Kidneys are less than 1 % body mass, but they use as much as 10% of total oxygen consumption. This project focuses on the situation when kidneys lack of oxygen supply. This problem occurs in diabetic kidneys and the nephropathy seems to be one of the most severe diabetic complications, often ending with kidney transplantation.

The main mediator of metabolic response to hypoxia (lowered oxygen concentration) is hypoxia-inducible factor, HIF-1, controlling the expression of the numerous genes having HRE (hypoxia response element) in their regulatory region. The vital role of HIF-1 is shifting oxidative metabolism to unaerobic energy production – it activates glycolysis and there are also some reports on stimulatory action of HIF-1on the activity of gluconeogenesis (glucose synthesis *de novo* from non-carbohydrate precursors) in liver, but there are no data on HIF-1 effect on renal glucose production, which is also considered to be an important source of systemic glucose, especially during diabetes.

Functional HIF-1 is composed of two subunits: α and β. While the latter one is synthesized constitutively, HIF-1α level is precisely regulated – under aerobic conditions is hydroxylated and degraded. However, it seems likely that is some situations the increase in HIF-1α content might be achieved due to factors other than hypoxia itself. The issue of high glucose concentration (hyperglycemia) effect on the activity of HIF-1 is of special interest, but the reports are full of discrepancies.

Thus, the aim of the present project is to explain the mechanisms responsible for the stimulation of HIF-1α expression in renal proximal tubules under hyperglycemic conditions and to elucidate the role of HIF-1 in the regulation of renal gluconeogenesis.

The experiments will be performed on the cell cultures of: immortalized human proximal tubules (HK-2), primary proximal tubules of diabetic type 2 patient (Clonetics™ Diabetic Renal Proximal Tubule Epithelial Cells; D-RPTEC) and control primary tubules (Clonetics™ Normal Human Renal Cells; RPTEC). Throughout the experiments aimed to study gluconeogenesis primary tubules isolated from rabbit kidneys will be also applied. The cells will be cultured under either normoxic or hypoxic (1% oxygen) conditions. Then the following parameters will be examined, *e.g.* activity, expression and posttranslational modifications of the selected proteins (enzymes, transcription factors, *etc.*) and the efficiency of the selected transcription factors binding to the regulatory regions of target genes. The effect of hypoxia and HIF-1 activation on gluconeogenesis will be examined tracking the changes in the intercellular content of the intermediates.

It is expected that the results obtained during the realization of the present project will significantly broaden the knowledge of HIF-1 function in renal proximal tubules, especially under diabetic conditions. This data might turn out to be really useful in terms of postulated, although arousing controversy, application of HIF-1 activity modulators in the therapy of chronic kidney diseases, including diabetic nephropathy. The latter one seems to be a serious challenge for contemporary medicine, as, according to the World Health Organization (WHO), there are about 350 million people all over the world, *i.e.* 6% of the adult population, suffering from diabetes and this number is still increasing.