Knockout mice lacking GLUT4 glucose transporters
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The physiopathology of non-insulin-dependent diabetes mellitus (NIDDM) is still a hot issue in endocrinology. The disease is associated with a defect in insulin secretion as well as markedly impaired glucose uptake in response to insulin. Katz et al. (Nature, 377, 151–155) have disrupted the murine GLUT4 gene in an effort to build up a new model of tissue-specific (i.e. mainly muscular) insulin resistance. Strikingly, they show that knockout mice lacking GLUT4 transporter do not develop diabetes.

Glucose transport is one of the main components maintaining glucose homeostasis. Glucose uptake is mediated by a family of different specific transporters ensuring facilitated glucose diffusion through the membrane. GLUT1 is ubiquitous and found mainly in erythrocytes, placenta and the blood–brain barrier. Because of its low K_m, it supplies in concert with GLUT3 the constant level of glucose needed by the brain. GLUT2, expressed preferentially in the liver and in the pancreas, works together with glucokinase in regulating insulin secretion and entry of glucose into the hepatocyte. The uptake of glucose by insulin-sensitive tissues involves the GLUT4 glucose transporter, which is expressed in muscles and adipose tissue. Skeletal muscle is quantitatively the main tissue responsible for the disposal of glucose under the effect of insulin. It is now well known that insulin induces translocation of GLUT4 transporters from an intracellular compartment to the cell surface, thereby enhancing glucose transport. Muscle contraction can also stimulate glucose transport via the same translocation mechanism. This process of insulin-stimulated glucose uptake is defective in various physiological and pathological conditions such as diabetes, obesity, high-fat diet and ageing, all characterized by insulin resistance. In obese rat strains, both genetic (Zucker rats) and experimentally induced (ventromedial lesion of the hypothalamus or fed a high-fat diet), there is a decrease of GLUT4 concentration in adipose tissue probably associated with an alteration in GLUT4 translocation in muscle in response to insulin.

Non-insulin-dependent diabetes mellitus is characterized by defects in both insulin secretion and insulin action in peripheral target tissues. Adipocytes and muscle from patients with NIDDM display markedly impaired glucose uptake in response to insulin. Nevertheless, no GLUT4 gene mutation has been related to any defect in insulin sensitivity. GLUT4 protein and mRNA are markedly decreased (by 85%) in adipose tissue from NIDDM patients and may be the main contributor to insulin resistance in this tissue. The precise molecular mechanism of GLUT4 translocation defect in muscle is unknown. Transgenic mice overexpressing GLUT4 exhibit relative hypoglycaemia as well as a diminished hyperglycaemic response during glucose tolerance tests and show a higher rate of insulin-stimulated glucose utilization than control mice (2). In db/db mice, a genetic animal model of NIDDM with hyperglycaemia, insulin resistance and a defect in glucose transport, the transfection and overexpression of human GLUT4 gene markedly improved glycaemic control and overcame the glucose transporter translocation defect (3).

Thus, GLUT4 is of particular importance as it is the site of a rapid adaptation of glucose transport in adipose tissue and muscle after carbohydrate-induced insulin secretion. It may also represent a promising target for therapeutic management of patients with NIDDM.

In order to further delineate the role of GLUT4 in glucose homeostasis, Katz et al. have disrupted the murine GLUT4 gene. They observed that GLUT4-null mice do not develop diabetes although they display insulin resistance. Further, these animals reveal a reduction in adipose tissue, a cardiac hypertrophy and a reduced longevity.

Male GLUT4-null mice have moderate hypoglycaemia during the fasting state and a 20% increase in fed glycaemia, contrasting with normal fasting and post-prandial blood glucose levels exhibited by the females. However, male and female knockout mice show a normal fasting insulin level but a great increase in post-prandial insulin level. Thus, subnormal post-prandial glycaemia in GLUT4-null mice was achieved at the expense of a post-prandial insulin secretion increase. This hyperinsulinaemia is likely to raise hepatic glucose utilization and so compensate for the reduced muscle uptake of glucose. The glycaemic response to an oral glucose tolerance test (OGTT) carried out on 10-week-old GLUT4-null mice was also subnormal in both sexes. In addition, the GLUT4-null mice display a reduced drop of glycaemia during an insulin tolerance test, indicating an expected decreased sensitivity to insulin. This normoglycaemia after a carbohydrate load, in spite of decreased sensitivity to insulin, is somewhat puzzling. It would be interesting to follow up the metabolic parameters in older mice to search for deterioration of glucose tolerance and to study the consequence of hyperinsulinaemia on islet function and structure.

To further elucidate the compensatory mechanisms developed to maintain nearly normal levels of blood
glucose despite a lack of GLUT4. Katz et al. studied the expression of the five GLUT in various tissues. GLUT1 was overexpressed by 1.5-fold in the heart but this upregulation cannot be of great importance for the disposal of glucose. GLUT2 was overexpressed by 1.7-fold in the liver but no upregulation of GLUT1. GLUT3 or GLUT5 was found in skeletal muscle, which brings forward additional evidence for reduction of glucose uptake by muscle.

The consequences of the lack of GLUT4 on glucose, fat metabolism and growth were also studied. Fasted and fed lactate levels were greatly reduced in GLUT4-null mice, suggesting a reduced muscle glycolytic pathway due to a reduced muscle glucose uptake. Free fatty acid (FFA) levels were also lower in GLUT4-null mice.

GLUT4 is also a main transporter in the adipocytes, so it is not surprising that GLUT4-null mice have a reduction in body weight, a dramatic reduction in adipose tissue and, for example, no ovarian fat pad. GLUT4-null mice also developed an important heart hypertrophy (1.5-fold of weight-matched control). Hyperinsulinaemia and high utilization of FFA are known to be risk factors for diabetic cardiovascular disease and certainly contribute to cardiac hypertrophy and decreased longevity. Overexpression of GLUT1 in the heart, inducing a compensatory constant increase of glucose uptake, may also contribute to cardiac hypertrophy. Finally, although GLUT4-null mice can nearly maintain normoglycaemia, they die at 5–7 months prematurely, probably because of their cardiac abnormality.

Katz et al. have developed a highly interesting model of knockout mice. The absence of diabetes despite severe muscle insulin resistance highlights the debate on the primum movens of NIDDM: insulin secretion defect or insulin resistance. The adaptive changes balancing the lack of insulin-regulated glucose transport have to be clarified further. The comparison of the response to oral administration and to intraperitoneal administration of glucose could show if the animals have decreased their glucose absorption. Direct evaluation of glucose uptake by muscle has not yet been performed by Katz et al. It would be particularly interesting to assert this reduction and compare it to that of other diabetic models. A study of post-prandial production of glucose-6-phosphate by the liver and of the glycogen store in the liver could also give information about the hepatic compensatory response to the lack of GLUT4.

The search for the adaptive mechanisms that allow mice to cope without GLUT4 will certainly help in understanding the NIDDM metabolic features and natural history. The study of the consequences of chronic hyperinsulinaemia without hyperglycaemia present in this model is of great interest, particularly with respect to the cardiovascular system.

References

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Dichlorodiphenyltrichloroethane and androgen receptor

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A recent paper from William Kelce et al. (Nature, 1995; 375:581–585) points out that the major metabolite of dichlorodiphenyltrichloroethane (DDT), 1,1-dichloro-2,2-bis(p-chlorophenyl)ethy lene (p,p'DDE), is a potent androgen receptor antagonist and can damage male reproduction. According to the authors, DDT and its major metabolite could be one of the factors responsible for the increasing male tract abnormalities reported in humans and animals. Indeed, various recent studies have reported an increased incidence of hypospadias and cryptorchidism and an increased incidence of testicular cancer (1). A recent study has shown that during the past 20 years there has been a decline in the concentration and motility of sperm and in the percentage of normal spermatozoa in fertile men in the Paris region (2). It has been hypothesized that all these changes have a common origin and may be related to environmental exposure or to a change in life style which has occurred during a period of increased exposure to oestrogenic chemicals that are known to induce male reproductive tract disorders.

The discovery of DDT in the middle of this century was a major step in the fight against various diseases and their vectors, particularly in tropical countries.