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Role of AMPK and its possible interactions in metformin therapy and physical exercise-Research perspectives

Lucas Eduardo Campos de Oliveira[1], Luiz Augusto da Silva[2,3*], Jéssica Wouk[3], Vinícius Müller Reis Weber[1], Camila da Luz Eltchechem[3], Pablo de Almeida[2], Julio Cesar Lacerda Martins[2], Flavia Angela Servat Martins[2], Carlos Ricardo Maneck Malfatti[1,3], Raul Osiecki[4]

[1]Physical Education Department, Midwest State University of Paraná, Guarapuava, Paraná, Brazil.
[2]Physical Education Collegiate, Faculdade Guairacá, Guarapuava, Paraná, Brazil.
[3]Post-graduation of Pharmaceutical Science, Midwest State University of Paraná, Guarapuava, Paraná, Brazil.
[4]Physical Education Department, Federal university of Paraná, Curitiba, Paraná, Brazil.

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ABSTRACT

Insulin resistance results in increased blood glucose, called hyperglycemia, leading to the onset of diabetes mellitus. A better function in glucose uptake caused by metformin and physical exercise are interesting strategies for the control of hyperglycemia. Studies demonstrate expressive and beneficial results of physical exercise associated with metformin in response to the activation of a protein called AMPK, which stimulates Glut4 translocation, which improves the glucose sensitivity and hyperglycemia reduction. The present review seeks understanding on the effects of physical exercise and Metformin on the AMPK enzyme in the metabolism of glucose in diabetic people.

INTRODUCTION

It is well known that type 2 diabetes *mellitus* (T2DM) is a chronic degenerative disease that can cause a number of deleterious effects on the health of the individual, such as neuropathy, heart disease, nephropathy, and others (Sanz *et al*., 2010). This disease has been growing exponentially, reaching around 422 million people worldwide (NCD Risk Factor, 2016). T2DM (90% of cases) is characterized by muscle cells inability to respond to insulin, causing compensatory responses, generating a state of insulin hypersecretion, which may lead to the development of other chronic degenerative diseases (Weyer *et al*., 2001; Maiorana *et al*., 2001; Coughlan *et al*., 2014).

Therefore, it is necessary to seek therapies that can improve the health of these patients, avoiding the development of subsequent diseases, such as endothelial dysfunctions, cardiac problems, neuropathies, nephropathy, retinopathy, and worsening of clinical and quality of life's patient (Maiorana *et al*., 2001). Considering that great part of these complications arises from problems in glucose uptake by the cell and accumulation of fatty acids in the bloodstream, the action of AMP-activated protein kinase (AMPK), an enzyme sensitive to intracellular energetic concentrations, stands out. Energy levels are low by stimulating glucose uptake by the cell, oxidation of fatty acids and decreased hepatic glucose production, activation of this protein kinase provides improvements in insulin sensitivity improving metabolic health (Coughlan *et al*., 2014).

* *Corresponding Author*
Midwest State University (UNICENTRO), Campus CEDETEG, Guarapuava-PR, 85040-080, Brazil; e-mail: lasilva7 @ hotmail.com; Tel.:+554299697341d.

Pharmacological and physiological strategies that have the principle of AMPK activation are gaining great research interest in the treatment of diseases such as T2DM (Ruderman *et al*., 2013). Currently, advances in research in the health area allow us to envision positive perspectives for the treatment of this disease based on the interaction between pharmacological factors, such as metformin, which shows improvement in insulin sensitivity and also in therapy based on life, emphasizing the roles of diet and physical exercise for the improvement of the diabetic patient (Bianchi *et al*., 2017; Sahay and Sahay, 2002).

In this direction, the present study aims to review the available literature on information between the interaction of drug therapy with metformin in conjunction with the practice of physical exercise, focusing on the function of protein kinase activated by AMP (AMPK), pointing out possible mechanisms for This work in synergy.

ROLE OF METFORMIN IN T2DM TREATMENT

Metformin has been widely used for the treatment of T2DM because of its effect on improving insulin sensitivity. In the class of biguanides, metformin chlorhydrate is a substance derived from guanidine, active compound of the medicinal plant *Galega Officinalis* (Graham *et al*., 2011). One of its effects, it is possible to observe partial inhibition of hepatic neoglycogenesis, which is directly linked to a decrease in insulin resistance, leading to a decrease in glucose in the fasted state and increasing the insulin sensitivity of peripheral tissues such as skeletal muscle. It also decreases intestinal glucose uptake and improves glucose uptake and utilization in general (Gosg *et al*., 2012, Zou *et al*., 2004).

Sakar *et al*. (2002) sought to assess whether metformin could regulate intestinal glucose transport and thereby improve insulin sensitivity. As a result, the researchers observed redistribution in glucose transporters, reducing excessive glucose uptake and a consequent improvement in the glucose tolerance test. Considering that the hyperinsulinemia framework can bring several deleterious effects to health, the interest in the use of this drug for general health improvement is gaining great interest by the scientific community. Its clinical application has shown good results in several aspects of health in general, such as reduction of vascular problems (such as stroke, acute myocardial infarction and peripheral vascular disease) (UKPDS, 1998). Marchetti *et al*. (1998), showed in their work an effect on the alteration in the metabolic process of lipids, increasing the amount of free fatty acids, thus bringing a possible benefit to the mobilization and use of fat as an energy substrate.

Studies indicate that among the positive effects provided by this substance is the activation of AMPK (Ruderman *et al*., 2013). This activation triggers intracellular cascades and this signaling may mediate many of the beneficial effects noted, such as alteration in gene transcription and stimulatory mechanisms for glucose uptake, such as mitochondrial biogenesis and increase of glucose transporters to the cell membrane (Zou *et al*., 2004).

Cai *et al*., (2016) demonstrated in his study with sixty patients diagnosed with endometrial carcinoma that treatment with Metformin increased the activation of AMPK and that this activation was directly related to the improvement in the individuals' condition. Thus, the use of metformin in addition to improvements in glucose metabolism may provide improvements to other complications resulting from T2DM (Unnikrishnan *et al*., 2016).

METFORMIN AND AMPK RELATION

According to Zou *et al*. (2004), AMPK had increased activation by metformin in hepatocytes and skeletal muscle in rats. In the study by Musi *et al*. (2003) metformin exerted increased AMPK activity in skeletal muscle in humans.

To understand these mechanisms, some studies have sought to uncover actions of Metformin on AMPK, which could lead to an increase in AMPK activity by metformin, by AMPK threonine 172 phosphorylation. Another way of action of Metformin could be by activation of the liver enzyme kinase B1 (LKB1) and consequently activation of AMPK, by processes not fully understood (Ruderman *et al*., 2013; Zhou *et al*., 2001; Hardie, 2003).

In the work of Zang *et al*. (2004), the main modification caused by metformin in the metabolism of fatty acids is mediated by the activation of AMPK, in which HMGCoA reductase and Acetyl-CoA carboxylase (ACC), inactivation of cholesterol and fatty acids synthesis in hepatocytes Which leads to a decrease in their production and a consequent decrease in lipidemia, a decrease in hepatic steatosis and an increase in the insulin sensitivity of liver cells. The action of metformin on the activation of LKB1 for AMPK stimulation and consequently its cellular actions are illustrated in figure 1.

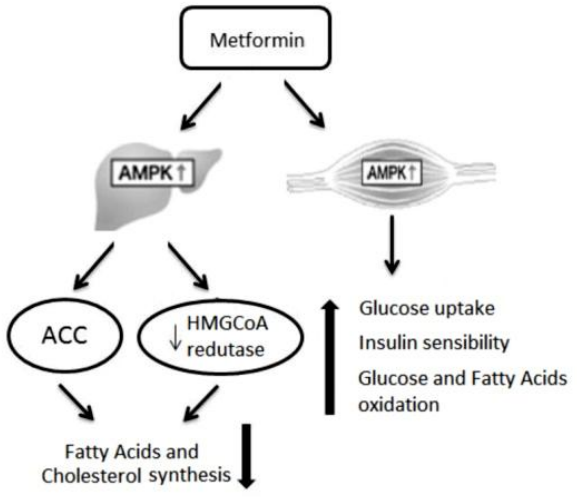

Fig 1: Activation of LKB1 by metformin leading to the subsequent activation of AMPK in several tissues where it is noticed a decrease in the synthesis of fatty acids and cholesterol in the hepatocyte better uptake of glucose by the skeletal muscle and their respective metabolic regulation providing increased sensitivity to insulin.

AMPK AND PHYSICAL EXERCISE RELATION

The main mechanism proposed by the beneficial effects of physical exercise on glucose metabolism permeates through the

activation of AMPK (Colberg *et al*., 2010). To understand these processes, Kemp *et al*. (2003) found that AMPK is very sensitive to moments that cause a decrease in the energy state of the cell, similarly to what happens in the practice of physical exercise, where successive contractions stimulate energy expenditure, and thus, reduce ATP. AMPK activation is shown in different intensities and durations of physical exercise (McGee and Hargreaves, 2006; Wasserman and Halseth, 1998).

Even with the evidence that AMPK promotes greater uptake of glucose by the skeletal muscle in the contractile process, its role in carbohydrate metabolism is not completely known, some evidence suggests that AMPK regulates glucose and glycogen metabolism, stimulating the glycolytic pathway through Enzymatic activation of phosphofructokinase 2 PFK-2 (Hardie, 2003; Kemp *et al*, 2003).

PHYSICAL EXERCISE AND METFORMIN ASSOCIATION

The possible effect of Metformin (150 mg/kg/day) and physical exercise (1h/day) on rats reduced serum glucose in relation to control, but when analyzed in isolation, the effects did not show significant differences in biomarkers Such as cholesterol, triglycerides and cholesterol, however, the authors conclude that adding exercise to pharmacological therapies can add beneficial effects to treatment (Tang e Reed, 2001).

According to Malin *et al*. (2001) observed the association between physical exercise and metformin on AMPK activation in skeletal muscle and observed that this combination could be more effective for stimulation after 12 weeks, interventions improved insulin sensitivity, but the largest increase was observed after Intervention only with exercise and in conclusion the authors suggested that metformin in exercise therapy could attenuate the effects.

Metformin (200mg/day) does not increase insulin sensitivity after physical exercise when compared to exercise alone, and when AMPK activity is evaluated, it was shown 3 times higher after exercise at 65% VO_{2max}, but with no association with metformin (Sharoff *et al*., 2010).

Based on the evidence that metformin would attenuate the insulin sensitivity promoted by exercise, we sought to evaluate the effects of both on insulin resistance individuals among a group taking their daily dose after exercise. As a result, the researchers found that glucose tolerance was similar to that of the control group, but the energy expenditure during the activity was 9% higher with the combination with metformin and this was due to the higher oxidation of carbohydrates (Ortega *et al*., 2014)

FUTURE PERSPECTIVES AND CONCLUSIONS

Based on the data presented, there are potential mechanisms to obtain benefits of treatment with metformin in combination with exercise for the treatment of T2DM in an efficient manner, however, further research is needed to analyze the effect of the combination on different exercise protocols and different metformin dosages, considering that some studies have observed attenuation of the beneficial effects of exercise to the timing and drug dosages at different times of the day, considering the drug half-life and its active principle so that it is possible to analyze possible daily distributions of exercise and metformin with The purpose of obtaining the best results, allocating each one in the best possible scenario in the treatment of T2DM and its complications.

However, more research is needed with different physical activity protocols, involving intense training, resistance training, high intensity interval training and its combination with metformin to evaluate the respective responses to each exercise.

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