Incretins: What is known, new and controversial in 2013?

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Abstract

Glucagon-like peptide (GLP)-1 action involves both endocrine and neural pathways to control peripheral tissues. In diabetes the impairment of either pathway may define different subsets of patients: some may be better treated with GLP-1 receptor agonists that are more likely to directly stimulate beta-cells and extrapancreatic receptors, while others may benefit from dipeptidyl peptidase (DPP)-4 inhibitor treatments that are more likely to increase the neural gut–brain–pancreas axis. Elevated plasma concentrations of GLP-1 associated with agonist treatment or bariatric surgery also appear to exert neuroprotective effects, ameliorate postprandial and fasting lipids, improve heart physiology and protect against heart failure, thereby expanding the possible positioning of GLP-1-based therapies. However, the mechanisms behind GLP-1 secretion, the role played by proximal and distal intestinal GLP-1-producing cells as well as the molecular basis of GLP-1 resistance in diabetes are still to be ascertained. The pharmacological features distinguishing GLP-1 receptor agonists from DPP-4 inhibitors are discussed here to address their respective positions in type 2 diabetes.

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Keywords: Incretins; Autonomic nervous system; DPP4; Heart; GIP

Résumé

GLP-1, que savons-nous, nouveautés et contradictions ?

Nous confirmons que l’action du GLP-1 est endocrine et neurologique. Cette dernière action définit l’axe intestin-cerveau-périphérie. Leurs influences respectives sur la glycémie et altération au cours du diabète conduiraient à des actes thérapeutiques propres puisque les inhibiteurs DPP4 recruteraient préférentiellement l’axe nerveux alors que les agonistes agiraient directement sur les récepteurs des cellules bêta-pancréatiques et extra-pancréatiques. La forte concentration sanguine en agoniste atteinte lors des traitements ou par le GLP-1 natif lors de chirurgies bariatriques extra-pancréatiques. La forte concentration sanguine en agoniste atteinte lors des traitements ou par le GLP-1 natif lors de chirurgies bariatriques serait à l’origine du contrôle des lipides et de la protection cardiocérébrale récemment identifiée, suggérant un positionnement sur les risques cardiovasculaires et neurologiques. Les mécanismes de la sécrétion des incretines par l’intestin proximal et distal ainsi que les mécanismes du dysfonctionnement du GIP au cours du diabète ont été rediscutés. Les positionnements différentiels des agonistes du récepteur au GLP-1 et des DPP4i furent discutés en fonction des caractéristiques physiopathologiques des patients diabétiques de type 2.

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Mots clés : Incretines ; Système nerveux autonome ; DPP4 ; Cœur ; GIP

1. Introduction

The incretins glucagon-like peptide (GLP)-1 and gastric inhibitory peptide (GIP) are released by the gut during a meal and contribute to the enhancement of glucose-induced insulin secretion [1]. The major drawback preventing the use of native GLP-1 in the treatment of diabetes is linked to its rapid degradation through proteolysis by dipeptidyl peptidase (DPP)-4. GLP-1-based therapeutic strategies, which are now on the market for the treatment of type 2 diabetes, are using DPP-4-insensitive GLP-1 receptor agonists and DPP-4 inhibitors (DPP-4i). However, our understanding of the physiological roles and modes of actions of the incretins is continuously growing, leading to the
possibility of a pharmacological repositioning of the incretin-based therapies. As an example, the dogma of a direct endocrine role of gut-released GLP-1 on stimulation of glucose-induced insulin secretion has been recently challenged by new original data [2–4]. Indeed, the control of energy metabolism by GLP-1 leading to reduced food intake and body weight is now associated with activation of a neuronal gut–brain–peripheral tissue axis. As this pathway may be more effectively activated by DPP-4i, this may have implications for the selection of patients more likely to respond to the treatment.

This analysis is in line with the new recommendations by the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) [5] and also supports the concept of personalized medicine, where the treatment is adapted to the patient’s particular physiological features. Similarly, the mechanisms through which glucose/lipids increase incretin secretion remains elusive and most likely are not simply associated with the direct detection of nutrients by K (GIP-secreting) and L (GLP-1-secreting) cells. More complex interactions with other nutrients, bile acids and microbiota need to be considered to provide an explanation for the endocrine mechanism. Again, greater knowledge of these issues would help in the development of new clinical trials to adapt therapeutic strategies aiming for better control of type 2 diabetes. Eventually the growing evidence of the extrapancreatic action of GLP-1-based therapies on, for example, neurological [6,7] and cardiovascular physiology will allow the possible use of GLP-1 receptor agonists and DPP-4i in new clinical applications. In general, the next decade should bring new physiological understandings and clinical evidence of better treatments for type 2 diabetes and its associated complications.

2. Glucagon-like peptide-1 and cardiovascular positioning

Large sets of data are now available regarding the extrapancreatic action of GLP-1, most notably on postprandial and fasting lipids, heart physiology and cardioprotective effects that suggest a place for GLP-1-based therapies in the control of cardiovascular risk factors [8,9]. Some clinical trials with GLP-1 receptor agonists and DPP-4i are now looking at these issues, and the results should be available within the next few years [10]. Already, recent studies have shown that the DPP-4i are associated with significantly fewer cardiovascular events [11]. To position GLP-1-based therapies in the control of cardiovascular risk factors, clinical trials using cardiovascular co-morbidities as the primary criteria are needed.

However, despite the vast amount of data available from animal models, the molecular mechanisms through which GLP-1-based therapies affect cardiovascular function are still unknown, and could be different for GLP-1 receptor agonists and DPP-4i, as they each recruit different mechanisms to control glycaemia. Although the presence of GLP-1 receptors on cardiac cells has been documented [12], the means through which endogenous GLP-1 or GLP-1-based therapies affect the function of cardiac cells is not yet known. Furthermore, the DPP-4i, which also show some cardiovascular effects [13], most probably act through mechanisms not directly involving the GLP-1 receptor at the surface of cardiac cells. Instead, DPP-4i may be acting indirectly through an integrated whole-body response. Thus, the effect of GLP-1 on heart rate and heart protection may be diverse, thereby allowing it to affect different subpopulations of diabetic patients.

3. Glucagon-like peptide-1 and neuroprotection

Recent evidence in the literature has demonstrated a neuroprotective role for GLP-1. This prompted a discussion on whether the concentrations of circulating GLP-1, reached when using GLP-1 receptor agonists or following bariatric surgery, could have an impact on these central mechanisms and contribute to the prevention of neurodegenerative diseases in humans [6,7]. It is now considered that GLP-1 serves as a neurotransmitter that might protect against excitotoxic cell death and oxidative injury [14]. However, although strongly supported by preclinical observations, dedicated clinical trials in humans are required to validate the possible impact of GLP-1 on neuroprotection. As regards the possible central effect of GLP-1, it is still a matter of debate whether GLP-1 can efficiently cross the blood–brain barrier to reach the brain nuclei where its receptors are located. The specific pharmacology of the different GLP-1-based therapies may thus affect distinct regions of the brain that would not otherwise be physiologically activated during everyday life. It was also suggested that GLP-1 neurons present in the caudal nucleus tractus solitarius in the brain stem might regulate autonomic nervous activity through their projection towards the dorsomedial and paraventricular hypothalamic nuclei, the ventrolateral periaqueductal gray and the thalamic paraventricular nucleus [15]. For this reason, these cells could be important GLP-1 targets for regulating eating habits, gastric emptying, pancreatic endocrine secretion and cognition, for example. Thus, the important questions are whether GLP-1-based therapies can target these brain areas and what their respective roles are in comparison to gut GLP-1-producing cells.

4. Glucagon-like peptide-1 and bariatric surgery

A tremendous amount of data is now available to demonstrate the efficacy of bariatric surgery in the treatment of obesity and even diabetes [16]. Their remission is attributed in part to the large GLP-1 secretion observed immediately after surgery [17]. However, what triggers the increased rate of GLP-1 secretion is unclear, but could be caused by the direct contact of nutrients with ileal and colonic L cells or mediated by intestinal microbiota [18]. Exclusion of the foregut, which secretes GIP as well as other peptides [19], may also contribute to the overall beneficial therapeutic effects of surgery.

It is certain that bariatric surgery offers an opportunity to decipher the role of incretins and other intestinal peptides in coordination with gut microbiota and bile acids in the control of glucose homeostasis. The respective impact of these factors on insulin secretion and action, and on remission and relapses in body weight and glycaemic control, needs to be deciphered in order to design new therapeutic strategies for the treatment.
of type 2 diabetes and even obesity. Biomarkers defining the patients most likely to succeed and at risk of relapses should be identified to avoid patients at high risk of failure undergoing the surgery. However, the current hypoglycaemic risk observed in some patients following bariatric surgery [20,21] could be attributable to some extent to incretin-induced insulin secretion, which contradicts the glucose-dependency dogma of incretin action. For this reason, major clinical trials should be performed as well as essential fundamental studies to understand the molecular mechanisms of hypoglycaemia and appetite [22].

Bariatric surgery may also lead to an increase in beta-cell mass through both the anti-apoptotic and pro-proliferative effects of both GLP-1 and GIP. This effect was discussed as a way to explain the success rate of the operation in the treatment of diabetes. The rate of success or failure depends on the patient’s islet plasticity and, as a consequence, the question of bariatric surgery in type 1 diabetic patients was also raised. Although this concept is still in its early stages, it should be considered in the near future. It was also mentioned that the reasons for relapses in body weight loss and glycaemic control need to be studied intensively to prevent some patients undergoing the major surgical procedure only to fail to reach the therapeutic goal in the long-term. It was also suggested that, after surgery, patients should eat energy-dense food almost continuously (E. Naslund, personal communication). Being in a continuous fed state hampers the beneficial effects of fasting and feeding periods, but preserves the metabolic flexibility required for normal control of energy homeostasis.

5. The gut, carbohydrates and glucagon-like peptide-1 secretion

Besides protecting GLP-1 and GIP against degradation with DPP-4i and using agonists to activate the GLP-1 receptor, an alternative therapeutic strategy could rely on increasing GLP-1 secretion, the control of which is still not completely understood. Bile acids are emerging as important inducers of GLP-1 secretion [23], which could lead to novel pharmaceutical strategies possibly in combination with DPP-4i. L cells express the bile acid receptor TGR5 as well as other G protein-coupled receptors that bind different lipid species and activate GLP-1 secretion. These observations suggest that a complex relationship between lipid absorption and bile acid production and their modification by intestinal microbiota might modulate GLP-1 secretion.

Another major topic of discussion was whether the gradient in the abundance of GLP-1-producing L cells observed from the foregut to the distal gut is associated with functional differences between these cells and, in particular, whether secretion is controlled similarly by different nutrients. Electrogenic transport of glucose in the duodenum and ileum, for instance, may proceed at different rates and thus have different effects on plasma membrane depolarization, as the luminal concentration of glucose is most likely different between the proximal and distal gut regions. It was also suggested that the origins of glucose in the foregut and distal gut are probably different. The foregut could be absorbing simple carbohydrates, while the distal gut could more likely be absorbing slow-release carbohydrates. This would mean that different nutritional signals might allow the body to adapt differently according to the type of carbohydrate absorbed. Again, by contributing to hydrolysis of the different types of carbohydrates, the gut microbiota may further influence the pattern of GLP-1 secretion.

It was also concluded that the distribution of incretin cells along the intestinal tract might therefore correspond to a differential capacity to respond to the quality and quantity of nutrients present in the different segments of the intestine. This is an important point in the context of the use of sodium-dependent glucose transporter (SGLT)1/2 inhibitors that reduce the uptake of glucose in the duodenum while increasing its concentration in the distal gut. By further increasing GLP-1 secretion, could this process be involved in the anti-diabetic effect of SGLT inhibitors? In any case, dapagliflozin and canagliflozin, which are specific SGLT2 inhibitors that block 90% of the glucose reuptake in the kidney, are most likely not involved in the process. SGLT2 is not expressed in the intestine, but only in the kidney. Thus, SGLT2 inhibitors are not likely to have an impact on GLP-1 secretion.

6. Could gastric inhibitory peptide be revisited for the treatment of type 2 diabetes?

GIP has been neglected in the treatment of diabetes because it does not retain its insulinotropic effects in diabetic patients [24]. However, on revisiting GIP as a putative anti-diabetic agent, its lipogenic role in animal models suggests that using this peptide in the treatment of type 2 diabetes may have the unwanted effect of increasing body weight gain [25]. Yet, numerous anti-diabetic strategies increase body weight, including insulin therapy, sulphonylureas and thiazolidinediones, which suggest that increasing body weight gain is not necessarily incompatible with an anti-diabetic strategy. The type of fat rather than its mere quantitative accumulation is also important in determining the development of insulin resistance. It is now clearly established that a fat depot characterized by metabolic inflammation, such as that due to the infiltration of immune cells, causes insulin resistance [26]. However, no data are available regarding either the pro- or anti-inflammatory effects of GIP, and such information is necessary before any conclusions can be drawn on that point.

Likewise, as glucagon secretion is increased by GIP and could worsen glycaemia, should GIP antagonists rather than agonists be used? Some answers are related to the time of the day that agonists and antagonists are used. Inhibition of glucagon secretion in a fasting state requires the use of GIP receptor antagonists, whereas receptor agonists can be used in the fed state to enhance insulin secretion even when glucagon secretion is increased as well.

The impaired insulinoitropic activity of GIP in type 2 diabetes was also addressed in terms of the molecular reasons related to the impaired function. The consensus was that the reduced number of GIP receptors at the surface of beta-cells is responsible for the impairment, although the mechanisms responsible for this reduced number remains unknown and needs to be addressed. The impairment also appears to affect all diabetic patients, as no
type 2 diabetic has ever shown satisfactory insulin secretion in response to GIP administration. Although yet to be ascertained, the origin of the impaired GIP insulinotropic effect is most likely associated with glucolipotoxicity and other diabetes-associated dysmetabolic factors. This suggests that, following treatment and with improved metabolic control, the factors hampering GIP-regulated insulin secretion could be reduced and thus alleviate their inhibitory action. This means that GIP-based therapies could be used secondarily, notably in those considering DPP-4-resistant GIP analogues, and might even be considered to further adjust glycaemic control [27].

7. Pharmacological specificities of glucagon-like peptide-1-based therapies and anti-diabetic use

DPP-4i and GLP-1 receptor agonists (including GLP-1 and exendin-4 analogues) are characterized by two different modes of action in the control of glycaemia. DPP-4i mostly engages in the activation of the GLP-1-dependent gut–brain axis [2, 28], whereas GLP-1 receptor agonists directly target pancreatic beta-cells and the brain in some cases. In addition, differences in food intake, energy expenditure, gastric emptying and body weight loss can be found between the two strategies. Thus, two classes may be proposed, and their positioning will depend on patients’ characteristics such as age, body weight and social environment. It is proposed that DPP-4i and GLP-1 receptor agonists might be used as add-ons to each other rather than sequentially. It is also clear that the pharmacokinetic differences between each of the DPP-4i because of their different hydrophilic or hydrophobic properties or half-lives may lead to a differential distribution of the molecules in the body. It has been proposed that intestinal DPP-4 could be a major target of DPP-4i for improving glucose control compared with blood DPP-4 [28]. This suggests that molecules mainly inhibiting intestinal DPP-4 may have a slightly different mode of action in the control of glycaemia, although the short-term anti-diabetic effects analyzed in human clinical trials have shown no differences so far. Likewise, the GLP-1 receptor agonists with long or short half-lives most likely also have slightly different modes of action. Short-acting molecules could mainly inhibit gastric emptying and eventually insulin secretion during food intake, whereas long-acting ones could preferentially reduce glucagon secretion and promote long-term control of insulin secretion. However, more head-to-head randomized clinical trials have to be done to delineate the evidence for differential therapeutic efficacy among the different types of DPP-4i and GLP-1 agonists.

8. Conclusion and prospective

Over the past few years the amount of data on the modes of action of incretins and the corresponding clinical evidence has dramatically increased, thereby allowing new understandings while leading the way to new clinical applications in the treatment of diabetes and corresponding co-morbidities. The promising fields of investigation now extend to the brain, cardiovascular system and lipid metabolism as well as to other gut peptides such as GIP and peptide YY. A clear possibility for the future is that, in addition to the current advances, the scientific and clinical communities will devise large European preclinical and clinical trials to, first, gain more precise insights on the physiological modes of action of the incretins and related peptides and, second, to identify through head-to-head and add-on trials the subgroups of patients for whom current and near future therapeutic strategies could best be adapted to improve treatment and allow more individualized therapy. More important, it is also expected that these trials will provide further knowledge on how to prevent the long-term failure of therapeutic strategies as well as the adverse events associated with type 2 diabetes.

Disclosure of interest

Remy Burcelin has received honoraria from Merck Sharp & Dohm, Sanofi-Aventis, Bristol-Myers Squibb, Lilly, DuPont Danisco and Physiogenex. Bernard Thorens has received honoraria from Eli Lilly and Novo Nordisk.

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