MedNut Mail

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

Glucose transporters and AMPK

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Editorial

AMPK (adenosine monophosphate-activated protein kinase) is an energy sensor in the cells. It rebalances adenosine triphosphate (ATP) levels in times of stress, and thus is important in a range of physiological functions. Our focus is on the various pathways that AMPK utilises to stimulate GLUT4 translocation.

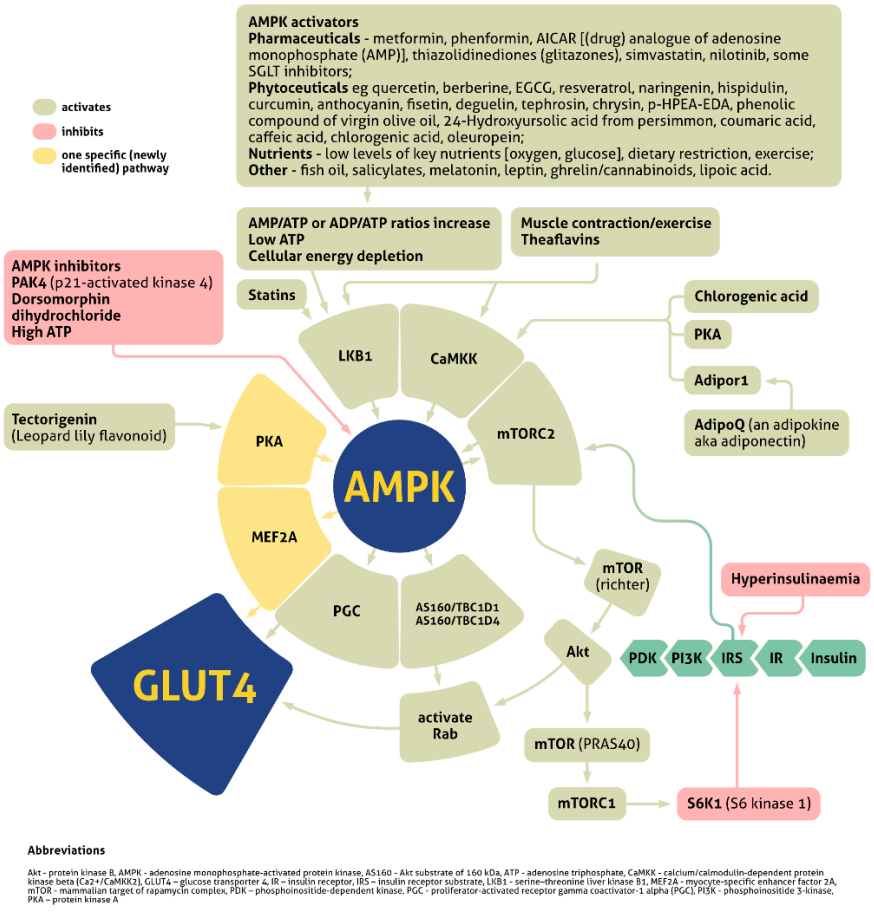
AMPK exerts multiple mechanisms of action to influence GLUT4 translocation, including interactions that –

- **directly** affect insulin-independent pathways;
- **indirectly** affect insulin-dependent pathways.

The flowchart below identifies some of the key factors in AMPKs pathways that impact GLUT4 translocation. The image is sufficiently self-explanatory to not require explanation!

Some Key factors the impact AMPKs stimulation of GLUT4 translocation

Some of AMPKs key factors that impact GLUT4 translocation



Abbreviations

Akt - protein kinase B, AMPK - adenosine monophosphate-activated protein kinase, AS160 - Akt substrate of 160 kDa, ATP - adenosine triphosphate, CaMKK - calcium/calmodulin-dependent protein kinase beta (Ca2+/CaMKK2), GLUT4 – glucose transporter 4, IR – insulin receptor, IRS – insulin receptor substrate, LKB1 - serine–threonine liver kinase B1, MEF2A - myocyte-specific enhancer factor 2A, mTOR - mammalian target of rapamycin complex, PDK – phosphoinositide-dependent kinase, PGC - proliferator-activated receptor gamma coactivator-1 alpha (PGC), PI3K - phosphoinositide 3-kinase, PKA – protein kinase A

Limited evidence indicates AMPK may also stimulate GLUT1.

AMPK is primarily activated by 2 key pathways, being LKB1 and CaMKK. A third pathway has been recently identified, being Tectorigenin -> PKA -> AMPK -> MEF2A -> GLUT4.

Vitamin D

Limited evidence indicates vitamin D can increase AMPK phosphorylation and consequently increase glucose uptake.

Glucose transporters and AMPK

GLUTs 1-14 primarily facilitate glucose absorption and cellular uptake. Inhibition means increased loss of glucose and therefore likely activation of AMPK. The current evidence regarding AMPK involvement primarily focuses on GLUT4 which is predominantly situated in muscle.

SGLTs 1,2,4,5,6 primarily facilitate glucose absorption and renal reabsorption. Inhibition means increased loss of glucose and likely activation of AMPK via CaMKK.

SWEET1 primarily facilitates the excretion of glucose from cells. Inhibition means reduced glucose availability and likely activation of AMPK.

Clinical considerations

The AMPK/GLUT4 pathway is very complex with multiple inputs that can influence the pathway to stimulate GLUT4 translocation. Key nutrients involved in the activation of various interactions in the many pathways are not identified. Key nutrients include calcium, phosphate and magnesium, and likely various vitamins and other minerals. Inadequate availability of any of the key nutrients will alter the AMPK/GLUT4 pathway at various points. Much of this information seems to be a well-kept secret.

Strategies that reduce insulin resistance also reduce the requirement for AMPK.

Both pharmaceutical and phytoceutical evidence is steadily increasing regarding their impacts on the AMPK/GLUT4 pathway. Evidence relating to direct and indirect impacts of vitamins and minerals on this pathway remains remarkably limited.

Clinical Questions

Apart from dietary changes to modify insulin resistance, would you consider recommending dietary changes to further manipulate AMPK expression and thus glucose uptake? If so, how would you do that?

Conclusions

AMPK can alter GLUT4 translocation via several direct and indirect pathways. AMPK also has sufficient capability to influence both insulin-dependent and insulin-independent impacts on GLUT4 and therefore glucose absorption.

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: hypernatraemia, hypomagnesaemia, PA stage 2

Other: pain, deafness, hypothyroid, GORD, vit D def, IDA

Biochemistry with Pharmaconutrition Consequences

Na:	139	mmol/l	Hb:	109	g/L	Albumin:	36	g/L	BSL:		mmol/l
K:	4.3	mmol/l	Lymph:	1.0		Total Protein:		g/L	HbA1C:		
Urea:	6.1	mmol/l	MCV:	92	mmol/l	B12:	345	pmol/L	INR:		
Creatinine:	0.73	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:	2.34	mIU/L

Other: eGFR 62, ferritin 133, T4 14.5, vit D 81, C diff neg

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
Aspirin	C, Fe, folate, E	☑	NV				☐				☐	☐	☑
Esomeprazole	B1, B12, Ca, Fe, Mg, Zn (40 m	☑	NV	CD	↑		☑				☑	☐	☐
EUTROXSIG	A, Ca, carnitine, Fe, Iodine, Li,	☑	V	D	↓		☐				☐	☐	☑
Fluoxetine	Na	☑	NV	CD	↑	↓	☑				☑	☑	☐
PANAMAX	Fe	☐	NV	CD			☐				☐	☐	☐

Transporter-mediated interactions and nutrients

Transporter¤	OCT1¤		OCT2¤		OAT1¤		OAT3¤		GLUT1¤		P-gp¤		SMVT¤	
Nutrients-·Substrates¤	B1,·choline¤		B1,·choline¤		B2,·B5,·pyridoxic·acid·(B6),·B7,·B9¤		B5,·B6,·carnitine,·B2¤		DHA¤		B3,·B5,·B6,·B12,·vit·D¤		B5,·B7,·iodide¤	
Nutrients-·Inh¤	¤		¤		¤		¤		¤		vit·A¤		B5,·B7¤	
DRUG¤	**Sub¤**	**Inh¤**	**Sub¤**	**Inh¤**	**Sub¤**	**Inh¤**	**Sub¤**	**Inh¤**	**Sub¤**	**Inh¤**	**Sub¤**	**Inh¤**	**Sub¤**	**·Inh¤**
aspirin¤	¤	¤	¤	¤	¤	Y¤	Y¤	¤	¤	Y¤	Y¤	¤	¤	Y¤
esomeprazole¤	¤	Y¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤
Fluoxetine¤	Y¤	Y¤	¤	Y¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤
paracetamol¤	¤	¤	¤	¤	¤	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,·DHA-·dehydroascorbic·acid·(vitamin·C)¤														

Comments – medication and nutrition effects only

Data summary

Biochemistry

Recent relevant available biochemistry indicates -

- low Hb - associated with increased risk of falls, and poor appetite. Currently prescribed esomeprazole.

Glycaemia

Currently prescribed 4 medications that alter glycaemic status.

Pharmaconutrition

The side effects profile of Mrs ADF's prescribed medicines include -

- 2 that include anaemia, hyponatraemia, altered taste, dry mouth, tremor, impaired magnesium status, impaired calcium status;
- 3 that include altered potassium, constipation, weight changes, sweating;
- 4 that include nausea, diarrhoea, impaired Fe status;
- 5 that include vomiting.

Vitamin C (960 mg/day) attenuates aspirin-induced gastric injury.
Caffeine increases aspirin absorption by altering gastric pH.
Aspirin inhibits vitamin C absorption by either inhibiting vitamin C binding to albumin, or by inhibiting/regulating/modulating GLUT1 (glucose transporter 1) uptake of vitamin C as DHA (dehydroascorbic acid).

- If there is concurrent administration of a vitamin C intervention and the drug then advisable to administer vitamin C prior to drug as vitamin C does not impact drug absorption whereas the drug does.
- Aspirin has a negative impact on folate status - the mechanism of action remains speculative.

Esomeprazole decreases B12, vitamin C, magnesium, zinc and iron absorption, likely decreases calcium absorption, and decreases thiamine availability.

Drug-coffee interaction – coffee sequesters thyroxine resulting in a 55% reduction in drug absorption.

Regular monitoring sodium levels recommended whilst fluoxetine prescribed.

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. Paracetamol'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 absorption of paracetamol. Consequently, the authors advise different administration times from each other for the drug and iron.

Frusemide ceased one month ago. Since both esomeprazole and frusemide have been prescribed until recently, and both decrease magnesium availability, advisable to clarify magnesium status.

Membrane transporters

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 Mrs ADF's prescribed medications include -

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

The duration of drug inhibition of transporters currently remains unknown.

Bowel management

- no regular interventions prescribed;
- oral PRN aperient prescribed;
- no Nurse Initiated interventions administered.

Staff comments

Staff advise Mrs ADF always says she is hungry but doesn't always eat when offered food, and doesn't always eat all that is offered.

Observations

Mrs ADF is a small, slender, pale, charming lady who was sitting the Day Room when I went to speak to her - she responded to my presence but was not always reliable in her responses to my questions, and often repeated the same several items of information.

Mrs ADF has remained weight stable about 43-45 kg for the last 6 months.

PharmacoNutrition comments

PPI prescription

Since Mrs ADF is pale and is prescribed esomeprazole, advisable to check iron levels and if low then short term (90-120 days) intervention recommended however it is unlikely an oral intervention will be successful whilst esomeprazole is prescribed.

Strategies to increase iron intake include -

- concurrent administration of an iron tablet, with a probiotic such as yakult or vaalia to protect the beneficial gut microbiota;
- non-oral intervention

It seems to me there is an increasing preference for non-oral to minimise enhancing infections and impacting gut microflora.

Concurrent prescription of esomeprazole and thyroxine results in increased thyroxine dose. If esomeprazole is ceased then advisable to closely monitor thyroid

function as Mrs ADF is at risk of overmedication and consequent weight loss.

Given its impacts on key nutrients such as iron, zinc and magnesium, 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).

Food restrictions

Staff have frequently expressed concern regarding Mrs ADF's loose bowels and have introduced food restrictions (gluten and lactose) as a management strategy. Prescribed drugs impacts do not appear to have been considered - 4 include diarrhoea as a side effect. Advisable to determine whether the gluten and lactose restrictions are to proceed and if so then diagnoses are required. Food restrictions in the absence of a diagnoses is deemed to be deprivation and punishment.

UTIs

Staff commented Mrs ADF has frequent UTIs. Serial infections decrease immunity and if frequent then the body may not have time to fully recover from the last infection before the next one is diagnosed. Zinc is very important in immune function however the combination of esomeprazole and frusemide prescriptions (both of which decrease zinc availability), and the frequency of UTIs indicates the immune function is likely compromised. Advisable to check zinc status and if low then intervention recommended; the effectiveness of the zinc supplement is compromised whilst esomeprazole prescribed.

Nutritional factors that may be useful to include UTI management include -
- vitamin A – has an adjuvant effect in conjunction with antimicrobial therapy. Currently prescribed eutroxsig therefore advisable to monitor status;
- vitamin C – has been found to confer benefit, and currently prescribed aspirin. Advisable to ensure any vitamin C intervention is administered before aspirin administration to ensure full benefit of both interventions;
- zinc – recurrent UTIs deplete immune system and consequently zinc status. Currently prescribed esomeprazole and frusemide and both decrease zinc availability therefore advisable to check zinc status.

Anaemia

Currently prescribed 4 medicines that impact iron status via various mechanisms of action. Advisable to administer iron intervention at different times from aspirin, esomeprazole, eutroxsig, and panamax to minimise these drug-nutrient interactions.

Pain

Mrs ADF's diagnoses include arthritis and therefore chronic pain. Nutritional factors that may be useful to consider in pain management include -

- 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. Whilst not considered part of the pain management armament, Vitamin C it won't cause harm and evidence suggests it may confer benefit. Currently prescribed esomeprazole which decreases conversion of vitamin C to its active form, and aspirin which inhibits vitamin C distribution.

- low B12 - exacerbates elevated TNF- α which is an inflammatory response marker; elevation of the inflammatory response can include a pain response. Currently prescribed esomeprazole 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 diagnosed with hypomagnesaemia, and also currently prescribed esomeprazole which decreases magnesium absorption.

Falls

Mrs ADF's diagnoses include falls. Nutritional factors that may be useful to ensure within acceptable ranges include –

- potassium - important in muscle function. Currently prescribed esomeprazole therefore advisable to monitor status;

calcium - more likely to be low if potassium or magnesium low; important in muscle function. Currently prescribed esomeprazole and eutroxsig therefore advisable to monitor status;

- B12 - is important in the righting reflex when a person stumbles. Currently prescribed esomeprazole therefore advisable to monitor status;

- zinc – can decrease food intake through altered sense of taste and poor appetite, and consequently reduced muscle mass. Currently prescribed esomeprazole therefore advisable to monitor status;

- magnesium - magnesium is important in vitamin D activation, de novo carnitine production, and muscle function, amongst other functions. Currently diagnosed with hypomagnesaemia and also currently prescribed esomeprazole which significantly decreases magnesium availability;

- thiamine –is important in balance and position sense. Currently prescribed which directly and indirectly impacts thiamine status therefore advisable to monitor status;

- carnitine - carnitine is both absorbed and produced de novo, and is important in a range of muscle functions. Currently prescribed eutroxsig therefore advisable to monitor status.

Deafness

Mrs ADF's diagnoses include deafness. Nutritional factors to ensure within acceptable ranges include –

- B12 - currently prescribed esomeprazole therefore advisable to monitor B12;
- vitamin C - inadequate dietary intake associated with deafness. Currently prescribed esomeprazole which reduces conversion of vitamin C to its active form and aspirin which inhibits vitamin Cs distribution;
- zinc - inadequate zinc status has been associated with impaired hearing. Currently prescribed esomeprazole and eutroxsig therefore advisable to monitor zinc status;
- 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 esomeprazole which decrease thiamine availability both directly and indirectly.

Wound healing

Mrs ADF's diagnoses include a Stage 2 pressure area. Nutritional interventions that support to wound healing include -

- adequate status of B12, magnesium, zinc and iron. Currently prescribed esomeprazole which compromises their status;
- acceptable iron status. Currently prescribed aspirin, esomeprazole, eutroxsig and paracetamol which all negatively impact iron availability;
- adequate vitamin C - important in collagen formation and the strength of the collagen; both topical application and increased oral intake confer benefit. Currently prescribed aspirin and esomeprazole which decrease vitamin C availability.

Vitamin C is important in collagen formation and the strength of the collagen; the proton pump inhibitors reduce availability of active vitamin C. It is likely wound healing will be delayed, and of poor quality whilst there is reduced availability of active vitamin C. It is also likely vitamin C interventions are unlikely to be effective whilst a proton pump inhibitor is prescribed.

Mrs ADF is in the difficult position of being prescribed a proton pump inhibitor and having a wound that is unlikely to heal properly whilst a proton pump inhibitor is prescribed. Advisable to consider

- whether proton pump inhibitor prescription is still required;
- if suppression of gastric acidity is still required and whether it could be managed with an H2 antagonist such as ranitidine (there is a general belief that they cause less nutritional harm than proton pump inhibitors);
- if the proton pump inhibitor intervention can be ceased until the wound is healed.

What else would you include?

Please read this as it is important …

The information in this article is provided to support Health Professionals. It is not an exhaustive protocol and Health Professionals are advised that adequate professional supervision is accessed to ensure that Duty of Care obligations with respect to safe administration of medicines is met for each consumer.

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