



LUND UNIVERSITY

The dynamic incretin adaptation and type 2 diabetes.

Ahrén, Bo

Published in:
Journal of Clinical Endocrinology and Metabolism

DOI:
[10.1210/jc.2011-0299](https://doi.org/10.1210/jc.2011-0299)

2011

[Link to publication](#)

Citation for published version (APA):
Ahrén, B. (2011). The dynamic incretin adaptation and type 2 diabetes. *Journal of Clinical Endocrinology and Metabolism*, 96(3), 620-622. <https://doi.org/10.1210/jc.2011-0299>

Total number of authors:
1

General rights

Unless other specific re-use rights are stated the following general rights apply:
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

JCEM

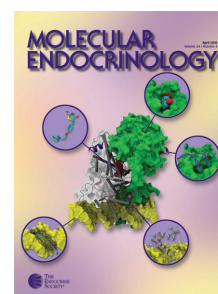
THE JOURNAL
OF CLINICAL
ENDOCRINOLOGY
& METABOLISM

The Dynamic Incretin Adaptation and Type 2 Diabetes

Bo Ahrén

J. Clin. Endocrinol. Metab. 2011 96: 620-622, doi: 10.1210/jc.2011-0299

To subscribe to *Journal of Clinical Endocrinology & Metabolism* or any of the other journals published by The Endocrine Society please go to: <http://jcem.endojournals.org/subscriptions/>



The Dynamic Incretin Adaptation and Type 2 Diabetes

Bo Åhrén

Department of Clinical Sciences Lund, Lund University, 221 84 Lund, Sweden

In 1932, Dr. Jean La Barre (1) of Belgium introduced “incretin” as the name of a substance in the gut mucosa that produces hypoglycemia when injected in normal but not in pancreatectomized experimental animals. He and Dr. Hans Heller (2) of Austria suggested almost simultaneously that this could be the basis for diabetes therapy. The incretin concept was further developed in the early 1960s when it became possible to determine the insulin level in blood. Then the famous experiments comparing the influence of *iv* vs. oral glucose administration on insulin secretion were undertaken. The results showed that oral glucose elicited a much larger insulin response than an *iv* glucose infusion (3, 4). This was confirmed in a study when glucose levels were the same after oral vs. *iv* glucose administration (5) and, with similar technique, has also been demonstrated to exist in mice (6), providing a tool for investigating incretin mechanisms in more detail. The incretin function has key physiological impact on glucose homeostasis after oral glucose. This is illustrated by results in healthy humans that the glucose excursion is very similar after ingestion of 25, 50, or 100 g due to an increase in the incretin effect matching the increased glucose load and preventing hyperglycemia (5).

The incretin effect is largely attributed to the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). They are both released from enteroendocrine cells after oral glucose, and they both augment glucose-stimulated insulin secretion (7). GIP and GLP-1 are also released after ingestion of nonglucose macronutrients (both proteins and lipids) (8). This may suggest that the incretin concept is broader than only augmenting insulin secretion after oral glucose. However, whether the incretin hormones are of importance for the insulin response to nonglucose stimuli also remains to be established.

During recent years, the interest in the incretin concept has been intensified because pharmacological therapy of type 2

diabetes has been developed based on the antidiabetic action of GLP-1 (9). In addition to stimulated insulin secretion, these actions include inhibited glucagon secretion, induction of satiety, and delay in gastric emptying. Today, clinically introduced incretin-based therapy exists in terms of injectable GLP-1 receptor agonists and of orally available inhibitors of the enzyme dipeptidyl peptidase-4 (DPP-4), which raise endogenous GIP and GLP-1 levels by preventing inactivation of the incretin hormones (9).

An important discussion has evolved as to whether the incretin function is impaired in type 2 diabetes and, if so, whether this contributes to the pathophysiology of the disease. A first study on this topic compared the insulin and C-peptide responses to oral glucose (50 g) vs. *iv* glucose when plasma glucose levels were matched, and the study was performed in both healthy subjects and subjects with type 2 diabetes (10). The results showed that more than 70% of the insulin response to oral glucose was mediated by the incretin hormones in healthy subjects, whereas the corresponding figure in subjects with type 2 diabetes was less than 40%, *i.e.* the results suggested that incretin function is markedly impaired in type 2 diabetes. At the same time, the study showed that the GIP response to oral glucose was the same in healthy and diabetic subjects (GLP-1 was not determined). Therefore, this study suggested that it is impaired action of incretin hormones rather than impaired incretin hormone secretion that explains the defective incretin function in type 2 diabetes. This conclusion was supported by other results showing that the insulin secretory response to *iv* GIP is indeed markedly impaired in type 2 diabetes (11). It was later shown that the insulinotropic action of *iv* GLP-1 is also impaired in type 2 diabetes, albeit not as much as the response to GIP (12).

Other studies have, however, shown defective incretin hormone secretion in type 2 diabetes, making this

area somewhat controversial (13, 14). Several explanations may be offered for this apparent inconsistency, such as different techniques of measuring the incretin hormones, different patient populations in the different studies with different degrees of glycemic control and treatment, and different protocols of the studies including different times for the washout of treatment. It is also possible that after ingestion of a mixed meal, non-glucose macronutrients contribute to the response, and there might be differences in impairment in type 2 diabetes between different macronutrients. A recent meta-analysis showed there are factors that inhibit incretin hormone secretion (increased body weight, high glucagon) and factors that increase incretin hormone secretion (old age, high free fatty acids), and careful studies to compare the secretion in different groups need to control for these confounders (15). Until such studies have been performed, the conclusion seems to be that there is no indication of a generalized defect in incretin hormone secretion in all patients with type 2 diabetes (15).

In this issue of *JCEM*, Bagger *et al.* (16) present a new study with novel data of great interest in this context. The authors decided to study the dynamic increase in incretin function by increasing oral glucose loads in nondiabetic and diabetic subjects to examine whether the adaptation in incretin function is impaired in type 2 diabetes. They therefore challenged healthy volunteers and subjects with type 2 diabetes with three different doses of oral glucose (25, 50, and 125 g). They confirmed in healthy subjects that both the incretin hormone secretion and the incretin effect (*i.e.* the insulin response after oral *vs.* iv glucose) are increased by increasing the glucose load, resulting in the same glucose peak after the three different challenges. More importantly, however, they showed for the first time that this dynamic incretin function is impaired in type 2 diabetes. A marked impairment in incretin function was seen after all three glucose loads in the diabetic subjects, and quantitatively, the incretin effect after 125 g glucose in diabetic subjects was similar to the effect after 25 g glucose in healthy subjects. This markedly impaired incretin effect in type 2 diabetes patients was associated with higher glucose levels compared with the healthy subjects; more importantly, the glucose peak increased when the glucose load increased in type 2 diabetes patients (which was not the case in nondiabetic subjects). In other words, the incretin function was not sufficiently increased by oral glucose to prevent hyperglycemia in diabetic subjects. Hence, the study shows that: 1) the incretin function is impaired in type 2 diabetes; 2) this is mainly due to a defective dynamic incretin adaptation to the increased glucose load; and 3) this defective incretin adaptation seems to contribute to prandial hyperglycemia in type 2 diabetes.

The study by Bagger *et al.* (16) also showed that both GIP and GLP-1 responses to the increasing glucose challenge were augmented, *i.e.* for both GIP and GLP-1, higher plasma levels were observed by increasing the glucose load. They also found that these responses were the same in healthy and diabetic subjects. Hence, this study confirms the recent meta-analyses showing that incretin hormone secretion after oral glucose seems preserved in diabetes (15). Therefore, a main conclusion of the novel study is that the defective up-regulation of the incretin function by increasing oral glucose challenges in type 2 diabetes is not caused by a defective increase in incretin hormone levels, but instead is largely caused by defective islet effects of the incretin hormones.

Bagger *et al.* (16) also estimated gastric emptying in their study by applying the acetaminophen absorption technique. They demonstrated that gastric emptying was reduced by increasing the glucose load, and they showed that this reduction was the same in healthy subjects and in type 2 diabetes patients. This finding has several interesting consequences. First, it suggests that inhibition of gastric emptying after ingestion of a high amount of glucose may be a physiological response to prevent hyperglycemia. Second, it suggests that this gastric effect of oral glucose is preserved in type 2 diabetes, *i.e.* impairment of this effect is not a mechanism underlying postprandial hyperglycemia.

The study thus clearly suggests that an impaired dynamic incretin function in type 2 diabetes contributes largely to the insulin deficiency and postprandial hyperglycemia. Two important aspects evolve from this:

- 1) Is this a cause or an effect of type 2 diabetes? Islet dysfunction is seen early during the development of type 2 diabetes. Recently, it was actually shown to precede the development of impaired glucose tolerance (17). Does defective incretin function contribute to this islet dysfunction? A previous study has suggested that this is not the case, but rather that the defective incretin effect in type 2 diabetes is a reflection of impaired glucose homeostasis and not a primary phenomenon (18). However, longitudinal long-term follow-up studies of the dynamic incretin adaptation to increasing glucose loads are required to solve this.
- 2) To what extent is the impaired incretin hormone effect on insulin secretion in type 2 diabetes a reflection of a global generalized islet dysfunction *vs.* a more specific defect in β -cell incretin hormone receptor signaling? Delineating this, which requires experimental tools, may offer novel ways to develop the incretin-based therapy.

This nice piece of work by Bagger *et al.* (16) thus presents interesting novel and conceptually new information for our understanding of incretin physiology and pathophysiology. The work is an example of sound interventional physiology studies in a clinical context. The strength of this integrative approach is evident from the important basic and clinical implications of the results. The study also opens novel avenues for creative studies to further understand the incretin system and for future development of incretin-based therapy of type 2 diabetes.

Acknowledgments

Address all correspondence and requests for reprints to: Dr. Bo Åhrén, Department of Clinical Sciences Lund, B11 BMC, 221 84 Lund, Sweden. E-mail: Bo.Ahren@med.lu.se.

Disclosure Summary: The author has nothing to declare.

References

1. La Barre J 1932 Sur les possibilités d'un traitement du diabète par l'incrétine. *Bull Acad R Med Belg* 12:620–634
2. Heller H 1935 Über das insulotrope Hormon der Darmschleimhaut (Duodenin). *Arch Exp Pharmacol* 177:127–133
3. Elrick H, Stimmler L, Hlad Jr CJ, Arai Y 1964 Plasma insulin responses to oral and intravenous glucose administration. *J Clin Endocrinol Metab* 24:1076–1082
4. McIntyre N, Holdsworth CD, Turner DS 1964 New interpretation of oral glucose tolerance. *Lancet* 2:20–21
5. Nauck MA, Homberger E, Siegel EG, Allen RC, Eaton RP, Ebert R, Creutzfeldt W 1986 Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. *J Clin Endocrinol Metab* 63:492–498
6. Åhrén B, Winzell MS, Pacini G 2008 The augmenting effect on insulin secretion by oral versus intravenous glucose is exaggerated by high-fat diet in mice. *J Endocrinol* 197:181–187
7. Holst JJ, Vilsbøll T, Deacon CF 2009 The incretin system and its role in type 2 diabetes mellitus. *Mol Cell Endocrinol* 297:127–136
8. Carr RD, Larsen MO, Winzell MS, Jelic K, Lindgren O, Deacon CF, Åhrén B 2008 Incretin and islet hormonal responses to fat and protein ingestion in healthy men. *Am J Physiol Endocrinol Metab* 295:E779–E784
9. Åhrén B 13 January 2011 GLP-1 for type 2 diabetes. *Exp Cell Res* 10.1016/j.yexcr.2011.01.010
10. Nauck M, Stöckmann F, Ebert R, Creutzfeldt W 1986 Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia* 29:46–52
11. Nauck MA, Heimesaat MM, Orskov C, Holst JJ, Ebert R, Creutzfeldt W 1993 Preserved incretin activity of glucagon-like peptide 1 [7–36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type 2 diabetes mellitus. *J Clin Invest* 91:301–307
12. Kjems LL, Holst JJ, Vølund A, Madsbad S 2003 The influence of GLP-1 on glucose-stimulated insulin secretion: effects on β -cell sensitivity in type 2 and non-diabetic subjects. *Diabetes* 52:380–386
13. Toft-Nielsen MB, Damholt MB, Madsbad S, Hilsted LM, Hughes TE, Michelsen BK, Holst JJ 2001 Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *J Clin Endocrinol Metab* 86:3717–3723
14. Åhrén B, Carr RD, Deacon CF 2010 Incretin hormone secretion over the day. *Vitam Horm* 84:203–220
15. Nauck MA, Vardarli I, Deacon CF, Holst JJ, Meier JJ 2011 Secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down? *Diabetologia* 54:10–18
16. Bagger JJ, Knop FK, Lund A, Vestergaard H, Holst JJ, Vilsbøll T 2011 Impaired regulation of the incretin effect in patients with type 2 diabetes. *J Clin Endocrinol Metab* 96:737–745
17. Åhrén B 2009 β - and α -cell dysfunction in subjects developing impaired glucose tolerance: outcome of a 12-year prospective study in postmenopausal Caucasian women. *Diabetes* 58:726–731
18. Knop FK, Vilsbøll T, Højberg PV, Larsen S, Madsbad S, Vølund A, Holst JJ, Krarup T 2007 Reduced incretin effect in type 2 diabetes: cause or consequence of the diabetic state? *Diabetes* 56:1951–1959