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

Breast Cancer Resistance Protein and pharmaconutrition

Y Coleman

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BCRP TRANSPORTER AND PHARMACONUTRITION

Editorial

Breast Cancer Resistance Protein (BCRP) seems to be an initial defence against environmental insults such as phototoxic skin lesions, and xenobiotic absorption, and seems to prefer to excrete toxic substances via the biliary pathway. BCRP overlaps with P-glycoprotein (aka P-gp, or MDR1) and to a lesser extent with MRP1 (Multi Resistance Protein) – whether there are additive or synergistic interactions with either or both of these other transporters is still to be determined.

BCRP roles include -

- restricting brain penetration of drugs;
- contributing to the protection of cells from exposure to toxic xenobiotics;
- transporting a wide range of endogenous compounds, such as steroid metabolites, urate, porphyrins, and environmental contaminants;
- tissue and cellular protection;
- mediating homeostasis of physiological substrates;
- defining a new blood type, the Jr(a-) blood type which does not express BCRP;
- preventing the accumulation of cadmium and protecting against toxicity, a response that is impaired by the Q141K variant;
- reducing cellular protoporphyrin IX levels (an important precursor to biologically essential prosthetic groups such as heme, cytochrome c, and chlorophylls) in the plasma membrane of mature erythrocytes. Elevated cellular accumulation of heme and protoporphyrin IX is associated with formation of membrane lipid-damaging reactive oxygen species.

BCRP is expressed epithelium of small intestine and colon (maximal expression in the duodenum and a gradual decrease along the GI tract to the rectum), liver, gallbladder, alveolar (lungs), pancreas, adrenal gland, sebaceous glands, kidney, muscle tissues, mature erythrocytes, blood-brain barrier, prostate, uterus, cervix, endothelium (inner wall of blood vessels), testis, placenta, and mammary glands

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Endogenous and food-based substances that are substrates include –

- Folic acid,
- Riboflavin,
- Uric acid,
- Vitamin K3,
- Dehydroepiandrosterone sulfate (DHEA),
- Glutathione (GSH),
- Sphingosine 1-phosphate,
- isobutyryl carnitine,
- PPIX (heme precursor),
- arginine,
- Estradiol-17b glucuronide,
- Estrone 3-sulfate,
- Genistein,
- Hesperetin conjugates (flavonoid),
- Kaempferol (flavonoid),
- 2- arachidonoyl glycerol,
- urolithin A (derived from ellagic acid) found to have anti-inflammatory and chemo preventive properties.

Early animal evidence indicates riboflavin is a suitable specific endogenous probe for BCRP activity, including predictability of transporter activity in vivo.

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

1. **Inherited metabolic disorders** – there do not seem to be any examples;

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. the ABCG2 c.421C>A variant resulted in poor response to the substrates allopurinol (increased risk of developing gout) and rosuvastatin (consequent higher risk of myopathy);
    b. SNP polymorphisms are responsible for more than 90% of all interindividual genetic variations in BCRP;
    c. multiple common and rare variants of BCRP are independently associated with gout;

3. **Epigenetics** – molecular events that can affect gene expression without changes of the DNA sequence such as DNA methylation, histone modifications, and non-coding RNAs;

4. **Environmental** – likely to manifest at any age and is dependent upon the environmental insult; identified causes include –
    a. Inhibition of vitamin D2;
    b. inhibition by dietary components such as cranberry juice, oleic acid, quercetin, xanthine, curcumin, and flavonoids (common polyphenolic compounds found in foods and herbal products);
    c. inhibition by the popular laxative Senna;
    d. there is currently speculation whether gender, age, and circadian rhythms can impact BCRP;
    e. the diagnosis of diabetes seems to be a factor in BCRP regulation which indicates the effectiveness of BCRP substrates may be altered, and the authors suggest prescription of BCRP substrate drugs to people with diabetes should be based on their BCRP function;
    f. The up-regulation of BCRP expression in Alzheimer's disease can be interpreted as either/and a compensatory response to try and reduce the Aβ peptide burden by enhancing efflux of Aβ peptide across the blood brain barrier, and/or a mechanism to protect the brains by reducing oxidative stress and inflammatory responses;
    g. BCRP is the key mediator in the pathophysiology of Erythropoietic protoporphyria (EPP) as BCRP inhibition will decrease the accumulation of PPIX in the skin and prevent EPP phototoxicity;
    h. BCRP inhibition reduces its capacity to protect placental cells in those with IUGR;
    i. Inhibition by cannabidiol;
    j. hypoxic environments such as low oxygen environment, and being at high altitude, indicate oxygen levels are important in regulating BCRP expression;
    i. plastic pollution is becoming a threat to human health as initial evidence has identified four likely BCRP inhibitors including - Dicyclohexal phthalate, Octrizole, 2,2'-Methylenebis(6-tert-butyl-p-crescol), 2,2'-Methanediylbis(6-cyclohexyl-4-methylphenol).

BCRP overexpression -

- can be caused by Focused Ultrasound (FUS) application (fully recovered within two weeks),
- is associated with multi drug resistance (MDR) in diseases,
- decreased anti-viral drug efficacy.

Dietary fibres can also alter the expression and functions of intestinal BCRP in humans by increasing BCRP transporter expression along the small intestinal tract in both sexes.

It is interesting that some research is focussing on foodstuffs and their potential to alter BCRP function. So how should we use this knowledge? At present the evidence is very limited and clinical application has not been considered, therefore there seem to be 2 scenarios –

1. Very stable dietary intake and very stable health condition – just monitor for change;
2. Instability in dietary intake and/or health status – note the instability and the potential for a drug-transporter to be part of the cause in your report, advise relevant other health professionals, and further to discussion with other health professionals possibly advise some level of stability in dietary intake and monitor for change.

What actions will you initiate when you see someone whose prescribed medicines alter BCRP function, will you –

- clarify adequacy of dietary intake of folic acid, riboflavin, vitamin K and vitamin D, request blood tests for folic acid, riboflavin, vitamin K and vitamin D, and then compare findings?
- If there is disagreement between oral intake and blood test results, will you question inhibition of the transporters?
- recommend nutrient interventions be administered at different times from the prescribed medicines?
- suggest utilising riboflavin to try and monitor BCRP status, especially in those with diabetes?

Conclusions

BCRP seems to be a powerful membrane transporter that we don't know a lot about. There seems to be an increased risk for potential food-transporter and nutrient-transport interactions that may alter health outcomes.

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: IDC, epilepsy, kidney stones

Biochemistry with Pharmaconutrition Consequences

Na:		mmol/l	Hb:	113	g/L	Albumin:	34	g/L	BSL:		mmol/l
K:		mmol/l	Lymph:	1.8		Total Protein:		g/L	HbA1C:	5.1	
Urea:		mmol/l	MCV:	93	mmol/l	B12:		pmol/L	INR:		
Creatinine:		mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:		mIU/L

Other: Ca 2.71, Ca corr 2.83

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
Clonazepam		☐		NV	C	↕	↕	☐		↑		☐	☑	☐
COLOXYL WITH S		☐			D			☐				☐	☐	☐
		▩						▩				▩	▩	▩

Extra drug: microlax enema

Transporter-mediated interactions and nutrients

Transporter	OCT1		OCT2		OCT3		OCT6		OCTN1		OCTN2		MATE1/2	
Nutrients - Sub	B1, choline, carnitine		B1, choline, creatinine		B1		carnitine		carnitine		carnitine		B1, creatinine	
Nutrients - Inh														
Location	intestines, liver		kidney		intestines, liver, kidney		testis, endometria		Intestines, kidney		Intestines, liver, kidney		kidney	
DRUG	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**
Atenolol	Y		Y											Y
Maxolon	Y		Y	Y										
Metformin	Y	Y	Y		Y								Y	
Nexium		Y												
Sertraline		Y	Y		Y								Y	
Sub – substrate, Inh – inhibitor, B1 - thiamine														

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

Data summary

Biochemistry

Relatively recent available biochemistry indicates -
- low Hb - associated with increased risk of falls, and poor appetite;
- low albumin - typical indicator of nutritional status; influenced by inflammatory response; advisable to recheck status.

"Old" biochemistry showed -
- low vit D - currently no vitamin D intervention prescribed therefore advisable to recheck vitamin D status and if still low then review current vitamin D management strategy;
- elevated ferritin - typically indicates mobilisation of iron stores which indicates inadequate iron intake therefore advisable to clarify iron status.

Glycaemia

Currently prescribed 0 medication that alters glycaemia.

BSLs
before breakfast - 5.1-6.9; recommended range 4-6;
tested weekly;
reportable limits: < 2 and > 15;

advisable to recheck HbA1c and clarify current glycaemic status.

Pharmaconutrition

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

Calcium and vitamin D interventions recommended whilst clonazepam prescribed.

Bowel management

Regular interventions prescribed,
No PRN interventions prescribed,
Nurse Initiated aperient administered 1 x April.

Staff comments

Staff advise a very good appetite and increasing independence.

Observations

Mrs AGX is a small, slender lady with a lovely smile and who was sitting in the Day Room when I went to speak to her - she smiled in agreement when staff commented on her good appetite and independence.

As can be seen from the weight graph, Mrs AGX has gained weight in the last year.

Pharmaconutrition assessment

What would you include?

Medications have profoundly and positively changed health outcomes however they do generally come with some nutritional harms. By identifying and addressing the nutritional harms, optimal health outcomes are closer to being achieved.

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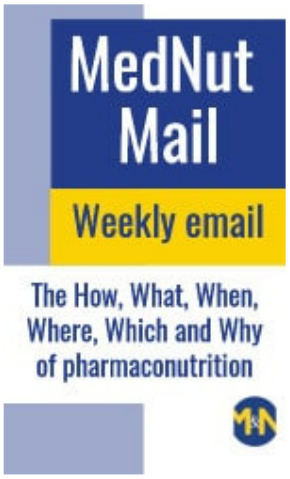

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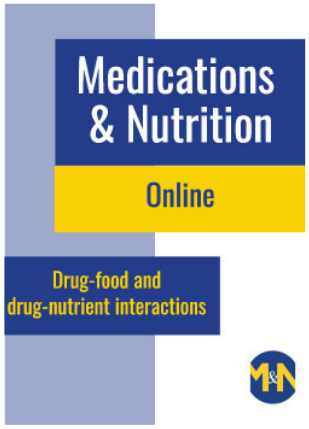

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