Metabolism
Clinical and Experimental
VOL 49, NO 10, SUPPL 2 OCTOBER 2000

EDITORIAL

Type 2 Diabetes: To Stimulate or Not to Stimulate the β Cell

Erol Cerasi

NOT THAT THE EARLIER history of humanity has been much brighter, but the 20th century has excelled as a century of dogmatic-fanatic views, and dictatorships to impose them. One is ashamed to admit that we diabetologists have not fared much better. Are type 2 diabetic patients hyperinsulinemic? Are type 2 diabetics hypoinsulinemic? Is insulin resistance the truth and the only truth in type 2 diabetes? Is insulin deficiency the truth and the only truth in type 2 diabetes? Sounds familiar? If one-sided views were for academic debate only one would not care so much; the problem is that one-sided views have had a major impact on patient-care attitudes, and there is no justification for the type 2 diabetic patient to bear the burden of our biases.

Whether it is because dogmatics have run out of steam, or because (hopefully) some degree of common sense has dawned on all of us, we are starting to realize that biology is never as simple, that both insulin deficiency and insulin resistance have their place under the sun, that in fact, with few exceptions, there exists no type 2 diabetic patient with pure β-cell or pure peripheral defect. The debate is now more on a quantitative level: which is more important, which one comes earlier? Also here, it seems that type 2 diabetes is so heterogeneous that all the proponents of all the theories may gain satisfaction regarding at least some of their patients. Nonetheless, a consensus seems to emerge: at some stage of the development of type 2 diabetes, as the disease progresses, be it as a primary, genetically controlled factor or in response to deteriorating metabolic milieu, β-cell function (and perhaps viability) declines, and increasingly poses a threat to overall metabolic control. It therefore stands to reason to strengthen the function of the β cells of type 2 diabetic patients, and this supplement, which relates the papers presented at the workshop "Gliclazide Modified Release Once Daily in Type 2 Diabetes: Molecular Action to Vascular Protection" held in Mexico City on November 5, 2000, is exactly about this, and how the new sulfonylurea preparation, gliclazide modified release, can help us achieve the goal.

Three aspects struck me when reviewing the papers of this supplement:

First, as somebody who has spent his life stressing the importance of the rapid dynamics of insulin release, the last thing that my intuition would dictate is to generate slow-release preparations for insulin secretagogues. Too bad if reality does not fit the theory (!): the detailed description and analysis of the clinical effects of gliclazide modified release by Harrower and by Crepaldi in this volume convince us that this drug is efficient, does not cause hypersecretion of insulin in the postabsorptive state, and hence presents a very low risk of hypoglycemia. Why the latter? It has been shown that gliclazide–β-cell sulfonylurea receptor (SUR1) interactions are readily reversible, and the drug lacks active metabolites that might have prolonged effects. As an alternative explanation, gliclazide may not entirely behave as a classical sulfonylurea on insulin release; this molecule indeed seems to be much more glucose-dependent in its insulinotropic effect than other drugs presently in clinical use, insulin secretion therefore being reduced when near-normoglycemia is reached (unpublished in vitro observations by S. Efendic and E. Cerasi support this view).

Second, being focused on metabolic and especially blood glucose control, I would not expect a sulfonylurea drug to have direct hemorrheologic effects independently from its correcting effect on the metabolic milieu. Yet, as described by Jennings in this volume, gliclazide has indeed such effects, fully characterized in experimental systems but also observed in many clinical studies. This seems to be the consequence of the aminoazabicyclo[3.3.0]octane ring in the gliclazide molecule, which has free radical scavenging effects. This characteristic of gliclazide certainly adds to its attractiveness. The full clinical

From the Department of Endocrinology and Metabolism, Hebrew University–Hadassah Medical Center, Jerusalem, Israel.

Address reprint requests to Erol Cerasi, MD, PhD, Department of Endocrinology and Metabolism, Hadassah University Hospital, PO Box 12000, 91120 Jerusalem, Israel.

Copyright © 2000 by W.B. Saunders Company

0026-0495/00/4910-2001$10.00/0
doi:10.1053/meta.2000.17821

implications of the free radical scavenging properties of gliclazide remain to be explored. There is presently major interest in the role that oxidative stress may play in the deterioration of β-cell function and survival in type 2 diabetes; whether gliclazide may show a beneficial effect in this context is definitely worth investigating.

The third aspect relates to the debate on whether sulfonylureas may be "cardiotoxic." For someone like myself who belongs to the "University Group Diabetes Program generation," this is not a trivial issue, despite the absence of excess cardiovascular morbidity and mortality in sulfonylurea-treated type 2 diabetics in the United Kingdom Prospective Diabetes Study. At least at the intellectual level, it is highly satisfying to read the paper by Gribble and Ashcroft in this volume, where they show that gliclazide has very low affinity for the cardiac type sulfonylurea receptor (SUR2A); thus, there does not seem to exist even theoretical possibilities for a "cardiotoxic" effect of gliclazide, let alone clinically demonstrated effects.

Back to the title: yes, we must stimulate the β-cell in type 2 diabetes, and gliclazide modified release seems to be efficient and safe for doing so in a once-daily formulation. It will be for the future to provide us with even more efficient molecules capable of entirely normalizing the defective insulin secretory capacity of the type 2 diabetic patient.