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)ethylene (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.
where malaria, yellow fever, trypanosomiasis, typhus, etc. were responsible for millions of deaths. However, although its use was restricted in Europe 20 years ago due to its solubility in all body fats and its half-life of about 100 years, it has still been found in the fat of seals in the Arctic Ocean and in the sullage discharged in European rivers. Dichlorodiphenyltrichloroethane is still widely used in tropical countries and a ban on its use seems well-nigh impossible. Finally, even in developed countries. DDT remains an environmental problem because of its long half-life, its accumulation and concentration in the entire food chain, its ubiquity in human fat and its well-known oestrogenic effects.

The discovery that, in vivo and in vitro, p,p′DDE is a potent androgen antagonist is of cardinal importance and shows that collecting information to examine the level of accumulation of these metabolites in man and the real risk of these chemicals to humans must be considered as a priority.

Kelce et al. report that the major metabolite of DDT, p,p′DDE, inhibits androgen binding to the androgen receptor as well as androgen-induced transcriptional activity. In vivo, it inhibits androgen action in fetal, pubertal and adult male rats. The authors studied the inhibition of the binding of the synthetic androgen (3H)R1881 to androgen receptor (AR) by five environmental chemicals: chlороdecone (Kepone), p,p′DDT (the main component of DDT), o,p′DDT (second component of DDT), p,p′DDE (main metabolite of DDT with slow degradation and excretion), diethylstilboestrol and 17β-oestradiol using cell-free binding assays in rat ventral prostate cytosol. The metabolite p,p′DDE displays an important dose-dependent competitive inhibition of (3H)R1881 binding to androgen receptor, with its inhibition constant similar to that of diethylstilboestrol. In contrast to diethylstilboestrol, 17β-oestradiol, chlороdecone and o,p′DDT, p,p′DDE is a very poor competitor of oestrogen binding to the oestrogen receptor (ER) and binds the AR 200 times more effectively than the ER.

Hydroxyflutamide (antiandrogen) and p,p′DDE were equally effective in inhibiting androgen-induced transcriptional responses through AR in in vitro transcriptional studies. This was not the consequence of a cytotoxic effect of p,p′DDE, as this metabolite did not affect dexamethasone-induced glucocorticoid receptor transcriptional activity. In summary, these in vitro studies indicate that p,p′DDE is a main androgen receptor antagonist with a nearly equivalent potency to that of the antiandrogen hydroxyflutamide.

To confirm, in vivo, the importance of these results, fetal, pubertal and adult Long-Evans rats were treated with p,p′DDE. Prenatal exposure during 4 days to 100 mg p,p′DDE/kg induced a reduced anogenital distance at birth and retained thoracic nipples on postnatal day 13, underscoring the prenatal antiandrogen activity of p,p′DDE.

In addition, 21-day-old rats were exposed to 100 mg p,p′DDE/kg/day for 36 days to determine its effect on the onset of puberty. Exposure to p,p′DDE delayed the onset of puberty by 5 days without inducing retarded growth or reducing testosterone levels. The antagonistic effect of p,p′DDE was also present in adult rats. Exposure of adult rats to 200 mg p,p′DDE/kg/day for 4 days induced a significant decrease of seminal vesicle weight and a significant decrease of ventral prostate weight.

In summary, in vitro and in vivo studies indicate that p,p′DDE is an important AR antagonist. The levels of p,p′DDE able to inhibit AR transcriptional activity are comparable to the levels that can accumulate in humans from highly contaminated environments. For example, the DDT serum levels of persons living in DDT-treated dwellings in South Africa (where DDT was widely used in the fight against malaria) were twofold higher than the concentration required to inhibit AR transcriptional activity in cell culture.

These data also highlight the need for more intense research efforts designed to establish the risk of DDT to man. Only clinical reports can confirm a relationship between the damage of the human male reproduction system and past and present DDT exposure.

References


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