Postprandial lipaemia is associated with increased plasma glucagon levels and inadequate glucose-induced suppression of glucagon secretion in healthy men

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Background and Aims

A great wealth of studies has been published on the effect of lipids on insulin sensitivity and insulin secretion (1-2). The role of plasma lipids in the regulation of glucagon secretion, however, has received much less attention. Previous studies on the effect of lipids on glucagon secretion have led to conflicting results (3-4). Abnormalities in glucagon secretion have been implicated in the development of type 2 diabetes for a long time. Some thirty years ago, Unger and Orci proposed that in addition to absolute or relative insulin deficiency, an elevated plasma glucagon level plays a key role in the pathogenesis of diabetes (5). More recent studies revealed that in addition to elevated plasma glucagon levels, reduced glucose-induced supression of glucagon secretion represents another feature of insulin resistant states (6-7). We have recently demonstrated that postprandial lipemia through elevation of triglyceride-rich lipoproteins induces insulin resistance in vitro in cultured skeletal muscle cells and in vivo in healthy male subjects independently of NEFA levels (8). The aim of the present investigation was to study the effect of postprandial lipemia on plasma glucagon levels as well as on glucose-induced suppression of glucagon secretion in vivo in healthy men. Our study design enabled us to assess the role of plasma NEFA levels in the regulation of glucagon secretion.

Materials and Methods

In a crossover study including 7 healthy volunteers, two experiments using two fat-enriched meals were performed on each volunteer. Meal 1 was designed to raise plasma levels of both TGRLs and NEFAs, and Meal 2 to raise TGRLs only. Two consecutive IVGTTs were performed, one postabsorptively and the other postprandially, i.e. 3 h after meal consumption. Glucose-induced suppression of glucagon concentration was calculated as the difference between nadir and basal glucagon levels (GISG) and as the area of infrabasal glucagon concentration during 0 to 60 min of the IVGTTs (AGISG), respectively.

Results

Plasma glucagon levels measured immediately before the IVGTTs rose from 80.7±18.2 postabsorptively to 104.2±17.5 ng/l postprandially with Meal 1 (P=0.017) and from 86.1±16.2 to 106.8±30.1 ng/l with Meal 2 (P=0.028). Both GISG and AGISG did not differ between postabsorptive and postprandial states with either of the two meals. However, as compared to their respective postabsorptive values, postprandial GISG and AGISG were inadequate since the acute insulin response to glucose (AIR) was approximately 2-fold higher during postprandial lipemia than postabsorptively with either meal.

Conclusion

Since Meals 1 and 2 induced comparable changes in postprandial glucagon kinetics, we conclude that these changes are caused by elevated postprandial levels of TGRLs independently of plasma NEFA levels or, alternatively, through insulin resistance induced by TGRLs.

References:
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2. Madison LL, Seyffert WA, Jr., Unger RH, Barker B: Effect on plasma free fatty acids on plasma glucagon and serum insulin concentrations. Metabolism 17:301-304, 1968
3. Dumonteil E, Magnan C, Ritz-Laser B, Ktorza A, Meda P, Philippe J: Glucose regulates proinsulin and prosomatostatin but not proglucagon messenger ribonucleic acid levels in rat pancreatic islets. Endocrinology 141:174-180, 2000
4. Fujiwara K, Maekawa F, Dezaki K, Nakata M, Yashiro T, Yada T: Oleic acid glucose-independently stimulates glucagon secretion by increasing cytoplasmic Ca2+ via ER Ca2+ release and Ca2+ influx in the rat islet α-cells. Endocrinology, 2007
5. Unger RH, Orci L: The essential role of glucagon in the pathogenesis of diabetes mellitus. Lancet 1:14-16, 1975
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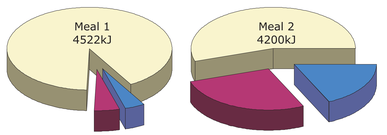
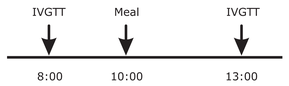
7. Ahren B, Larsson H: Impaired glucose tolerance (IGT) is associated with reduced insulin-induced suppression of glucagon concentrations. Diabetologia 44:1998-2003, 2001
8. Pedrini MT, Niederwanger A, Kranebitter M, Tautermann C, Ciardi C, Tatarczyk T, Patsch JR: Postprandial lipaemia induces an acute decrease of insulin sensitivity in healthy men independently of plasma NEFA levels. Diabetologia 49:1612-1618, 2006

Experimental Design



Meal 1
350 ml whipped cream
10 g cacao powder
1 ml artificial sweetener

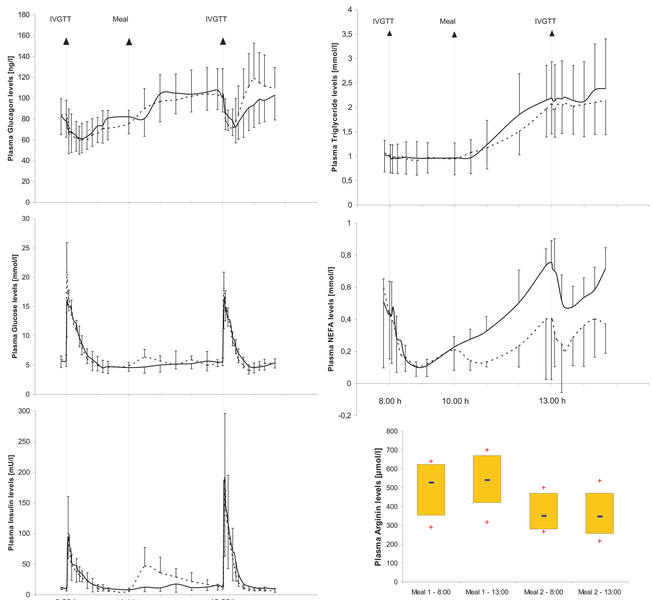
Meal 2
192 ml whipped cream
10 g cacao powder
1 ml artificial sweetener
100 g low-fat milk powder
10 g maltodextrin
160 ml water



IVGG
An IVGTT was performed postabsorptively at 08.00 and postprandially at 13.00 using the protocol described by Bergman with minor modifications.

Bergman RN, Ider YZ, Bowden CR, Cobelli C (1979) Quantitative estimation of insulin sensitivity. Am J Physiol 236:E667-E677

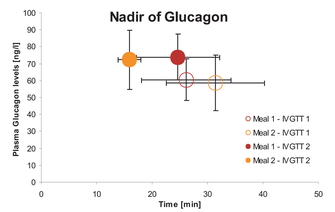
Plasma levels

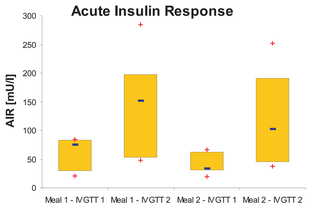


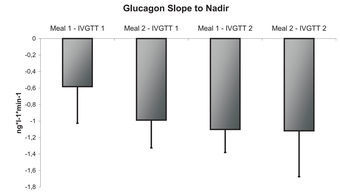
Mean±SD plasma profiles of glucagon, glucose, insulin, triglycerides and NEFAs on the days of the experiments. Intravenous glucose boli and Meals were provided at the times indicated. Continuous line: Meal 1; broken line: Meal 2

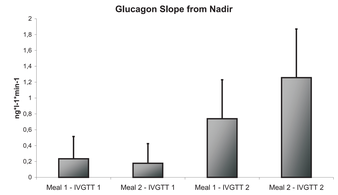
Lower right panel: Plasma Arginin levels determined by the method of sakaguchi with minor modifications in an ELISA-Reader. (Median±25%, minimum and maximum)

Calculated Data

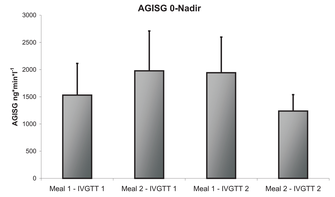


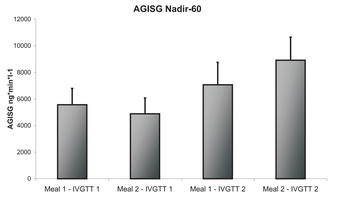






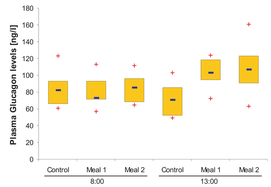
The downward slope to Nadir showed no statistical difference. By contrast, the upward slope was steeper in the postprandial state than postabsorptively with Meal 2 whereas with Meal 1 a statistical difference was not reached.





AGISG showed no difference between postabsorptive and postprandial states with either of the two meals over the whole time of the IVGTT. Additionally, AGISG was considered in parts, seperated by the nadir, revealing no difference.

Control



Missing Data / further Work
- GIP
- GLP1

Plasma Glucagon levels prior to each ivGTT. Data from a control experiment without a meal is shown. Contrary to either of the two meals, the control experiment showed decreased plasma glucagon levels at 13:00. (Median±25%, minimum and maximum)