Basic science

Thiazolidinediones make good sense

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Thiazolidinediones (TZDs) are the 'new kids on the block' for the treatment of type 2 diabetes. This new class of antidiabetic drug produces a gradual improvement in glycaemic control by amplifying insulin action in adipose tissue, skeletal muscle and liver. It is this reduction in target tissue insulin resistance that has led to the categorisation of TZDs as insulin-sensitising agents.

The first TZD used for the treatment of type 2 diabetes (troglitazone) was withdrawn following reports of hepatotoxicity, but other TZDs (e.g. rosiglitazone and pioglitazone) were introduced in the UK in 2000. Moreover, such is the potential of these new oral agents that five to six other TZDs or related compounds are currently undergoing clinical trials.

The review by Fürnsinn and Waldhäusl emphasises the importance of obtaining a better understanding of how the direct TZD effects on the target tissues lead to the slowly generated antihyperglycaemic action of these exciting new drugs.

The authors focus particularly on the role of the nuclear peroxisome proliferator-activated receptor-gamma (PPARγ), considered to be the predominant molecular target for TZDs. However, it is clear from this comprehensive review that PPARγ-agonist effects of TZDs in adipose tissue are not the sole cause of lowered blood glucose concentrations. Indeed, considerable evidence is provided to indicate that TZDs may exert both direct and PPARγ-independent effects on glucose metabolism in muscle and liver.

To further complicate the picture, it is becoming apparent that TZDs may also act directly on the insulin-producing pancreatic β-cell. Studies of rosiglitazone treatment in animal models of type 2 diabetes have shown a lowering of blood glucose and amelioration of disease associated with an increase in functional β-cell mass.

The authors make some interesting closing remarks, including advice that researchers should seek to avoid undue bias towards single molecular drug targets, as in the case of PPARγ. This is particularly wise counsel when seeking new pharmacological approaches to the treatment of complex conditions such as type 2 diabetes, which evolve through a combination of interdependent factors such as insulin resistance, β-cell dysfunction and dyslipidaemia.

DIABETOLOGIA

How do TZDs affect different tissues?

Readability	✓ ✓ ✓ ✓
Applicability to practice	✓ ✓ ✓
WOW! factor	✓ ✓ ✓ ✓

1 Thiazolidinediones (TZDs) are becoming increasingly important in the treatment of type 2 diabetes, but the molecular mechanisms by which they affect glucose homeostasis are unclear.

2 One hypothesis emphasises the effects of peroxisome proliferator-activated receptor (PPAR) on adipose tissue, suggesting that insulin sensitisation is triggered indirectly by changes in circulating concentrations of adipocyte-derived non-esterified fatty acids and peptide hormones.

3 A second hypothesis proposes that TZDs improve glucose homeostasis independently from the actions of adipose tissue, by direct interaction with muscle and liver.

4 To further elucidate the mechanisms of antidiabetic TZD action, the interdependence of adipogenic and antidiabetic action needs to be established.

5 In addition, the relative share of direct and indirect TZD actions on skeletal muscle, liver and adipose tissue needs to be elucidated.

Fürnsinn C, Waldhäusl W (2002) Thiazolidinediones: metabolic actions in vitro. *Diabetologia* **45**: 1211–23

Diabetes not linked to NKT cell defect

Readability	✓ ✓
Applicability to practice	✓ ✓
WOW! factor	✓ ✓ ✓

1 Defects in interleukin (IL)-4-producing CD1d-autoreactive natural killer T (NKT) cells have been implicated in autoimmune insulin-dependent diabetes mellitus (IDDM).

2 However, the identification of NKT cells in these studies was based on indirect methods.

3 In this study, a direct, highly specific CD1d tetramer-based methodology was used to test whether humans with IDDM have associated NKT cell defects.

4 NKT cell numbers in healthy subjects were considerably lower than previously estimated.

5 In addition, NKT cell numbers and cytokine-secreting functions were not signfiicantly altered in a large group of diabetic and prediabetic patients when compared with controls.

THE JOURNAL OF CLINICAL INVESTIGATION

6 These results contradict previous conclusions and directly challenge the notion that autoimmune diabetes in humans is caused or aggravated by an NKT cell defect.

Lee PT, Putnam A, Benlagha K et al (2002) Testing the NKT cell hypothesis of human IDDM pathogenesis. *The Journal of Clinical Investigation* **110**(6): 793–800

'If the abnormalities constituting the metabolic syndrome result from independent physiological processes, attempts to study a global syndrome phenotype may be counterproductive.'

DIABETES

Redefining the metabolic syndrome

Readability	✓ ✓ ✓
Applicability to practice	✓ ✓ ✓
WOW! factor	✓ ✓ ✓ ✓

1 The combination of insulin resistance, dyslipidaemia, hypertension and obesity has been described as a 'metabolic syndrome' that is a strong determinant of type 2 diabetes.

2 Factor analysis was used to identify components of this syndrome in 1918 Pima Indians, and prospective analyses were conducted to evaluate associations of identified factors with the incidence of diabetes.

3 Four unique factors with different associations with the incidence of diabetes were identified, each reflecting a proposed component of the metabolic syndrome: insulinaemia, body size, blood presure and lipid metabolism.

4 Insulinaemia was strongly associated with diabetes incidence. Body size and lipids, but not blood pressure, also significantly predicted diabetes.

5 Correlations among these variables therefore seem to reflect distinct metabolic processes.

6 These findings have implications for research and clinical practice: if the abnormalities constituting the metabolic syndrome result from independent processess, then attempts to study a global syndrome phenotype may be counterproductive.

Hanson RL, Imperatore G, Bennett PH, Knowler WC (2002) Components of the 'metabolic syndrome' and incidence of type 2 diabetes. *Diabetes* **51**: 3120–7

DIABETES

Mitochondrial function linked with β-cell growth

Readability	✓ ✓ ✓
Applicability to practice	✓ ✓
WOW! factor	✓ ✓ ✓

1 Rapamycin, an inhibitor of mTOR (mammalian target of rapamycin), has a role in preventing rejection in pancreatic islet transplant recipients.

2 Characterisation of the insulin signalling cascade that modulates mTOR has been a major focus of investigation. In addition, nutrients can activate mTOR independent of insulin.

3 β-cells express components of the insulin signalling cascade and use nutrient metabolism to affect insulin secretion.

4 Studies suggest that increases in mitochondria-derived ATP, through enhanced substrate flux, may be responsible for the ability of nutrients to activate mTOR signalling in β-cells.

5 Optimisation of mitochondrial function is thus important for insulin secretion and may also significantly impact the growth and proliferation of β-cells through mTOR signalling pathways.

McDaniel ML, Marshall CA, Pappan KL, Kwon G (2002) Metabolic and autocrine regulation of the mammalian target of rapamycin by pancreatic β-cells. *Diabetes* **51**: 2877–85

'Optimisation of mitochondrial function is not only important for insulin secretion but may also significantly impact the growth and proliferation of β-cells through mTOR signalling pathways.'

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IRS-2: linking insulin action and β-cell function

Readability	✓ ✓ ✓ ✓
Applicability to practice	✓ ✓
WOW! factor	✓ ✓ ✓ ✓

1 The insulin receptor substrate (IRS)-2 branch of the insulin/insulin-like growth factor (IGF)-signalling pathway is a common element in the peripheral insulin response and pancreatic β-cell growth and function.

2 This relation creates a link between tissues that respond to insulin and the pancreatic cells that sense blood glucose levels and secrete insulin.

3 Failure of IRS-2 signalling might explain the loss of compensatory hyperinsulinaemia during prolonged periods of peripheral insulin resistance.

4 Moreover, inhibition of IRS proteins suggests a common molecular mechanism for insulin resistance during acute injury or infection, or the sensitivity of β-cells to autoimmune destruction.

5 IRS-2 seems to play a pivotal role in determining the specificity of relevant signalling cascades. Future work will establish the extent of its role and its value for therapeutic intervention.

White MF (2002) IRS proteins and the common path to diabetes. *American Journal of Physiology, Endocrinology and Metabolism* **283**: E413–22

CLINICAL ENDOCRINOLOGY

Studying the genetics of diabetes

Readability	✓ ✓ ✓ ✓
Applicability to practice	✓ ✓
WOW! factor	✓ ✓ ✓

1 Multiple gene effects, and metabolic and environmental factors, contribute to the pathogenesis of type 2 diabetes mellitus (T2DM) and insulin resistance.

2 This complexity hinders the search for susceptibility genes and has led to the use of several different approaches.

3 This article first looks at studies of monogenic forms of DM and insulin resistance, including maturity-onset diabetes of the young and mitochondrial diabetes.

4 Next, candidate genes predisposing to T2DM or insulin resistance are reviewed. These are often selected on the basis of current knowledge about the biochemical and metabolic defects in T2DM and insulin resistance.

5 Finally, genome-wide scan studies are discussed.

6 By adopting such a range of complementary approaches, the roles of genes in the pathogenesis of insulin resistance and T2DM are beginning to be understood.

McIntyre EA, Walker M (2002) Genetics of type 2 diabetes and insulin resistance: knowledge from human studies. *Clinical Endocrinology* **57**: 303–11