Role of genetic variability in systems of receptor-mediated and enzymatic defence against glycation in the long-term consequences of diabetes mellitus

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Abstract
Diabetes mellitus is the most common metabolic disease, and has late complications that are due to chronic hyperglycaemia. Altered carbohydrate and lipid metabolism together with impaired detoxification of carbonyl substrates and impaired trapping of oxygen radicals are responsible for cell damage in diabetes. Variable functional capacity of detoxifying systems could contribute to differing susceptibility to the development of complications. Identification of genetic variants responsible for modulating relevant intermediate phenotypes in diabetics could help to define individual risk profiles and to modify therapeutic strategy accordingly.

Introduction
Among many other diseases, diabetes mellitus is the one in which non-enzymatic glycation plays an unequivocal role in its long-term consequences (manifested primarily as an adverse effect on the capillary vasculature known as diabetic microangiopathy). Well known epidemiological facts about prevalence in the population, increasing incidence and the expected number of affected subjects in the near future place diabetes (especially Type II) in the centre of intensive research targeted at both primary prevention of the disease and secondary prevention of its complications.

Concept of diabetic complications, and main components affecting their development
Diabetes of all types is associated with chronic hyperglycaemia. The cumulative degree of hyperglycaemia depends, in addition to the duration of the disease itself, largely on the success of therapeutic management and the patient’s co-operation. However, to reach completely physiological glycaemia is nearly impossible. Due to theoretical and practical limitations, it is difficult to obtain a physiological daily profile of insulinaemia by exogenous administration in Type I diabetes or, similarly, to overcome or influence efficiently insulin resistance in Type II diabetes. Therefore chronic diabetes is always associated with some degree of hyperglycaemia, and this is reflected in its long-term clinical consequences. From whence it follows that the term ‘complication’ (meaning something that might eventually happen) is not ideal, since hyperglycaemia and diabetic microangiopathy (whether clinically manifested or not) are constantly present. It is broadly accepted that hyperglycaemia is causally responsible for the long-term consequences of diabetes. In addition, the existence of other factors that modulate the course of hyperglycaemia-induced processes is accepted. A simplified model of microangiopathy risk prediction would include three main components: (i) therapeutic compensation (the most powerful and influential tool, as proved by large prospective studies [1,2]), (ii) duration of disease (although difficult to determine precisely in case of Type II diabetes) and (iii) individual susceptibility to hyperglycaemia-induced damage.

Important pathogenic mechanisms of diabetic complications – carbonyl and oxidative stress
Hyperglycaemia results in a number of alternative metabolic pathways arising from intermediate products of glycolysis [polyol and hexosamine pathways, Maillard reaction in a broad sense leading to the production of AGEs (advanced glycation end products), 2-oxoaldehyde production and de novo synthesis of diacylglycerol], which lead to (i) direct toxic effects and tissue remodelling, (ii) changes in cell signalling due to activation of protein kinase C, and (iii) nuclear factor-κB-activated expression of a number of genes. There is a substantial degree of ‘co-operation’ among particular pathways, which usually (and unfortunately in the case of diabetes) amplify one another. Reactive oxygen species, whose production correlates with the level of hyperglycaemia, are common and crucially important denominators of this amplification [3].
Much attention has been paid in recent years to systems dealing with the metabolic consequences of hyperglycaemia – mainly carbonyl and oxidative stress [4,5]. These include physiological detoxifying enzymatic systems and several types of scavenger receptors for modified molecules. A summary of the most important detoxifying systems is presented in Table 1. Receptors [particularly RAGE (receptor of AGEs)] are probably phylogenetically part of an ancient non-specific immune defence system, and also act as regulators of cell differentiation, as demonstrated by the existence of many other ligands in addition to AGEs. Enzymatic detoxification includes reactions catalysed by aldose reductase, the glyoxalase system, 2-oxoaldehyde dehydrogenase, aldehyde dehydrogenase and some other enzymes [5]. From the broader point of view, the enzymatic detoxification system could also include antioxidant enzymes, [5]. From the broader point of view, the enzymatic defence against glycation in health, disease and therapeutics 1365

Table 1 | Summary of receptor and enzymatic detoxifying systems operative in diabetes, and their ligands and substrates

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Ligands</th>
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<tbody>
<tr>
<td>RAGE</td>
<td>AGES (applies to all)</td>
</tr>
<tr>
<td>LF-L (lactoferrin-like polypeptide)</td>
<td>Non-AGE: amphoterin, amyloid β peptide, S100/ calgranulins, transthyretin</td>
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<tr>
<td>AGER-1 (p60 ~ OST-48, oligosaccharyltransferase)</td>
<td>(applies to RAGE)</td>
</tr>
<tr>
<td>AGER-2 (p90 ~ 80K-H, protein kinase C substrate)</td>
<td></td>
</tr>
<tr>
<td>AGER-3 (galectin-3)</td>
<td></td>
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<tr>
<td>Macrophage receptor type II</td>
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</table>

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate</th>
</tr>
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<tbody>
<tr>
<td>Glyoxalase I</td>
<td>Methylglyoxal</td>
</tr>
<tr>
<td>Glyoxalase II</td>
<td>Glyoxal</td>
</tr>
<tr>
<td>2-Oxoaldehyde dehydrogenase</td>
<td>Glucose</td>
</tr>
<tr>
<td>Aldehyde dehydrogenase</td>
<td>3-Deoxyglucosone</td>
</tr>
</tbody>
</table>

Results of association studies – scavenger receptors, and detoxifying and antioxidant enzymes

A prevailing experimental method in the study of genetic susceptibility to diabetic complications is a candidate gene approach. The use of linkage studies is limited due to inherent features of the problem (polygenic pattern, weak effect of single variants, late manifestation of disease, not enough complete multi-generation families etc.).

RAGE has attracted considerable attention since its isolation and characterization in 1992 [6]. Several groups...
studied polymorphism in the RAGE gene and around 30 substitutions have been described [7–11]. The functional effects of some of them – increased transcriptional activity, enhanced ligand binding or an indirect effect on antioxidant status – were described for promoter polymorphisms −429T/C and −374T/A, exon variant G82S and intron polymorphisms 1704G/T and 2184A/G respectively [11–13]. Positive as well as negative associations of several of them with diabetic nephropathy or retinopathy have been published recently [9,11,14–16]. Very few polymorphisms have been detected in other AGE receptors, and none of these were associated with diabetic microangiopathy [8]. Genetic studies on the relationship between variability in detoxifying enzymatic systems and diabetic complications are much sparser, although they are equally logical candidates.

Despite promising findings, scepticism is still necessary. One has to be careful when evaluating these associations because rather limited sample sizes, ethnically different populations and different clinical outcomes were analysed. Moreover, a particular gene always behaves as a unit; therefore the whole intragenic ‘haplotypes’ should be studied rather than isolated polymorphisms. Finally, even strong associations have to be seen as a part of a mosaic of multigenic clusters, and appropriate statistical tools have to be employed.

Conclusions
Knowledge of ‘deglycation’ systems, their genetic variability and identification of particular risk alleles could help further to minimize the long-term consequences of diabetes. In the situation when preventing the disease itself is not yet effective, the patient population could at least be stratified according to the risk of developing complications, in terms of their onset, rate of progression, severity and organ distribution. This would allow a more individualized approach, variably aggressive therapy, differently timed complication screening, etc. Also, drugs specifically targeting these systems could be developed and applied more effectively.

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References

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