Endocrine (2019) 64:43–47
https://doi.org/10.1007/s12020-018-1808-9

ORIGINAL ARTICLE

Effects of exenatide and liraglutide on postchallenge glucose disposal in individuals with normal glucose tolerance

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Received: 4 September 2018 / Accepted: 29 October 2018 / Published online: 8 November 2018

Abstract

Purpose Glucagon-like peptide–1 receptor agonists (GLP-1RAs) are categorized as short- or long-acting types, but information regarding differences in the effects of these two types on postprandial glucose disposal has been limited. We have now investigated the effects of exenatide and liraglutide (short- and long-acting GLP-1RAs, respectively) on glucose disposal during an oral glucose tolerance test (OGTT).

Methods Fourteen healthy volunteers with normal glucose tolerance underwent three OGTTs, which were performed without pharmacological intervention or after a single administration of exenatide or liraglutide at 30 min and 10 h, respectively, before test initiation. The three OGTTs were performed with intervals of at least 7 days between successive tests and within a period of 2 months.

Results Exenatide, but not liraglutide, markedly decelerated the peak of both plasma glucose and serum insulin levels during the OGTT, with the peaks of both glucose and insulin concentrations occurring at 150 min after test initiation with exenatide compared with 30 min in the control condition or with liraglutide. Exenatide and liraglutide reduced the area under the curve for plasma glucose levels during the OGTT by similar extents, whereas that for serum insulin levels was reduced only by exenatide.

Conclusions Our results suggest that exenatide decelerates the increase in plasma glucose levels through inhibition of glucose absorption and that it exerts an insulin-sparing action after glucose challenge.

Keywords Exenatide · Liraglutide · Oral glucose tolerance test · Japanese

Introduction

Glucagon-like peptide–1 receptor agonists (GLP-1RAs) exert beneficial effects in the treatment of type 2 diabetes mellitus, including a potent glucose-lowering effect associated with a low frequency of hypoglycemia, as well as an antiobesity action [1, 2]. The treatment of type 2 diabetes with these drugs is thus associated with a favorable clinical outcome [3, 4], in particular with regard to the prevention of cardiovascular events [5, 6].

The glucose-lowering effect of GLP-1RAs is mediated by multiple mechanisms including the stimulation and suppression of insulin and glucagon secretion, respectively, from pancreatic islets as well as inhibition of gastric emptying and deceleration of glucose absorption from the small intestine [7–10]. The actions of GLP-1RAs on the gastrointestinal tract likely contribute to the reduction in postprandial glucose levels [10, 11] and to the appetite suppression induced by this class of drugs [12, 13], with the latter effect also being related to their antiobesity action [14, 15].

GLP-1RAs are generally categorized into short- and long-acting types [1, 16]. Among GLP-1RAs commercially available to date, exenatide and lixisenatide belong to the former category, whereas liraglutide, exenatide extended

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release, albiglutide, and dulaglutide belong to the latter. Although information regarding differences in the effects of the short- and long-acting types of GLP-1RA on postprandial glucose disposal is limited, some clinical studies showed that treatment with a short-acting drug resulted in a greater reduction in postprandial glycemia than did that with a long-acting GLP-1RA [17, 18].

To provide further insight into the pharmacological properties of GLP-1RAs, we have now investigated the effects of exenatide and liraglutide on glucose disposal during an oral glucose tolerance test (OGTT). To avoid secondary effects of drug treatment, as well as effects of metabolic defects or of tachyphylaxis induced by repeated drug administration, we examined the effects of a single injection of each agent in healthy volunteers with normal glucose tolerance (NGT).

Materials and methods

Study subjects

This exploratory, open-label, single-center study was approved by the ethics committee of Kobe University Graduate School of Medicine (approval no. 230021), conforms to the provisions of the Declaration of Helsinki, and is registered in the University Hospital Medical Information Network (UMIN000006858). Volunteers who had not been diagnosed with diabetes mellitus were recruited at the Division of Diabetes and Endocrinology of Kobe University Hospital from January to March 2012. All the individuals provided written informed consent to participation in the study. Exclusion criteria included: (1) a postprandial plasma glucose concentration of >200 mg/dL; (2) allergy to exenatide or liraglutide; (3) pregnancy or possibility of pregnancy; (4) a hemoglobin A_{1c} (HbA_{1c}) level of ≥6.1%; (5) severe renal or liver dysfunction; and (6) a declaration of otherwise inappropriate by an investigator. Individuals who did not know their recent HbA_{1c} or postprandial plasma glucose levels were not excluded. Enrolled volunteers first underwent a blood test for determination of HbA_{1c} level and then were subjected to a 75-g OGTT in the morning after an overnight fast.

Since this research was an exploratory pilot study, there was no theoretical basis for calculating a number of necessary cases for statistically significance. We performed this study with 14 subjects based on the number of subjects in previous reports studying the effect of GLP-1 RAs on insulin secretion, in which 9–12 subjects were recruited [12, 19].

Protocol of pharmacological intervention

Subjects whose glucose tolerance was categorized as NGT (fasting plasma glucose concentration of <110 mg/dL and plasma glucose level at 120 min after glucose ingestion of <140 mg/dL) and whose HbA_{1c} level was ≤ 6.0% underwent two additional 75-g OGTTs with subcutaneous injection of 5 μg of exenatide or 0.9 mg of liraglutide before test initiation (Fig. 1). Given that the peak serum levels of exenatide and liraglutide occur at ~30 min and ~10 h, respectively, after a single injection [20, 21], these drugs were injected 30 min and 10 h, respectively, before initiation of the OGTT. The three OGTTs were performed with intervals of at least 7 days between successive tests and within a 2-month period. Blood samples were collected 30 min and immediately (0 min) before, as well as 5, 10, 15, 30, 60, 120, 150, and 180 min after the ingestion of glucose for the measurement of plasma glucose and serum insulin concentrations.

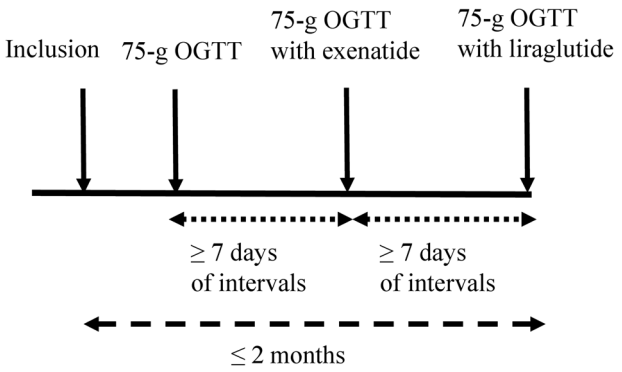

Fig. 1 Study protocol

We recruited 14 volunteers, all of whom were found to be categorized as NGT and to have an HbA_{1c} level of ≤6.0%. All the subjects then completed the two additional OGTTs with pharmacological intervention. Notable adverse events including hypoglycemia were not apparent after the administration of liraglutide or exenatide.

Statistical analysis

Data are presented as means ± SD and were analyzed with the paired Student's *t* test with the use of SPSS version 11.0 for Windows (SPSS, Chicago, IL). A P value < 0.05 was considered statistically significant.

Results

Characteristics of the study subjects are shown in Table 1. Plasma glucose concentrations at all time points with the exception of 180 min were significantly lower during the OGTT performed with prior administration of liraglutide compared with that performed without pharmacological intervention (Fig. 2a). In contrast, plasma glucose levels during the OGTT performed after exenatide administration

Table 1 Characteristics of the study subjects

Characteristic	
Males/females	8/6
Age (years)	29.5 ± 5.3
Body weight (kg)	56.8 ± 9.9
Body mass index (kg/m^2)	20.6 ± 2.2
HbA_{1c} (%)	5.2 ± 0.2

Data are means ± SD

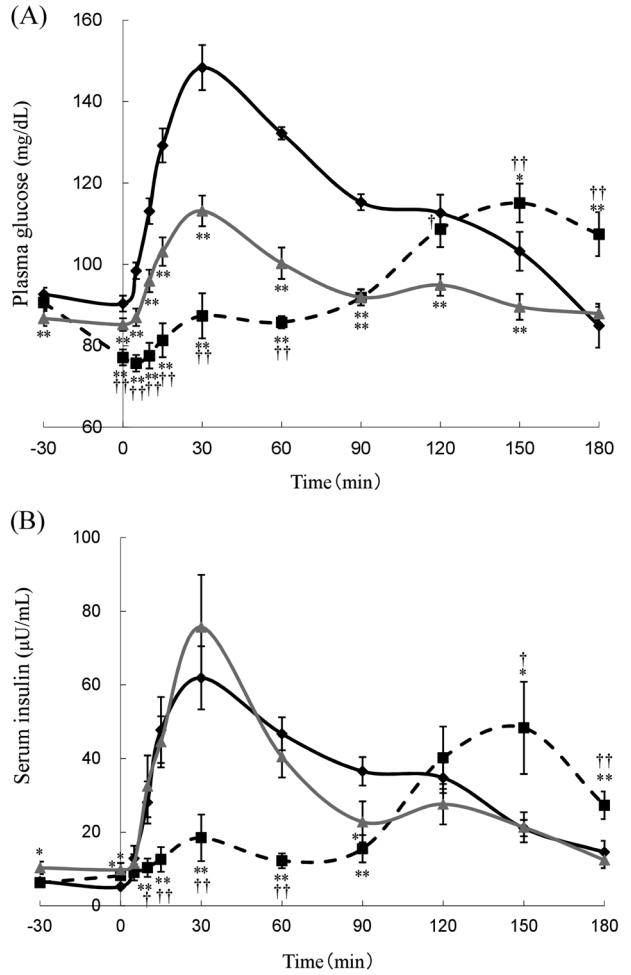

Fig. 2 Plasma glucose **a** and serum insulin **b** levels during OGTTs performed either with no pharmacological intervention (diamonds and black line) or after administration of exenatide (squares and black dotted line) or liraglutide (triangles and grey line). Data are means ± SD ($n = 14$). *$P < 0.05$, **$P < 0.01$ versus corresponding value for no pharmacological intervention; †$P < 0.05$, ††$P < 0.01$ versus corresponding value for liraglutide

were lower from 0 to 90 min, similar at 120 min, and greater at 150 and 180 min compared with those for the OGTT performed without drug treatment (Fig. 2a). Peak glucose levels during the OGTTs performed after liraglutide administration or without pharmacological intervention both occurred at 30 min, whereas that for the OGTT performed after exenatide injection was markedly delayed and did not occur until 150 min.

The serum insulin concentration at 30 min after initiation of the OGTT with liraglutide tended to be higher than that for the OGTT performed without pharmacological intervention, although this difference was not statistically significant (Fig. 2b). The serum insulin level at 90 min after test initiation was lower in the presence of liraglutide than in the absence of drug. Serum insulin levels during the OGTT performed after exenatide administration were lower at 10, 15, 30, 60, and 90 min, similar at 120 min, and greater at 150 and 180 min compared with those for the OGTT performed without intervention (Fig. 2b). Peak insulin levels during the OGTTs performed with liraglutide or without drug administration both occurred at 30 min, whereas that during the test performed after exenatide administration was again markedly delayed until 150 min.

The area under the curve (AUC) for plasma glucose concentration was significantly smaller during the OGTTs performed with liraglutide or exenatide than during that performed without pharmacological intervention, whereas the values for the tests performed in the presence of either of the two drugs were similar (Fig. 3a).

The AUC for serum insulin concentration was significantly smaller for the OGTT performed with exenatide than for that performed without drug, whereas the AUC for the test performed with liraglutide was similar to the control value (Fig. 3b).

Discussion

We here investigated the effects of exenatide and liraglutide on plasma glucose and serum insulin concentrations during an OGTT. As far as we are aware, this is the first study to directly compare the effects of GLP-1RAs on glucose disposal during an OGTT. We found that plasma glucose levels during the early phase of the glucose challenge test (before 90 min) were lowered to a significantly greater extent by the administration of exenatide than by that of liraglutide. Serum insulin levels during the early phase were also markedly suppressed by exenatide, suggesting that the glucose-lowering effect of exenatide during this phase is attributable largely to the inhibition of glucose absorption. In contrast, plasma glucose concentrations during the late phase of the test (after 90 min) were higher after the administration of exenatide than after that of liraglutide. Serum insulin levels during the late phase of the test performed with exenatide increased in parallel with the increase in plasma glucose levels, suggesting that a large portion of ingested glucose was absorbed during this phase in the presence of exenatide. This finding is thus again consistent with the notion that exenatide decelerated the

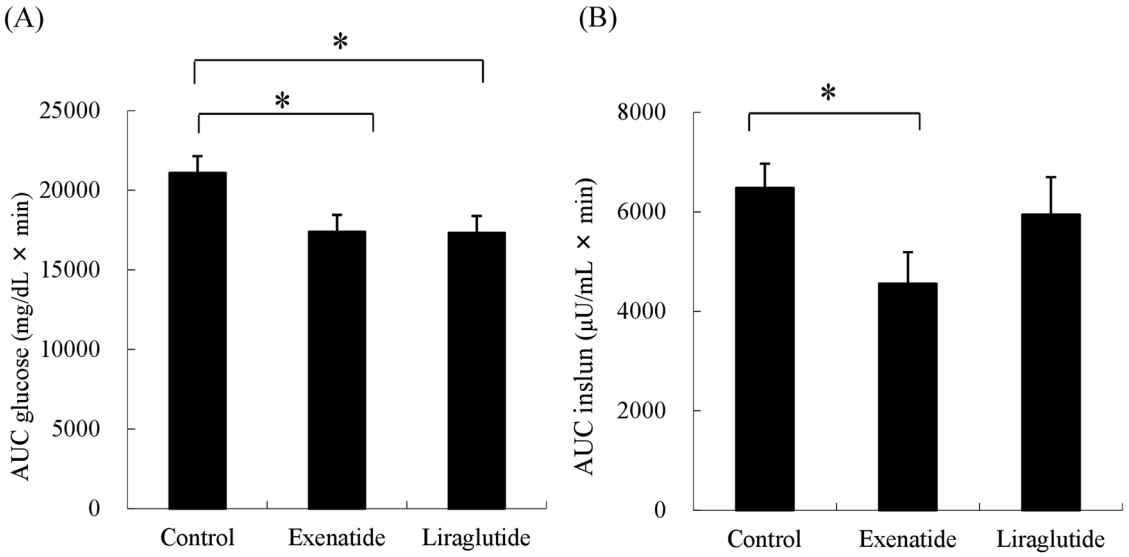

Fig. 3 AUC for plasma glucose **a** and serum insulin **b** concentrations during OGTTs performed either with no pharmacological intervention or after administration of exenatide or liraglutide. Data are means ± SD ($n = 14$). *$P < 0.05$

increase in plasma glucose levels through the attenuation of glucose absorption.

GLP-1RAs inhibit gastric emptying [9, 10], which likely contributes to the deceleration of glucose absorption and to the consequent amelioration of postprandial hyperglycemia induced by these drugs. Continuous intravenous infusion of exenatide was recently shown to impair the absorption of glucose administered via an intraduodenal tube [22], indicating that exenatide also attenuates glucose absorption in a manner independent of the inhibition of gastric motility. Under this condition, serum insulin levels were found to be lower during the early phase and higher during the late phase of the intraduodenal glucose challenge test compared with those under the control condition [22]. Our results now suggest that exenatide decelerates glucose absorption even when administered via the clinical route (subcutaneous injection) and at a clinically relevant dose. Given that liraglutide did not decelerate the peak of elevated plasma glucose, it is possible that the effect on glucose absorption of liraglutide is weaker than that of exenatide. Although the AUC values for plasma glucose concentration during the OGTT were similar after the administration of exenatide or liraglutide, the AUC for serum insulin level was smaller than the control value only after the administration of exenatide, indicating that exenatide exerts an insulin-sparing effect in the postprandial state.

There are several limitations to our study. First, we recruited subjects with NGT to avoid secondary effects of the treatment of diabetes. It remains to be determined whether the two GLP-1RAs have similar differential effects on postprandial glucose disposal in individuals with type 2 diabetes mellitus. Exenatide impaired the absorption of glucose administered via an intraduodenal tube in both individuals with type 2 diabetes and healthy volunteers [22]. Second, although the design of our study, in which the same subjects underwent the three OGTTs within a relatively short period, should have helped to mitigate the influence of interindividual variability, the number of subjects was relatively small. Finally, given that our study was based on a single administration of each drug, we could not evaluate the influence of tachyphylaxis on the gastrointestinal tract, which is thought to occur during long-term treatment with GLP-1RAs [19] and should be taken into account in clinical usage of this class of drugs.

In summary, we have shown that exenatide markedly decelerated the increase in plasma glucose and serum insulin levels during an OGTT likely through inhibition of glucose absorption. Exenatide, but not liraglutide, reduced the AUC for serum insulin level whereas both drugs similarly lowered the AUC for plasma glucose concentration, indicative of a greater insulin-sparing effect of exenatide. It is thus possible that exenatide is a better option for patients who exhibit substantial postprandial hyperglycemia with hyperinsulinemia. It remains to be determined whether the findings of the present study are applicable to other short- and long-acting GLP-1RAs.

Acknowledgements We thank Yuki Nishimoto, Kei Yoshino, Takehito Takeuchi, Hiroshi Miura, and Yasushi Nakagawa for assistance with data collection.

Compliance with ethical standards

Conflict of interest T.M., K.S., and W.O. have received lecture fees from Novo Nordisk; Y.H., K.S., and W.O. have received lecture fees

from Eli Lilly; and Y.H. and W.O. have received lecture fees from Astra Zeneca. W.O. has received research support from Novo Nordisk, Eli Lilly, and Astra Zeneca.

Ethical approval This exploratory, open-label, single-center study was approved by the ethics committee of Kobe University Graduate School of Medicine (approval no. 230021), conforms to the provisions of the Declaration of Helsinki, and is registered in the University Hospital Medical Information Network (UMIN000006858).

Informed consent All the individuals provided written informed consent to participation in the study.

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