Metformin Reverses Hexokinase and 6-Phosphofructo-1-Kinase Inhibition in Skeletal Muscle, Liver and Adipose Tissues from Streptozotocin-Induced Diabetic Mouse

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Diabetes *mellitus* (DM) is a chronic disease characterized by high blood glucose levels. Glycolysis is a metabolic pathway that consumes glucose, being regulated mainly by hexokinase (HK), phosphofructokinase (PFK) and pyruvate kinase. Activation of this pathway may contribute to decrease glycemia, ameliorating this diabetic symptom. Metformin is a biguanide wideworld used to treat type 2 DM. However, it has been shown that this drug decreases blood glucose concentration and stimulates glucose consumption rate in type 1 DM models, although the mechanism of metformin action is not completely known. In this study we investigated the role of metformin on HK and PFK activities of different mammalian tissues from streptozotocin-induced diabetic mice. Diabetic animals were intraperitoneally injected with metformin for three days, once a day. The treatment decreases the glycemia and increases lactacidemia in an insulin-independent manner. HK and PFK activities are reduced in diabetic mice when compared to control individuals, an effect abrogated upon the treatment with metformin. Additionally, the treatment of diabetic mice with metformin increases the cytoskeleton-bound PFK activity in skeletal muscle which has been described to activate the enzyme. In liver this treatment just decreased the soluble PFK activity but doesn't alter the PFK activity distribution in adipose tissue. The purified HK and PFK activities are not modified by metformin *in vitro*. In conclusion, our results suggest that elucidation of the mechanisms responsible for HK and PFK activation could reveal potential therapeutic targets for the prevention or treatment of diabetes. Supported by FAPERJ, CNPq, FAF/FECD, Pronex.
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