MedNut Mail

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

Organic Anion Transporters (OATs) and pharmaconutrition

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Editorial

Role/function

OATs are primarily influx transporters albeit some are bidirectional, that with their multi-specific binding pockets are able to transport a wide variety of anionic and cationic substances into the kidney and then regulate their rate of excretion.

OATs are important rate limiters in -

the transfer of small organic molecules	including endogenous factors such as antioxidants, carnitine, citrate, citrulline, CMPF (3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid - a furan fatty acid metabolite found in fish oils, vegetable oils, butters, and other foods and disrupts pancreatic β cell function, leading to glucose intolerance); creatinine, dehydroascorbic acid (vitamin C), deoxycarnitine, flavin mononucleotide and folic acid, homovanillic acid (HVA), mannitol, melatonin, mercury, niacin, nicotine, pantothenic acid, pyridoxal, pyridoxate, pyridoxic acid (pyridoxine), salicylate, sorbitol, urate (uric acid salt) and uric acid
across epithelial barriers	including kidney, liver, brain, eye, intestine, olfactory, placenta
and between body fluid compartments	Including blood-central nervous system, blood-urine, intestine-blood, blood-bile, blood-placenta, and others

OATP Isoforms

There are 11 known human isoforms as summarised -

OAT1	**Included in drug discovery processes to minimise drug-drug interactions**
Role	prefers hydrophilic compounds; important in the regulation of gut microbe–dependent metabolism, and the mediation of host and microbiome communication; transports uric acid and prostaglandin E2 (a downstream product of arachidonic acid metabolism);

	important in the regulation of systemic lipid metabolism and potential lipid-mediated signalling, regulation/modulation of proximal tubule energy metabolism and intracellular signalling within the proximal tubule, regulation of tryptophan metabolism and clearing tryptophan-related metabolites from the circulation by promoting their uptake by the kidney; may function in the sensing of odorants and/or short chain fatty acids.
Location	basolateral membrane of the renal proximal tubule cells, choroid plexus of the brain, eye, olfactory, placenta.
Substrates	folic acid, pantothenic acid, pyridoxic acid (pyridoxine), uric acid, creatinine, homovanillic acid (HVA), mercury.
Inhibitors	lithospermic acid, rosmarinic acid, salvianolic acid A, salvianolic acid B, tanshinol, Geranium tuberosum, Camphorosma Lessingii, Polygonum hydropiper, decaffeoylquinic acid, ginkgolic acid, ursolic acid, wedelolactone, baicalein, wogonin, luteolin, quercetin, viscidulin III, 18-b glycyrrhetinic acid, rhein (a lipophilic anthraquinone in rhubarb).
Biomarker	kynurenic acid – a metabolic intermediary from tryptophan metabolism, 4-pyridoxic acid (pyridoxine).
OAT2	
Role	minor contribution to the uptake of many negatively charged organic substances such as cyclic nucleotides and creatinine.
Location	basolateral membrane of renal proximal tubule cells, sinusoidal membrane of hepatocytes (liver), choroid plexus (brain), small intestine, lung, heart, skeletal muscle, corneal epithelium of the eye, placenta, red blood cells.
Substrate	niacin, pyridoxic acid (pyridoxine), homovanillic acid (HVA), salicylate.
OAT3	**Included in drug discovery processes to minimise drug-drug interactions**
Role	prefers hydrophobic compounds;

	transports uric acid, metabolites associated with flavonoids, tryptophan, phenylalanine and tyrosine, bile acids, endogenous metabolites; important in metabolite and signalling pathways; important in xenobiotic metabolism such as dietary components and benzoates; important regulator in tryptophan metabolism; modulates the levels of metabolites flowing through intestine, liver, and kidney; mediates the renal secretion of bile acids; is a crucial mediator of metabolic waste removal; important in the regulation of gut microbe–dependent metabolism, as well as inter-organismal communication between the host and microbiome; may have a role in the sensing of odorants and/or short chain fatty acids.
Location	basolateral membrane of the renal proximal tubule cells, brain capillary endothelium and choroid plexus, cerebrospinal fluid (CSF) to the blood, eyes, retinal vascular endothelial cells, liver, testes.
Substrate	pantothenic acid, carnitine, citrate, citrulline, melatonin, mannitol, sorbitol, salicylate, creatinine, uric acid, pyridoxal, pyridoxate, pyridoxic acid (pyridoxine), dehydroascorbic acid (vitamin C), deoxycarnitine, flavin mononucleotide (folic acid), homovanillic acid CMPF (3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid - a furan fatty acid metabolite found in fish oils, vegetable oils, butters, and other foods).
Inhibitors	lithospermic acid, rosmarinic acid, salvianolic acid A, salvianolic acid B, tanshinol; flavonoids – (strongest to weakest) Galangin, Chrysin, Kaempferol, Oroxylin A, Wogonin, Apigenin, Luteolin, Gossypetin, Quercetin, Mulberrin, Eriodictyol, Fisetin, Daidzein, Taxifolin, Apigetrin, Isoquercetin, Wogonoside, Myricetin; Anchusa azurea, Astracantha microcephala, Chaerophyllum bulbosum, Echium russicum, Glycyrrhiza glabra (licorice), Juncus

	effusus, Juniperus oblonga, Mentha longifolia, Primula macrocalyx, Symphytum asperum, Thymus kotschyanus; dicaffeoylquinic acid, ginkgolic acid, dioscorealide B, wedelolactone, oroxylin A, wogonin, luteolin, viscidulin III, scullcapflavone II, rhein (a lipophilic anthraquinone from rhubarb).
Biomarkers	kynurenic acid – a tryptophan metabolite, 4-pyridoxic acid (pyridoxine).
Upregulator	Vitamin D
OAT4	
Role	uric acid transporter; contributes to reabsorption of organic anions, including uric acid, from the urine back into proximal tubular cells; mediates the reabsorption of perfluorinated chemicals.
Location	the apical membrane (urine side) of the renal proximal tubule cells, brain, adrenal gland, placenta.
Substrate	pyridoxic acid (pyridoxine), uric acid.
Inhibitors	dicaffeoylquinic acid, glycyrrhetinic acid, catechin.
OAT5	
Role	involved in liver detoxification processes.
Location	sinusoidal membrane of hepatocytes (liver), almost exclusively in embryonic and adult liver, kidneys.
OAT6	
Role	exact role in the olfactory mucosa remains undefined, can interact with volatile odorants (e.g., propionate, butyrate), may function in the sensing of short chain fatty acids.
Location	olfactory - nasal epithelia, testes.
OAT7	

Role	involved in liver detoxification processes.
Location	sinusoidal membrane of hepatocytes (liver).
OAT8	
Location	kidney, liver.
OAT9	
Location	liver.
Substrate	carnitine.
OAT10	
Role	transports nicotine and uric acid, the reabsorption of substances from the tubular fluid.
Location	apical membrane of renal proximal tubule, small intestine, colon, brain, heart.
Substrate	uric acid, nicotine.
URAT1	
Role	uric acid homeostasis, uric acid transporter - mainly responsible for the reabsorption of urate via monocarboxylates exchange, coupled to maintenance of the redox state, the reabsorption of substances from the tubular fluid, mediates the reabsorption of perfluorinated chemicals, important in reactions related to ROS (Reactive Oxygen Species aka Reactive Substances) detoxification and maintaining cellular redox via peroxidation reactions relying on Vitamin C metabolism, maintenance of cofactors in the reduced state.
Location	apical membrane (urine-facing side) of the renal proximal tubule, liver, smooth muscle, lung.
Substrate	urate.

Transporter deficiencies

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

1. **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.

   There are many identified OAT-related polymorphisms, for example several OAT4 and URAT1 SNPs are associated with the urate handling anomalies of hyperuricaemia and hypouricemia;

2. **Epigenetic - e**pigenetic regulatory mechanisms are dynamic, potentially inheritable, processes which alter transcriptional activity without affecting DNA sequence and represent a key mechanism for the response to environmental and other changes.

   There is increasing evidence of epigenetic regulation of OAT transporter expression levels with potential functional consequences.

3. **Environmental** – likely to manifest at any age and is dependent upon the environmental insult -

   Identified inhibitors include –

   a. cigarette smoke condensate (CSC) cis-inhibited OAT substrate uptake in OAT1- and OAT3-transfected HEK293 cells, in a concentration-dependent manner;

   b. EGCG (epigallocatechin-3-gallate) is an abundant, potent catechin representing 50−80% of the total catechins, is a component of green tea, and inhibits -

      - OAT1 - mixed-type inhibition,
      - OAT3 - competitive inhibition.

      The low EGCG availability in usual tea drinking quantities is unlikely to cause harm, however the risk of harm is increased if there is consumption of high-dose EGCG supplements, and/or consumption of a green tea extract supplement containing multiple inhibitors, and/or decreased renal function such as in the elderly and chronic kidney disease.

   Consequences of inhibition -

   a. OAT1 unavailability alters many metabolic pathways including fatty acid, carnitine, biotin, and many others;

   b. OAT3 unavailability alters many metabolic pathways including tryptophan, phenylalanine and tyrosine, pyridoxine, benzoate, and others;

c. substrates being at risk of decreased renal elimination which means increased plasma exposure to xenobiotics and endogenous metabolites;
d. OAT1/3 inhibition conferring protection against mercury-induced renal damage;
e. increased plasma pCS concentrations (a uremic toxin) in diagnosed Chronic Kidney Disease even with only one OAT1/3 inhibitor prescribed;
f. partial inhibition or competition for OAT1 may increase the risk of metabolic syndrome in part through altering lipid metabolism;
g. uric acid-induced reduction in OAT1 membrane distribution which can be normalised with folic acid.

OAT1 and OAT3 inhibition can confer either harmful or beneficial impacts. For example, concurrent administration of the antiviral nucleoside analogue cidofovir and the strong OAT1 and OAT3 inhibitor probenecid prevents cidofovir-induced nephrotoxicity – proposed mechanism of action is inhibition of cidofovir uptake.

Can we use transporter inhibition as a strategy to increase nutrient uptake or improve nutritional health? There is now an increasing number of examples whereby drug inhibition of a transporter is a means for increasing cellular or organ uptake of a second drug. I suggest the precedent is established, and all we have to do is

(a) try and find some evidence in the nutrition sphere,

(b) start discussions in team meetings and possibly with treating GPs about trialling this intervention option, and

(c) for those in a position to trial then monitor excessively, document and publish.

What actions will you initiate when you see someone prescribed some medicines that are transported by an OAT will you –

- clarify adequacy of dietary intake of folic acid, pantothenic acid, pyridoxine, niacin, vit C and carnitine, request blood tests, and then compare findings?
- question whether elevated creatinine and/or uric acid levels are related to the disease or the treatment?
- if there is disagreement between oral intake and blood test results, will you question altered expression of one or more OATs?
- recommend nutrient interventions be administered at different times from the prescribed medicines?

Conclusions

The primary function of OATs is to transport substances to organs and cells, and therefore are very important in the utilisation of a range of nutrients. As is now becoming increasingly common with pharmaceutical interventions, we need to be considering how to utilise transporter function to optimise nutritional health.

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:

Other: iatrogenic hyperthyroidism, PA ® heel

Biochemistry with Pharmaconutrition Consequences

Na:	141	mmol/l	Hb:	138	g/L	Albumin:	37	g/L	BSL:		mmol/l
K:	4.2	mmol/l	Lymph:	1.7		Total Protein:	69	g/L	HbA1C:		
Urea:	5.0	mmol/l	MCV:	89	mmol/l	B12:		pmol/L	INR:		
Creatinine:	0.048	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:	4.46	mIU/L

Other: eGFR > 60, T4 21.4, T3 3.9, vit D 89

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
Amlodipine		☑		NV	CD	↕	↕	☑				☑	☑	☐
Cholecalciferol	(1/day)	☐						☐				☐	☐	☐
COLOXYL WITH S		☐			D			☐				☐	☐	☐
OXYNORM		☐		NV	CD		↕	☑	↓			☑	☑	☐
Paracetamol		☐		NV	CD			☐				☐	☐	☐
Thyroxine	(50 mcg/day) A, Ca, carnitine,	☑		V	D	↓		☐				☐	☐	☑
		▩						▩				▩	▩	▩

Extra drug: norspan, enprocal (100 mL tds)

Comments – medication and nutrition impacts (direct and indirect) only

Data summary

Biochemistry

Relatively recent available biochemistry indicates elevated TSH + elevated T4 - thyroxine dose modified.

Glycaemia

Currently prescribed 4 medications that alter glycaemia, being amlodipine, oxycodone, paracetamol, levothyroxine.

Pharmaconutrition

Currently prescribed 5 medications that include diarrhoea as a side effect.

Currently prescribed 4 medications that include vomiting as a side effect.

Currently prescribed 3 medications that include nausea, constipation sweating and tremor as side effects.

Chronic use of coloxyl + senna may promote excessive loss of water and electrolytes, especially potassium, and their regular monitoring recommended.

Amlodipine impairs zinc status.

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.

Thyroxine triples urinary excretion of carnitine.

Bowel management

Regular aperient prescribed,

No PRN interventions prescribed,

No Nurse Initiated interventions administered.

Staff comments

Staff advise Mrs ACI is often drowsy at breakfast and midday meals and that the drowsiness impacts on her food intake. Staff also commented Mrs ACI wakes as the day progresses and that she eats well in the evenings - from these comments it seems Mrs ACI is an owl rather than a fowl.

Observations

Mrs ACI is a small pale frail lady who was sitting in a fallout chair in the Day Room - she told me she eats well and that the food tastes as good as what she had at home - she refused to answer further questions as she does not know me.

As Mrs ACI is pale and is currently prescribed paracetamol, advisable to check iron levels and if low then short term intervention recommended.

Mrs ACI's weights are unavailable as she broke her femur resulting in hospitalisation, and then was unable to be weighed for some time therefore adequacy of dietary intake and thyroxine intervention are unknown.

If weekly weighs identify a weight loss trend, then advisable to clarify thyroid function status.

Thyroxine dose is directly related to weight status and as weight status changes so does drug effectiveness therefore advisable to closely monitor thyroid function and weight status during the healing process.

Both vitamin D and amlodipine are P-gp substrates and inhibitors – vitamin D levels are well within acceptable range however is that due to the cholecalciferol intervention, or amlodipine inhibiting P-gp?

Nutritional factors that contribute to wound healing include -

- weight gain of at least 2-3 kg - indicates adequate energy consumed to free protein for wound healing duties and some extra energy to store as fat for an emergency; weight loss delays the wound healing process and currently prescribed thyroxine therefore advisable to clarify adequacy of the thyroxine intervention, especially since an elevated TSH is noted.

Mrs ACI's diagnoses include falls - nutritional factors that may be useful to consider in falls management include -

- loss of weight – prescribed thyroxine which may alter thyroid function and therefore weight status, therefore advisable to clarify adequacy of the thyroxine intervention, especially since an elevated TSH is noted;

- low iron – currently prescribed paracetamol therefore advisable to check status;

- low carnitine - carnitine is both absorbed and produced de novo, and is important in a range of muscle functions; thyroxine decreases carnitine availability therefore advisable to clarify status.

What else would you include?

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