Incretin Hormone and Insulin Responses to Oral *Versus* Intravenous Lipid Administration in Humans

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Context: The incretin effect is responsible for the higher insulin response to oral glucose than to iv glucose at matching glucose levels. It is not known whether this effect is restricted to glucose only.

Objective: The aim of the study was to examine whether insulin and incretin hormone responses are higher after oral *vs*. iv challenge of a lipid emulsion with matching triglyceride levels in humans.

Design, Settings, and Participants: A lipid emulsion (Intralipid) was administered orally (3 ml/kg) or iv (variable infusion rates to match triglyceride levels after oral ingestion) in healthy lean males (n = 12) at a University Clinical Research Unit. Samples were collected during 300 min.

Main Outcome Measures: We measured the suprabasal area under the curve for insulin, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and the insulin secretory rate based on C-peptide levels by deconvolution.

Results: Triglyceride levels increased similarly after oral and iv lipid; also, glucose and free fatty acid levels were similar in the two tests. Oral lipid elicited a clear insulin and C-peptide response, whereas no insulin or C-peptide responses were observed during iv lipid. Total and intact GIP and GLP-1 levels both increased after oral lipid administration but were not significantly altered after iv lipid.

Conclusions: At matching triglyceride levels and with no difference in glucose and free fatty acid levels, oral lipid ingestion but not iv lipid infusion elicits a clear insulin response in association with increased GIP and GLP-1 concentrations. This may suggest that the incretin hormones also contribute to the islet response to noncarbohydrate nutrients. **(*J Clin Endocrinol Metab* 96: 2519–2524, 2011)**

The insulin response is higher after oral glucose than during iv glucose infusion at similar glucose levels (1). This is attributed to the incretin effect by the two incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), both released from enteroendocrine cells located in the gut wall in response to nutrients entering the bowel. These incretin hormones exert their insulinotropic effect by potentiating glucose-induced insulin secretion from the β-cells of the pancreas (2). The incretin effect accounts for up to 70–80% of the insulin secreted after oral glucose (3). However, whether the incretin hormones are also of importance after nonglucose ingestion has not been established. It is known that lipid ingestion is associated with an insulin response (4, 5), which may be due to the absorbed lipids directly stimulating insulin secretion (6). However, lipid ingestion is also known to elicit a release of the incretin hormones (4), and incretin hormones may, therefore, contribute to the insulin response to lipid ingestion. To examine this possibility, we have compared insulin

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Abbreviations: AUC, Area under the curve; FFA, free fatty acid; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GPR, G protein-coupled receptor; ISR, insulin secretion rate.

secretion and the GIP and GLP-1 responses to oral ingestion *vs.* iv infusion of a lipid emulsion at matching triglyceride levels in healthy humans. The lipid emulsion (Intralipid) contained soybean oil long-chain triglycerides (53% linoleic acid, 23% oleic acid, and 11% palmitic acid) (7). The iv infusion rate of the lipid emulsion was selected to match the triglyceride levels after oral lipid emulsion administration.

Subjects and Methods

Subjects

We examined 12 male volunteers with body mass index of 20–28 kg/m^2 (mean ± SD, 21.9 ± 2.0 kg/m^2) and an age range of 20–28 yr (mean ± SD, 23.2 ± 2.2 yr) who had no history of diabetes or gastrointestinal diseases and who did not take any medication. The study was approved by the Regional Ethics Committee of Lund, Sweden, and all subjects gave written informed consent before entry into the study.

Study protocol

The subjects came to our clinical research unit on three different occasions (visits A, B, and C) at 0800 h after an overnight fast (no food after 2200 h) and were provided with an antecubital vein catheter. At visit A, two baseline samples were taken, and then subjects ingested 3 ml/kg (equivalent to 6 kcal/kg) of a lipid emulsion (300 mg/ml Intralipid; Fresenius Kabi AB, Uppsala, Sweden) at t = 0, after which samples were taken at specified time points as indicated in Figs. 1–3. At visit B, the lipid emulsion was infused at three different rates in each individual to tailor the infusion rate for each individual to match the triglyceride levels after oral lipid ingestion. Two different protocols were used. In the first eight subjects, the lipid emulsion was infused in the stepwise increases of 0.5, 1.0, and 1.5 ml/min. The highest infusion rate was consistently found to result in triglyceride levels markedly exceeding that of the lipid ingestion and, therefore, in the four remaining subjects, a lower infusion rate step-wise protocol was used in which the lipid emulsion was infused at 0.25, 0.5, and 1.0 ml/min. In all individuals, the range of triglyceride concentrations during the iv infusion covered the range of triglyceride levels after oral lipid ingestion, and therefore, it was possible to design an appropriate infusion protocol for the final visit C to match the triglyceride levels observed at visit A, after the oral lipid ingestion. Thus, for each individual, the slope of the increase in triglyceride levels during the lipid infusions at visit B was calculated. This slope was compared with the change in triglyceride levels after oral lipid in each individual to estimate the infusion rate required during an iv intralipid to copy the individual triglyceride curves as obtained from visit A. Hence, the triglyceride levels obtained from the oral ingestion of lipid were used as templates to individually tailor the infusion rate at visit C. At visit C, two baseline samples were taken, and the participants were given 3 ml/kg of water together with iv lipid emulsion to match the triglyceride curves from visit A. The individual infusions of lipid emulsion started at the time point when an increase in triglyceride levels was observed after oral intralipid ingestion, *i.e.* at different time points in different individuals (ranging from t = 0 to t = 110 min). Similarly, infusions were stopped at different time points ranging from t = 240 (n = 5) or t = 300 min (n = 7) according to decline in triglyceride levels after oral intralipid. The total infused dose of the lipid emulsion ranged from 42 to 136 ml (mean, 81 ml or 1.2 ml/kg). Additional blood samples were taken throughout the 300-min study period. The blood samples from visits A and C were analyzed for triglycerides, free fatty acid (FFA), glucose, insulin, C-peptide, and intact and total GLP-1 and GIP.

Analyses

Blood samples, collected into chilled tubes containing EDTA (7.4 mmol/liter) and aprotinin (500 KIU/ml; Novo Nordisk, Bagsvaerd, Denmark), were immediately centrifuged at 4 C, and plasma was frozen at −20 C. Glucose was measured using the glucose oxidase method. Triglyceride and FFA levels were analyzed with colorimetric assays (Wako Chemicals, Neuss, Germany). Insulin levels were analyzed using Luminex xMAP Multiplexing technology (Millipore Corp., Billerica, MA), and glucagon and C-peptide were analyzed using double antibody RIA (Linco Research, St. Charles, MO). Blood samples for determining GIP and GLP-1 were collected into chilled tubes containing EDTA and aprotinin with addition of diprotin A (0.1 mmol/liter; Bachem, Bubendorf, Switzerland). GLP-1 concentrations were determined with RIA, using an N-terminally specific guinea pig anti-GLP-1 antiserum (Linco Research) for intact GLP-1 and a C-terminally directed antiserum (code no. 89390) for total GLP-1 (8). For intact GIP, an antiserum (code no. 98171), which is specific for the intact N terminus of GIP, was used. Total GIP was analyzed using a newly developed assay, employing a C-terminally directed antiserum (code no. 80867) raised in rabbits immunized with a C-terminal fragment of GIP [GIP (28–42)] conjugated to keyhole limpet hemocyanin via its N terminus. This assay has broadly the same specificity and characteristics as the previously published assay using antiserum R65 (9), recognizing equally both intact GIP (1–42) and the primary metabolite, GIP (3–42).

Calculations and statistics

Insulin secretion rate (ISR) was calculated from the C-peptide concentrations by deconvolution (10). Means ± SEM are shown. For all variables, incremental areas under curves (AUC) after meal ingestion were calculated by the trapezoid rule during the initial 30 min and the entire 300-min period. Incremental concentrations were obtained by subtracting baseline values; therefore, a positive AUC represents an increment above baseline, whereas a negative AUC indicates a reduction below baseline. Nonparametric paired *t* test was used for estimation of differences in response to oral *vs.* iv ingestion. P values < 0.05 were considered significant.

Results

Triglycerides, FFA, and glucose (Fig. 1)

Triglyceride levels were well matched after the oral ingestion at visit A and during the variable lipid emulsion infusion at visit C. There were no significant differences in regard to FFA or glucose between the two challenges.

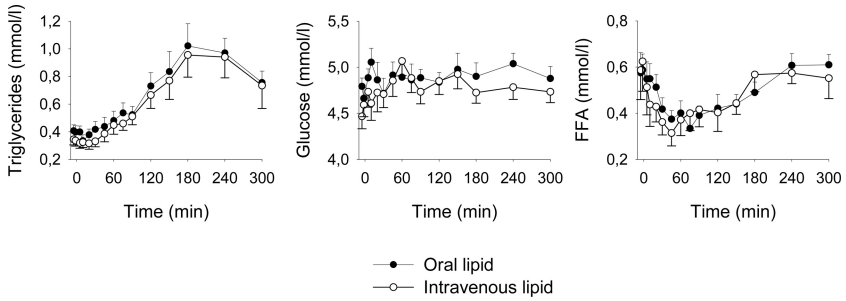

FIG. 1. Plasma triglycerides, glucose, and FFA after oral ingestion of 3 ml Intralipid/kg and after iv Intralipid infusion to match the triglyceride levels after oral challenge in healthy volunteers (n = 12). There were no significant differences in triglycerides, glucose, or FFA levels between the two tests. Means ± SEM are shown.

Insulin, C-peptide, ISR, and glucagon (Fig. 2 and Table 1)

After the oral lipid challenge (visit A), insulin levels rose during the first 20 min and then remained at an elevated level throughout the entire 300-min study period. In contrast, during the iv infusion with matching triglyceride levels, insulin levels remained at baseline and did not change significantly, and accordingly, the 300-min $AUC_{insulin}$ was higher after the oral than after the iv challenge. Similarly, C-peptide levels increased after the oral lipid ingestion but did not change significantly during the iv lipid infusion. This resulted in a greater $AUC_{C\text{-}peptide}$ during the oral than during the iv lipid challenge. ISR rapidly rose after oral lipid to a peak after 30 min, after which it decreased but remained elevated throughout the study period. In contrast, no change in ISR was seen after iv lipid; in fact, ISR did not exceed baseline levels during the iv lipid administration. This was reflected in a higher incremental mean ISR for the oral challenge than for the iv challenge, both for the initial 30 min (22.1 ± 6.0 *vs.* −1.2 ± 3.7 pmol/min/m^2; $P = 0.008$) and for the entire 300 min (12.7 ± 3.7 *vs.* 2.0 ± 4.1 pmol/min/m^2; $P = 0.041$). Figure 2 and Table 1 show the glucagon data. Glucagon tended to be higher during the first 30 min after oral ingestion, but the difference did not reach significance. Glucagon levels did not change significantly after iv lipid.

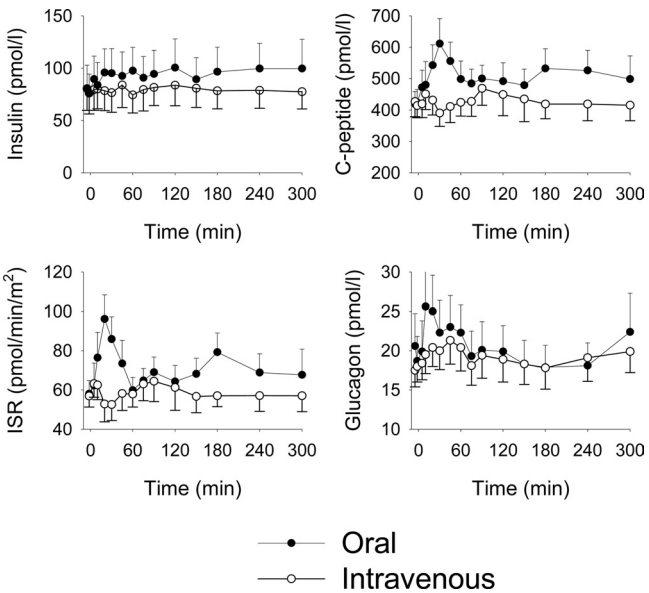

FIG. 2. Insulin, C-peptide, the ISR, and glucagon after oral ingestion of 3 ml Intralipid/kg and after iv Intralipid infusion to match the triglyceride levels after oral challenge in healthy volunteers (n = 12). Statistical analysis was performed using the 30- and 300-min AUC for the parameters as shown in Table 1. Means ± SEM are shown.

Incretin hormones (Fig. 3 and Table 1)

After oral lipid, intact and total GIP increased to a peak after approximately 60 min, after which they remained elevated for another 2 h, whereas GIP concentrations were unchanged after iv lipid. The later peak after the oral lipid meant that $AUC_{intact\ GIP}$ for the first 30 min (59 ± 57 pmol/liter × min) did not differ significantly from that after iv lipid (−7 ± 29 pmol/liter × min; $P = 0.35$), whereas $AUC_{intact\ GIP}$ was significantly higher after oral lipid for the entire 300 min (2.9 ± 0.4 nmol/liter × min) than after iv lipid (0.25 ± 0.10 nmol/liter × min; $P = 0.002$). Similarly, $AUC_{total\ GIP}$ for the first 30 min (137 ± 94 pmol/liter × min) did not differ significantly from that after iv lipid (−24 ± 77 pmol/liter × min; $P = 0.18$), whereas $AUC_{total\ GIP}$ was significantly higher after oral lipid for the entire 300 min (9.2 ± 0.78 nmol/liter × min) than after iv lipid (−0.25 ± 0.42 nmol/liter × min; $P = 0.002$). Intact and total GLP-1 also rose rapidly to a peak 30 min after oral lipid ingestion, after which they decreased, although the levels remained above baseline during the length of the study. This was evident from a higher $AUC_{intact\ GLP\text{-}1}$ after oral lipid than during iv lipid for both the first 30 min (81.4 ± 26.1 *vs.* −1.6 ± 2.3 pmol/liter × min; $P = 0.002$) and for the entire 300 min (1.28 ± 0.20 *vs.* 0.24 ± 0.08 nmol/liter × min; $P = 0.002$). Similarly, $AUC_{total\ GLP\text{-}1}$ was higher after oral lipid than during iv lipid, both during the initial 30 min (191 ± 112 *vs.* −50 ± 25 pmol/liter × min; $P = 0.026$) and during the entire 300 min (4.0 ± 0.67 *vs.* 0.12 ± 0.42 nmol/liter × min; $P = 0.005$).

Discussion

In this study, we show that oral lipid administration was associated with increased insulin secretion compared with iv lipid administration. Because triglyceride levels were matched on the two experimental days and glucose and

TABLE 1. Suprabasal AUC for insulin, C-peptide, and intact and total GIP and GLP-1 and the incremental ISR for 30 and 300 min after oral lipid ingestion and during iv lipid infusion to match the triglyceride levels after oral challenge in healthy humans (n = 12)

	Oral lipid	Intravenous lipid	*P*
30 min			
$AUC_{Insulin}$ (pmol/liter × min)	261 ± 72	13 ± 70	0.041
$AUC_{C\text{-}peptide}$ (pmol/liter × min)	995 ± 303	204 ± 119	0.028
Incremental ISR (pmol/min/m^2)	22.1 ± 6.0	−1.2 ± 3.7	0.008
$AUC_{glucagon}$ (pmol/liter × min)	83.5 ± 40.7	55.6 ± 20.3	NS (0.61)
$AUC_{intact\ GIP}$ (pmol/liter × min)	59 ± 57	−7 ± 29	NS (0.35)
$AUC_{total\ GIP}$ (pmol/liter × min)	137 ± 94	−24 ± 77	NS (0.18)
$AUC_{intact\ GLP\text{-}1}$ (pmol/liter × min)	81.4 ± 26.1	−1.6 ± 2.3	0.002
$AUC_{total\ GLP\text{-}1}$ (pmol/liter × min)	191 ± 112	−50 ± 25	0.026
300 min			
$AUC_{Insulin}$ (nmol/liter × min)	9.1 ± 2.1	4.9 ± 1.1	0.023
$AUC_{C\text{-}peptide}$ (nmol/liter × min)	28.0 ± 6.6	18.7 ± 4.2	0.050
Incremental ISR (pmol/min/m^2)	12.7 ± 3.6	2.0 ± 4.1	0.041
$AUC_{glucagon}$ (nmol/liter × min)	1.3 ± 0.8	1.5 ± 1.3	NS (0.70)
$AUC_{intact\ GIP}$ (nmol/liter × min)	2.9 ± 0.4	0.25 ± 0.10	0.002
$AUC_{total\ GIP}$ (nmol/liter × min)	9.2 ± 0.78	−0.25 ± 0.42	0.002
$AUC_{intact\ GLP\text{-}1}$ (nmol/liter × min)	1.28 ± 0.20	0.24 ± 0.08	0.002
$AUC_{total\ GLP\text{-}1}$ (nmol/liter × min)	4.0 ± 0.67	0.12 ± 0.42	0.005

Means ± SEM are shown. *P* indicates the probability level of random difference between the two tests. NS, Not significant.

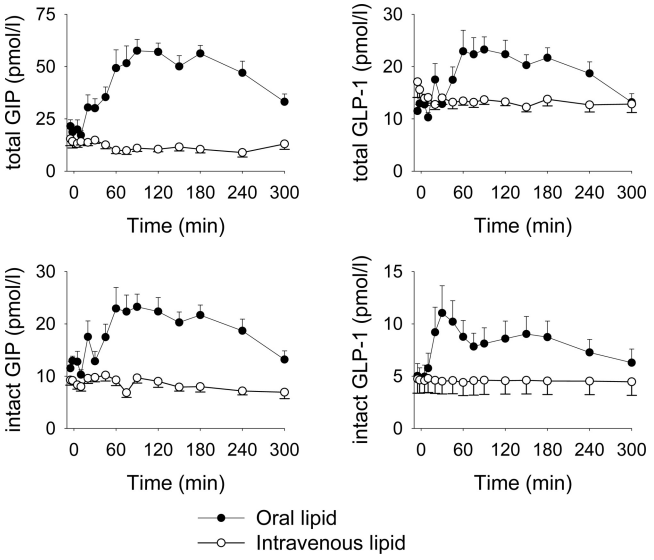

FIG. 3. Plasma total and intact GIP (*left*) and GLP-1 (*right*) after oral ingestion of 3 ml Intralipid/kg and after iv Intralipid infusion to match the triglyceride levels after oral challenge in healthy volunteers (n = 12). Statistical analysis was performed using the 30- and 300-min AUC for the parameters as shown in Table 1. Means ± SEM are shown.

FFA levels did not differ, it is unlikely that the difference in the insulin responses to the two challenges is related to plasma triglyceride, FFA, or glucose. The results are thus similar to previous reports after oral *vs.* iv glucose administration with matched glucose levels (3). This incretin effect after oral glucose has been attributed to GIP and GLP-1, because: 1) both incretin hormone levels are clearly increased by oral, but not by iv, glucose (3); 2) both GIP and GLP-1 augment glucose-stimulated insulin secretion (11, 12); and 3) the incretin effect is impaired by antagonists to GIP and GLP-1 (13–15) and in incretin hormone receptor knockout animals (15).

In the present study, we also found that oral ingestion but not iv administration of a lipid emulsion increased GIP and GLP-1 secretion, as reflected by increased concentrations of total GIP and total GLP-1. It has previously been demonstrated in several studies that oral lipids stimulate GIP and GLP-1 secretion (4, 16), and the mechanisms underlying lipid-stimulated incretin hormone secretion are starting to emerge. Thus, fatty acids with longer chain length appear to have a more pronounced effect (17), and unsaturated fatty acids seem more potent than saturated fatty acids (18). Digestion of the fatty acids seems important for their ability to cause incretin hormone release because the lipase inhibitor, orlistat, diminished GIP and GLP-1 responses to fat ingestion (19–21). At the enteroendocrine cellular level, G protein-coupled receptors (GPR119, GPR40, and/or GPR120) might serve as sensors for the ingested fat in mediating the incretin hormone release (22–24), although other mechanisms may also be involved (25). The crucial point in the present study is whether the increased incretin secretion evoked by the oral lipids, which was true for both total and intact concentrations of the hormones (intact incretins being the active form of the hormones), is responsible for the increased insulin secretion—in other words, whether lipids evoke a similar incretin effect as is well known for glucose. In support of this notion, it has previously been shown that both GIP and GLP-1 in physiological concentrations increase insulin secretion also at euglycemia (12, 26). Antagonists to GLP-1 and GIP receptor activation may clarify this point.

Lipid may stimulate insulin secretion through a direct action on the β-cells. It has thus been known for a long time that fatty acids, as metabolic substrates, stimulate

β-cell secretion through fuel oxidation in mitochondria (27). Fatty acids may also stimulate the generation of specific signals in the β-cells, such as acyl coenzyme A, which in turn stimulate insulin secretion (27). Finally, fatty acids may also through an extracellular action stimulate β cell GPR, mainly GPR40, which may result in stimulated insulin secretion (28). In our study, however, triglyceride and FFA levels were similar after oral *vs.* iv lipid administration, making direct actions of fat molecules on β-cell function less likely to explain the different degree of stimulation of insulin secretion.

Finally, another possibility for the oral lipid ingestion to stimulate islet function as distinct from the iv lipid infusion is through an activation of the autonomic nervous system by oral lipids because the autonomic nervous system contributes to insulin secretion after food ingestion (29). This would be supported by a recent suggestion that dietary fat activates vagal efferent nerves in the upper intestine in rats (30). However, a study examining a potential activation of the autonomic nervous system after fat ingestion did not find any evidence for this in humans (31). Nevertheless, this possibility needs to be examined in more detail.

It is noteworthy in this study that circulating glucose was not reduced by oral lipid, in view of the stimulated insulin secretion and the slight elevation of insulin levels. The reason for this is not known but could be explained by a simultaneous increase in glucagon. In the present study, there was a trend toward increased glucagon levels during oral lipid, although this did not reach statistical significance. In addition, oral lipid absorption may have produced higher hepatic levels of gluconeogenic substrates, which could have counteracted the suppressive effects of the slight hyperinsulinemia. It is also noteworthy that FFA levels declined during the initial hour after both oral and iv lipid administration. This is not readily explained by insulin because insulin levels increased only after oral lipid, although portal insulin levels were not determined and might be altered after iv lipid, resulting in a rapid inhibition of lipolysis. The regulation is, however, complex, and a slight reduction in FFA levels was previously observed after water ingestion without any nutrients (4). The mechanism behind the transient reduction in FFA therefore needs further investigation by more careful analyses of lipid turnover.

In conclusion, we have found that oral ingestion of lipids in contrast to iv lipid infusion stimulates incretin secretion, which is associated with an increased insulin response despite similar levels of glucose, FFA, and triglycerides. We suggest that incretin hormones may contribute to the higher insulin secretion after oral *vs.* iv lipid administration, although other mechanisms may also have contributed.

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