Novel Insights Into the Regulation of Postprandial Lipemia by Glucagon-Like Peptides: Significance for Diabetes

Gerald F. Watts and Dick C. Chan

Glucagon-like peptide-1 (GLP-1) and GLP-2 are peptide hormones encoded by the proglucagon gene that are cosecreted in equimolar amounts from enteroendocrine L-cells of the intestine in response to nutrients, primarily carbohydrates and fats (1). Most is known about GLP-1, which stimulates the pancreatic secretion of insulin in a glucose-dependent manner while inhibiting the secretion of glucagon, gastric emptying, and satiety. This tonic effect maintains glucose homeostasis and is chiefly controlled by the enzymatic degradation of the peptide in the circulation by dipeptidyl peptidase-4 (DPP-4) (2). This has led to the development of new therapies for diabetes, including GLP-1 receptor analogs and inhibitors of DPP-4 (3).

By contrast to GLP-1, the physiological and therapeutic roles of GLP-2 are less clear. GLP-2 inhibits postprandial gastric motility/secretion and intestinal hexose transport and has a trophic effect on intestinal epithelium that implies a specific role in intestinal repair processes (4). GLP-2 may antagonize the effects of GLP-1 on glucose homeostasis by enhancing the pancreatic release of glucagon but could also have a cooperative, short-term effect on satiety. Its biological actions are mediated by a specific G-protein–coupled receptor.

Recent studies have also suggested that GLP-1 and possibly GLP-2 may be involved in regulating fat absorption and chylomicron biogenesis (5–8), pointing to a regulatory role in postprandial lipid metabolism. This has implications for atherogenesis and vascular disease in diabetes and insulin-resistant states. GLP-1 may improve while GLP-2 may aggravate postprandial lipemia, but exactly how these biological actions are intertwined in health and disease remains unclear.

In this issue of *Diabetes*, Adeli and colleagues (9) report a well-designed set of experiments investigating the time-dependent effects of GLP-1, GLP-2, and the coinfusions of both gut peptides on postprandial chylomicron metabolism in chow-fed and fructose-fed male Syrian golden hamsters. An olive oil load was administered via oral gavage and intravenous dosing regimens were used that achieved physiological concentrations of the peptides. Poloxamer was administered to protect newly formed chylomicrons from catabolism and enable estimation of their secretion. The short-term (30 min) intravenous infusion of GLP-1 reduced whereas GLP-2 increased postprandial apolipoprotein (apo) B48 and triglyceride concentrations and chylomicron particle secretion in the chow-fed hamsters. The acute coinfusion of both peptides resulted in a net increase in these indices of postprandial lipemia, but this was reversed to a dominant effect of GLP-1 in experiments that sampled over 2 and 6 h and after administration of a DPP-4 inhibitor. With the more prolonged infusions, GLP-1 had a dominant effect over GLP-2 in decreasing chylomicron particle secretion. The acute inhibitory effects of GLP-1 on chylomicron secretion were augmented by including glucose in the oral fat load. In the fructose-fed hamsters, postprandial lipemia was enhanced compared with the chow model, with a more pronounced response to GLP-2 and impaired response to GLP-1.

How valid are these studies? The Syrian golden hamster is an accepted model for studying glucose and lipid metabolism because the fructose-fed state reflects diet-induced insulin resistance and dyslipidemia (10); however, only male animals were studied. The experiments were designed to simulate the acute and prolonged physiological responses of the GLPs to a fat load. However, the oral challenge of fat alone does not represent a mixed meal, noting that glucose has a major modulating effect on the release of both GLPs and insulin. Measurement of chylomicron particle turnover was based on an indirect method in which particle catabolism was artificially blocked and secretion estimated using noncompartmental analysis. Chylomicron biogenesis integrates a complex series of processes and is most appropriately studied using endogenous labeling with tracers and multicompartmental modeling (11). The effects of the GLPs on the catabolism of postprandial chylomicrons cannot be strictly excluded in this experimental model.

The findings are physiologically significant, however. After initial luminal hydrolysis of dietary triglycerides, chylomicron biogenesis by the enterocyte involves the reesterification of fatty acids and sn-2-monoacylglycerol by diglyceride acyltransferase followed by stepwise lipidation of apoB48 by microsomal triglyceride transfer protein to form the mature chylomicron particle (12). Under physiological conditions, insulin partially inhibits these processes by reducing lipogenesis in the enterocyte, enhancing degradation of intracellular apoB48, and decreasing the expression of microsomal triglyceride transfer protein (13,14). GLP-1 augments these effects via its incretin response, but GLP-2 appears to antagonize them by increasing lipid absorption via CD36/fatty acid translocase (7). The current study proffers a temporal dimension to these events: release of GLP-1 initially slows chylomicron biogenesis, but its duration of action is curtailed by more rapid catabolism by DPP-4 relative to GLP-2, which in turns facilitates
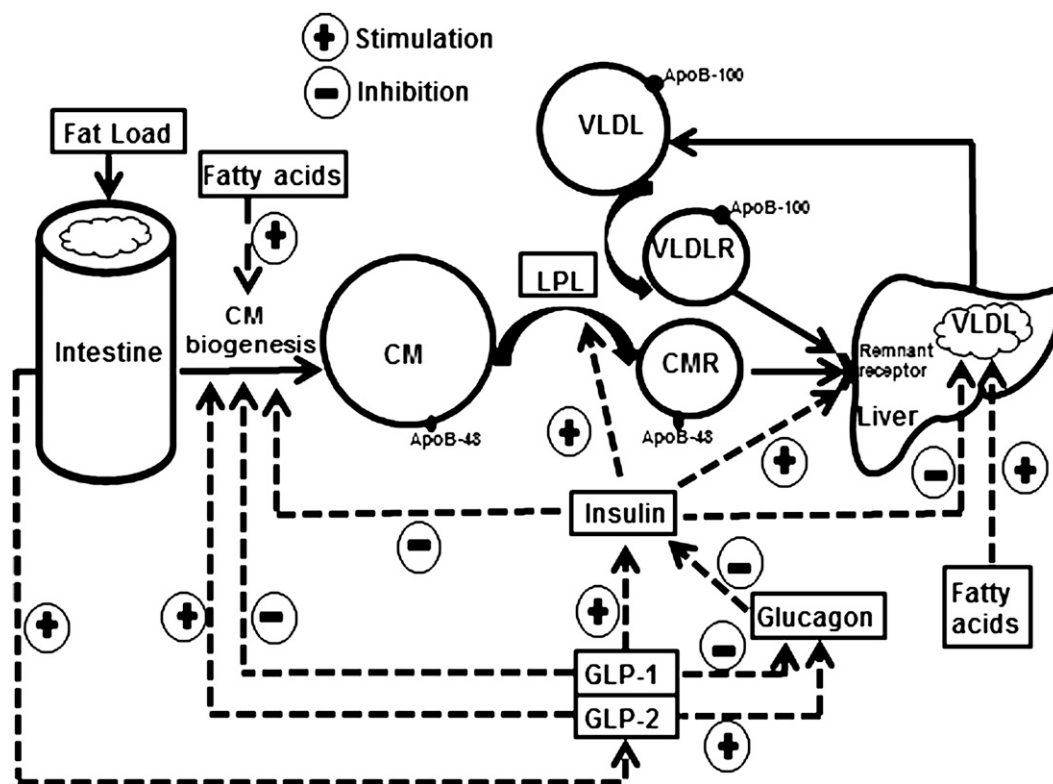
FIG. 1. Potential role of GLP-1, GLP-2, insulin, and glucagon in regulating the postprandial metabolism of chylomicron and VLDL particles. GLP-1 and GLP-2 have opposing effects on chylomicron metabolism in response to dietary fat load. GLP-1 inhibits intestinal chylomicron biogenesis, stimulates insulin secretion, and suppresses glucagon secretion, whereas GLP-2 stimulates chylomicron biogenesis and glucagon secretion. Under normal physiological conditions, insulin inhibits chylomicron and VLDL synthesis and secretion but stimulates lipoprotein lipase LPL and hepatic receptor activities, thereby enhancing the removal of chylomicron and VLDL remnant particles by liver. Postprandial dyslipidemia in type 2 diabetes may result from an imbalance in the secretion and catabolism of GLP-1 and GLP-2, together with the effect of insulin resistance and increased availability of fatty acids to enterocyte and hepatocyte. CM, chylomicron; CMR: chylomicron remnant; LPL, lipoprotein lipase; VLDLR, very-low-density lipoprotein remnant.

biogenesis over a longer period. The physiological co-ordination of these actions may be most relevant to the so called "ileal brake" phenomenon (15), whereby GLP-1 increases the delivery of fat to the ileum thereby activating a satiety signal and GLP-2 acts to complete the absorption of fat in the proximal intestine. Whether increased absorption of fat by GLP-2 also mediates satiety remains unclear. Insulin modulates the impact of GLPs on chylomicron secretion but critically also accelerates the turnover of chylomicron particles by stimulating their catabolism by lipoprotein lipase and hepatic receptors (12,16). The relative effects of GLP-1 and GLP-2 on gastric emptying, intestinal motility, and lymphatic and splanchnic blood flow as well VLDL and apoC3 metabolism and their consequence for postprandial chylomicron metabolism remain to be investigated.

The pathophysiological significance of this study relates to the mechanism of increased production of chylomicrons in insulin resistance and type 2 diabetes (12,16,17). The roles of impaired insulin signaling, inflammation, increased availability of fatty acids, and enhanced lipogenesis in accelerating chylomicron secretion by enterocytes have been well emphasized. Enterocytic resistance to the direct effects of GLP-1, as well as increased sensitivity to GLP-2, may augment postprandial lipemia in insulin resistance by increasing chylomicron biogenesis. Figure 1 summarizes the potential role of GLP-1, GLP-2, insulin, and glucagon in regulating the postprandial metabolism of chylomicron and VLDL particles (FIG. 1).

These findings also further explain the mechanism of action of DPP-4 inhibitors in improving dyslipidemia by sustaining the action of GLP-1 relative to GLP-2 (3). Whether specific inhibition of GLP-2 can mitigate postprandial dyslipidemia remains untested. Activation of GLP-2 may conversely be useful in treating injury or dysfunction of intestinal mucosal epithelium, including ischemic damage and short bowel syndromes (18). Specific regulation of GLP-mediated mechanisms may have less potential for managing of diabetic dyslipidemia than improvement in glycemic control with more rigorous lifestyle interventions and use of statins and triglyceride regulating agents, including fibrates, n-3 fatty acids, and niacin (19).

Beyond beneficial effects atherogenic dyslipidemia, GLP-1 may directly mitigate the risk of vascular disease in diabetes by improving endothelial function and blood pressure and decreasing inflammation (20). Whether GLP-2 augments or antagonizes these effects also warrants further investigation.

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