MedNut Mail

The How, What, Which, Where, When and Why of pharmaconutrition

Glucose transporters SWEETs

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27th August 2024

https://medicationsandnutrition.com/mednut-mail/

Editorial

The glucose transporter SWEET1 is a relatively recent discovery that not much is known about it. The SWEETs are predominantly found in plants, and the only known human transporter is SWEET1.

The primary function of glucose is as a key energy source for physiological function. Many organs can derive energy from fats and proteins in times of glucose shortage, however the brain is fully dependent upon glucose as its energy source.

Three families of glucose transporters have now been identified and each family has distinct physiological functions and working mechanisms –

1. GLUTs (glucose transporters) - sodium-independent glucose transporters. Refer Glucose Transporters (GLUTs);

2. SGLTs (sodium glucose linked transporters) - sodium-dependent glucose cotransporters;

3. SWEETs (sugars will eventually be exported transporters) – uniporter ie membrane transporter that passively transports glucose across cell membranes.

Isoform

SWEET1	
Role	widely-expressed glucose efflux (from cell to blood) transporter present in glucose producing cells. may also supply glucose for lactose synthesis in mammary glands.
Location	intestine, liver, epididymis, mammary glands, plasma membrane, endoplasmic reticulum, extracellular space, vacuoles, nucleus, and lysosomes
Substrates	glucose.
Biomarker	a serum-based diagnostic and prognostic biomarker in breast cancer.

The pharmaceutical sector is now showing interest in SWEET1 which means drug development is not far behind.

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Clinical considerations

The presence of so many glucose transporter systems indicate glucose's importance in physiological function. Further, awareness of the existence of this new glucose transport system broadens the concept of glucose utilization.

Speculatively, the similarity between glucose and vitamin C molecules infers vitamin C may also be transported by SWEET1.

Clinical questions

There is so little information available about the SWEET1 glucose transport system that clinical questions are currently redundant!

Conclusions

The glucose transporter SWEET1 is a recent discovery with minimal evidence available. As its functions and roles becomes apparent, so will we be able to integrate it into our clinical practice.

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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: hyperlipidaemia, deafness, blindness

Other: biliary colic - not for cholecystectomy, vit D def

Biochemistry with Pharmaconutrition Consequences

Na:	141	mmol/l	Hb:	122	g/L	Albumin:	33	g/L	BSL:		mmol/l
K:	4.2	mmol/l	Lymph:	2.4		Total Protein:		g/L	HbA1C:		
Urea:	5.5	mmol/l	MCV:	98	mmol/l	B12:		pmol/L	INR:		
Creatinine:	0.109	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:		mIU/L

Other: eGFR 55, Ca 2.27, Ca corr 2.38, phos 0.98, Mg 0.84, CRP 20

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
Candesartan	Zn, B2		☑	NV	D			☑				☐	☐	☐
Clopidogrel			☑	N	CD	↓		☑				☐	☐	☐
Escitalopram			☐	NV	CD	↕	↓	☑				☑	☐	☑
Frusemide	Ca, Cl, K, Mg, Na, Zn, B1, (40		☑	NV	CD		↓	☐				☑	☐	☑
GASTRO - STOP			☑	NV	C			☑				☑	☐	☐
Metformin	Mg, Zn, B1, B6, B12, folate (1		☐	NV	D	↓	↓	☑				☐	☐	☑
Paracetamol	Fe		☐	NV	CD			☐				☐	☐	☐
Simvastatin	E, CoQ10		☑	NV	CD			☑				☐	☐	☐
TOPROL-XL	B2		☐	NV	CD	↑		☑				☑	☐	☑
VITA-D GEL CAPS	(2 tabs/day)		☐					☐				☐	☐	☐
Warfarin	D		☑	NV	D			☑				☐	☐	☐

Extra drug: augmentin duo forte

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Transporter-mediated interactions and nutrients

Transporter	OCT1		OCT2		OCT3		THTR2		OCTN1		MATE1		MATE2	
Nutrients - Substrates	B1, choline		B1, choline		B1, choline, carnitine		B1, B6		Carnitine, choline		B1		B1, B2	
Nutrients - Inh									vit D, choline					
DRUG	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**
Amoxicillin component	Y													
candesartan														
Clopidogrel		Y		Y										
Escitalopram		Y		Y										
Furosemide														
Loperamide	Y													
Metformin	Y	Y	Y		Y		Y	Y	Y		Y		Y	
paracetamol														
Metoprolol				Y										
Simvastatin														

Sub – substrate, Inh – inhibitor, B1 – thiamine, B2 – riboflavin, B3 – niacin, B5 – pantothenic acid, B6 – pyridoxine, B7 – biotin, B9 – folic acid, B12 – cobalamin, NMN – N-methylnicotinamide

Transporter	OAT1		OAT2		OAT3		P-gp		OATP1B1		OATP2B1			
Nutrients - Sub	B5, pyridoxic acid (B6), B7, B9, B2		B3, pyridoxic acid (B6), vit C		B5, B6, carnitine, B2		B12, vit D, B6, B3, B5		vit D		Vit D			
Nutrients - Inh			B3				vit A		Vit D def		Vit D def			
DRUG														
Amoxicillin component														
candesartan		Y				Y								
Clopidogrel														
Escitalopram														
Furosemide	Y			Y										
Loperamide							Y							
Metformin														
paracetamol		Y												
Metoprolol														
Simvastatin		Y				Y	Y		Y		Y			

Sub – substrate, Inh – inhibitor, B1 – thiamine, B2 – riboflavin, B3 – niacin, B5 – pantothenic acid, B6 – pyridoxine, B7 – biotin, B9 – folic acid, B12 – cobalamin, NMN – N-methylnicotinamide, TYR - tryptophan

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Comments – medication and nutrition effects only

Data summary

Biochemistry

Recent relevant available biochemistry indicates -

- elevated MCV - advisable to check B12 levels. Currently prescribed metformin. There is disagreement between pathology ranges and research findings with regard to appropriate B12 levels – the authors of a neuro-imaging study recommend B12 interventions once levels are less than 300 pmol/L.

- low albumin - typical indicator of nutritional status; influenced by inflammatory response. Currently prescribed 6 medications that are impacted by altered albumin status.

Glycaemia

BSLs

- before breakfast - 4.7-8.7; recommended range 4-6.

- tested weekly.

- reportable limits: < 4.0 and > 20.0.

- advisable to check HbA1c and clarify overall glycaemic control.

Diabetes drugs - metformin has a duration of 12 hours.

Diabetes drugs coverage

- before breakfast BSLs - minimal, if any, coverage by previous evening's metformin;

- before evening meal BSLs - minimal, if any, coverage by previous evening's metformin.

Currently prescribed 2 medications that alter glycaemia.

Pharmaconutrition

Side effects profile from the currently prescribed medicines -

- 9 medications that include nausea and vomiting.
- 8 medications that include diarrhoea.
- 7 medications that include constipation and altered taste.
- 6 medications that include weight changes.
- 5 medications that include appetite changes.
- 4 medications that include dry mouth, sweating, altered zinc status .

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Candesartan causes altered sense of taste unrelated to zinc status - Mr ADB has commented much of the food has an unacceptable taste.

Clopidogrel is a CYP1A2 substrate (can be carried by the transporter). CYP1A2 substrates include caffeine, retinol, melatonin, phosphatidylcholine; inhibitors include grapefruit juice and inducers include coffee; drug's metabolism inhibited by caffeine therefore drug will remain active in the body for longer.

Escitalopram-coffee interaction - drug forms a complex with caffeine which results in delayed dissolution and consequent decreased absorption of the drug.

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

Metformin decreases availability of B12, Mg, An, B1, B6 and B9 - there is now a recommendation for B12 status to be monitored on a regular basis ie at least annually.

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

Paracetamol is a CYP1A2 substrate (can be carried by the transporter). CYP1A2 substrates include caffeine, retinol, melatonin, phosphatidylcholine, inhibitors include grapefruit juice and inducers include coffee; drug's metabolism inhibited by caffeine therefore drug will remain active in the body for longer.

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.

Currently prescribed Vital-D (2/day). Advisable to check vitamin D levels and if still low then review current vitamin D management strategy.

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.

Advisable to check lipid levels and clarify current status. There is variability between pathology laboratories with regard to appropriate lower acceptable cholesterol level - some pathology ranges have set the lower acceptable limit at 3.5, others 3.0, and some do not set a lower limit. Cholesterol is important in brain structure and function amongst many other roles.

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Some of the identified membrane transporters alter the absorption and/or organ and cellular uptake of a range of nutrients. Inhibition of membrane transporters means blood test results may be unreliable. To clarify nutrient status advisable to conduct blood tests at least one hour before administration of relevant prescribed medicines. A concurrent detailed Diet History is also essential to corroborate adequacy of intake of all affected nutrients. Further, all affected nutrients to be monitored on a regular basis ie at least annually. Unreliable blood test results due to inhibition of transporters by prescribed medications, is raising concern in some clinical publications.

Nutrients that are affected by Mr ADB's prescribed medications include -

- substrates - thiamine, riboflavin, niacin, pantothenate, pyridoxine, biotin, folate, B12, vitamin C, vitamin D, carnitine and choline;
- inhibitors – niacin, choline, vitamin A, vitamin D def.

The duration of drug inhibition of transporters currently remains unknown.

Bowel management

- regular intervention prescribed – no.
- PRN interventions prescribed – no.
- Nurse Initiated interventions administered – no.

Staff comments

Staff commented that historically Mr ADB often bought food outside and that now he is only consuming the food provided inhouse.

Observations

Mr ADB is a big-framed man of size - as I haven't seen him for some time I was shocked at the amount of weight he appears to have lost. I do not consider further loss of weight to be desirable and commented upon this to him.

As can be seen from the weight graph, Mr ADB's weight has fluctuated during the last 12 months, with a recent apparent loss associated with hospitalisation and a toe amputation.

Pharmaconutrition comments

Mr ADB's diagnoses include diabetes. There are a number of nutritional interventions to improve insulin sensitivity or reduce insulin resistance including -

- vitamin D within acceptable range - current intervention may not be adequate to attain adequate range. Early evidence indicates low vitamin D is a predictor of

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peripheral insulin resistance and elevated inflammatory response markers and currently prescribed warfarin and metformin**;**

- magnesium – is important in glycaemic control and inadequate intake may impair insulin synthesis, secretion and signalling pathways; in fact there is evidence of an inverse correlation between magnesium status and diabetes incidence. Currently prescribed furosemide and metformin which significantly decrease magnesium availability, and currently no intervention. Advisable to review status;

- thiamine - people with diabetes have a significantly increased urinary excretion of thiamine; thiamine is important in glycaemic control; currently also prescribed furosemide and metformin which further decrease thiamine availability;

- biotin – evidence indicates biotin is important in a number of steps in carbohydrate metabolism; currently prescribed 4 x OAT1 drugs whereby biotin is affected;

- TNF-α – evidence indicates TNF- α has systemic effects that result in insulin resistance and NIDDM; low B12 status exacerbates elevated TNF- α and currently prescribed metformin therefore advisable to check B12 status;

- zinc – is integral to insulin formation, and enhances insulin sensitivity through stimulation of insulin receptors; inadequate intake may impair insulin synthesis, secretion and signalling pathways. It is important in the glucose metabolism, protects the mitochondria from oxidative stress and glycation, and altered glomerular function, as well as modifying the inflammatory response pathway and activation of the polyol pathway (a part of intracellular signalling and metabolism) and currently prescribed candesartan, furosemide and metformin therefore advisable to check status;

- potassium - important in the glucose metabolism, and functions in β-cells; inadequate intake may impair insulin synthesis, secretion and signalling pathways; currently prescribed furosemide therefore advisable to monitor status;

- calcium - important in the glucose metabolism, and functions in β-cells; inadequate intake may impair insulin synthesis, secretion and signalling pathways; currently prescribed furosemide therefore advisable to monitor status.

Falls

Mr ADB's diagnoses include falls - nutritional factors that may be useful to ensure within acceptable ranges include –

- potassium - important in muscle function, currently prescribed furosemide therefore advisable to clarify status;

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- calcium - more likely to be low if potassium or magnesium low; important in muscle function, currently prescribed furosemide therefore advisable to clarify status;
- vitamin D – increasing vitamin D intake increases muscle strength and decreases falls (Sato et al, 2013); currently prescribed colecalciferol and warfarin therefore advisable to clarify vitamin D status;
- B12 - is important in the righting reflex when a person stumbles; prescribed metformin therefore advisable to check status;
- iron – important in many physiological functions, currently prescribed paracetamol therefore advisable to check status;
- zinc – can decrease food intake through altered sense of taste and poor appetite, and consequently reduced muscle mass; currently prescribed candesartan, furosemide and metformin therefore advisable to check status;
- magnesium - magnesium is important in vitamin D activation, de novo carnitine production, and muscle function, amongst other functions. Also currently prescribed furosemide and metformin which significantly decrease magnesium availability. Magnesium is an intracellular ion therefore serum levels are unlikely to detect early depletion of status Advisable to clarify magnesium status;
- thiamine –is important in balance and position sense. Currently prescribed furosemide and metformin therefore advisable to monitor status.

Deafness

Mr ADB's diagnoses include deafness - nutritional factors to ensure within acceptable ranges include –

- B12 and/or folate - currently prescribed metformin therefore advisable to check B12 status and if low then intervention recommended;
- vitamin D - associated with low-frequency and speech-frequency hearing loss; currently prescribed warfarin therefore advisable to clarify status;
- zinc - inadequate zinc status has been associated with impaired hearing; currently prescribed candesartan, furosemide and metformin therefore advisable to check zinc status and if low then intervention recommended;
- thiamine – associated with bilateral hearing loss and proposed mechanism of action is that thiamine transporter OCT2 is expressed in the hair cells of the cochlea therefore interruptions to thiamine accessibility are likely to impact hair cell function; currently prescribed furosemide and metformin which decrease thiamine availability both directly and indirectly.

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Warfarin

Mr ADB has been prescribed warfarin for at least 6 years; warfarin antagonises vitamin K availability and a stable intake is required. Vitamin K is important in a range of body functions including the clotting cascade, bone health, glycaemic control, lipid metabolism, and production of myelin sheaths and neuronal membranes; and low vitamin K status is now being associated with cognitive impairment. Given the duration of warfarin prescription it is likely Mr ADB is low in vitamin K and has probably depleted his vitamin K stores. Advisable to check vitamin K intake for 3 days and clarify adequacy of intake - aiming for a minimum intake of 120 mcg/day; if inadequate intake of vitamin K and/or low blood vitamin K levels then a short term (90-120 days) vitamin K intervention may be appropriate.

What else would you include?

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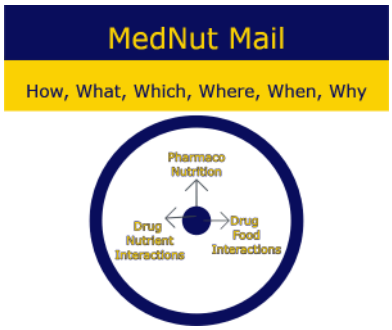

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