Brief Communication

Metformin + Sodium-glucose Co-transporter-2 Inhibitor: Salutogenic Lifestyle Mimetics in a Tablet?

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Abstract

Salutogenesis is an accepted approach for chronic disease management. Calorie restriction and exercise are two evidence based salutogenic interventions in diabetes treatment. Calorie restriction mimetics and exercise mimetics may be used as pharmacological tools to help manage diabetes in a sulutogenic manner. This article discusses the biochemical basis and pharmacology of metformin and sodium glucose cotransporter 2 inhibitors. It describes how a combination of these drugs can be used as a calories restriction and exercise mimetic, to help improve diabetes control.

Keywords: AMPK activation, canagliflozin, cardiovascular outcomes, dapagliflozin, empagliflozin

Salutogenic Lifestyle

The benefits of a salutogenic (factors which promote health and well-being) lifestyle on health and longevity are well known. There is ample evidence to show that calorie restriction and exercise improve physical health and enhance the quality of life. Calorie restriction has also been shown to prolong the life span, whereas exercise has been shown to improve the brain function.[1,2]

Exercise Mimetics and Calorie Restriction Mimetics

Not all individuals, however, are able to practice, and sustain, calorie restriction and/or exercise. This inability may be due to a variety of factors, including biomedical limitations, insufficient psychological willpower, and/or lack of social support. Various drugs have been developed in an effort to achieve the benefits of calorie restriction and exercise, in such persons. These drugs are termed as calorie restriction mimetics (CRMs) and exercise mimetics (EMs), respectively.[3,4] Such drugs, which overlap with commonly used glucose-lowering agents, work through a few pathways including 5′-adenosine monophosphate-activated protein kinase (AMPK) [Tables 1 and 2].

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5′-Adenosine Monophosphate-activated Protein Kinase and Metabolism

AMPK is a ubiquitous cellular energy sensor, which maintains bioenergetic homeostasis by monitoring and modulating adenosine monophosphate (AMP): adenosine triphosphate (ATP) (and adenosine diphosphate [ADP]: ATP) ratios. High AMP concentration (or high AMP: ATP ratio) stimulates AMPK, which in turn promotes catabolic and inhibits anabolic processes, thus leading to conservation of falling ATP levels. AMPK is also regulated by various hormones, including insulin, which is a potent inhibitor of the enzyme. Other inhibitors include leptin and triiodothyronine (T3), whereas known activators are ghrelin and adiponectin.[5]

A glucose-lowering drug which inactivates or inhibits AMPK, therefore, will act as an insulin mimetic or insulin sensitizer and may reduce insulin requirement in persons with diabetes. Such a molecule should be the drug of choice in persons with "maladaptive anabolism" or overweight/obesity, where catabolic processes need to be activated to maintain

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Table 1: Glucose-lowering salutogenic lifestyle mimetics

Class	Example	Action	CVO
Biguanides	Metformin	CRM EM	Beneficial
GLP1RA	Liraglutide Exenatide QW	CRM CRM	Beneficial
SGLT2i	Canagliflozin Dapagliflozin Empagliflozin	CRM EM	Safe Beneficial
AGIs	Acarbose Voglibose	CRM	Beneficial in prediabetes

CRM: Calorie restriction mimetic, CVO: Cardiovascular outcome, EM: Exercise mimetic, QW: Once weekly, SGLT2i: Sodium-glucose co-transporter-2 inhibitor

Table 2: Exercise mimetics

Target pathway	Drug	Status
AMPK	AICAR	Banned by World Anti-Doping Agency
AMPK	Metformin; SGLT2i	Approved for use in diabetes
SIRT 1	Resveratrol	Nutraceutical
PPAR 8	GW501516	Banned by World Anti-Doping Agency
AMPK-SIRT 1-PGCIα	Epicatechin	Nutraceutical

AMPK: Adenosine monophosphate-activated protein kinase, SGLT2i: Sodium-glucose co-transporter-2 inhibitor

homeostasis. These medications may be more helpful if they have proven CRM and EM properties.

5′-Adenosine Monophosphate-activated Protein Kinase and the Kidney

Many ion channels, transporters, and pumps are regulated by AMPK in the kidney, and AMPK-dependent regulation of membrane transport proteins is gradually being understood. Treatment with AMPK activators may prevent renal damage in various conditions, including acute ischemia, diabetes mellitus, and polycystic kidney disease, by acting, at least partly, on the regulatory effects of AMPK on solute transport.[6] Thus, AMPK-activating glucose-lowering drugs may improve renal outcomes as well.

Salutogenic Pharmaceutical Lifestyle Mimetics

A recently proposed AMPK-based classification of glucose-lowering drugs, in fact, is based on their effect of AMPK. Activators of AMPK include metformin and the thiazolidinediones. Incretin-based therapies have mixed action on AMPK receptors in various tissues.[7,8]

Metformin acts by binding to the AMPK-γ subunit of AMP and/or ADP, activating the kinase through allosteric effects, and promoting phosphorylation of Thr172 on the AMPK-α subunit. This activates AMPK and restores energy homeostasis by promoting catabolic processes, such as fatty acid oxidation, and inhibiting anabolic pathways, including fatty acid synthesis.[9] Thus, metformin can be classified as a combined CRM and EM.

Sodium-glucose Co-transporter-2 Inhibitors

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a newly developed class of drugs which are proven to have glucose-lowering efficacy and beneficial cardiovascular outcomes.[10] Their action on AMPK suggests that they may act as CRM and EM.[11,12]

The phosphorylation of AMPK-α (at Thr172) and acetyl-CoA carboxylase (ACC; at Ser79) is increased by empagliflozin. This finding implies that empagliflozin activates AMPK and enhances fat oxidation in skeletal muscle.[13]

Another study has found that although dapagliflozin and empagliflozin both activate AMPK, very high concentrations are required for this effect. In comparison, canagliflozin demonstrates AMPK activation at levels which are similar to those seen in therapeutic concentrations.[14]

The effects of phlorizin and its aglycone form, phloretin, have also been studied. Phloretin activates AMPK and promotes phosphorylation of AMPK and ACC at concentrations slightly higher than canagliflozin, whereas phlorizin has minimal effect, that too at much higher concentrations.[15]

Combined Salutogenic Lifestyle Mimetics

Such research opens up the possibility of using metformin and SGLT2 inhibitor as salutogenic lifestyle mimetics (SLMs), or salutogenic pills, which mimic both calorie restriction and exercise. In no way do we support the use of SLMs as a preferred alternative to lifestyle management (LSM). However, the SLMs may serve a useful therapy in persons who are incapable of, unwilling to, or unable to follow a healthy lifestyle. They may also be used as adjuncts to LSM, and as part of preventive pharmacotherapeutic regimens in both prediabetes and diabetes.

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Conflicts of interest

There are no conflicts of interest.

References

1. López-Lluch G, Navas P. Calorie restriction as an intervention in ageing. J Physiol 2016;594:2043-60.
2. Viña J, Rodriguez-Mañas L, Salvador-Pascual A, Tarazona-Santabalbina FJ, Gomez-Cabrera MC. Exercise: The lifelong supplement for healthy ageing and slowing down the onset of frailty. J Physiol 2016;594:1989-99.
3. Kalra S, Jacob JJ, Gupta Y. Newer antidiabetic drugs and calorie restriction mimicry. Indian J Endocrinol Metab 2016;20:142-6.
4. Handschin C. Caloric restriction and exercise "mimetics": Ready for prime time? Pharmacol Res 2016;103:158-66.
5. Hardie DG, Ashford ML. AMPK: Regulating energy balance at the cellular and whole body levels. Physiology (Bethesda) 2014;29:99-107.
6. Pastor-Soler NM, Hallows KR. AMP-activated protein kinase

regulation of kidney tubular transport. Curr Opin Nephrol Hypertens 2012;21:523-33.
7. Kalra S. Classification of non-insulin glucose lowering drugs. J Pak Med Assoc 2016;66:1497-498.
8. Dutta D, Kalra S, Sharma M. Adenosine monophosphate-activated protein kinase-based classification of diabetes pharmacotherapy. J Postgrad Med 2017;63:114-21.
9. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, *et al.* Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest 2001;108:1167-74.
10. Madaan T, Akhtar M, Najmi AK. Sodium glucose CoTransporter 2 (SGLT2) inhibitors: Current status and future perspective. Eur J Pharm Sci 2016;93:244-52.
11. Kalra S, Gupta Y, Patil S. Sodium-glucose cotransporter-2 inhibition and the insulin: Glucagon ratio: Unexplored dimensions. Indian J Endocrinol Metab 2015;19:426-9.
12. Kalra S, Jain A, Ved J, Unnikrishnan AG. Sodium-glucose cotransporter 2 inhibition and health benefits: The Robin Hood effect. Indian J Endocrinol Metab 2016;20:725-29.
13. Xu L, Nagata N, Nagashimada M, Zhuge F, Ni Y, Chen G, *et al.* SGLT2 inhibition by empagliflozin promotes fat utilization and browning and attenuates inflammation and insulin resistance by polarizing M2 macrophages in diet-induced obese mice. EBioMedicine 2017;20:137-49.
14. Hawley SA, Ford RJ, Smith BK, Gowans GJ, Mancini SJ, Pitt RD, *et al.* The Na+/Glucose cotransporter inhibitor canagliflozin activates AMPK by inhibiting mitochondrial function and increasing cellular AMP levels. Diabetes 2016;65:2784-94.
15. Fan HT, Morishima S, Kida H, Okada Y. Phloretin differentially inhibits volume-sensitive and cyclic AMP-activated, but not Ca-activated, Cl(-) channels. Br J Pharmacol 2001;133:1096-106.