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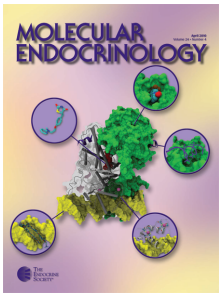

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Editorial

The Dynamic Incretin Adaptation and Type 2 Diabetes

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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

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Abbreviations: GIP, Glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1.

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, nonglucose 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.

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