GLP-1: What is known, new and controversial in 2010?

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Abstract

Over the past 2 years, more than 1300 manuscripts have been published on glucagon-like peptide-1 (GLP-1) and yet, what do we know about it for sure? The European Club for the Study of GLP-1 (EuCSGLP-1) has debated the latest controversies concerning GLP-1, including both fundamental and clinical aspects, and concluded that the control of glucose metabolism by GLP-1 requires paracrine activation of the enteric nervous system to regulate numerous physiological functions. This involves—but is not limited to—the endocrine pancreas, liver, cardiovascular system, gastric-emptying and the brain. For this reason, the role of GLP-1 as an endocrine hormone has come under question. As systemic concentration of the peptide was not thought to be relevant to its physiological action, it was proposed that dipeptidyl peptidase-4 (DPP4) inhibitors would involve the control of enteric, rather than circulating, DPP4 activity to effectively regulate glycaemia. In any case, the concomitant insulinotropin and glucagonostatic roles of GLP-1 were believed to be of equal importance to glucose control. Another important question was related to the role of GLP-1 on beta cell apoptosis, regeneration and differentiation in type 2 diabetic patients. Although evidence in vitro showed that GLP-1 controls these functions, such effects remain elusive in humans in vivo. Nevertheless, the consensus was that GLP-1 could control glucose responsiveness, one of the first impaired physiological functions at the onset of diabetes. The therapeutic efficiency of GLP-1 would be related to the initial restoration of glucose competence, while an increase of beta cell mass has not yet been demonstrated. From a clinical and fundamental point of view, it was concluded that, at the onset of diabetes, an initial triggering of GLP-1 secretion—by metformin coupled with a DPP4 inhibitor—would help to activate the gut–peripheral axis and, hence, restore adequate regulation of glycaemia. GLP-1 analogues would certainly be helpful in association with long-acting insulin (albeit off-label) in patients with impaired beta cells and GLP-1 secretory potential. However, a reliable and routine feasible test to systematically assess dynamic insulin secretion is essential. More important, factors that influence therapeutic response, such as compliance and lifestyle, as well as pharmacokinetics and dosing, disease duration, age, gender, ethnicity, patients’ clinical characteristics, autonomic nervous system integrity and genotype characteristics also need to be considered. A few innovative perspectives have been debated, such as the recently discovered cardiovascular protective effects of the native GLP-1 peptide and its degradation product GLP-19-36, as well as the neuroprotection offered by GLP-1. Although still considered speculative, these perspectives remain hopeful and promising.

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Résumé

GLP-1, que savons-nous ? Nouveautés et contradictions.

Plus de 1300 manuscrits ont été publiés depuis 2008 concernant le GLP-1 et cependant, que savons-nous avec certitude ? Le Club européen pour l’étude du GLP-1 (EuCSGLP-1) a débattu des récentes controverses cliniques et fondamentales à ce sujet. Nous concluions initialement que le contrôle glycémique du GLP-1 nécessitait une activation paracrine du système nerveux entérique afin de réguler en cascade les nombreuses fonctions biologiques qui lui sont associées. Celles-ci correspondent notamment, mais pas seulement, à l’action du GLP-1, via le système entérique, sur le pancréas endocrine, le foie, le système cardiovasculaire, la vidange gastrique et le cerveau. Ainsi, l’action entéroparacrine du GLP-1 suggérerait que ce peptide ne soit pas réellement considéré comme une hormone. En effet, sa concentration circulante systémique ne semble pas avoir de rôle physiologique. Ainsi, nous avons proposé que le contrôle glycémique par les inhibiteurs de la dipeptidylpeptidase-4 (DPP4) implique également l’activation du système nerveux entérique et que les effets glucagonostatiques et insulinotropiques du GLP-1 sont d’une importance similaire. Le rôle du GLP-1 sur l’apoptose des cellules bêta insulinosécrétrices, leur régénération et différenciation représente un sujet...
1. Roundtable topics

1.1. Rémy Burcelin (Toulouse, France)

1.1.1. Enteric versus brain GLP-1 and glucose-sensing: what do we know so far, and is it important for the physiological role of GLP-1?

This question introduced the concept of glucagon-like peptide-1 (GLP-1) as a gut-released peptide activating the gut–brain–peripheral axis. In response to a meal, GLP-1 is rapidly secreted and almost immediately degraded by dipeptidyl peptidase-4 (DPP4). The half-life of the peptide (<1 min) and its low circulating concentration were considered incompatible with an endocrine effect of a peptide that could reach beta cells and trigger insulin secretion by binding to beta cell GLP-1 receptors. However, in the light of recent data, paracrine activation of the enteric nervous system by GLP-1 acting on the brain relay can be considered the main physiological function of the peptide in the regulation of pancreatic secretions and overall glucose metabolism. As this conclusion questioned the concept of GLP-1 as a trigger of beta cell GLP-1 receptors and its role in the control of glucose-induced insulin secretion, localized production of GLP-1 by neural terminal ends was suggested. Another hypothesis was that the moderately increased circulating GLP-1 concentration might require other cAMP-producing peptides, such as PACAP, to act in synergy with GLP-1 to stimulate insulin secretion.

The cross-talk between GLP-1 and other peptides was also illustrated by the fact that GLP-1 can modulate the action of other peptides, such as leptin and ghrelin, and notably in the brain. However, although GLP-1 is detected in brain-stem nuclei projecting towards the hypothalamus, where GLP-1 receptors are found, it is still unclear whether this axis is indeed functional in physiological situations. In the absence of receptor-occupancy tools, there is currently no way to truly assess any effect (there is no clear pharmacological way to assess the gain or loss of function).

There is a definite need for models of cell-specific GLP-1 receptor knockout to identify the relevance of brain GLP-1 on physiology. Furthermore, the putative targeting of brain GLP-1 receptors by circulating GLP-1 has been discussed and found to be irrelevant, at least in part, in the triggering of hypothalamic nuclei not in contact with the blood circulation. However, while this may be true in a physiological situation when pharmacological concentrations are reached, such as during the treatment of diabetes with analogues, it cannot be ruled out that some nuclei would be reached by the peptide and, hence, could trigger brain functions such as food intake or gastric-emptying. Nevertheless, direct evidence is still necessary, as different analogues diffuse differently across the blood–brain barrier.

Linked to these pharmacological differences is the suggestion that diverse physiological effects may be found between GLP-1 receptor agonists in the control of food intake, gastric-emptying and even pancreatic hormone secretion. As DPP4 inhibitors certainly do not induce high enough circulating concentrations of GLP-1, this suggests that analogues and inhibitors might regulate glycaemia through different GLP-1-dependent pathways. From a clinical viewpoint, these pharmaceutical strategies could be considered different and, thus, additive.

1.2. Richard Carr (Copenhagen, Denmark)

1.2.1. GLP-1 and heart/vessel targeting: are there evidence and indications of a promising future?

Over the past 3 years, there has been a growing body of evidence to suggest that GLP-1 could be considered a regulator of cardiovascular function. As a consequence, pharmacological approaches could be theoretically used to treat hypertension, ischaemia and heart failure. In the first debate on the relevance of GLP-1 as a suitable molecule for reducing the size of infarcts, the current evidence is from preliminary data—mostly animal studies—showing that a GLP-1 receptor agonist can reduce infarct size in the isolated rat heart, and that this effect can be reversed by preventing cAMP production. Most of these observations were made in preconditioned situations, whereas the relevance in humans largely depends on post-conditioned situations. More studies are certainly required in the post-ischaemic situation.
In humans, clinical trials remain scarce and indirect. A recent study showed that DPP4 inhibitors improved left ventricular function, as measured by dobutamine stress Doppler echocardiography. There was a consensus that the blood-pressure-lowering effect (mostly reduction of systolic blood pressure) is consistently seen with all incretin-based therapies, and is probably secondary to both acute and chronic vasodilatory effects. Interestingly, whether this now well-established effect of GLP-1 is glucose-dependent remains unknown, but would be worthy of study.

The pharmacological relevance of the cardiovascular effect was also debated. The fact that GLP-1 can still protect against ischaemia in GLP-1 receptor knockout mice argues against a direct role of GLP-1. It was shown that GLP-1\textsubscript{7-36} and GLP-1\textsubscript{9-36} share some effects at high doses that are well within the pharmacological range, suggesting a specific GLP-1\textsubscript{9-36} receptor. However, no clear dose–response effect can be seen with the use of pharmacological doses consistent with a physiological effect.

The precise location of GLP-1 receptors are thought to be in left ventricular myocytes, and not in Purkinje fibres. However, in the absence of any direct demonstration on isolated cardiomyocytes, it is difficult to draw any firm conclusions. In summary, as no genetic or pharmacological study has demonstrated the presence of a second receptor to GLP-1 byproducts, the idea that GLP-1\textsubscript{7-36} would need to be degraded (into GLP-1\textsubscript{9-36}) to control cardiovascular effects remains unproven. Indeed, no further speculation can be made that could lead to any clinical therapy. R. Carr’s own preliminary data, from a rat model \textit{ex vivo}, showed that a DPP4 inhibitor reduced infarct size, but only at high ambient glucose levels (11 mmol/L), while the effect was lost at lower glucose levels (5 mmol/L). This intriguing observation was discussed in the light of potential glucose-sensing molecular mechanisms that might explain how changes in glucose concentration could potentiate GLP-1 cardiovascular effects, although no evidence was proposed and the question remains open to further analyses.

1.3. Bernard Thorens (Lausanne University, Switzerland)

1.3.1. GLP-1 and beta cell apoptosis: what is the evidence that the mechanism does or does not exist in humans?

The anti-apoptotic role of GLP-1 is now established in rodents \textit{in vitro} and mostly on isolated human beta cells. However, so far, it has not been demonstrated in humans \textit{in vivo} and is still a key question, as it might be considered a major therapeutic effect of the peptide in the treatment of type 2 diabetes. To address this point, it should be remembered that the beta cell mass is the result of the combined effects of neogenic, anti-apoptotic and replicative mechanisms. Therefore, all the arguments suggesting that GLP-1 could be controlling these factors were examined.

Although there is virtually no evidence \textit{in vivo} to suggest a role of endogenous GLP-1 on these functions, the use of analogues that dramatically increase systemic GLP-1 concentrations needs to be discussed in terms of its usefulness in the treatment of type 2 diabetes. Indeed, a 1-year treatment with GLP-1 analogues, followed by a washout period, could not sustainably improve beta cell function, as the patients rapidly returned to their initial diabetic status. This conclusion, however, is open to criticism, as it could reflect the fact that more than 1 year is needed to detect any improvement in beta cell mass and to induce durable changes. A second argument is related to the putative reduction in beta cell mass at the time of diagnosis of type 2 diabetics, and over the time course of the disease, that is thought to be the triggering feature of fasting hyperglycaemia. However, this latter argument is challenged by the fact that bariatric surgery can nearly restore glucose-induced insulin secretion and glycaemic profiles in type 2 diabetic patients within a short time (a few days), well before the occurrence of body-weight normalization. This suggests that the beta cell mass was easily recruited and was, in fact, sufficient to control glycaemia. This conclusion hampers the role of a putative beta cell mass reduction, at least at the onset of type 2 diabetes.

It was further noted that pregnancy corresponds to a physiological situation associated with hyperinsulinaemia and increased beta cell mass. Whether or not changes in GLP-1 concentration are associated with this situation remains unknown, but requires further study. Along this line of investigation, the molecular mechanisms that could help to control beta cell mass, starting with apoptosis and proliferation, were also discussed. An innovative hypothesis was that the recently described autocrine IGF-2/IGF-1 receptor pathway could be involved in humans \textit{in vivo} in physiological GLP-1 or pharmacological situations. GLP-1 could stimulate IGF-1 receptor expression by beta cells that, in turn, are activated by the autocrine secretion of IGF-2. By activating the IGF-1 receptor–Akt signalling pathway, the beta cells are protected against apoptosis and their proliferation is induced, thus augmenting glucose competence.

It is also worth mentioning that GLP-1 could also trigger the expression of beta cell proliferation genes, and that the prolonged activation of this pathway \textit{via} the continuous administration of GLP-1 could favour an increase in beta cell mass. However, whether or not overt activation would still lead to nesidioblastosis remains unclear.

Several molecular mechanisms (fast and strong) that limit the ability of GLP-1 signalling to stimulate proliferation were reminded to be key regulators of the physiological beta cell mass. These would be important physiological regulatory mechanisms to prevent the overt proliferation of beta cells that could lead to deleterious hypoglycaemia. Hence, the control of these regulators could be considered the putative therapeutic targets in type 2 diabetes to increase beta cell mass, provided that over-proliferation can be avoided.

Another major pathway of analysis is related to the anti-stress effect of GLP-1—notably, endoplasmic reticulum (ER) stress—on beta cells. This appears to be a better pathway for control of the beta cell mass, as regeneration is a slow process and beta cell replication appears to be associated with increased apoptotic vulnerability. Thus, improving the anti-stress activity of GLP-1 could further and rapidly improve beta cell mass by reducing apoptosis.
Besides reduced beta cell mass, impaired beta cell glucose competence was mentioned as being present at the onset of diabetes. Glucose competence could be targeted first by GLP-1-based therapies and be responsible for the rapid improvement in glycaemia. However, impaired glucose competence needs to be distinguished from impaired first-phase insulin secretion.

An important question was related to the putative role of other cAMP-inducing hormones, such as PACAP, GIP and glucagon, which can potentiate GLP-1-induced insulin secretion. The increased concentrations of circulating GLP-1 during a meal—which remains far from the affinity constant to its receptor—could, in association with other glucose-induced factors such as the autonomic nervous system and other insulino trophic peptides, restore the endocrine activity of beta cells. Thus, from a physiological point of view, a regulatory role of GLP-1 could be related to its daily production and could, even at low doses, control beta cell mass when associated with other co-factors.

1.4. Carolyn Deacon (Copenhagen, Denmark)

1.4.1. Mechanism of action of DPP4 inhibitors: do we have evidence that insulin secretion is involved, through which mechanism does stabilization of active GLP-1 peptide control glycaemia, and is GLP-1 involved?

Dipeptidyl peptidase-4 (DPP4) is an endoprotease that degrades half the circulating GLP-1 within less than 1 min and GIP (glucose-dependent insulino tropic peptide) within 5–7 min. This means that most circulating incretins are present as metabolites that can no longer stimulate glucose-induced insulin secretion. Indeed, it has been shown that only about 12% of secreted GLP-1 reaches beta cells as the intact peptide. This simple concept already suggests that GLP-1 could act as a paracrine hormone. As a consequence, the systemic value of intact GLP-1 is increased three- to fourfold by DPP4 inhibitors, a low concentration of which may still be able to directly stimulate insulin. However, portal vein GLP-1 concentrations are much higher and, following DPP4-inhibitor treatment, intact GLP-1 levels in the portal vein may be considered high enough for potent activation of the gut–brain and gut–beta cell axes, suggesting improvement of the incretin effect.

There are as yet unpublished data from our patients treated with DPP4 inhibitors showing a similar effect of these inhibitors on insulin secretion during oral, as well as intravenous, glucose administration. This suggests that DPP4 inhibitors do not enhance the incretin effect per se but, instead, the insulin secretory response to glucose. This unexpected result is also a reminder that the mechanisms of DPP4-inhibitor-improved glycaemia have not yet been fully unravelled and that other, as yet unidentified, mediators of DPP4 inhibitors may have caused these effects. PACAP is a suggested candidate, as well as peptides released by the terminal ends of neurons in the vicinity of beta cells. Thus, it is important to identify the precise location of DPP4 activity to fully elucidate the main sites of action of inhibitors that lead to improved glycaemic control. The enteric area was strongly suggested as an important target of these inhibitors, while inhibition of the soluble (circulating) form of DPP4 was thought to be less important, as plasma DPP4 represents only a tiny amount of whole-body DPP4.

Other peptide substrates of DPP4, such as peptide YY (PYY), were also discussed, and it appears that, in humans, part of the improvement in glycaemic control induced by DPP4-inhibitor treatment might be related to the effect of DPP4 on other substrates. Food intake, gastric-emptying and other functions may also be targeted by other peptides and, thus, contribute to glycaemic control.

As for the role of GLP-1 in lymph, GLP-1 concentrations are high, and almost no DPP4 activity has been described. Although it has been thought that lymph could be considered a way for GLP-1 to escape DPP4 degradation, the lymph flow rate is extremely low and, thus, is unlikely to account for much of the GLP-1 entering the systemic circulation. Ultimately, it was concluded that, although the precise site of action of DPP4 inhibitors remains unknown, it appears to be more than probable that the enteric location of the enzyme is key for explaining the role of inhibitors in improving glycaemic control. It is very likely that the inhibitors lead to enhanced activation of the local neurons and, thus, are able to control a wide range of physiological actions in which the regulation of insulin and glucagon secretion has a similar impact on glycaemic control.

1.5. Sten Madsbad (Copenhagen, Denmark)

1.5.1. GLP-1-related therapies, inhibitors and analogues: which therapy for which patient?

GLP-1-based therapeutic strategies for the treatment of type 2 diabetes comprise long-lasting GLP-1 analogues and DPP4 inhibitors. Both strategies are thought to belong to the same family of therapeutic strategies. However, based on the recent literature and the above discussions, it is clear that their modes of action and targeted cells are different. Hence, they could belong to different classes. This conclusion led to the question of which patients were more likely to benefit more from which therapy?

To answer this question, it is worth bearing in mind that GLP-1 analogues lead to a 10-fold higher circulating GLP-1 concentration than do DPP4 inhibitors, and that different GLP-1 concentrations are required for different physiological actions, such as insulin secretion, gastric-emptying and food intake. Clinically speaking, each type of treatment is associated with a different clinical outcome. Despite the fact that HbA1c-lowering is considered similar with both strategies in patients with similar phenotypes, their weight reduction, blood pressure and gastrointestinal symptoms are different. In addition, as already mentioned above, the use of DPP4 inhibitors requires that patients still have some remaining potential capacity for GLP-1 secretion. In contrast, patients with a considerably reduced beta cell capacity would be more likely to be treated with GLP-1 analogues, as pharmacological GLP-1 concentrations could then be achieved. Furthermore, cost and convenience should also be considered according to the given patient. Thus, the treatment algorithm used to determine the most suitable therapy could be based on the identification of clinical and demographic predictive factors.
These physiological considerations, reflected in guidelines around the world (such as the American Diabetes Association [ADA], European Association for the Study of Diabetes [EASD], the UK’s National Institute for Clinical Excellence [NICE] and the Canadian Diabetes Association [CDA]), represent another set of arguments. Indeed, in both the current EASD and ADA guidelines, DPP4 inhibitors are not included and GLP-1 analogues are only recommended as the second-line therapy. In addition, the NICE guidelines propose stopping treatment if no reduction of HbA1c greater than 0.5% is obtained after 6 months of treatment with DPP4 inhibitors. With the GLP-1 analogue liraglutide (1.2 mg/d) for patients with a body mass index (BMI) greater or equal to 35 kg/m² treatment should be continued only if a beneficial metabolic response is observed (defined as a reduction of at least 1% in HbA1c and, in the case of triple-therapy regimens, weight loss of at least 3% of initial body weight). The CDA has finally proposed using DPP4 inhibitors and GLP-1 analogues as a second-line of treatment. Accordingly, body weight is a factor to consider, as well as the association of other molecules as the second or third line of treatment. Ultimately, it was concluded that, besides metformin as the first-line molecular strategy, DPP4 inhibitors followed by GLP-1 analogues could be used as a general treatment algorithm. The criterion of overweight was important when considering GLP-1 analogues compared with sulphonylureas or thiazolidinediones. It was also emphasized that incretin-based therapy may be especially suitable for elderly patients who are at high risk of hypoglycaemia or who have difficulties in self-monitoring their glycaemia. It was also again repeated that, based on clinical outcomes such as renal and hepatic insufficiency, GLP-1-based therapies need to be proposed with caution.

In general, from the physiological, social and economic points of view, it was agreed that the optimal use of glitamins in the treatment algorithm could be as an add-on to metformin as a dual therapy. In addition, the majority favoured the initial use of glitamins in combination with metformin in a single pill specifically for patients with a high baseline HbA1c to improve compliance. However, it should be borne in mind that, as yet, no trial has evaluated the durability of such an initial combination, nor are there outcome data showing any longer-term benefit for the patient. More important, the philosophical approach is different, as the use of such an initial combination means not waiting for the failure of one drug before adding the other. Finally, the potential value of a GLP-1 and insulin combination (which currently represents about one-third of its use, albeit still off-label) was debated. It was concluded that long-lasting insulin combined with a GLP-1 analogue might allow for a reduction in daily insulin doses (basal insulin only, as mixed insulin would no longer be necessary), with some expected benefits for both weight and hypoglycaemia.

1.6. Bo Ahren (Lund, Sweden)

1.6.1. GLP-1 mimetics and DPP4 inhibitors: who are the responders and non-responders?

How to predict the responders and non-responders to incretin-based therapies is a key question, to which the answer remains elusive. This difficulty led NICE to its current pragmatic approach of recommending continuing the drug only if a sufficient beneficial metabolic response is observed after the initial 6-month ‘test’ period.

Indeed, there are a number of possible explanations for the different response rates with any single drug, ranging from factors related to the drug (pharmacokinetics and dosing characteristics) to patient compliance and disease state (progressive, with pathophysiological differences in, for example, insulin secretion, beta cell mass and function, or glucagon secretion) and patient characteristics (such as age, gender, ethnicity, lifestyle, obesity, fat distribution, autonomic nervous system integrity and genotype characteristics).

When analyzing published reports of incretin-based therapy to identify the responders vs non-responders, the most consistent finding was the better response obtained in patients with a higher initial HbA1c. However, the discussion pointed out the intriguing fact that, usually, the end result across studies remains surprisingly similar whatever the baseline: for example, in all studies of incretin-based therapy added to metformin, approximately the same HbA1c (7.2–7.4%) was reached after 6 months, regardless of the initial HbA1c. Other patient characteristics reported in clinical trials, such as baseline BMI, gender, age and duration of diabetes, do not appear to predict response rates. One major limitation is, however, that studies have not stratified for these characteristics. Furthermore, data on islet function is generally not included in clinical studies and, when it is—for example, in relation to insulin secretion—only the poorer indices of beta cell function are reported. Results based on these indices are difficult to interpret most probably because these indices are only weakly related to insulin secretion. It was shown that with sitagliptin, for example, a higher baseline HOMA-B (homeostasis model assessment for beta cell function) score was associated with a lower clinical response, suggesting that patients with the least insulin secretion would respond the best. However, with liraglutide, patients with higher levels of C-peptide at baseline had a better response, suggesting better responses in those with better insulin secretion. This discrepancy clearly illustrates the need for better and more reliable indices of beta cell function that can also be used in clinical studies. In addition, there was a clear consensus that the HOMA-B score is a poor and useless index of beta cell function (as a good index should take insulin sensitivity into account, and not reflect only the fasting state).

Furthermore, it was agreed that the use of meal test data at baseline would be acceptable for lack of a better index, although it is evident that there is a need for a common and standardized way to easily assess insulin secretion in large studies (where the gold-standard hyperglycaemic clamp test is not possible). As for the HOMA-IR (homeostasis model assessment for insulin resistance), the consensus was that it appears to be slightly more reliable, although it mostly reflects insulin sensitivity in the liver.

Even fewer data are available for glucagon. Interestingly, however, glucagon may be the best predictor of efficacy: in an earlier study conducted by Arhen’s team, patients treated with a DPP4 inhibitor with the greatest reduction in postpran-
dial glucagon also had the best response in terms of glucose control.

A recent study evaluated predictors of the sustainability of response to treatment with vildagliptin as an add-on to metformin, and found that HbA1c, BMI, fasting plasma glucose, weight and disease duration were not predictive of a sustained response to treatment. The only significant predictor was age, which was also seen with sulphonylurea treatment. On debating the reason why age is important for a sustained effect, it appears that, in older subjects, different pathophysiological mechanisms of insulin secretion may be responsible for islet sensitivity and, thus, may play a role in such patients’ improved glucose control.

An additional factor that may potentially play an important role in regulating the GLP-1 response to a meal is the intestinal microflora. For this reason, it was suggested that a study should be designed to assess how changes in the intestinal microbiota might correlate with the GLP-1 response (secretion), as seen in patients who have undergone bypass surgery.

In the end, however, it was agreed that studies should be designed to evaluate responders vs non-responders. Yet, doubts were also raised as to whether or not there is truly such a thing as ‘non-responders’ to these therapies. Following extensive discussion, the assembly remained unconvinced that patients not responding to any GLP-1 therapy actually exist; instead, it may be that the degree of response varies widely among patients. It was also proposed that the ‘one-dose-fits-all’ concept may be as wrong here as it is with insulin, as what matters is exposure at specific locations.

1.7. Baptist Gallwitz (Tubingen, Germany)

1.7.1. GLP-1 and neuroprotection: is this mechanism relevant?

Recent data have shown that GLP-1 may be considered a neuroprotector against oxidative stress and amyloid deposition in the brain. Consequently, GLP-1 might have positive effects against neurodegenerative diseases such as Alzheimer’s and Parkinson’s disease, and might even stimulate neurogenesis. These data appear to be consistent with the broader protective effects of GLP-1 against oxidative stress-induced beta cell apoptosis and cardioprotection. In general, these new sets of data can be considered promising, although considerably more molecular and pharmacological work is still required. Older data showing the positive effects of GLP-1 on memory, learning and neuroprotection were also debated. These data appear to be controversial, as many experimental drawbacks were raised. Indeed, a seed of doubt was sown in the audience regarding the putative role of GLP-1 as a neuroprotector. The evidence was related to the effect of GLP-1 on certain neuroblastoma cell lines, where changes in the signalling pathways studied were modest and did not follow dose–response patterns. However, the evidence in vivo was convincing, such as the prevention and reversal of apoptosis induced by neural lesions, as was also a model of Huntington’s disease, thereby suggesting that more of this concept may be seen in future. The concept is consistent with the idea of protection against hypoglycaemia-induced neural lesions. Thus, GLP-1-based therapies might be able to prevent the deleterious effects of hypoglycaemia on the central nervous system, although this still needs to be accurately documented.

1.8. Filip Knop (Copenhagen, Denmark)

1.8.1. GLP-1, DPP4 and glycaemic control through glucagon secretion: which is doing what to glycaemia, and what are the therapeutic advantages and clinical consequences?

A growing body of evidence shows the importance of GLP-1 in the control of glucagon secretion and its role in glycaemic regulation. However, the mechanisms through which GLP-1 controls glucagon secretion remain unclear.

Under hyperglycaemic conditions, glucagon secretion is thought to be decreased by the combined inhibitory effects of glucose and insulin secretion (the intra-islet hypothesis), along with somatostatin and concomitantly secreted molecules such as zinc and amylin. On the other hand, hypoglycaemia is a strong stimulus for glucagon secretion. In addition, the autonomic nervous system that regulates catecholamine secretion as well as, most probably, other neurohormones released locally, also act as stimulators of glucagon secretion. It is noteworthy that, other than the neuropeptides known to activate glucagon secretion besides GLP-1, which has a glucagonostatic effect, little is known of other inhibitory peptides. Thus, the origin of this peculiar function is worthy of investigation.

The role of glucagon on glycaemic control is important, as it is believed to be responsible for 50% of fasting hepatic glucose production. For this reason, it has been suggested that the glucagonostatic effect of GLP-1 might regulate fasting glycaemia—which is considered surprising for a peptide secreted in the fed state. This has led to the suggestion that either the basal GLP-1 secretion rate or basal GLP-1 receptor activity might be involved in the regulation of fasting glycaemia. This hypothesis was followed by a discussion of what goes wrong during diabetes. First, circulating glucagon concentrations are increased and, second, postprandial hyperglycaemia fails to decrease it. There is also a delay in the glucagonostatic effect of postprandial hyperglycaemia. Furthermore, as in most type 2 diabetic patients arginine tests are still an effective way to regulate glucagon secretion, it was concluded that impaired glucagon regulation was specific to glucose. Thus, the glucosesensing mechanisms responsible for glucose-regulated glucagon secretion are impaired in type 2 diabetes.

This conclusion was further supported by the argument that an oral glucose load is less efficient than isoglycaemic intravenous glucose administration to regulate glucagon secretion in type 2 diabetic patients. Interestingly, GLP-1-based therapies appear to restore the glucose competence of these glucose sensors, which might secondarily regulate glucagon secretion. Thus, the brain, pancreas and enteric glucose sensors may be involved in the glucagonostatic effect of GLP-1.

In addressing the direct regulation of glucagon secretion by GLP-1, a subset of alpha cells expressing the GLP-1 receptor were mentioned as possibly responsible for some of the glucagonostatic effect of GLP-1. Similarly, GLP-1 might stim-
ulate somatostatin secretion and secondarily inhibit glucagon secretion. These hypotheses were further discussed along with arguments for the role of GLP-1 in type 1 insulinopenic patients, thereby demonstrating a non-insulin-dependent route for regulation of glucagon secretion. In the end, the main conclusion was that a balance between glucagon stimulatory factors (such as GIP and GLP-2) and inhibitory factors (such as glucose, insulin, GLP-1 and somatostatin) would favour the suppression of glucagon secretion in controls, whereas the opposite effect would be seen in type 2 diabetics.

Pharmacologically speaking, GLP-1 analogues, receptor agonists and DPP4 inhibitors are all suitable for reducing glucagon concentrations. Although these molecules are characterized by different modes of action, their effects on glucagon are nevertheless similar. Hence, another hypothesis is that all of these approaches might restore glucose competence. Ultimately, an important consensus was reached: that the glucagonostatic and insulinotropic actions of GLP-1 are equally important in the control of glycaemia. Thus, it was proposed that the reduction of glucagon secretion by GLP-1 is of primary importance in the regulation of basal glycaemia and inhibition of hepatic glucose production following the initial meal test.

2. Conclusion

This recent meeting of the EuCSGLP-1 led to the conclusion that the numerous metabolic and vascular functions regulated by GLP-1 require a complex gut–brain–peripheral axis in which glucose-sensitive units and the autonomic nervous system are major players. Validation of GLP-1 analogues, receptor agonists and DPP4 inhibitors as regulators of glycaemia through different mechanisms would also allow the elaboration of new therapeutic strategies. Although individualized therapy could be based on the sensitivity of patients to these treatments, more phenotype studies are required and, certainly, more pharmacological evidence is needed for the future validation of the role of GLP-1 in cardioprotective, neuroprotective, glucagonostatic, beta cell-regenerative and anti-apoptotic functions, which should be considered in the near future as important paths of investigation. Although much progress has taken place over the past 2 years, considerably more needs to be made in the coming years. GLP-1 secretory mechanisms along with GIP interactions also need to be elucidated.

Conflict of interest statement

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