PLASMA triglycerides have since long been recognized as a risk for cardiovascular disease. Recently, large population studies have further used this relationship and established a usefulness in the regulation of triglyceride homeostasis. The autonomous nervous system, consisting of parasympathetic and sympathetic nerves, has been related to triglyceride metabolism by regulating adipose tissue activation and liver triglyceride homeostasis. The hypothalamus is the center of nerve signaling to densely innervated abdominal organs such as adipose tissue and liver. Hence, hepatic triglyceride production, reflected by very-low-density lipoprotein-triglyceride secretion, was attenuated during intracerebroventricular injection of neuropeptide Y in hyperinsulinemic mice as well as in rats. More pronounced is the abnormal postprandial lipid response. Most of the circulating triglycerides are originating from dietary origin and provide an instrumental role for the intestine in triglyceride homeostasis. Yet, the regulation of the process of the intestinal lipid absorption is still largely unknown.

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The central regulation of the brain may be instrumental in the regulation of triglyceride homeostasis. The autonomous nervous system, consisting of parasympathetic and sympathetic nerves, has been related to triglyceride metabolism by regulating adipose tissue activation and liver triglyceride homeostasis. The hypothalamus is the center of nerve signaling to densely innervated abdominal organs such as adipose tissue and liver. Hence, hepatic triglyceride production, reflected by very-low-density lipoprotein-triglyceride secretion, was attenuated during intracerebroventricular injection of neuropeptide Y in hyperinsulinemic mice as well as in rats. In line, neuropeptide Y signaling decreases sympathetic outflow to adipose tissue resulting in decreased lipolysis in white as well as brown adipose tissue. In contrast, stimulation of the melanocortin-driven neurons induces more catabolic effects represented by increased white adipose tissue lipolysis, brown adipose tissue activation, and reductions in hepatic very-low-density lipoprotein-triglyceride secretion and hepatic triglyceride content.

After ingestion of a meal, the small intestine rapidly secretes various hormones including the incretin hormone glucagon-like protein-1 (GLP1) that has been implicated as an important regulator of satiety through MC4R (melanocortin 4 receptor)-mediated sympathetic nerve activity in different animal models. Also, GLP1 directly affects triglyceride homeostasis by reducing hepatic and adipose tissue lipid stores. Indeed, it has been shown that exogenous increases in plasma GLP1 including inhibitors of the enzyme dipeptidyl peptidase 4 (that degrades GLP1) and longacting GLP1 receptor agonists rapidly reduce plasma triglyceride levels and hepatic triglyceride stores. As GLP1 is synthesized in L-cells located in the small intestine, it has already been suggested that GLP1 may affect intestinal lipid absorption and thus postprandial triglyceride excursions. However, the role of the central nervous system in this process has never been investigated.

Farr et al. tested the hypothesis that central GLP1-mediated neuronal signaling may underlie chylomicron secretion in an insulin-resistant environment using the Syrian hamster, a unique model, which closely resembles the human lipoprotein features with apoB48 synthesis only in the intestine and apoB100 production in the liver. Chylomicron secretion was measured after an oral dose of olive oil and Pluronic F-127, a compound that inhibits lipoprotein lipase-mediated lipoprotein clearance. When GLP1 receptor agonist was administered intracerebroventricularly, it resulted in a significant reduction in postprandial plasma triglyceride-rich lipoprotein (TRL)-apoB48 and triglycerides, suggesting an important role for central GLP1 in intestinal chylomicron secretion. Indeed, intracerebroventricular administration of a GLP1R antagonist has a similar effect on postprandial lipid response, whereas a smaller effect was noted on intracerebroventricular injection of a dipeptidyl peptidase 4 inhibitor. Peripheral administration of the GLP1 agonist also reduces postprandial TRL-triglycerides and apoB48 response independent of cerebral GLP1R activation. In conclusion, one can postulate that endogenous GLP1 exerts its triglyceride reducing effect through interaction with both peripheral GLP1 receptors and GLP1-receptors located on central neurons in which MC4R signaling is involved.

What do we learn from these studies with regard to human (postprandial) triglyceride physiology in insulin resistance? Dipeptidyl peptidase 4 inhibitors (which are currently in phase III clinical development phase) have all shown to improve postprandial plasma TRL-triglycerides and apoB48 levels, whereas no changes were found in hepatic very-low-density lipoprotein secretion and plasma triglycerides and apoB100 levels. A similar observation was made for the GLP1 receptor agonist exendin 4. In line, kinetic stable isotope-based studies reveal that exendin 4 affects chylomicron secretion independent of changes in bodyweight, satiety, and gastric emptying. Thus, the reported lack of effect on GLP1 on hepatic lipoprotein metabolism in humans may
be a consequence of the absence of GLP1 receptors in the liver. However, GLP1 involves a central (brain)signaling as GLP1 receptor blockade by exendin 3 to 39 was able to block the effect of exendin 4 on food intake and satiety. Overall, the GLP1 analogues and the dipeptidyl peptidase 4 inhibitors are excellent drugs to improve insulin sensitivity in patients with type 2 diabetes mellitus, yet their effect on plasma lipids remains to be studied.

**Disclosures**

None.

**References**


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