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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.

Objectives
To compare GLUT4-mRNA expression in myocardial samples of diabetic and non diabetic patients undergoing cardiac surgery.

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 extracorporeal 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 OGTT, 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. J Clin Basic Cardiol 2004; 7: 8–10.

Key words: glucose transport, gene expression, real time PCR, hypertension
absolute density of the house-keeping gene G3PDH. 32P-la-
belled human GLUT4-cDNA had been used for hybridisa-
tion. While control values tended to be around 100 RODs
(97.0 ± 10.4), NIDDM-patients showed RODs of around
half of that, when corrected for the house-keeping gene.

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

Discussion

The interrelation between disturbances in glucose-metabo-
list, hypertension and myocardial ischemic disease has been
known for a long time and thus has been the subject of investi-
gation in a multitude of trials, publications and experimen-
tal studies [c.f. 10–19]. Insulin resistance and reactive hyper-
insulinemia occur not only with obesity, impaired glucose
tolerance or non-insulin-dependent (type 2) diabetes melli-
tus, 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-exist-
ence 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, inappropria-
te vasoconstriction, structural changes of the cardiovascular
system [21–23] as to its stiffness, but also unfavourable dis-
tribution 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
e elucidated completely as yet, trans-membrane glucose trans-
port is certainly crucial in this setting [1–9].

GLUT4, the insulin-dependent transmembrane glucose
facilitative transport molecule, plays a decisive role in insu-
lin-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 normoten-
sive (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 hyper-
tensive 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 hyper-
tension. We then concluded that defective GLUT4-expres-
sion 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 de-
velopment 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 vas-
cular GLUT4-involvement in the development of hyperten-
sion in animals [29] and still no reports can be found on
GLUT4 in human myocardium. Despite the scant experi-
mental 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 myo-
cardial ischemia, such as the gating properties of specific ion-
channels, intracellular ion-homeostasis, electrical phenom-
ena, 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]. Myo-
cardial ischemia increases glucose uptake through transloca-
tion of GLUT1 and GLUT4 from an intracellular compart-
ment 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 con-
trolling 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 in-
crease in glucose uptake and metabolism by the ischemic
myocardium helps to protect myocardial cells from irrevers-
bile 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 diabe-
tes 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

Figure 1. Northern Blot of total RNA with 32P-labeled human GLUT4-
cDNA of patients with NIDDM, IDDM and controls. Rehybridization
with a human G3PDH-cDNA probe to correct for equal amounts of
RNA. Quantification was performed by laser scanner and is expressed
in optical densities.
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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