Non-insulin-dependent diabetes mellitus: new drugs?

In the Western world the incidence of non-insulin-dependent diabetes mellitus (NIDDM) is increasing at an almost epidemic rate. There is no simple explanation for this, in agreement with the fact that the aetiology of NIDDM remains elusive. It is generally accepted that NIDDM, to a large extent, is a genetic disorder that is polygenic with a high rate of transmission and a complex pattern of inheritance. However, a sedentary lifestyle and obesity seem to be major contributing factors to the current increases in incidence.

Current approaches to treatment

Because of its high incidence (more than 2% of the population in many Western countries suffers from NIDDM) and the associated morbidity and mortality, NIDDM has become a major health hazard, and efficient treatment is in great demand. Unfortunately, the treatment that can be offered at present is highly unsatisfactory. Admittedly, treating NIDDM is not a simple matter. Because NIDDM is associated with obesity and a sedentary lifestyle, the logical approach would be to prescribe physical exercise and dietary restriction. This approach indeed forms the basis for all NIDDM treatment, but turns out, in clinical practice, to be most inefficient.

Although everybody realizes that measures to improve compliance with exercise and diet regimens are of paramount importance, there is an obligation, at the same time, to provide the best possible symptomatic treatment, in particular with a view to preventing or reducing complications. It has been clearly shown that glycaemic control, i.e. attempting to keep blood glucose concentrations as normal as possible, is essential for the prevention of complications[1]. Many approaches in NIDDM treatment are, therefore, directed at reducing blood glucose levels. Of these, parenteral insulin therapy remains the most efficient treatment known, but is associated with a high incidence of hypoglycaemic events and further weight increases. Therefore, this is usually postponed for a long time, perhaps too long. In fact, 50% of patients have micro- or macrovascular complications at the time of diagnosis.

At a conference organized by IBC, entitled *Non-Insulin Dependent Diabetes: Advances in Understanding & New Therapeutic Targets*, which was held in December 1996 in Amsterdam, the above-mentioned issues were discussed. The conference did not bring forward a new miraculous cure for NIDDM but, in addition to reviewing the status of the current therapeutic armoury, it introduced new areas of research that may be of relevance in future drug development programmes.

Insulin sensitizers

Part of the conference was devoted to the thiazolidinediones, which are insulin sensitizers[2] originally developed from fibrate lipid lowering agents. Although their antidiabetogenic effects were discovered fortuitously, they illustrate that a drug target in diabetes therapy should not necessarily be sought on the direct pathway from insulin secretion to insulin action. The thiazolidinediones are high-affinity ligands for peroxisome proliferator-activated receptor γ (PPARγ), an orphan member of the nuclear hormone receptor superfamily expressed in high levels in adipose tissue. PPARγ turns out be a central regulator of adipocyte gene expression and differentiation[3]. The thiazolidinediones seem to act in concert with insulin to regulate transcription of a wide range of insulin-responsive genes. Some of their most conspicuous actions are increases in the insulin receptor and GLUT 4 (glucose transporter) numbers in adipose tissue.

In animal models of insulin resistance thiazolidinediones improve glycaemic control, reduce hyperinsulinaemia and hypertriglyceridaemia, and seem to be able to prevent or significantly delay the onset of severe diabetic complications, including hypertension and nephropathy, and to prevent terminal β-cell exhaustion. In humans the effects are perhaps not so dramatic, but still clinically interesting. However, concern must be directed towards safety issues; weight gain, left-ventricular hypertrophy and adipogenesis in bone marrow seem to be related directly to the mechanism of action of the drugs. Also, the fact that their effect may be exerted mainly on adipose tissue is of some concern because human insulin resistance most commonly results from abnormalities of skeletal muscle glucose handling.

Insulin resistance and TNFα

A most exciting presentation was given by Dr Gökhan Hotamisligil from Harvard University (Cambridge, MA, USA), who described the possible role of tumour necrosis factor α (TNFα) in obesity and insulin resistance[4]. Virtually all animal models of insulin resistance are associated with increased levels of TNFα, and neutralization studies in obese rats result in increased insulin sensitivity. TNFα seems to impair insulin-receptor signalling by a mechanism that also involves insulin receptor substrate-1 (IRS-1). Excitingly, mice with a targeted mutation in adipocyte fatty-acid-binding protein develop dietary obesity, but neither insulin resistance nor diabetes, and these animals are unable to express TNFα in their adipose tissue. Thus, the pathways involved in TNFα formation and action may be new potential targets in treating insulin resistance.

Glucagon-like peptide-1

The most efficient acute treatment of hyperglycaemia in NIDDM, apart from insulin, is infusion of glucagon-like peptide-1(GLP-1), an intestinal insulinotropic and glucagonostatic hormone, which brings about complete normalization of blood glucose levels in virtually all patients with NIDDM[5]. In addition, this hormone has recently been implicated in the regulation of food intake and thus may be useful for simultaneous obesity and diabetes treatment. However, because GLP-1 is rapidly metabolized, a stable form of the peptide must be developed before it can be considered for clinical use.

Animal models

Among the animal models of obesity and insulin resistance, the agouti mouse has attracted justified interest[6], because it appears that a protein overexpressed as a result of the agouti mutation is an inhibitor of the melanocortin-1 and -4 receptors. The melanocortin-4 receptor is a hypothalamic target for the melanocyte-stimulating hormone, known to play an important downstream role in the signalling pathway by which the hypothalamus responds to obesity, i.e. by reducing food intake and increasing energy expenditure and sympathetic activity. Thus, mice carrying the yellow agouti mutation become obese and develop a yellow (rather than brown) fur coat. Mice with a targeted disruption of the melanocortin-1 receptor become obese but do not exhibit discoloration of the fur.

Clearly, here are some new, exciting targets for obesity and insulin-resistance research. Other presentations updated the delegates on the regulation of insulin gene transcription by nutrients, and on the mapping of the genes for NIDDM and obesity in the Goto-Kakizaki (GK) rat, a rat strain outbred by selection for glucose intolerance, which may serve as a particularly useful genetic model for human NIDDM.

Diabetic complications

An important part of the conference was devoted to new approaches to understanding and treating diabetic complications. Pharmacological reduction of 'advanced glycation end products' using substances such as aminoguanidine has a remarkable beneficial effect in animal studies[7], and recent studies suggest that neurotrophins such as nerve growth factor and and neurotropin-3 may improve diabetic neuropathy[8]. Deficiences in essential fatty acids have been reported in diabetic rodents, and in such animals evening primrose oil ameliorates neuropathy, possibly by normalizing the capacity to produce prostacyclins[9].

Perhaps the most important message from the conference was not to narrow the scope when searching for new ways of treating NIDDM.

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