Response to Schmitz

In an otherwise enticing article by Schmitz et al. (1) in the February 2002 issue of Diabetes Care, the authors make several assertions that are difficult to support by the data presented in the article.

The authors discuss “early-phase” insulin secretion numerous times throughout their article and seem to consider this term the same as “acute phase” insulin secretion (CONCLUSIONS, paragraph two, line 13: “[. . .] early-phase insulin release is one of the first defects to appear as type 2 diabetes develops”). Based on this assumption, they conclude that the study drug did indeed improve “early-phase” insulin secretion (presumably within 10 min after administration, by their definition) (CONCLUSIONS, paragraph 2, line 9) but there are no data presented in their article to support this contention.

As best as I could tell, Schmitz et al. measured blood samples 43 times over 24 h, but the intervals of measurement are not given. Even if they measured insulin levels at 1-min intervals after oral glucose administration, would this be equivalent to insulin secretion after intravenously administered glucose? Perhaps I am missing something here, but are these two terms interchangeable (acute-phase insulin release and early-phase insulin secretion)?

I would greatly appreciate it if the authors could clarify this point for me.

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Response to Block

I thank Dr. Block (1) for the interest in our article (2) and the editor for the opportunity to clarify the point raised. As stated several times in our article (RESULTS, Table 2, CONCLUSIONS), we define the early-phase period (i.e., where insulin secretory rates were calculated) as the initial 30 min of the prandial phase. The calculation of insulin secretion was as noted based on measurements of insulin and C-peptide, utilizing the classic combined model. Samples were drawn every 10 min during this part of the prandial period.

The cardinal issue in our article is the effect of the insulin secretagogue repaglinide on the meal-induced insulin secretion, which is influenced by several nutrients, release of incretin hormones, etc. In CONCLUSIONS we discuss twice the intravenous glucose-induced early-phase insulin release (presumably what Dr. Block refers to as acute-phase insulin release) to notice another important aspect of type 2 diabetes pathophysiology. In the same paragraph, meal-induced insulin release was discussed as it appears from the references. We felt that the message was clear and it was easy for the general reader to distinguish between these two issues.

The allegation of the authors trying to equate meal-induced insulin secretion to intravenously glucose-induced early-phase insulin secretion warrants a comment. Oral insulin secretagogues are developed to reduce glycermia during daily life conditions (e.g., meals), but of course in the interest of gaining insight into mode of action, it may be of relevance to explore their effects on unphysiological insulin challenges (e.g., intravenous glucose). The immediate insulin secretion elicited by the latter stimulus is now demonstrated to be related to a pool of insulin which is in equilibrium with insulin released from the other insulin stores (pool of insulin secreted in response to exogenous insulin challenges). The early-phase insulin secretion after meal ingestion is probably ascribable to a combination of release from this pool and initially undocked vesicles.

So, to some extent, it may be two sides of the same coin. Both a reduced meal-induced and intravenously glucose-induced early-phase insulin secretion are abnormalities often present in healthy prediabetic individuals (3,4). Clearly the two modes of stimulating the B-cell are only partially comparable. Nevertheless, our study deals with clinical pharmacology and insulin and glucose dynamics during daily life conditions of type 2 diabetic individuals after administration of an insulin secretagogue. In this context, we did not find it of relevance to compare this daily life condition in terms of insulin release with an (unphysiological) intravenous glucose challenge. One almost gets the impression from Dr. Block’s comment that restoration of intravenously glucose-induced insulin secretion is even more pivotal than restoring the daily-life, meal-induced, early-phase insulin secretion.

Moreover, it is important to state that our study drug (repaglinide) convincingly improved insulin secretion during the initial 30 min of the prandial periods, but we never reported that this took place within 10 min after administration. I kindly ask Dr. Block to read our article again to solve this misinterpretation.

Finally, I thank Dr. Block for giving us the opportunity to emphasize the importance of defining insulin secretion (e.g., early-phase, very early-phase, acute-phase, first-phase insulin secretion to a given challenge) very carefully.

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References

COMMENTS AND RESPONSES

On Combination Therapy of Diabetes With Metformin and Dipeptidyl Peptidase IV Inhibitors

Recently, data were presented showing that metformin increased plasma active glucagon-like peptide (GLP)-1(7–36NH2) concentrations in obese nondiabetic male patients (1), and it was suggested that metformin was a di-
rect dipeptidyl peptidase (DP) IV inhibitors. Contradiction of this hypothesis is simply found by examining the modes of action of metformin and of the DP IV inhibitors. Although the specific molecular target of metformin is still unknown, bioguanides generally act to sensitize peripheral tissues to insulin action (particularly, skeletal muscle) and inhibit hepatic gluconeogenesis and glycogenolysis (2–4). In contrast, DP IV inhibitors act to enhance the insulin response to a meal, via preservation of intact bioactive incretins, GLP-1(7–36NH2) and GIP(1–42OH) (5–10). Notably, metformin does not improve glucose tolerance via an increase in circulating insulin levels, implicating different antidiabetic mechanisms for metformin and DP IV inhibitors.

Unfortunately, Mannucci et al. (1) did not measure total GLP-1 (GLP-1(7–36NH2) + GLP-1(9–36NH2)) levels in their study. An increase NH2-terminal intact GLP-1 was interpreted as indicating protection from degradation by DP IV, and the possibility of an increase in total GLP-1 levels, yielding a proportional rise in intact GLP-1 concentrations, was not considered. This possibility is consistent with prior studies examining glucagon and GLP-1 levels after metformin treatment (11–13). A simplistic interpretation of these findings would be that metformin either enhances the glucose sensitivity of the islet α-cell and enteroendocrine 1-cell, the secretory rate of these cells, or increases transcription/translation of the proglucagon gene, resulting in greater hormone release with metformin treatment. Regardless, we initiated a series of in vitro biochemical studies to test the hypothesis of Mannucci et al., but were unable to duplicate their earlier work or support this hypothesis by other means (13).

Traditional treatment of type 2 diabetes begins with diet control and oral monotherapy (metformin, sulfonylureas, acarbose, or certain glitazones), and as the disease progresses, combinatorial treatment follows, until finally insulin injections are required to achieve glycemic control (3). Considering the different modes of action of DP IV inhibitors (enhancing the postprandial insulin response due to active incretin preservation) and metformin or glitazones (sensitizing peripheral tissue to insulin), we predict that type 2 diabetic patients receiving combinatorial treatment of these therapies will produce an even greater (additive) antidiabetic effect. However, because both DP IV inhibitors and sulfonylureas enhance insulin release, the potential of combination therapy with these agents is doubtful. A corollary to our hypothesis was recently published by Zander et al. (14), who found that subcutaneous infusion of GLP-1 had an additive antidiabetic effect when given in combination with metformin; it was also commented that data were inconsistent with the findings of Mannucci et al. Direct testing using laboratory models of type 2 diabetes and clinical trials will ultimately confirm or refute our prediction on combination therapies.

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References

Response to Hinke et al.

We agree with Hinke et al. (1) that metformin acts mainly through the inhibition of hepatic glucose output and the enhancement of periph-
eral insulin sensitivity, through unidentified molecular mechanisms in the liver and skeletal muscle. However, it has been observed that metformin could enhance glucose-induced insulin secretion in some experimental conditions (2), although the relevance of this effect for the antihyperglycemic action of metformin is questionable. Furthermore, glucagon-like peptide (GLP)-1 has been shown to increase insulin sensitivity and non-insulin-mediated glucose disposal (3,4), suggesting that DPP-IV inhibitors, which increase GLP-1 levels, could be expected to improve insulin sensitivity as well as insulin secretion.

Our study (5) has shown that the increase of GLP-1 levels after an oral glucose load determined by metformin, consistent with previous reports, is not due to drug-induced differences in glycemia or insulinemia; in fact, this effect can also be observed in isoglycemic and isoinsulinemic conditions, i.e., during a hyperinsulinemic-euglycemic clamp. The contribution of enhancement of secretion and inhibition of degradation to the increase of GLP-1 levels during metformin therapy needs to be elucidated through further specifically designed studies, as was clearly stated in our study. The measurement of total GLP-1, as suggested by Hinke et al., would be of little use in this respect; in fact, total GLP-1 should obviously be expected to be increased, even in the case of metformin inhibiting degradation without stimulating secretion. In vitro or ex vivo experimental models, such as isolated intestinal L-cells or perfused ileum, would be more informative for the study of the effects of metformin on GLP-1 secretion.

We also agree with Hinke et al. that, theoretically, the combination of DPP-IV inhibitors (acting mainly via the increase of early postprandial insulin secretion) and metformin (acting mainly through the enhancement of insulin sensitivity and suppression of hepatic glucose output) could be useful in the treatment of type 2 diabetes. However, the choice of therapeutic combinations should be based on evidence derived from clinical studies rather than on theoretical consideration. Demuth et al. (6) reported that the Probiodrug DPP-IV inhibitor P32/98 has a significant hypoglycemic effect in type 2 diabetic patients treated with sulfonylureas, but it does not reduce blood glucose in those already treated with metformin. We agree with Hinke et al. that other DPP-IV inhibitors could have a more favorable profile of action when given in combination with metformin, but we advise greater caution in designing future therapeutic scenarios when so little sound clinical evidence is available.

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