Central Nervous System Regulation of Intestinal Lipoprotein Metabolism by Glucagon-Like Peptide-1 via a Brain–Gut Axis

Sarah Farr, Christopher Baker, Mark Naples, Jennifer Taher, Jahangir Iqbal, Mahmood Hussain, Khosrow Adeli

Objective—Intestinal overproduction of atherogenic chylomicron particles postprandially is an important component of diabetic dyslipidemia in insulin-resistant states. In addition to enhancing insulin secretion, peripheral glucagon-like peptide-1 (GLP-1) receptor stimulation has the added benefit of reducing this chylomicron overproduction in patients with type 2 diabetes mellitus. Given the presence of central GLP-1 receptors and GLP-1–producing neurons, we assessed whether central GLP-1 exerts an integral layer of neuronal control during the production of these potentially atherogenic particles.

Approach and Results—Postprandial production of triglyceride-rich lipoproteins was assessed in Syrian hamsters administered a single intracerebroventricular injection of the GLP-1 receptor agonist exendin-4. Intracerebroventricular exendin-4 reduced triglyceride-rich lipoprotein-triglyceride and -apolipoprotein B48 accumulation relative to vehicle-treated controls. This was mirrored by intracerebroventricular MK-0626, an inhibitor of endogenous GLP-1 degradation, and prevented by central exendin9–39, a GLP-1 receptor antagonist. The effects of intracerebroventricular exendin-4 were also lost during peripheral adrenergic receptor and central melanocortin-4 receptor inhibition, achieved using intravenous propranolol and phentolamine and intracerebroventricular HS014, respectively. However, central exendin9–39 did not preclude the effects of peripheral exendin-4 treatment on chylomicron output.

Conclusions—Central GLP-1 is a novel regulator of chylomicron production via melanocortin-4 receptors. Our findings point to the relative importance of central accessibility of GLP-1–based therapies and compel further studies examining the status of this brain–gut axis in the development of diabetic dyslipidemia and chylomicron overproduction. (Arterioscler Thromb Vasc Biol. 2015;35:1092-1100. DOI: 10.1161/ATVBAHA.114.304873.)

Key Words: apolipoprotein B-48 ▪ central nervous system ▪ chylomicron ▪ glucagon-like peptide-1

Insulin resistance and the metabolic syndrome are frequently associated with postprandial dyslipidemia, characterized by the overproduction of chylomicrons by the intestine. Lipolysis of these triglyceride-rich apoB48-containing particles generates atherogenic remnants, contributing to the heightened risk of cardiovascular disease observed in patients with type 2 diabetes mellitus. It is therefore critical to understand how intestinal lipoprotein metabolism is regulated.

See accompanying editorial on page 1048

The gut-derived hormone glucagon-like peptide-1 (GLP-1) has received attention as an insulin secretagogue and as a regulator of lipid metabolism. Patients with type 2 diabetes mellitus who received chronic treatments or a single injection of the GLP-1 producing neurons, we assessed whether central GLP-1 exerts an integral layer of neuronal control during the production of these potentially atherogenic particles.

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The gut-derived hormone glucagon-like peptide-1 (GLP-1) has received attention as an insulin secretagogue and as a regulator of lipid metabolism. Patients with type 2 diabetes mellitus who received chronic treatments or a single injection of the GLP-1 receptor (GLP-1R) agonist exendin displayed significantly lower postprandial levels of circulating triglycerides and apoB48 (a marker of chylomicron particles). Similar findings have been obtained from healthy humans, rats, mice and hamsters during postprandial GLP-1R stimulation and from mice treated with sitagliptin, an inhibitor of dipeptidyl peptidase-4 (DPP-4), which mediates GLP-1 degradation. A role for GLP-1 in regulating intestinal lipoprotein metabolism is not surprising given that its secretion is enhanced in response to lipid ingestion and that postprandial dyslipidemia occurs alongside impaired GLP-1 production in patients with type 2 diabetes mellitus.

The manner by which GLP-1 confers these intestinal effects remains unclear. Direct action of GLP-1 on enterocytes is supported by reductions in apoB48 secretion from primary enterocytes treated with exendin-4 ex vivo. However, the involvement of a brain–gut axis is an alternative possibility. The nucleus of...
the solitary tract in the brain stem contains GLP-1–producing neurons that project to GLP-1R–expressing hypothalamic nuclei. Intracerebroventricular injections of exendin-4 can activate hypothalamic nuclei such as the paraventricular and arcuate nuclei (ARC). These regions, in turn, innervate the intermediolateral nucleus (IML) of the spinal cord, which mediates sympathetic outflow to the periphery. Intracerebroventricular injections of GLP-1 have been shown to increase sympathetic nerve activity in white adipose tissue, thereby reducing lipogenic gene expression and demonstrating central control over peripheral lipid metabolism. Furthermore, intracerebroventricular exendin-4 reduced gastric tone in rats, demonstrating central control over gastrointestinal function. Finally, activation of the IML can be induced by melanocortin-4 receptor (MC4R) agonists, and exendin-4–induced satiety is associated with activation of ARC proopiomelanocortin neurons, which produce the MC4R ligand α-melanocyte-stimulating hormone.

Given that peripheral GLP-1 can modulate chylomicron secretion and that central GLP-1 has important effects on peripheral lipid metabolism and sympathetic signaling, we sought to characterize a potential role for central GLP-1 in regulating chylomicron production. Our findings demonstrate a novel, central pathway of control over intestinal lipoprotein metabolism. Insight into the physiology of this brain–gut interaction, as presented here, may have important implications for identifying new targets for the treatment of diabetic dyslipidemia and potential central disruptions during insulin resistance.

### Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

### Results

#### Central GLP-1R Stimulation Reduces Postprandial Chylomicron Secretion

To examine the potential involvement of central GLP-1Rs in regulating chylomicron secretion, fat-loaded hamsters received intracerebroventricular exendin-4 or vehicle, and postprandial triglyceride-rich lipoprotein (TRL) production was examined. Central exendin-4 treatment significantly reduced plasma triglyceride levels compared to vehicle. Intravenous adrenergic receptor antagonists also reduced TRL levels, indicating a role for sympathetic signaling in chylomicron output.

![Figure 1](http://atvb.ahajournals.org/)

Figure 1. Central glucagon-like peptide-1 receptor stimulation reduces chylomicron production, which can be prevented by sympathetic inhibition. Fat-loaded hamsters received intracerebroventricular (ICV) exendin-4 (n=4), MK-0626 (n=8) or H2O (n=8), and Pluronic F-127. Some groups additionally received ICV exendin9–39 (n=4–5) or intravenous adrenergic receptor antagonists (n=3–5). A and D, Plasma triglyceride (TG), (B and E) triglyceride-rich lipoprotein (TRL)-TG, and (C and F) TRL-apoB48 levels (n=3–5). Vehicle (Veh), exendin-4 (Ex4), MK-0626 (MK), exendin9–39 (Ex9–39), adrenergic receptor antagonists (AR antag). Veh vs Ex4, #Ex4 vs Ex4+Ex9–39, ^Veh vs MK, $MK vs MK+Ex9–39, and &Ex4 vs Ex9–39. 1, P<0.05; 2, P<0.01; and 3, P<0.001. Analysis by 2-way ANOVA with Bonferroni post-test. Mean±SEM shown.
and TRL-triglyceride levels (Figure 1A and 1B; Table I in the online-only Data Supplement), their area under the curve (AUC; Table III in the online-only Data Supplement), and their rates of accumulation relative to vehicle-treated controls (vehicle versus exendin-4 TRL-triglyceride slope; \( P<0.001 \); Table II in the online-only Data Supplement). These changes occurred alongside reductions in TRL-apoB \(_{48} \) levels (−62.58% difference at 6 hours), indicating the secretion of fewer chylomicrons (Figure 1C). Effects of exendin-4 on TRL production could not be accounted for by changes in plasma insulin (AUC, \( P=0.79 \); Figure 1A in the online-only Data Supplement) or glucose levels (AUC, \( P=0.43 \); Figure 1B in the online-only Data Supplement).

Exendin-4 is a GLP-1 mimetic with a prolonged half-life because of its DPP-4 resistance and constitutes an exogenous form of receptor stimulation. To confirm that central GLP-1 is physiologically relevant, the DPP-4 inhibitor MK-0626 was given by intracerebroventricular injection to stimulate GLP-1Rs with endogenous GLP-1, and only in regions where GLP-1 is naturally produced. Although the magnitude of the effect was milder, MK-0626 significantly reduced plasma and TRL-triglyceride levels (Figure 1A and 1B; Table I in the online-only Data Supplement), and the rate of TRL-triglyceride accumulation (vehicle versus MK slope; \( P=0.02 \); Table II in the online-only Data Supplement). MK-0626 also induced a trend toward reduced TRL-apoB \(_{48} \) levels (Figure 1C). The effects of exendin-4 and MK-0626 occurred despite the absence of changes in gastric emptying rates during the first hour of the study (\( P=0.37 \); Figure IIA in the online-only Data Supplement).

Furthermore, effects on plasma and TRL-triglyceride levels were negated by intracerebroventricular pretreatment with the GLP-1R antagonist exendin9–39 (TRL-triglyceride slope, exendin-4 versus exendin-4+exendin9–39; \( P=0.0001 \) and MK versus MK+exendin9–39; \( P=0.039 \); Figure 1A and 1B; Tables I–III in the online-only Data Supplement). Reductions in TRL-apoB \(_{48} \) levels were also negated by exendin9–39 (Figure 1C), confirming that the observed reductions in TRL production were mediated by central GLP-1Rs.

To further characterize this brain–gut communication, the effects of intracerebroventricular exendin-4 were assessed during impaired sympathetic signaling. In the presence of \( \alpha \)- and \( \beta \)-adrenergic receptor antagonists, intracerebroventricular exendin-4 was unable to alter plasma and TRL-triglyceride levels (Figure 1D and 1E), their rate of accumulation (exendin-4 versus AR antag+exendin-4 TRL-triglyceride slope; \( P=0.028 \); Table II in the online-only Data Supplement), and TRL-apoB \(_{48} \) levels (Figure 1F). This indicates that sympathetic pathways are important in conferring GLP-1–mediated brain to gut signaling.

### MC4Rs Are Key Regulators of the Effects of Central GLP-1R Stimulation on Chylomicron Production

Given that MC4Rs can modulate sympathetic nerve activity\(^{17} \) and MC4Rs have been linked to GLP-1’s satiety effects,\(^{18} \) we examined a role for MC4Rs in regulating chylomicron production. Fat-loaded hamsters received an intracerebroventricular injection of the MC4R agonist Ro-273225, the MC4R antagonist HS014, or vehicle and TRL production was examined. Similar to GLP-1R stimulation, MC4R agonism significantly reduced the number of chylomicrons produced, reflected in TRL-apoB \(_{48} \) levels (vehicle versus MC4R ag, 75.39% difference at 6 hours; Figure 2C). MC4R agonism also induced a trend toward reduced plasma and TRL-triglyceride levels, whereas MC4R antagonism caused the opposite trend. Although neither of these changes were significant relative to vehicle-treated hamsters, the difference between them was significant (Figure 2A and 2B). This was also seen in the rate of plasma-triglyceride accumulation (MC4R antag versus MC4R ag, \( 3.26\pm0.43 \) versus \( 2.19\pm0.31 \) mmol/L per hour; \( P=0.046 \)) and TRL-triglyceride accumulation (0.59±0.12 versus 0.33±0.076 mmol/L per hour; \( P=0.056 \)). Given the ability of MC4Rs to regulate apoB \(_{48} \) output, their involvement in mediating the effects of central GLP-1 was assessed. Interestingly, no difference was observed in plasma or TRL-triglyceride levels between hamsters treated with intracerebroventricular exendin-4 or vehicle during MC4R antagonism.

**Figure 2.** Central melanocortin-4 receptors (MC4Rs) play a role in intracerebroventricular (ICV) exendin-4–mediated changes in chylomicron production. Fat-loaded hamsters received ICV MC4R agonist (n=10) or H\(_2\)O (n=7), and Pluronic F-127. Some groups additionally received ICV MC4R antagonist in the presence (n=9) or absence (n=5) of ICV exendin-4. **A.** Plasma-triglyceride (TG), **B** triglyceride-rich lipoprotein (TRL)-TG, and **C** TRL-apoB \(_{48} \) levels (n=5). MC4R agonist (MC4R ag), MC4R antagonist (MC4R antag), \(^{\dagger}\)MC4R ag vs MC4R antag, \(#\)MC4R antag vs MC4R antag+Ex4, \(^{\ast}\)vehicle (Veh) vs MC4R ag, \(\S\)MC4R ag vs MC4R antag+Ex4. 1, \( P<0.05 \); 2, \( P<0.01 \). Analysis by 2-way ANOVA with Bonferroni post-test for A and B, and 1-way ANOVA for C. Means±SEM shown.
Peripheral GLP-1R Stimulation Reduces Postprandial Chylomicron Secretion

Previously, we demonstrated that acute intraperitoneal exendin-4 lowered TRL-triglyceride and TRL-apoB_{48} levels in mice and hamsters ≤2 hours after fat load. To study the interplay between central and peripheral pathways of regulation, it was important to determine whether peripheral exendin-4 also had prolonged postprandial effects. In an 8-hour time course, intraperitoneal exendin-4 significantly lowered large TRL-triglyceride levels (Figure 3B) and their rate of accumulation and AUC (Table IV in the online-only Data Supplement). There was also a significant reduction in the rate of small TRL-triglyceride accumulation, with a trend in AUC (Figure 3C; Table IV in the online-only Data Supplement), and a similar trend for the rate of plasma-triglyceride accumulation (Figure 3A; Table IV in the online-only Data Supplement). This amounted to significantly lower total TRL-triglyceride levels (calculated as the sum of large and small TRL-triglyceride) and their rate of accumulation and AUC (Figure 3D; Table IV in the online-only Data Supplement). Changes in large TRL-triglyceride levels were accompanied by a reduction in particle number, reflected in apoB_{48} (AUC vehicle versus exendin-4, 461.4±40.35 versus 285.7±68.94; P=0.044; Figure 3E). As expected, plasma insulin levels were significantly increased by exendin-4 at 4 hours (AUC, P=0.073), despite similar plasma glucose levels (AUC, P=0.22; Figure IIC and IID in the online-only Data Supplement), and gastric emptying was significantly delayed (P=0.013; Figure IIB in the online-only Data Supplement).

Peripheral GLP-1R Stimulation Can Reduce Chylomicron Secretion, Independent of Central GLP-1R Activation

Given that exendin-4 was previously shown to reduce apoB_{48} secretion from primary enterocytes ex vivo, we assessed whether peripheral receptors alone were sufficient to impair chylomicron secretion during central GLP-1R antagonism. Intraperitoneal exendin-4 alone significantly lowered the rate of TRL-triglyceride accumulation (intracerebroventricular vehicle/intraperitoneal vehicle versus intracerebroventricular vehicle/intraperitoneal exendin-4 slope; P=0.038; Table V in the online-only Data Supplement). In the presence of intracerebroventricular exendin9–39, these effects were maintained, with significant reductions in plasma and TRL-triglyceride levels (Figure 4A and 4B), AUC (Table VI in the online-only Data Supplement), and the rate of plasma-triglyceride accumulation (intracerebroventricular exendin9–39/intraperitoneal vehicle versus intracerebroventricular exendin9–39/intraperitoneal exendin-4 slope, P=0.0029; Table V in the online-only Data Supplement). There was also a trend toward a reduced rate of TRL-triglyceride accumulation (P=0.068; Table V in the

Figure 3. Peripheral exendin-4 reduces chylomicron production. Fat-loaded hamsters received intraperitoneal (IP) exendin-4 (n=6) or PBS (n=7), and Pluronic F-127. A, Plasma. B, large triglyceride-rich lipoprotein (TRL; S_{f}>400). C, small TRL (S_{f}100-400), and D, total TRL triglyceride (TG) levels (sum of large and small TRL-TG). E, Large TRL-apoB_{48} levels. *P<0.05, **P<0.01. Analysis by 2-way ANOVA with Bonferroni post-test. Mean±SEM shown.
This trend, suggesting reduced chylomicron output, was confirmed with significantly lower TRL-apoB48 levels, reflecting particle number (intracerebroventricular exendin-9–39/intraperitoneal vehicle versus intracerebroventricular exendin-4, 55.05% difference at 6 hours; Figure 4C). This indicates that peripheral GLP-1R activation can reduce chylomicron secretion independent of central GLP-1R signaling. The reverse experiment was also performed. Interestingly, the ability for intracerebroventricular exendin-4 to affect plasma and TRL-triglyceride levels (Figure 4D and 4E), their rate of accumulation (Table V in the online-only Data Supplement), or AUC (Table VI in the online-only Data Supplement) was lost during peripheral exendin-9–39 treatment (intraperitoneal exendin-9–39/intraperitoneal vehicle versus intraperitoneal exendin-9–39/intraperitoneal exendin-4 TRL-triglyceride slope; P=0.62). This could not be explained by changes in peripheral GLP-1 release during central GLP-1R stimulation (treatment effect on AUC, P=0.38; Figure III in the online-only Data Supplement). However, it should be noted that early on at 2 hours, a trend toward reduced plasma and TRL-triglyceride levels exists with intracerebroventricular exendin-4 treatment during peripheral GLP-1R antagonism (intraperitoneal exendin-9–39/intracerebroventricular vehicle versus intraperitoneal exendin-9–39/intracerebroventricular exendin-4, 8.25±0.78 versus 4.507±0.80 mmol/L plasma-triglyceride, P=0.013; 1.19±0.17 versus 0.60±0.17 mmol/L TRL-triglyceride, P=0.048; by Student t test). This suggests that central GLP-1R signaling may act independent of peripheral GLP-1Rs to reduce chylomicron production, but the capacity to maintain this lowering is eventually lost during peripheral GLP-1R antagonism.

Peripheral and Central GLP-1R Stimulation Limit Jejunal Triglyceride Availability and Microsomal Triglyceride Transfer Protein Activity

To examine mechanisms for the peripheral regulation of chylomicron production by GLP-1, lipid levels in the jejunum and its luminal contents (chyme) were measured. Intraperitoneal exendin-4 reduced jejunal triglyceride levels 2 hours after fat load (Figure 5A), confirmed by Oil Red O staining (Figure 5B). To examine whether this involved impaired lipid absorption, 3H-triglyceride was administered by gavage and intestinal 3H recovery was measured. Intraperitoneal exendin-4 decreased total 3H (Figure IVA in the online-only Data Supplement) and 3H-triglyceride levels (Figure IVB in the online-only Data Supplement) in jejunal tissue and increased

![Figure 4](http://atvb.ahajournals.org/figures/Figure4.jpg)
3H-triglyceride and 3H-fatty acid recovery from jejunal lumen contents (Figure IVC and IVD in the online-only Data Supplement). The latter increase was confirmed with a total triglyceride colorimetric assay ($P=0.0072$; Figure IVF in the online-only Data Supplement), suggesting that peripheral exendin-4 hinders jejunal fatty acid absorption. In addition, the relative distribution of 3H in each lipid species recovered from jejunal luminal contents was examined. Exendin-4 increased the percentage of 3H in triglyceride and induced a trend toward a lower percentage of 3H in fatty acids (Figure IVE in the online-only Data Supplement). In line with early reductions in lipid substrate, jejunal activity of microsomal triglyceride transfer protein (MTP), responsible for apoB48 lipidation, was significantly decreased at 6 hours (Figure 5C). This could not be explained by changes in MTP protein levels (Figure 5D). Interestingly, central GLP-1R stimulation induced similar trends of reducing 2-hour jejunal triglyceride levels (Figure VA and VB) and increasing triglyceride recovery from luminal contents (Figure VC in the online-only Data Supplement). Furthermore, intracerebroventricular exendin-4 significantly reduced jejunal MTP activity both at 2 and 6 hours (Figure VD in the online-only Data Supplement), with a trend toward lower MTP protein levels at 6 hour (Figure VE in the online-only Data Supplement). Overall, these findings suggest that prolonged inhibition of chylomicron secretion involves reduced jejunal triglyceride availability and MTP activity for chylomicron assembly during both peripheral and central GLP-1R stimulation.

**Discussion**

Previous studies from our group have demonstrated that GLP-1 induces rapid reductions in intestinal lipoprotein production in hamsters and mice. Similar findings have been obtained by administering a GLP-1R agonist or DPP-4 inhibitor to patients with type 2 diabetes mellitus, with important implications for diabetic dyslipidemia. GLP-1 in the brain has also been implicated in controlling peripheral lipid metabolism and gastrointestinal function. Here, we demonstrate a novel role for central GLP-1R stimulation in mediating prolonged reductions in chylomicron production. The finding that a central DPP-4 inhibitor alone, without any exogenous source of GLP-1, similarly reduces TRL-triglyceride levels and that central GLP-1R antagonism negates this effect additionally suggests that endogenously produced GLP-1 has access to GLP-1Rs on central neurons that regulate chylomicron production. This brain–gut communication seems to involve MC4R signaling and sympathetic pathways. Furthermore, we show that although these central pathways offer an important level of regulation, peripheral GLP-1R stimulation likely has more direct, independent effects on the gut. In fact, central...
stimulation may require peripheral receptors to confer its sustained effects. Figure 6 depicts our proposed model.

Given that ileal L cells release GLP-1 locally at the level of the intestine and our group has previously shown that exendin-4 can directly modulate apoB secretion from primary enterocytes, a role for central regulation may be unexpected. However, the ability of DPP-4 to rapidly degrade circulating GLP-1 supports the involvement of a neuronal network. Furthermore, it was recently shown that cholecystokinin, released on nutrient sensing in the proximal gut, can activate central GLP-1–producing neurons. This would serve as a fast-acting signal, enabling central GLP-1 to modulate chylomicron production immediately on food consumption, before nutrients reach ileal L cells to stimulate intestinal GLP-1 release. The clinical relevance of this central GLP-1 pathway is supported by the identification of GLP-1R mRNA in regions of the human brain, including the hypothalamus, and the ability for the human brain to bind GLP-1. Furthermore, in a mouse model of diet-induced obesity, the effects of intracerebroventricular GLP-1 on adipocyte metabolism are impaired, suggesting that defects in these central pathways may contribute to changes in metabolism in insulin-resistant states.

The specific regions of the brain that mediate the effects of central GLP-1 on chylomicron production have yet to be identified. However, the only neurons that express the proglucagon gene are located within the nucleus of the solitary tract and these neurons densely innervate hypothalamic nuclei such as the paraventricular nucleus and the ARC. Both of these regions highly express GLP-1Rs and are situated adjacent to the third ventricle where our intracerebroventricular injections were performed, and undergo activation after intracerebroventricular exendin-4 treatment. Furthermore, the ARC contains proopiomelanocortin neurons that produce α-melanocyte–stimulating hormone, and 68.1% of these proopiomelanocortin neurons express GLP-1R mRNA. In the present study, we showed that stimulating MC4Rs in the brain reduces chylomicron production, and that blocking these MC4Rs prevents central exendin-4 from reducing TRL output. It is plausible, therefore, that central GLP-1 leads to the activation of ARC proopiomelanocortin neurons, resulting in α-melanocyte–stimulating hormone production and stimulation of MC4Rs to impair chylomicron production. Indeed, a polymorphism near the MC4R gene is associated with lower postprandial triglyceride and small TRL-apoB levels. Interestingly, although MK-0626 mimicked these effects of intracerebroventricular exendin-4 and MC4R agonism, there is a paucity of evidence for the presence of DPP-4 in the brain. Another DPP-4 inhibitor, sitagliptin, has previously been shown to possess DPP-4–independent activities in stimulating L-cell GLP-1 secretion. The possibility that MK-0626 mediated its effects in a DPP-4–independent manner cannot be excluded.

Furthermore, the paraventricular nucleus is a region that highly expresses MC4Rs and has a well-documented role in regulating food intake by receiving stimulatory input from ARC proopiomelanocortin neurons. It is also a major source of sympathetic outflow to the periphery through its branches to IML neurons in the spinal cord, and these same neurons that branch to the IML undergo activation by intracerebroventricular exendin-4 treatment. Here, we showed that intracerebroventricular exendin-4 requires sympathetic pathways to mediate reductions in chylomicron output. Thus, it is possible that GLP-1–mediated stimulation of proopiomelanocortin neurons leads to the activation of paraventricular nucleus MC4Rs, thereby enhancing sympathetic outflow to the intestine. Alternatively, some ARC proopiomelanocortin neurons branch directly to the IML, which expresses MC4Rs, and MC4R agonists have been shown to activate these sympathetic preganglionic neurons in the spinal cord. Additional evidence supporting a link between GLP-1 and sympathetic signaling includes heightened postprandial norepinephrine levels in patients with type 2 diabetes mellitus receiving the DPP-4 inhibitor vildagliptin, enhanced activity of sympathetic nerve endings in adipose tissue after intracerebroventricular GLP-1 treatment, and impaired GLP-1 effects on intestinal motility during adrenergic receptor antagonism. Finally, β-adrenergic receptors are located on enterocytes, demonstrating their potential to respond to sympathetic neurotransmitters.

It is important to note that leakage of centrally administered compounds to the periphery during our studies is unlikely, given that the insulin and gastric emptying responses to central versus peripheral exendin-4 were different. If leakage was occurring, intracerebroventricular exendin9–39 should have partially blocked the effects of intraperitoneal exendin-4. Furthermore, we suspect that the central dose of exendin-4 (250 ng) would be diluted to such an extent in the periphery that effects would be negligible.

The ability for peripheral exendin-4 to maintain its effects on chylomicron production during central GLP-1R antagonism corresponds with previous findings that exendin-4 reduced enterocyte apoB secretion ex vivo where neuronal inputs were absent. Reduced chylomicron output with peripheral exendin-4 treatment was associated with impaired intestinal lipid availability. This finding is reminiscent of decreased hepatic lipid content in DPP-4–deficient rats and high-fat–fed apoE−/− mice treated with the GLP-1R agonist taspoglutide. Reductions in jejunal MTP activity may be secondary to this initial decrease in lipid substrate. Heightened dietary triglyceride levels in jejunal luminal contents suggests malabsorption and is supported by findings of heightened fecal triglyceride levels in taspoglutide-treated high-fat–fed apoE−/− mice. Furthermore, similar to our findings, a GLP-1 infusion was found to increase the triglyceride:monoacyl glycerol ratio in the intestinal lumen of rats, suggesting reduced triglyceride lipolysis. Indeed, in healthy humans, GLP-1 can reduce gastric and pancreatic lipase secretions, with the latter likely secondary to changes in gastric emptying. Gastric emptying was similarly affect by peripheral exendin-4 in our hands, thus potential contributions of maldigestion or direct effects of GLP-1 on enterocyte lipid absorption are areas for further study. Interestingly, central exendin-4 mirrored these effects on jejunal triglyceride levels, despite no change in gastric emptying. However, in contrast to peripheral findings, jejunal MTP activity was reduced both at 2 and 6 hours.
Central GLP-1 Reduces Chylomicron Output


**Significance**

To our knowledge, this is the first study to show the importance of the central nervous system and central glucagon-like peptide-1 in regulating the intestinal production of potentially atherogenic chylomicron particles. This brain–gut axis seems to involve melanocortin-4 receptors and sympathetic pathways, which may serve as potential therapeutic targets for treating conditions of postprandial dyslipidemia. Given that chylomicron overproduction is a common and harmful feature of insulin-resistant states, our study points to the importance of considering whether central accessibility of glucagon-like peptide-1–based therapies could be beneficial for treating diabetic dyslipidemia. It also compels further studies examining potential disruptions in central glucagon-like peptide-1 receptor signaling in insulin-resistant states.
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