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Metformin Delays Germination and Inhibits Growth of *Lens culinaris* Medik Seeds

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Abstract: Metformin is an AMPKinase activator which is often used for diabetes type II treatment. With the objetive to analyse the relevance of the AMPKinase in the growth of the plants, we exposed seeds of Lens culinaris Medik from the family of the *Leguminosae* to metformin and analyzed seeds germination and plant growth. Our results showed that metformin was able to diminish growth and delay germination of Lens culinaris Medik seeds suggesting that AMPKinase may have an important role in plant development and that the study of different AMPKinase activators and inhibitors in seeds germination and plant growth may be relevant in horticulture.
Keywords: Metformin, seeds, germination, plant growth, AMPKinase

INTRODUCTION

Metformin is an antidiabetic drug from the family of biguanides used in the treatment of Diabetes type II. Its action mechanism is not clear. However, it is able to induce an activation of the enzyme AMPKinase inducing an increase in catabolic metabolism and a decrease in the anabolism. AMPKinase, an enzime highly conserved, is expressed in eukariotal cells [1]. The AMPKinase is a multimeric enzyme composed by three subunits (alpha, beta and gamma) which is the responsible for switching the sort of cell metabolism. When AMPKinase is activated, cell metabolism change into an oxidative one with mitochondrial activation ATP increase and a major carbohydrate, lipidic and proteic catabolism. However, its inactivation induces an anabolic switch of cell metabolism with ATP decrease and an increase in lipidic, proteic and nucleic acid synthesis [1].

Therefore, AMPKinase behaves like a cell metabolism interruptor, switching metabolism from a catabolic one to an anabolic one and vice versa depending on cell metabolic needs [1]. Metformin is able to activate AMPKinase throught the kinase LKB1 which induces phosphorylation of its alpha subunit. On the other hand, metformin provokes an increase in AMP which activates AMPKinase by an initial inhibition of Complex I in mitochondrial respiratory chain [2] (Fig. 1). Lens culinaris Medik is a plant from the family of the Leguminosae whit a short germination period (24-48h) and with a fast growth, so it is a very good model to develop germination and growth experiments [3]. The objective of this article was to analyze the influence of metformin in the germination and plant growth using Lens culinaris Medik seeds as experimental model.

MATERIALS AND METHODS

Seeds of Lens culinaris Medik (n=30) were placed in containers over cotton sheets and fed with water (10 mL) twice per day including a treatment with metformin (1.7M, 170mM, 34mM, 17mM). A group of seeds (n=30) without treatment was used as a control. Root and stem germination and growth were measured at different times. Statistical analysis was carried out using the SPSS 17.0.

RESULTS AND DISCUSSION

In the seed control group, the root germination and stem complete germination ocurred at 24 and 60 h, respectively. By contrast, seeds treated with metformin (170 mM) showed a complete germination of roots at 36 hours and a complete stem germination at 108 hours (Fig. 2 A and B). In relation to root growth, metformin (170 mM) induced a less growth of seeds (9, 77 mm) that those used as a control (24,07 mm) after 144 h. In addition, stems were smaller after metformin exposure (11, 65 mm) in comparison to control (67, 53 mm) at the same time (Fig. 2 C and D). Interestingly, doses metformin at 1.7 M inhibited completely seeds germination, metformin at 17 mM had not any effect and metformin at 34 mM induce only a slightly delay in stem growth (data not shown).

Lens culinaris Medik seeds have been used to study the effect of some physical and chemical compunds. In fact, Akbal *et al*. [4] showed that mobile phone electromagnetic waves were able to modulate their root germination and growth while Sinha *et al*. [5] demonstrated a decrease in Lens culinaris Medik germination after gamma rays exposure. According to our results, metformin (170 mM) delayed root and stem germination of Lens culinaris Medik seeds. This metformin effect could be explained by its action mechanism including an activation of the AMPKinase which induce a change in seed and plant metabolism. Therefore, a decrease in lipid and protein synthesis, which are necessary for cell proliferation and growth, occurred in the seeds inducing a delay in their germination and growth. In addition, other mechanisms might be implicated in this phenomenon. In fact, Dong *et al*. [6] demonstrated that AMPKinase activation provokes an inactivation of the mTOR1 protein which normally enhances cell proliferation and growth. So, the inactivation of mTOR1 mediated by metformin could provoke a decrease in plant cell proliferation and growth and AMPKinase might have a central role in plant physiology. In this context, the AMPKinase inhibitors (i.e. dorsomorphin or compund C which may activate mTOR1 [7] could also increase plant growth and be useful in horticulture.

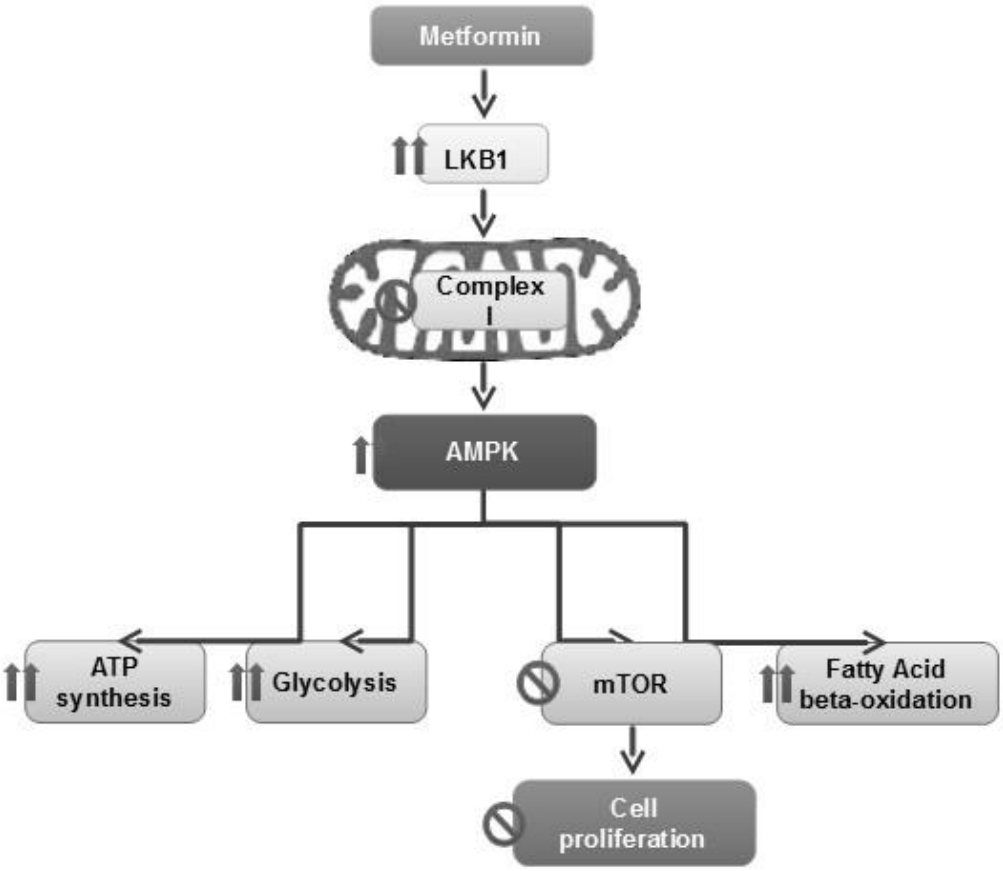

Fig-1: Metformin and AMPKinase. AMPKinase activation provokes an increase in ATP production, glycolysis and beta-oxidation. By contrast, its inactivation is responsible for a decrease in ATP production and a rise in gluconeogenesis, lipogenesis and pentosas cycle. Metformin is able to activate kinase LKB1 which inhibits the Complex I in the mitochondrial respiratory chain. Both processes are responsible for AMPKinase activation. In addition, AMPkinase activation induce a inhibition of mTOR and, consequently, a decrease in cell proliferation. By contrast, AMPKinase inhibition induce the opossite effect

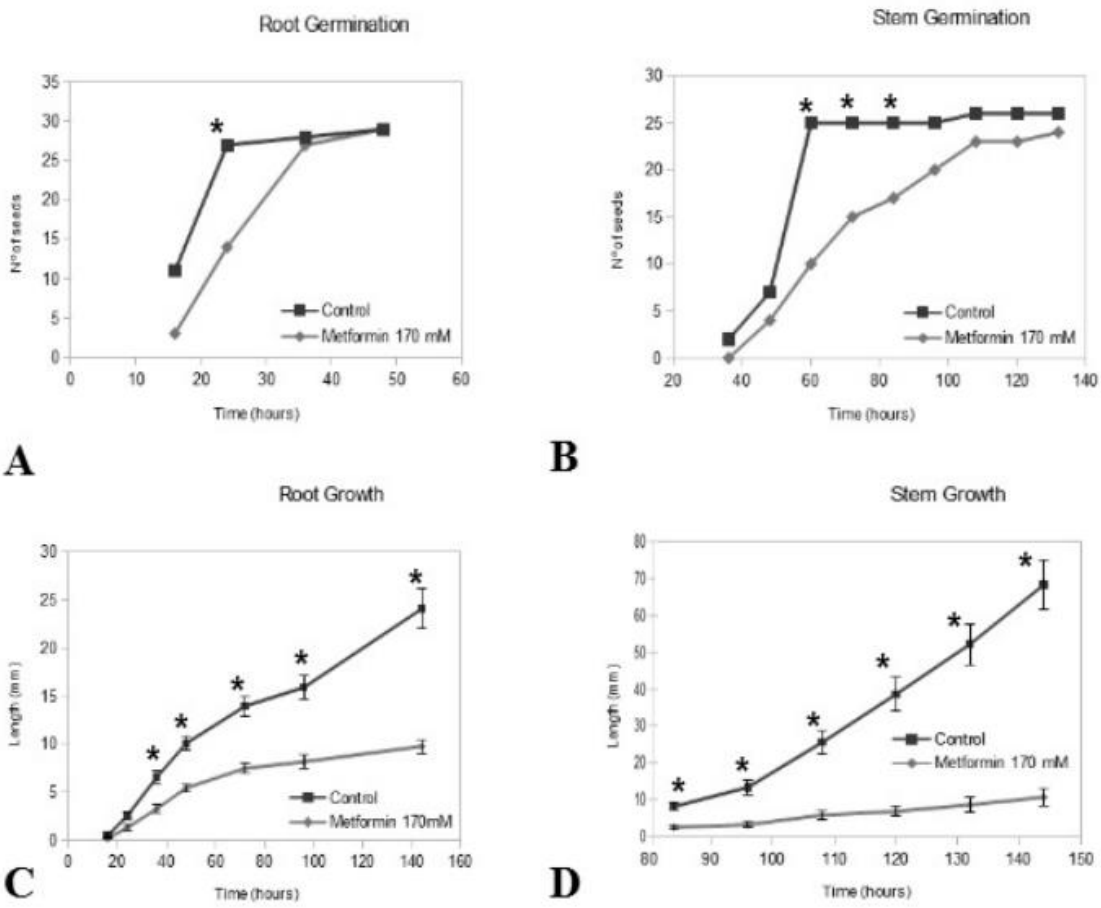

Fig-2: Effect of metformin in root and stem of *Lens culinaris* Medik . A and B, Effect of metformin (170 mM) in root and stem germination. C and D, effect of metformin (170 mM) in root and stem growth. Data represent the mean value ± SD of 30 replicates. (*) Significant differences between samples ($p<0.01$)

CONCLUSION

Metformin provokes a delay in germination and a growth inhibition of Lens culinary Medik seeds. This phenomenon, that could be related to AMPKinase signaling pathway, might be usefull in horticulture.

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