MedNut Mail

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

P-glycoprotein and pharmaconutrition

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Editorial

Permeability-glycoprotein is known as P-glycoprotein or P-gp or multidrug resistance protein (MDR1/2); it has a large and versatile drug-binding region that encompasses multiple and overlapping binding sites inside a large and flexible binding pocket lined with aromatic residues that can accommodate a large range of smaller or larger molecules or several molecules simultaneously, and is stereoisomer selective.

P-gp inducers - if small they act as modulators, if large they are "substrates," and can act as inhibitors eg quercetin, curcumin, caffeine.

P-gp inhibitors - are compounds that slow down the rate of P-gp ATPase activity (energy) and transport.

P-gp modulators - are compounds that interact with P-gp to either enhance or reduce the P-gp ATPase activity (dose dependent). Examples include GRAS/IIG compounds such as tannic acid, cholesterol, stearic acid, vitamin E, beta carotene, and glyceryl palmitate.

P-gp substrates - are compounds that show net efflux (higher active efflux by P-gp than passive influx) in a transport assay.

P-gp is an efflux transporter with low substrate specificity and high transport capacity that serves three major drug transport functions -

1. to restrict the distribution of its substrates into organs such as the brain, testes, placenta, and the gastro-intestinal tract;
2. to be an inherent barrier that protects the body from xenobiotics and other toxic substances;
3. to excrete its substrates from organs such as -
    a. the intestinal epithelium where it pumps back into the intestinal lumen,
    b. the liver where it pumps into bile ducts,
    c. the cells of the proximal tubular of the kidney where it pumps into urine-conducting ducts,
    d. the capillary endothelial cells where it pumps back into the capillaries.

In the intestinal lumen, P-gp effect is determined by substrate dose and rate of absorption –

- high dose and rapid absorption – transporters become saturated and therefore minimal impact;

- low dose and slow absorption – transporters hamper absorption ie significant impact.

P-gp also has important roles in many body functions such as -

- cholesterol metabolism and lipid homeostasis;
- transporting intrinsic substrates such as steroid hormones and β-amyloid;
- regulating vitamin D homeostasis;
- protecting organs from toxic substances;
- helping to maintain integrity of the Blood Brain Barrier (BBB), Blood Retina Barrier (BRB), Blood Testes Barrier (BTB), and the Blood Placenta Barrier (BPB);
- gendered functions – for example during Multiple Sclerosis relapses, testosterone levels decrease in women, but not in men;
- being important in immune function and the inflammatory response via a range of mechanisms;
- likely involvement in a range of neurological, neuroinflammatory and neurodegenerative conditions;
- probable synergistic action with CYP3A4 and with BCRP, as their combined actions modulate absorption of their substrates;
- likely conferring protection to reproductive organs and their processes;
- likely regulating ion channel activity via direct interaction;
- likely regulating aspects of ceramide glycosylation pathway (protects cells from ceramide-governed cytotoxicity).

P-gp levels of expression can be altered by food, gender, stress, Vitamin D Receptor, renal accumulation of toxic substances, and dietary fibre intake.

P-gp is inhibited or slowed down, with ageing, and when its load is large.

Changing the levels of P-gp expression is likely to alter the availability of a range of beneficial and harmful substances.

There are 2 known P-gp isoforms –

- MDR1 – functions as transporter of amphiphilic compounds including drugs and certain lipids, also regulates cell volume by influencing swelling, and activating chloride currents via a protein kinase C-sensitive phosphorylation site;

- MDR2 – functions primarily as a lipid transporter, and is also involved in apoptotic mechanisms and cellular stress.

Many papers refer to P-gp and it is unclear whether one or both isoforms are included in their findings.

P-gp is expressed throughout the human body, with higher expression in the gastrointestinal tract, small intestine and colon; brain and BBB; liver, bile and pancreas; kidney; lungs; skin; skeletal muscles; immune cells such as monocytes, dendritic cells, and T and B lymphocytes; endocrine tissues; adrenal cortex, spleen; placenta, endometrium, testes, BTB, pregnant uterus, hematopoietic stem cells, foetal membranes; retina, BRB; endoplasmic reticulum and the nuclear envelope; astrocytes.

There is limited agreement regarding P-gp expression in the intestinal tract with claims as follows -

- expression increases from the proximal small intestine to the distal small intestine, and then decreases in the colon in humans;
- negligible or very low expression in the first part of small intestine (duodenum and proximal jejunum) and high expression in the distal tract of ileum and colon.

Most substances that inhibit P-gp are actually P-gp substrates. Concurrent administration of two P-gp substrates means competition for uptake into the P-gp binding pocket which prevents efflux of the other ie competitive inhibition.

P-gp substrates and inhibitors are typically lipid-soluble and amphipathic molecules – nutrient substrates include folates, B12, vitamin D (out of the intestines and into the epithelium, and out of the bloodstream into the lumen), lipids.

P-gp 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.

   Genetic variants of the MDR1 gene may alter the expression and/or activity, and/or may cause mRNA instability, and thus interfere with the absorption, distribution and excretion of P-gp substrates with consequent interindividual variability in response.

   Thirty-eight SNPs have been reported with diverse frequencies in different populations.

   The variants may include –

- having variable frequencies across populations and being associated with differences in drug response;
- being linked to diseases with an inflammatory component, such as epilepsy, cancer, neurodegenerative diseases (Alzheimer disease, Creutzfeldt-Jakob disease, Parkinson's disease, etc), and autoimmune diseases such as systemic lupus erythematosus, inflammatory bowel disease, hepatic cirrhosis, autoimmune thrombocytopaenia, and rheumatoid arthritis, in which they cause resistance to a range of drugs;
- altering brain homeostasis and accelerating disease progression by exposing vulnerable CNS cells to damaging compounds during neuroinflammation;
- being considered predictive factors for the onset of cancer and autoimmune diseases in various populations;
- being associated with increased risk of developing Demyelinating Disease; carriers of these genotypes may present toxic accumulation of P-gp substrates.

2. **Epigenetics -** the expression of MDR1 is subject to epigenetic regulation via histone acetylation;
3. **Environmental** – P-gp inhibitors are typically either very high affinity substrates that bind non-competitively (not allowing other drugs to bind), or efficient inhibitors of ATP hydrolysis, either at the ATP binding site or by inhibiting protein kinase C (PKC); identified causes include –
   a. cranberry polyphenols, caffeine, melatonin, ellagic acid, furanocoumarin component in grapefruit juice, plant-based compounds including alkaloids, coumarins; flavonoids, lignans, saponins, terpenoids;
   b. quercetin, naringenin and ellagic acid in combination with verapamil (primary inhibitor test drug) having an additive or synergistic inhibitory effect on P-gp function. This indicates there is an increased risk of a drug-food interaction between P-gp substrate/inhibitor drugs and dietary polyphenols which are found in fruits, vegetables, wine, coffee, tea, others; even a weak P-gp inhibitory effect of an individual compound is likely to be amplified by the identified additive or synergistic interaction;
   c. retinol, 13-cis-retinoic acid and retinyl-acetate inhibiting P-gp;
   d. vitamin A palmitate, a GRAS-approved food ingredient, inhibiting P-gp ie indicating a potential food-or excipient-drug interaction;
   e. vitamin A deficiency likely decreasing P-gp expression in tissues;

f. calcitriol and calcipotriol inhibiting P-gp; it is not yet known whether calcitriol is a modulator and/or substrate of P-gp;

g. as efflux inhibitors, plastic compounds comprising one substrate compound and one inhibitor compound, can inhibit detoxification and thus increase resistance, with resultant cell death, carcinogenesis, and other diseases;

h. lipopolysaccharide (LPS) being an inflammatory agent that downregulates P-gp activity, is elevated in diabetes;

i. LPS downregulates P-gp activity, and up-regulates TNF-α;

j. decreasing P-gp expression in the epithelium of Irritable Bowel Disease patients (IBD) - decreased P-gp expression or function are associated with IBD;

k. being downregulated in Parkinson's Disease, likely resulting in reduced P-gp efflux at the BBB, and likely increasing toxic endogenous substrates and xenobiotics levels;

l. Focused Ultrasound-induced BBB opening is able to decrease P-gp expression for up to 3 days after sonication in both the treated and in the contralateral brain regions;

m. Reactive Oxidative Stress (ROS) downregulating P-gp expression - ultrasound exposure increases intracellular ROS production;

n. Salmonella typhimurium decreasing P-gp;

o. downregulation of P-gp at the BBB has also been linked to higher rates of obesity;

p. seemingly having a trans-generational effect as there was an observed higher incidence of birth defects in infants born to mothers who took P-gp substrate or inhibitor drugs during pregnancy;

q. sucralose and acesulfame potassium being competitive inhibitors of P-glycoprotein at concentrations as low as levels found in human plasma after drinking one non-nutritive sweetener (NNS)-sweetened beverage – whether they were consumed individually or in combination; longer NNS exposure times (~ 24–72 h) increased P-gp expression, whilst acute exposure (~ 30 min) caused competitive inhibition of P-gp efflux function;

r. P-gp being indirectly regulated via mechanisms that influence the activity of the protein in an acute and reversible manner without impacting its expression levels – for example -

    I. many substances can inhibit P-gp activity by acting as competitive substrates for transport;

II. sphingolipid signalling can differentially modulate P-gp transport activity, without affecting protein expression – fingolimod can rapidly and reversibly reduce P-gp export activity, whilst ceramide 1-phosphate (C1P) can increase P-gp transport activity at the BBB;

III. other mechanisms include vascular endothelial growth factor (VEGF) signalling, trafficking and internalisation, and alterations to the membrane lipid environment.

That P-gp regulates vitamin D status via its absorption from the intestines and resecretion of excess back into the intestines raises the question of the degree of effectiveness of high-dose vitamin D interventions – how much vitamin D really is being absorbed, and how much of that confers therapeutic benefit? For example how much vitamin D is absorbed, and retained, from a monthly 50,000 IU dose, or is a smaller daily dose of 1 x 1,000 IU mane, and 1 x 1,000 IU nocte, a more effective dose?

It seems to me that we really do need to know which nutrients and foodstuffs are P-gp substrates, which are inhibitors of, and inhibited by P-gp, and their therapeutic dose ranges. How can we, or any clinician, make optimal clinical decisions without this very important information?

What actions will you initiate when you see someone whose prescribed medicines are transported by P-gp, will you –

- clarify adequacy of dietary intake of folic acid, B12, vitamin D, and a range of lipids, request blood tests, and then compare findings?
- If there is disagreement between oral intake and blood test results, will you question altered expression of P-gp?
- recommend nutrient interventions be administered at different times from the prescribed medicines?

Conclusions

P-gp is a profoundly important membrane transporter that has significant consequences when inhibited in some manner. Our drug-nutrient and drug-food interactions knowledge and awareness in relation to P-gp function is lagging well behind our drug-drug knowledge and awareness, and certainly fits into the category of " … needed that yesterday …".

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: hypothyroidism, chronic facial pain, STML

Biochemistry with Pharmaconutrition Consequences

Na:	147	mmol/l	Hb:	141	g/L	Albumin:	42	g/L	BSL:		mmol/l
K:	4.8	mmol/l	Lymph:	1.5		Total Protein:	72	g/L	HbA1C:		
Urea:	5.7	mmol/l	MCV:	93	mmol/l	B12:		pmol/L	INR:		
Creatinine:	0.080	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:		mIU/L

Other: eGFR > 60, CRP 42, Fe 11, TRF 1.6, satn 28%, ferritin 287

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
Carbamazepine	B6, biotin, carnitine, D, folate,		☐	NV	CD	↑	↑	☑				☑	☐	☐
Clopidogrel			☑	N	CD	↓		☑				☐	☐	☐
EUTROXSIG	(100 mcg/day) A, Ca, carnitin		☑	V	D	↓		☐				☐	☐	☑
Fluoxetine	Na		☑	NV	CD	↑	↓	☑				☑	☑	☐
OSTELIN	(2/day)		☐					☐				☐	☐	☐
TARGIN			☐	NV	CD		↕	☑				☑	☑	☐
TROVAS			☑	NV	CD	↑	↓	☑				☐	☐	☐

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**
Clopidogrel		Y		Y										
Fluoxetine		Y		Y										
Targin				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[1]

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

Data summary

Biochemistry

No biochemistry results with a pharmaconutrition input.

Glycaemia

Currently prescribed 3 medications that alter glycaemia, being fluoxetine, Targin and atorvastatin.

Pharmaconutrition

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

Currently prescribed 5 medications that include nausea, vomiting, constipation, altered taste, weight changes, appetite changes as side effects.

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

Currently prescribed 3 medications that include hyponatraemia, altered lipids, dry mouth as side effects.

Carbamazepine decreases biotin and carnitine absorption and decreases availability of folate and vitamin D.

Regular monitoring sodium levels recommended whilst fluoxetine prescribed.

Trovas decreases CoQ10 availability - CoQ10 is required in the mitochondria for energy production; CoQ10 intervention recommended.

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

- conversion of sun 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.

Therefore, advisable to clarify cholesterol status and if low then review necessity for ongoing prescription of Trovas.

Bowel management

No regular intervention prescribed.

Oral PRN aperient prescribed.

No Nurse Initiated interventions administered.

Staff comments

Staff advise Mr ACH eats well.

Observations

Mr ACH is a tall, slender, pleasant man who was lying in bed when I went to speak to him - he told me he has a nasty taste in his mouth and that he is keen to stop the targin intervention.

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

Pharmaconutrition assessment

Evidence now indicates biotin is important in glycaemic control. Currently prescribed carbamazepine which decreases biotin absorption. Longterm inadequate biotin intake is associated with increased risk of developing diabetes, and also poor glycaemic control. Advisable to monitor biotin status on a regular basis.

Mr ACH is prescribed eutroxsig for his altered thyroid function. Eutroxsig dose is directly related to weight and if there is a change in weight then drug dose

effectiveness is altered. Mr ACH has lost weight is therefore at risk of overmedication. Advisable to check thyroid function.

Current standard advice is that soy-containing compounds and high fibre diets can decrease the intestinal absorption of levothyroxine and that dosage adjustment of levothyroxine may be necessary, in particular at commencement or completion of soy supplements. It is unlikely Mr ACH will be commenced on soy supplements.

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

- vitamin D – associated with muscle weakness and consequently falls; currently prescribed Trovas therefore advisable to clarify vitamin D status.

Mr ACH'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 Trovas which decreases vitamin D status. Advisable to check vitamin D levels and if still low then review current vitamin D management strategy.

- vitamin K - has been found to suppress the inflammatory cytokines and NF-kappaB and prevent oxidative, hypoxic, ischemic injury to oligodendrocytes and neurons – vitamin K deficiency therefore results in classic expression of the inflammatory response and consequently pain. Currently prescribed carbamazepine therefore advisable to monitor vitamin K status.

What else would you include?

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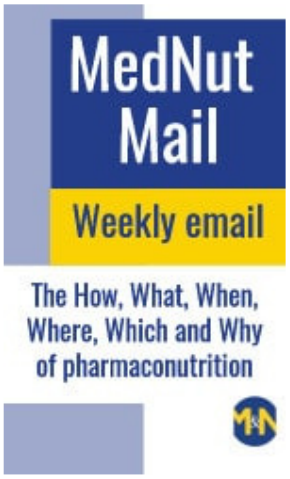

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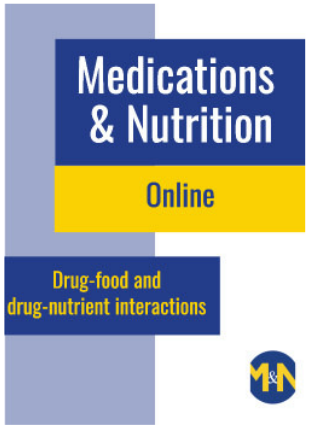

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