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Human Myocardial mRNA-Expression of Insulin-Dependent Transmembrane Glucose Transporter is Increased in Human IDDM and Decreased in NIDDM

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Transmembrane glucose transport and thus cellular high energy metabolism of the cardiovascular system depend largely on the insulin responsive GLUT4-isoform of the transmembrane glucose transport molecule. Several authors have shown that, in animals, myocardial GLUT4-mRNA expression is decreased in experimental diabetes. There are no data on humans as yet.

Here, we investigate probes of right atrial auricle from diabetic and non diabetic patients subjected to cardiac surgery which were snap frozen in liquid nitrogen. Semiquantitative PCR has been used in order to quantify GLUT4-mRNA using G3PDH as a house keeping gene.

Methods

Myocardial tissue probes derive from the right auricle of patients undergoing cardiac surgery. A small part of the right auricle is removed when the heart is put on extracorporal circulation and is normally wasted. The muscle piece (60–200 mg) will then be snap frozen in liquid NO and stored at −70 °C until homogenisation. Total RNA was isolated using guanidium thiocyanate, phenol-chloroform extraction and alcohol precipitation. Total RNA was hybridised with 32P-labelled human GLUT4-cDNA and re-hybridised with a human G3PDH-cDNA probe to correct for equal amounts of RNA. Quantification was performed by a laser scanner and is expressed in optical densities.

Results

Our results represent one of the first measurements of GLUT4-mRNA in human myocardial tissue. Seven patients had NIDDM (determined by OGT, HbA1C and insulin secretion), 7 had IDDM and 7 served as controls. Relative GLUT4-expression amounted to 97.0 ± 10.4 (±SEM) in the control group, 133.3 ± 15.2 in the IDDM-group and 49.1 ± 6.2 (± SEM) in the NIDDM-group. From these data we deduce that DM is initially associated with a decreased GLUT4-expression, the latter then being upregulated by external application of insulin.

Key words: glucose transport, gene expression, real time PCR, hypertension

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absolute transport molecules. Down-regulation of transmembrane 
insuline dependent glucose concentrations of serum insulin may cause the observed 
down-regulation of transmembrane insulin dependent glucose transport molecules.

The fact that insulin treated diabetic patients exhibit a down-regulated GLUT4-expression is surprising. However, the facilitated glucose entry into the cell in the presence of higher concentrations of serum insulin may cause the observed down-regulation of transmembrane insulin dependent glucose transport molecules.

**Discussion**

The interrelation between disturbances in glucose-metabolism, hypertension and myocardial ischemic disease has been known for a long time and thus has been the subject of investigation in a multitude of trials, publications and experimental studies [c.f. 10–19]. Insulin resistance and reactive hyperinsulinemia occur not only with obesity, impaired glucose tolerance or non-insulin-dependent (type 2) diabetes mellitus, but also in many non-obese [20], non-diabetic patients with essential hypertension and seem to be largely responsible for the development of hypertension. The common co-existence of genetic predisposition for hypertension with insulin resistance helps to explain the frequent, although temporally often dissociated, occurrence of hypertension together with dyslipidemia, obesity and type 2-diabetes in a given cohort.

In the pathogenesis of metabolic syndrome, inappropriate vasoconstriction, structural changes of the cardiovascular system [21–23] as to its stiffness, but also unfavourable distribution of liquid between the compartments play a key role. While the complete cascade of interactions between glucose-metabolism, KHK, obesity and hypertension has not been elucidated completely as yet, trans-membrane glucose transport is certainly crucial in this setting [1–9].

GLUT4, the insulin-dependent transmembrane glucose facilitative transport molecule, plays a decisive role in insulin-dependent cardiac glucose metabolism, apparently also for myocardial [24] and vascular stiffness [19] as well as in the context of osmolarity, compartmental water distribution and homeostasis [1]. As early as 1995, comparative studies using nuclear magnetic spectroscopy in heart of normotensive (WKY) and spontaneously hypertensive rats (SHR) have looked at glucose uptake during insulin stimulation as well as mRNA-expression of GLUT1 and GLUT4 [25]: in hypertensive rats, expression of GLUT4-mRNA as well as the amount of protein in the membrane had been decreased and cardiac hypertrophy increased by 59%. Similar results have been found in the afferent vessel of the renal glomeruli in experimental, streptozotocin-induced diabetes mellitus. In diabetic animals, GLUT4 as well as polypeptide expression and thus glucose uptake had been reduced. In this context, it has been speculated that the resulting decrease of GLUT4 could modulate renal blood flow and, in turn, lead to hypertension. We then concluded that defective GLUT4-expression may also occur in human myocardium of diabetics [8–10] as well as hypertensives [26]. Disturbed transmembrane glucose transport may also significantly contribute to the development of severe coronary heart disease [27] and diabetic cardiomyopathy [28]. In the context of hypertension, very few authors have looked at evidence for myocardial and vascular GLUT4-involvement in the development of hypertension in animals [29] and still no reports can be found on GLUT4 in human myocardium. Despite the scant experimental direct evidence, Ikegami et al have already postulated the GLUT4-gene as one of the target genes in essential hypertension when accompanied with insulin resistance [30].

In the present project we have intensified our investigational efforts focussed on the unknown role played by GLUT4 in the development of different forms of diabetes in the context of the above considerations.

**GLUT4 and Myocardial Ischemia**

Glucose and high energy metabolism play a pivotal role in the development of numerous salient characteristics of myocardial ischemia, such as the gating properties of specific ion-channels, intracellular ion-homeostasis, electrical phenomena, contractility and other phenomena [31–33]. Many of these aspects of myocardial ischemia are linked in one or the other way to transmembrane glucose transport, intracellular glucose metabolism and, in fact, to GLUT4 [34–36]. Myocardial ischemia increases glucose uptake through translocation of GLUT1 and GLUT4 from an intracellular compartment to sarcolemma. This appears to be a beneficial effect during ischemia and possibly recovery. Insulin and ischemia have additive effects to increase *in vivo* glucose utilisation and augment glucose transporter translocation [37]. Delivery of glucose to the glycolytic pathway appears to be a major controlling site of glycolysis in low-flow ischemia. Downstream regulation is then distributed along the pathway with no one site exerting greater inhibition than reduced glucose delivery [38]. While many experimental studies suggest that an increase in glucose uptake and metabolism by the ischemic myocardium helps to protect myocardial cells from irreversible injury [39], little or nothing is known in this context about human cardiac transmembrane glucose transport, GLUT4-expression and the interrelation between the latter and diabetes during ischemia.

The weakness of the study is twofold: on the one hand, the patient cohorts are relatively small and hence difficult to match concerning co-medications, age and co-morbidities. However, it can be argued that the differences between the groups are statistically relevant, and that the data are certainly valid to inspire larger investigations. Furthermore, it has to be argued that, in the present setting, it is difficult to retrieve sufficient human material in order to aim at larger cohorts. The second weakness targets the semiquantitative method of measurement. RT-PCR would certainly constitute a more
elegant methodological approach. Hence, inspired by the above measurements, we began to establish real-time PCR for the assessment of GLUT4-mRNA under various conditions. Further investigations on the subject are certainly needed in order to elucidate the role played by GLUT4 in the development of diabetes in humans.

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References

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