these fluid accumulation mechanisms, which depend on the continued function of cyst wall epithelium throughout the lifetime of the patient, ultimately contribute to the destructive impact of cysts on the surrounding parenchyma.

Maybe it goes without saying, but renal cysts are not so dull after all.

References


---

**Hyperglycaemia—pathophysiological aspects at the cellular level**

G. Wolf and F. Thaiss

Department of Medicine, Division of Nephrology and Osteology, University of Hamburg, Hamburg, Germany

**Introduction**

The concept of diabetic nephropathy has substantially changed in recent years. New biochemical and molecular aspects have emerged and have considerably increased the understanding of how diabetic nephropathy develops. The goal of this editorial is to summarize same recent aspects how hyperglycaemia at the cellular level may be linked to the functional and structural changes that characterize diabetic nephropathy.

**Cellular glucose uptake**

Glucose enters cells by different facilitative glucose transporters (GLUT) that have been characterized in various cell types. Six different transporter proteins, encoded by distinct genes, have been described (GLUT1 to GLUT5 and GLUT7). GLUT1–5 transporters have been found in glomeruli, glomerular mesangial, and tubular epithelial cells [1]. Since most GLUT transporters carry glucose into the cell independent of insulin, glucose gets into renal cells predominantly along a concentration gradient, even in insulin deficiency [1]. High extracellular glucose levels therefore induce high intracellular glucose concentrations. Overexpression of glucose transporters in transgenic mice has recently demonstrated that GLUT are necessary for the development of the characteristic changes of diabetic nephropathy, suggesting that high intracellular glucose concentrations are a prerequisite for these functional and structural changes of the kidney. The possible consequences of high intracellular glucose levels are mainly attributed to two theories, one is called the ‘osmolyte’ hypothesis and the other the ‘redox’ hypothesis (hyperglycaemic ‘pseudo-hypoxia’ [2–4]).

**The polyol pathway**

Elevated intracellular glucose levels are metabolized through the polyol pathway to sorbitol. This pathway is generated through the activation of the enzyme aldose reductase [2]. The intracellular accumulation of polyols induces hypertonicity, which results in an influx of fluid. This occurs because the polar nature of polyols prevents their facile penetration of membranes. The
increase in intracellular fluid resulting from polyol accumulation initiates changes in membrane permeability. The concentrations of potassium, glutathione, inositol, and adenosine triphosphate begin to decrease, whereas the concentrations of sodium and chloride ions increase. The activation of the polyl pathway by high glucose concentrations has been demonstrated in isolated glomeruli, glomerular mesangial cells, and tubuli [2]. As a consequence of intracellular sorbitol accumulation there is also a decrease of the intracellular myoinositol concentration. Mainly the membrane-bound fraction of inositol is decreased in hyperglycaemia [2]. The reduction of cell-membrane-bound inositol has profound consequences on the intracellular signalling processes through a disturbed activation of the IP3 pathway [2,5].

As a consequence of myoinositol depletion and altered intracellular signalling, Na+-K+-ATPase activity is decreased in a variety of cells in diabetes mellitus [6]. Changes in Na+-K+-ATPase activity in turn influences the regulation of sodium transport, vascular tone, and cellular proliferation. The increased intracellular sodium concentrations inhibit the Na+-Ca2+-exchanger, thus increasing intracellular calcium levels, which are elevated in most tissues in diabetic animals [7]. The increased availability of NADH may favour increased radical formation by other peroxidases such as GSH peroxidase. This pathway has been linked to an increased activation of NF-κB in glomerular mesangial cells, which may also be relevant for growth factor release in diabetes [9].

In addition, increased NADH/NAD ratios are the primary mechanism for an increased formation of nitric oxide (NO) in hyperglycaemia [4]. Hyperglycaemia induces an increased expression of the inducible form of NO synthase and an increased; release of NO in the cell culture medium as demonstrated for glomerular mesangial cells and macrophages [10]. This increased formation of NO might be responsible for glomerular hyperfiltration and hyperfusion which is seen in early diabetic nephropathy.

**Renal growth and extracellular matrix production**

Renal hypertrophy occurs early in diabetic nephropathy [11]. Several in vitro studies have recently demonstrated that hyperglycaemia per se has fundamental effects on cultured renal cells [12,13,15,16]. High glucose in the culture medium stimulates hypertrophy of murine proximal tubular cells [12]. This enlargement of tubular cells is mediated by autocrine induction of transforming growth factor beta (TGF-β). Moreover, high glucose medium and angiotensin II (ANG II) have additive effects on the induction of hypertrophy in renal tubular cells [13]. Since changes in the renin–angiotensin system have been described in diabetic nephropathy [2], potential increases in intrarenal ANG II may further foster the hypertrophy of tubular cells in the presence of hyperglycaemia. Stimulated renal expression of insulin-like growth factor 1 (IGF-1) appears to play a pivotal role in the development of the hypertrophy of the diabetic kidney [14]. However, whether IGF-1 is solely induced by hyperglycaemia in the absence of other metabolic abnormalities remains unclear [11]. In contrast to tubular cells, high ambient glucose concentration has a biphasic effect on growth of cultured mesangial cells [15]. Raising glucose concentration for 24 h has a significant proliferative effect on mesangial cells associated with the induction of immediate early growth response genes [15]. However, after 72 h of exposure to high-glucose-containing media a growth suppressive effect was observed. This late phase of glucose-induced mitogenic inhibition of mesangial cells was mediated by endocrine induction and bioactivation of TGF-β [15]. Furthermore, modification of extracellular matrix by non-enzymatic glycosylation also inhibits the proliferation of mesangial cells [16]. This change in mesangial cell growth behaviour is not limited to the in-vitro situation since glomerular mRNA levels for TGF-β, transforming growth factor

Mycophenolate mofetil (RS 61443): nothing new under the sun or an important break-through in the field of transplantation?

F. J. van der Woude
Department of Nephrology, State University Hospital, Leiden, The Netherlands

Introduction

Although transplantation of a kidney from a deceased donor has become a standard clinical procedure in North America and most countries within Europe, the steady loss of functioning transplants over time remains the most important problem to be solved. Long-term graft survival is characterized by failure rates that are essentially constant after about a year or two. The rate has not varied appreciably among cohorts defined in terms of transplant year [1]. Studies using multivariate analysis have shown that an acute rejection episode soon after transplantation is the single most important risk factor for chronic rejection [1,2]. Recently a cohort study of 482 consecutive patients who received a graft between 1983 and 1991 was made in our centre. Early vascular rejection occurring within 3 months after transplantation was the most important predicting variable of both early and late graft loss.

Use of cyclosporin A, less HLA-DR mismatching, and a cold-ischaemia time of short duration had a favourable influence on the development of vascular rejection [3]. In recent years many new immuno-suppressive drugs have been developed. While the majority of these drugs are excellent in preventing cell-mediated (interstitial) rejection, they do not equally inhibit the long-term immune responses mediated by antibodies against (endothelial) alloantigen of the donor, which may mediate vascular or chronic rejection [4].

Only mycophenolate mofetil seems to be especially promising for the treatment of vascular rejection, because of its potential to downregulate antibody production and to inhibit smooth muscle-cell proliferation in the vessel wall. Since the introduction of this drug in the clinic may turn out to be of clinical relevance, I will briefly discuss the rationale behind the design of the drug, data in experimental animal models, and clinical studies with the drug.

Why mycophenolate mofetil was designed

The development of mycophenolate mofetil was started by A. C. Allison; he tried to design a drug with reversible antiproliferative effects on lymphocytes more than on other cell types [5]. There are two major pathways involved in purine synthesis: the de novo and the salvage pathway. In the de novo pathway the ribose phosphate portion of purine nucleotides is derived from 5-phosphoribosyl-1-pyrophosphate (PRPP). PRPP is also used by the purine salvage pathways, including the major pathway catalysed by hypoxanthine-guanine phosphoribosyltransferase (HGPR Tase). Allison's therapeutic strategy depended on the fact that in human lymphocytes PRPP is inhibited by adenosine nucleotides (AMP and ADP) but activated by gua-