Changes associated with Na,K-ATPase in brain, kidney, heart and liver of the spontaneously diabetic Goto-Kakizaki rat

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Alterations in Na,K-ATPase activity, in isoenzyme expression and/or number of units of the pump present in the plasma membrane have been associated with diabetes. These changes were described in different organs and tissues such as brain, heart, kidney, among others, and may result from altered insulin levels. However, the vast majority of studies were conducted in animal models of chemically induced diabetes, which are not consensual models for type 2 diabetes (T2D). The major goal of this work was to investigate putative modifications in Na,K-ATPase enzymatic activity or expression in brain, kidney, heart and liver in T2D.

The Goto-Kakizaky rat (GK) strain was used as a model of spontaneously developed T2D, and Wistar rats as controls. Na,K-ATPase activity was assessed by the hydrolysis of ATP (Pi formed in the presence/absence of ouabain was measured using a colorimetric assay) and the isoenzymatic expression by Westernblot.

A decrease in Na,K-ATPase activity in renal and cardiac tissues from GK comparatively to controls (55.7% and 77.5%, respectively) was observed. The pump activity was similar in liver and brain tissues. In renal tissue, expression of α1-Na,K-ATPase was similar between GK and controls but α2- was 2.3x higher and α3- was detected only in GK. Contrastingly a decreased expression of α1- (49.5%) and α2-isoforms (67.6%) was found in cardiac tissue. Despite similar Na,K-ATPase activity in liver and brain tissues, α1-isoform expression was decreased (33.9%) in the liver from GK while in the brain an increase of α1-isoform (~2x) together with a decrease of α2-isoform (14.0%) expressions were observed.

It is unclear, except maybe for cardiac tissue where lower expression is potentially underlying the diminished pump activity in GK, whether the changes in isoenzyme expression is a key factor for differential Na,K-ATPase activity. Being responsive to complex regulation, other regulatory mechanisms may contribute to the impaired activity observed in kidney and heart.

These results have uncover changes in Na,K-ATPase activity and/or enzymatic expression in GK brain, kidney, heart and liver that may contribute to the undesirable conditions associated with T2D. This work highlight the relevance of further investigation about Na,K-ATPase regulation and role in physiopathology of T2D.

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Isozyme expression of isoforms α1, α2 and α3 of Na, K-ATPase were also analysed and changes were observed.

In the kidney, there was an expression of 0,009±0,002 and 0,021±0,006, in control rats and GK, respectively, or a significant increase in expression of the α2 isoform GK.

Already in the hepatic tissue, we observed a significant decrease in expression of the α1 isoform, registering an expression of 1,295±0,095 and 0,856±0,084, in control rats and GK, respectively.

In the brain, expression of the α1 isoform in the control and GK rats was 0,367±0,021 and 0,602±0,073, respectively, i.e. a significant increase in expression of this isoform in GK. In contrast, the α2 isoform, we observed a significant decrease in expression of GK, to which the recorded values of 0,043±0,003 and 0,037±0,001, in control rats and GK, respectively. Unlike isoform α1 and α2 to α3-Na, K-ATPase is not significantly different between control and GK rats for which we observed an expression of 0,765±0,047 and 0,684±0,044, respectively. Finally, expression of the α1 isoform in heart and GK rats control was 0,782±0,050 and 0,465±0,054, respectively. The expression of the α2 isoform was 0,037±0,011 and 0,012±0,004, in control rats and GK, respectively. Therefore, in cardiac tissue both α1 and α2 isoform experienced a significant decrease in GK.

In summary, our results point to a significant decrease in the activity of Na, K-ATPase in GK in renal and cardiac tissue. These changes may underlie the changes in isoenzyme expression also observed isoforms α1 and α2 and α3 Na, K-ATPase, which makes sodium pump an important therapeutic target for T2D.

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