Metformin downregulates mRNA expression of epithelial magnesium TRPM6 channel in intestine and kidney

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Backgrounds: Metformin is the first treatment of choice in diabetes mellitus. Recently, it has been shown that metformin induces low serum magnesium levels in type 2 diabetes patients. To date, the effect of metformin is only on clinical outcome, the molecular mechanism of metformin involved in Mg^{2+} homeostasis is completely unknown. The aim of this study is to investigate the impact of metformin on the mRNA expression of genes responsible for (re)absorption of Mg^{2+} in the kidney and in the intestine, and to give new insights into the molecular basis on Mg^{2+} uptake. To this end, mDCT15 and hCaco-2 cell lines were used as a cell model for kidney and intestine respectively.

Methods: Both cell lines were treated 24h with metformin (10mM). Only mDCT15 cells were incubated with AICAR (2mM) and insulin (10nM). AICAR was used as a positive control for AMPK phosphorylation. To determine the relative gene expression, total RNA was isolated and the real time quantitative PCR was performed. Western blot technique was used to determine the relative phosphorylation of AMPK. To assess magnesium absorption, $^{25}Mg^{2+}$ assay was carried out at 3 time points (0, 20, 40min) and $^{25}Mg^{2+}$ measurements were performed by inductively coupled plasma mass spectrometry (ICP-MS).

Results: Metformin significantly decreases *TRPM6* (epithelial Mg^{2+} channel) mRNA expression in mDCT15 and in hCaco2 cell lines. Contrary to metformin, AICAR increases significantly the expression of mRNA *Trpm6* in mDCT15 cells. Insulin did not show any significant difference in *Trpm6* mRNA expression in mDCT15 cells. *Slc41a1* (Na^{+}/ Mg^{2+} exchanger) mRNA expression is significantly increased by metformin and AICAR in mDCT15 cells. Metformin and AICAR reduce significantly $^{25}Mg^{2+}$ uptake in mDCT15 cells. Metformin decreases *Trpm6* mRNA expression independently of AMPK activation. Metformin might increase *Slc41a1* mRNA expression via AMPK pathway. Metformin might reduce Mg^{2+} uptake via AMPK pathway.

Conclusions: In diabetes type 2 patients, metformin could lower serum Mg^{2} levels through downregulating *TRPM6* mRNA expression in the kidney and in the intestine.

Keywords: Kidney, Intestine, TRPM6, Diabetes.