MedNut Mail

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

Multidrug Resistance Proteins (MRPs) and pharmaconutrition

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1st August 2023

https://medicationsandnutrition.online

Editorial

Role/function

Multidrug resistance proteins (MRPs) are efflux transporters and as such are responsible for the movement of a wide variety of both endobiotics (endogenous substances that influence the functioning of an organ or biological process. [Wiktionary]) and xenobiotics (foreign compounds not produced by an organism's metabolism, or biological substances present in excessive concentrations), across plasma and intracellular membranes, primarily into the bile duct. MRPs are important in both the regulation of physiological processes and the development of multidrug resistance.

Each MRP has unique physiological and pharmacological functions as well as unique membrane and tissue distributions. Although some MRPs may have some substrates in common only one MRP will export it.

MRP are involved in glutathione (GSH) homeostasis and export. MRP proteins both regulate GSH efflux, and also transport oxidized glutathione derivatives such as glutathione disulfide, S-nitrosoglutathione, glutathione-metal complexes, and other glutathione S-conjugates.

Since glutathione, which is ultimately a metabolic intermediary, is transported by so many of the MRP transporters, I backtracked its metabolic pathway –

Glutathione backtrack …!

inadequate glutathione is a cause of oxidative stress,

glutathione is derived from a combination of 3 amino acids – being cysteine, glutamate and glycine,

cysteine is the rate-limiting precursor for glutathione, and is derived from methionine metabolites,

methionine is derived from the B12 – folate cycle, (part of one-carbon metabolism) and ultimately regulates cysteine availability,

riboflavin is the rate limiter for one-carbon metabolism.

MRP Isoforms

There are 12 known human isoforms as summarised -

MRP1	**Long MRP**
Role	excretes a broad range of endogenous and exogenous substances; involved in inflammation, detoxification, and oxidative stress; transports organic anions, particularly glutathione conjugates, and works in tandem with the glutathione detoxification system; exports physiologically important molecules including proinflammatory molecules (e.g., leukotriene C4), hormones (e.g., estrogens and prostaglandins), and antioxidants (e.g., oxidized and reduced glutathione); regulates the availability of intracellular glutathione; inadequate availability of glutathione-dependent antioxidants is a cause of ferroptosis; protects placental cells from methyl-mercury-induced oxidative stress by both exporting the toxic metal and by maintaining the placental cells' GSH status in equilibrium; essential for the proper function of trophoblasts (important in early pregnancy); regulates intracellular redox status by extruding either reduced or oxidized GSH; utilized by astrocytes to provide neurons with substrates for GSH synthesis.
Location	ileum, kidney, placenta, brain, ubiquitous.
Substrates	B12, methyl mercury, organic anions, GSH conjugates, cysteinyl leukotrienes.
Inhibitors	kaempferol, myricetin.
Carriers	haptocorrin, transcobalamin.
MRP2	**Long MRP**
Role	a multi-specific organic anion transporter; important in the elimination process of xenobiotics and their metabolites from the bile and urinary systems;

	excretes into bile - bilirubin glucuronides, endogenous conjugates, such as leukotriene-C4 (LTC4) and conjugated bilirubin, paracetamol, and excretes into intestinal lumen – xenobiotics.
Location	kidney, liver, intestines, eyelids, some malignant human tumours.
Substrate	organic anions, glutathione, glucuronide, sulphate conjugates, GSH conjugates, cysteinyl leukotrienes.
Inhibitors	Rhein - a major metabolite of sennoside A and B.
MRP3	**Long MRP**
Role	can transport monoanionic bile acids; has an affinity for glutathione and glucuronate conjugates; confers a protective mechanism when MRP2 is absent or non-functional.
Location	liver, kidney, adrenal, pancreas, intestines, gallbladder, lungs, spleen.
Substrate	organic anions, monoanionic bile acids, GSH conjugates, cysteinyl leukotrienes.
MRP4	**Short MRP**
Role	important in cyclic adenosine monophosphate (cAMP) homeostasis in vascular smooth cells and cardiac myocytes, and mediates the urinary extrusion of cAMP and cGMP; transports various endogenous signalling molecules such as glutathione across the blood–brain barrier; important in the elimination process of xenobiotics and their metabolites from the bile and urinary system. essential in physiological processes, and its dysregulation is associated with the development of a range of diseases; important in platelet function such as release of lipid mediators, and aspirin resistance under certain conditions such as in patients after coronary artery bypass graft surgery; is quite inducible and plays a major role after intoxication by xenobiotics.

Location	kidney, prostate, lung, muscle, pancreas, testes, ovary, bladder, gallbladder, liver, almost all tissues and cell types.
Substrate	folic acid, eicosanoids, urate. organic anions, glutathione and GSH conjugates, cAMP, cGMP, conjugated steroids, cyclic nucleotides, nucleotide analogues, prostaglandins, leukotrienes, cysteinyl leukotrienes, leukotriene C4 [(LTC4) is a naturally occurring derivative of arachidonic acid[, prostaglandin E2 [(PGE 2) is derived from arachidonic acid].
Inducers	a single toxic dose of paracetamol induced mRNA expression with maximal effect at 12 h; ALT (alanine aminotransferases) as a marker of hepatic injury, was elevated further to a single toxic dose of paracetamol.
MRP5	**Short MRP**
Role	mediates the extrusion of cAMP and cGMP in urine; may partially mediate the composition of the aqueous and vitreous humors, as well as the redox status of other tissues in the front and/or back of the eye; the combined absence of MRP5 and MRP9 results in the poor transport and/or distribution of some metabolites such as heme, causing mitochondrial damage.
Location	ubiquitous, liver, placenta, cornea, carcinomas.
Substrate	organic anions, cAMP, cyclic guanosine monophosphate (cGMP), nucleotide/nucleoside analogues, GSH conjugates.
MRP6	**Long MRP**
Role	an organic anion transporter; mediates the transport of glutathione conjugates, LTC4 and N-ethylmaleimide S-glutathione (NEM-GS).
Location	liver, kidney.
Substrate	lipophilic anions, GSH conjugates, cysteinyl leukotrienes.
MRP7	**Long MRP**

Role	a lipophilic anion transporter, involved in phase III (cellular extrusion) of detoxification, does not directly transport GSH.
Location	heart, liver, skeletal muscle, kidney.
Substrate	lipophilic anions, GSH conjugates, cysteinyl leukotrienes.
MRP8	
Role	an organic anion transporter, important in the efflux of purine and pyrimidine nucleotide analogues including cAMP and cGMP, may also transport GSH conjugates.
Location	liver, brain, placenta, breasts, testes.
Substrate	cyclic nucleotides, GSH conjugates, cysteinyl leukotrienes.
MRP9	
Role	the combined absence of MRP5 and MRP9 results in the poor transport and/or distribution of some metabolites such as heme, causing mitochondrial damage.
Location	breast tissue, testes.
Substrate	GSH conjugates.
MRP10	
MRP11	**Short MRP**
MRP12	**Short MRP**

Transporter deficiencies

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

1. **Inherited metabolic disorder**

   Mutations in the MRP2 gene are associated with Dubin–Johnson syndrome, a condition that results in conjugated hyperbilirubinemia.

MRP2 transporter deficiency in genetic disorders can lead to jaundice.

Mutations found in the MRP6 gene are associated with genetic abnormalities of the autosomal inherited connective tissue disorder called pseudoxanthoma elasticum (PXE), which is the mineralization of elastic fibres in the skin, retina, and large blood vessels.

2. **Polymorphisms**

Variations of a specific DNA sequence that can involve either a single nucleotide (aka single-nucleotide polymorphism, or SNP), or a longer DNA sequence.

The Human Gene Mutations Database indicates almost 300 mutations of MRP4 are associated with diseases such as rheumatoid arthritis, leukemia, small cell lung cancer, inflammatory airway diseases, dysfunction of the blood-brain barrier, secretory diarrhea, and cardiovascular disease. Mutations that abolish MRP4 transporter function would sensitize developing embryos to toxic pesticides.

3. **Environmental**

Likely to manifest at any age and is dependent upon the environmental insult; inhibitors include -

Senna. Found to inhibit substrates in a dose dependent manner and therefore alters their effect. The authors advise caution if therapeutic MRP substrates such as prescribed medicines are administered concurrently with Senna.

Foodstuffs such as curcumin, **genistein, naringenin and its derivatives, quercetin,** salicylates, some flavonoids such as karanjin, likely others.

Sepsis. Early evidence indicates that sepsis-induced release of proinflammatory cytokines is responsible for suppression of PXR (pregnane receptor) a xenobiotic receptor involved in the regulation of transporter genes such as MRPs.

Other

The variability in clinical response expression seen between the sexes, ethnicities, and food intake, may be attributed to differing efflux transporters as they can alter P-gp, BCRP, and MRP2 transcript and protein expression levels. The authors suggest the sex, strain, feeding status, and quantification method in experimental models should be identified.

MRP2 alteration can be reversed with liver regeneration, if damage is not severe or if there is no ongoing damage. Ongoing graft damage slows, halts, or worsens recovery sub-clinically before presentation.

Paracetamol aka acetaminophen (APAP) overdose causes oxidative stress due to depletion of glutathione; MRP4 is upregulated as a compensatory mechanism during oxidative stress, consequently inhibition of MRP4 may further exacerbate liver injury and/or hamper tissue recovery.

Clinical Questions

What actions will you initiate when you see someone prescribed medicines that are transported by MRPs, will you –

- clarify adequacy of dietary intake of B12, B9 and B2, request blood tests, and then compare findings?
- question altered expression of one or more MRPs if there is disagreement between oral intake and blood test results?
- clarify if there is risk of high or sustained exposure to methyl mercury?
- recommend nutrient interventions be administered at different times from the prescribed medicines?

Conclusions

Multidrug Resistance Proteins are efflux transporters for multiple endogenous and exogenous substrates, and consequently are important in the regulation and protection of physiological processes. MRPs preferentially transport into the bile duct for waste disposal/elimination.

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:	asthma						

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
ASASANTIN SR	C, Fe		☑	NV	D			☑				☐	☐	☑
Atorvastatin			☑	NV	CD	↑	↓	☑				☐	☐	☐
Citalopram	Na		☐	NV	CD	↑	↕	☑		↑		☑	☑	☑
COLOXYL DROPS			☐					☐				☐	☐	☐
ENDONE			☐	NV	CD		↕	☑	↓			☑	☑	☐
Omeprazole	(20 mg/day) B1, B12, Ca, Fe,		☑	NV	CD	↑		☑				☑	☐	☐
PANADOL			☐	NV	CD			☐				☐	☐	☐
Ramipril			☐	NV	CD		↓	☑		↑		☑	☑	☑
TARGIN			☐	NV	CD		↕	☑				☑	☑	☐

Transporter-mediated interactions and nutrients

Transporter	OCT1		OCT2		OCT3	
Nutrients - Sub	B1, choline, carnitine		B1, choline, creatinine		B1	
Nutrients - Inh						
DRUG	Sub	Inh	Sub	Inh	Sub	Inh
Asasantin				Y		
Citalopram		Y		Y	S	
Omeprazole		Y		Y		Y
Targin				Y		

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

Data summary

Biochemistry

No recent relevant biochemistry available. Advisable to check plasma proteins (albumin, total proteins) as they are the primary transporters for three of the prescribed drugs and hypoproteinaemia may alter their effects.

Glycaemia

Currently prescribed 6 medications that alter glycaemia.

Pharmaconutrition

Currently prescribed 8 medications that include nausea, vomiting and diarrhoea as side effects.

Currently prescribed 7 medications that include altered taste and constipation as side effects.

Currently prescribed 5 medications that include hyponatraemia, altered appetite and dry mouth as side effects.

Currently prescribed 4 medications that include anaemia, altered potassium status, tremor, dysphagia and sweating as side effects.

Currently prescribed 3 medications that include altered thirst and altered weight status as side effects.

Vitamin C (960 mg/day) attenuates aspirin-induced gastric injury.

Asasantin may alter nicotinic acid availability.

Regular monitoring sodium levels recommended whilst citalopram prescribed.

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

There is increasing evidence that proton pump inhibitors such as omeprazole significantly impair magnesium absorption. Magnesium deficiency manifests as confusion, disorientation, personality changes, loss of appetite, depression, muscle cramps, tingling, numbness, hypertension, cardiac dysrhythmia, seizures. Magnesium is an intracellular ion therefore serum levels are unlikely to detect early depletion of status. 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. Advisable to clarify magnesium status.

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

Concurrent ingestion of paracetamol and iron resulted in 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.

Ramipril impairs zinc status.

Statins interfere early in the cholesterol metabolic pathway and consequently decrease -

- conversion of sunlight to vitamin D - vitamin D intervention recommended,

- production of CoQ10 - important in cellular energy production; CoQ10 intervention recommended,

- DHEA production - low DHEA associated with increased risk of metabolic syndrome; intervention recommended.

Bowel management

Regular aperient prescribed.

No PRN interventions prescribed.

No Nurse Initiated interventions administered.

Staff comments

Staff advise diminishing appetite.

Observations

Mr ACJ was asleep in bed in his room with a blanket pulled over his head so I couldn't even see him - I did not disturb him.

Mr ACJ has been losing weight for the last 6 months.

Pharmaconutrition comments

Loss of weight is associated with depletion of zinc status and zinc is important in a range of body functions, including sense of taste and release of the hunger hormone Neuropeptide Y. Since Mr ACJ has lost 10+ kg weight, advisable to check zinc levels and if inadequate then short term (90-120 days) intervention and recheck status prior to cessation of the intervention. Since Mr ACJ is also prescribed a proton pump inhibitor there is some doubt as to the effectiveness of a zinc intervention.

It is very difficult for elders to regain lost weight as less hunger hormone ghrelin is produced and the body is less sensitive to its effects, whilst the satiety hormones PYY and CKK are produced in larger volumes and the body is more sensitive to their effects. Long term prescription of medicines such as atorvastatin, citalopram, endone, ramipril and targin that have loss of appetite as a side effect will exacerbate the problem. In these circumstances weight stability is considered a success and weight gain a bonus.

Given there is sustained and seemingly ongoing weight loss, advisable to clarify whether current depression-management strategies are still effective.

Currently prescribed atorvastatin therefore advisable to check vitamin D levels and if low then intervention recommended.

Mr ACJ has been prescribed a proton pump inhibitor since admission 2½ years + previously, and likely before then. There is increasing evidence that longterm (3+ years) proton pump inhibitor prescription is associated with -

- altered gut microbiome;

- increased risk of food sensitivities at a level of peanut allergy, due to partial protein digestion;

- increased risk of coeliac disease due to partial protein digestion;

- increased risk of scurvy;

- generalised malnutrition due to impaired absorption of a range of nutrients such as B12, vitamin C, magnesium, zinc, iron, etc;

- altered gastric pH which reduces absorption dynamics of a range of drugs and nutrients. Altered drug availability is relatively easily identified however reduced nutrient absorption is rarely identified due to the non-specific nature of their signs and symptoms.

Consequently, advisable to consider reviewing current proton pump inhibitor prescription and consider -

- whether proton pump inhibitor prescription is still required,

- if suppression of gastric acidity is still required then could it be managed with an H2 antagonist such as ranitidine (there is a general belief that they cause less nutritional harm than proton pump inhibitors).

Mr ACJ's diagnoses include arthritis ie 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 atorvastatin which decreases vitamin D availability. Advisable to check vitamin D levels 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. 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 atorvastatin which decreases conversion of vitamin C to its active form ie reduced availability of active form.

- 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 omeprazole therefore advisable to check B12 status.

- 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 omeprazole which decreases magnesium absorption therefore advisable to clarify status.

The identified membrane transporters inhibit the absorption and/or organ and cellular uptake of thiamine and choline which means blood test results are likely to indicate normal or elevated status whereas these nutrients may be in the blood because they are prevented from entering relevant organs and cells. Advisable for blood tests to be conducted several hours after administration of relevant prescribed medicines.

What else would you include?

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