

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.

MARSHALL B. BLOCK, MD

Address correspondence to Marshall B Block, MD, Endocrinology Associates Pa, 3522 N Third Ave., Phoenix, AZ 85013. E-mail: ontheblock4m@yahoo.com.

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 glycemia 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 vesicles docked at the plasma membrane, whereas 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 β -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.

OLE SCHMITZ, MD

From the Department of Endocrinology, University Hospital of Aarhus, Aarhus, Denmark.

Address correspondence to Dr. Ole Schmitz, Department of Endocrinology, University Hospital of Aarhus, 8000 Aarhus C, Denmark. E-mail: ole.schmitz@ickf.au.dk.

References

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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-

