Insulin-Dependent Transmembrane Glucose Transport in Cardiovascular Disease

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In mammals, the transport of glucose across cell membranes occurs by facilitated diffusion. Several cDNAs encoding structurally related proteins with the properties of facilitative glucose transporters have been isolated and characterized (GLUT). These molecules regulate transmembrane glucose transport in various tissues. GLUT4 appears to be of special interest for several reasons, in particular because it is the only GLUT which is directly regulated/stimulated by insulin. It is found in various tissues like cardiac and skeletal muscles, as well as adipose tissue [1]. The isolation and characterisation of a monoclonal antibody that specifically recognised this “muscle-fat isoform”, GLUT4, revealed that it was a unique isoform, different from the glucose transporters present in erythrocytes, brain, kidney, jejunum and liver. It shows between 50 % and 70 % cDNA identity with GLUT1–3. Insulin causes a rapid and reversible increase in glucose transport activity via GLUT4 in cardiac and skeletal muscles [2].

**Function and Regulation of GLUT4**

While different types of muscle fibres contain different levels of GLUT4 proteins and gene expression as well as different insulin sensitivities, the nutritional state and contractile activity appear to regulate GLUT4 gene expression. Fasting, for example, results in a two- to threefold increase in GLUT4 protein and gene expression in mixed soleus and gastrocnemius muscle preparations [3]. Exercise training also increases GLUT4 protein levels in rat skeletal muscle [4], whereas there are conflicting results concerning patients with NIDDM: In skeletal muscle, Handberg and co-workers found no significant difference in the levels of GLUT4-mRNA and protein in biopsies from patients with and without NIDDM [5], whereas Dohn et al. found a significantly decreased expression of GLUT4 in skeletal muscle from insulin resistant patients [6]. In rat cardiac tissue of streptozotocin-diabetic rats, Eckel and Reinauer showed that GLUT4 mRNA is decreased [7]. Interestingly, our own group showed that in human NIDDM patients, GLUT4-mRNA expression is down-regulated [8], whereas it is up-regulated in IDDM [9]. The latter may be explained by the fact that the application of insulin stimulates the expression of GLUT4 mRNA [1].

**Glucose Metabolism, Molecular, Genetic and Structural Implications in the Development of Hypertension**

The multitude of humoral, structural, genetic and molecular mechanisms involved in the pathophysiology of hypertension and its development shall not be completely revealed in this context but has been subject of research and speculation for more than two centuries, beginning with the work of Stephen Hales (1677–1761) and the revolutionary publication of Scipione Riva-Rocci (1799–1869) [10–14]. Here, we shall only expand on one selected subject within the complex framework of hypertension: glucose metabolism.

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 [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 hypertension, 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 and hypertension has not been elucidated completely as yet, transmembrane glucose transport is certainly crucial in this setting [1–9].
**Insulin-Dependent Transmembrane Glucose Transport Molecule GLUT4 and Hypertension**

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 at 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 9%. 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, and were the first to demonstrate a decreased GLUT4 expression in the right auricle myocardium of non-diabetic, hypertensive patients, however, using semi-quantitative techniques and a small cohort of patients ([26] snap frozen, non-ischemic human material was difficult to retrieve). 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, already Ikegami et al. have postulated the GLUT4 gene as one of the target genes in essential hypertension when accompanied by insulin resistance [30]. In the present project, we wish to intensify our investigational efforts focussed on the unknown role played by GLUT4 in the development of hypertension using more sophisticated and complex techniques.

**GLUT4 and Myocardial Ischemia**

Myocardial ischemia has been the subject of research for more than three centuries, the first published experiment on coronary artery ligation in a dog came from Petri Chirac in 1698 (see facsimile). Since then, it has become clear that glucose and high-energy metabolism plays 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 way or the other to transmembrane glucose transport, intracellular glucose metabolism and, in fact, to GLUT4 [34–36]. Myocardial ischemia leads to an increase of 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 is known in this context about human cardiac transmembrane glucose transport, GLUT4 expression and the interrelation between the latter and coronary heart disease during ischemia.

Only one abstract on a small cohort of patients (3 subjects with reduced flow and metabolism, 5 with reduced flow and metabolism, 6 controls) has been published so far, which shows that disturbed transmembrane glucose transport via GLUT molecules may also significantly contribute to the development of severe coronary heart disease [27]. The contribution of GLUT4 to diabetic cardiomyopathy has also been discussed [28].

Literature indicates that downregulated GLUT4 may be a) involved in the development of hypertension and b) lead to less effective protection against myocardial injury. Further work is needed in order to elucidate this interrelation. Long-term results may lead to the development of new therapeutic strategies in the prevention of hypertension and the treatment of myocardial infarction.

**References:**


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