Evidence indicates non-food sources of magnesium > 300 mg/day are likely to cause side effects.

Bowel management

Regular aperients prescribed.

No PRN interventions prescribed.

No Nurse Initiated interventions administered.

Staff comments

Staff advise Mr AYM eats well .

Observations

Mr AYM is a tall, big-framed, well-covered, young man who initially did not want to speak to me, however ultimately agreed to do so. We discussed a number of issues and he told me -

- that prior to his fall (that resulted in his extended hospitalisation) he had limited vision and could not feel his feet;

- he was very low in a number of vitamins and minerals at time of hospitalisation, especially vitamin B12 and had several injections to increase his levels;

- he was commenced on heroin as a pain management strategy ie iatrogenically induced drug addiction (which was not made clear in the Notes), and then commenced on methadone in order to be managed in a Nursing Home.

Mr AYM's weight has fluctuated within a 10 kg range since admission; post recent hospitalisation his weight has seemingly dropped slightly; frusemide dose has not changed since admission.

We also discussed -

- increasing vitamin D dose to which he was agreeable,

- commencing vitamin C intervention - 500 mg bd to support pain management, and to reduce pain-induced oxidative stress,

- commencing a probiotic intervention such as inner health. Mr AYM is prescribed esomeprazole – proton pump inhibitors are associated with altering the gut microbiota population - this intervention may modify his gut environment.

Pharmaconutrition assessment

Zinc and copper share the same absorption mechanism and excessive zinc reduces copper absorption. Advisable to clarify both zinc and copper levels as copper deficiency can manifest as a myeloneuropathy.

Currently prescribed a significant pyridoxine intervention – possibly at the request of family – however advisable to clarify status and monitor on an ongoing basis ie at least 6-monthly.

Mr AYM's diagnoses include chronic pain - nutritional factors that may be useful to consider in pain management include -

- vitamin D - current intervention may not be adequate to attain adequate range. Evidence indicates increasingly brittle pain control with decreasing vitamin D levels. Currently prescribed levetiracetam which decreases vitamin D status directly, and esomeprazole and frusemide which decrease vitamin D status indirectly by decreasing magnesium availability (magnesium is important in the activation of vitamin D). Advisable to clarify vitamin D status and if still low then review current vitamin D management strategy.

- vitamin C - pain increases the reactive substances (formerly Reactive Oxygen Species) within cells. Vitamin C is important in quenching reactive substances and if there is insufficient vitamin C then cell status becomes compromised and the cells typically die which also causes pain. Advisable to consider a vitamin C intervention - the optimal intervention is 500 mg vitamin C/day (if more than 500 mg vitamin C administered at a time then the excess above 500 mg is not absorbed as the vitamin C transporters are overloaded). Vitamin C is not considered part of the pain management armament however it won't cause harm and evidence suggests it may confer benefit. Currently prescribed esomeprazole which decreases conversion of vitamin C to its active form, and both esomeprazole and frusemide decrease magnesium availability which is also important in activating vitamin C.

- low B12 exacerbates elevated TNF- α which is an inflammatory response marker; elevation of the inflammatory response can include a pain response and currently prescribed esomeprazole therefore advisable to clarify B12 status. There is

disagreement between pathology ranges and research findings with regard to appropriate B12 levels - neuro-imaging research indicates B12 interventions are effective once levels are less than 300 pmol/L.

- magnesium – proposed mechanism magnesium blocks the NMDA receptor channels in the spinal cord and thus limits the influx of calcium ie reduces the risk of excitotoxicity and consequent exacerbation of pain. Currently prescribed esomeprazole and frusemide which decrease magnesium availability - although a magnesium intervention is prescribed it is likely to be inadequate to meet Mr AYM's current requirements.

What else would you include?

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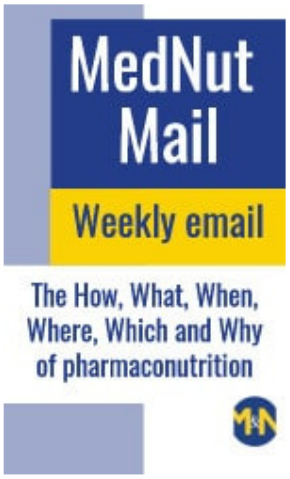

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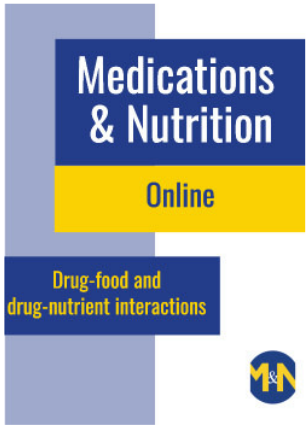

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