Description for the general public.

Long lasting elevated blood glucose level (hiperglycemia or diabetes) is often the main cause of a number of cardiovascular diseases and chronic kidney disease. The key factor for the renal dysfunction development might be excessive production and activity of local (paracrine) factors: adenosine (Ado, metabolite of ATP) might be increased in diabetes and bioavailability of vasodilator nitric oxide (*NO*) is often altered. Its level was found to be different depending of the stage of the disease: elevated in the onset phase but decreased at the established phase of diabetes, where it might be lower than in normoglycemic animals.

In the kidney, Ado acting through the purine P1 receptors (P1-R) can induce either vasoconstriction, through stimulation of A1, or vasodilation, via A2 receptor subtypes. In addition, Ado affects renal excretion by stimulation of P1-R localized in the renal tubules which mediate Ado action on sodium and water transport. Several studies showed that in diabetes the expression of individual P1-R subtypes could be differently modified, *e.g.* A2-R density was increased while that of A1-R was lowered; such complex pattern can significantly influence the actual role of adenosine in the kidney.

Restricted *NO* bioavailability reported in established phase of diabetes could be a reason for the disturbance of renal circulation, especially in the renal medulla, the region which is extremely sensitive to *NO* deficiency. The renal medulla is involved in the control of water and solute transport and, in consequence, long-term regulation of blood pressure (BP). It was often postulated that abnormal renal medullary function can result in kidney failure and associated disorders, such as hypertension.

In the project we will use the established model of diabetes induced in primarily normoglycemic rats with streptozotocin, an agent which inhibits insulin secretion. The main aim of our study is to establish if the abundance of individual P1-R (in cortex vs. medulla) is altered during development of diabetes (both in the onset and established phase), and if this is associated with altered renal tissue *NO* bioavailability. Remarkably, *NO* could mediate P1-R action. We will try to find out if the expected changes of P1 expression would have any discernible impact on renal haemodynamics and tubular transport.

It is planned to examine, if in conscious animals the STZ-induced diabetes induces changes in renal excretion of inflammation markers, of proteinuria (a marker of renal injury) and of *NO* metabolites (an index of renal *NO* production). The expression of individual P1-R will be estimated in kidney tissue harvested from animals rendered diabetic, at the onset and the established stage of the disease. Based on these results, in anesthetized animals we will investigate the impact of the individual P1-R on renal tissue *NO* bioavailability in situ (this will be accomplished using polarographic electrode probes placed in renal tissue), on blood perfusion of renal cortex and medulla, and on blood pressure, in rats in the onset or established stage of diabetes. We will verify if the role of specific P1-R depends on the phase of the diabetes.

Renal dysfunction, also that associated with intrarenal haemodynamic disturbances, is postulated to cause many pathological stages including hypertension. Long term exposure to hyperglycemia dramatically increases the risk of BP elevation. Therefore, investigation of the role of P1 receptors and their agonist adenosine, both known to be affected by hyperglycemia, seems to be crucial to the search for new strategies aimed at therapy of diseases like diabetes or hypertension.

The results might help explain the relationship of P1-R activity and *NO*, and also of the free radicals, in the control of renal circulation in individual kidney zones and of the renal tubular transport during the early and established stage of diabetes. Intrarenal interaction between purine P1 receptors and *NO* can also be crucial in BP control in different stages of hyperglycemia. The results obtained might provide a basis for preclinical research on the treatment of renal malfunction in patients with long term hyperglycemia associated with hypertension.