Motilin beyond gut motility: a novel role in the regulation of adipose tissue metabolism

Rolando Ceddia
School of Kinesiology and Health Science, Faculty of Health, York University, Toronto, Ontario, Canada
Submitted 8 August 2011; accepted in final form 8 August 2011

Motilin is a 22 amino acid peptide present predominantly in endocrine cells of the duodenal mucosa, although it can also be found in the myenteric plexus and the thyroid gland, as well as in the brain, with the highest concentration detected in the hypothalamus (3). The orphan G protein-coupled receptor (GPR38) has been identified as the human motilin receptor, which is mainly found in the gastrointestinal (GI) tract in a species-dependent manner (3). Motilin is well known for its GI motor-stimulating properties. Its plasma concentration increases cyclically every 90–120 min during the interdigestive fasting period to generate short intervals of strong peristaltic contractions from the stomach toward the duodenum and the small intestine. This pattern of peristaltic contractions is known as the phase III contraction of the migrating motor complex (8, 10). Most of the research regarding the role of motilin has focused on understanding the mechanisms underlying the motot-stimulating (prokinetic) properties of this peptide in the GI tract. This was further propelled by the observations that motilin could accelerate gastric emptying in patients with diabetic gastroparesis with important therapeutic applications for this peptide (5, 9, 11). The major interest has been to develop motilin agonists for the treatment of hypomobility disorders of the GI tract. In this context, very little is currently known about potential effects of motilin beyond its role in the regulation of GI tract motility. The article in this issue by Miegueu et al. (7) provides novel and compelling evidence that motilin, although apparently discrepant with the fact that the mRNA expression of GPR38 in subcutaneous human adipose tissue correlated positively with the homeostasis model assessment of insulin resistance (HOMA-IR) (7).

Most findings of Miegueu et al. (7) were obtained using murine and rat adipocytes, two species in which the genes coding for motilin and its receptors have been reported to exist only as pseudogenes (1, 4), therefore considered natural motilin knockouts (3). The study by Miegueu et al. provides an alternative view on this issue, since not only 3T3-L1 but also isolated primary rat adipocytes elicited functional responses to motilin. Furthermore, the concentration-dependent 125I-motilin binding profile and motilin-induced FA incorporation in 3T3-L1 adipocytes were inhibited by GPR38 and the growth hormone secretagogue receptor (GHSR) antagonists MB10 and [d-lys3]-GRP6, respectively (7). Thus, providing evidence that both the GPR38 and the ghrelin receptors mediate the lipogenic effects of motilin in adipocytes. These findings open up the possibility of exploring whole body and tissue-specific effects of motilin and of its synthetic agonists/antagonists utilizing rodents as models. This could quickly advance the understanding of the potential metabolic effects of motilin on various organs and tissues as well as to assess the broader physiological implications of using motilin as a prokinetic drug target for the treatment of hypomobility disorders of the GI tract.

The work by Miegueu et al. raises several important questions that need to be addressed. It is crucial that future experiments clearly identify signaling mechanisms by which motilin induces adipogenic effects. This could also provide insight into the potential cross-talk of motilin with other major hormones (i.e., insulin, ghrelin, catecholamines, and glucocorticoids) that regulate WAT metabolism and whole body energy homeosta-

Fig. 1. Motilin (Mot) binds to its receptors (Mr) and increases (+) glucose (Glu) and fatty acid (FA) uptake as well as triglyceride (TG) formation in adipocytes. Motilin also suppresses (−) FA release and increases the expression of genes involved in adipocyte differentiation and lipogenesis. PPARγ, peroxisome proliferator-activated receptor-γ; C/EBP, CCAAT enhancer binding protein; DGAT1, diacylglycerol acetyltransferase-1.

MOTILIN IS A 22 AMINO ACID PEPTIDE present predominantly in endocrine cells of the duodenal mucosa, although it can also be found in the myenteric plexus and the thyroid gland, as well as in the brain, with the highest concentration detected in the hypothalamus (3). The orphan G protein-coupled receptor (GPR38) has been identified as the human motilin receptor, which is mainly found in the gastrointestinal (GI) tract in a species-dependent manner (3). Motilin is well known for its GI motor-stimulating properties. Its plasma concentration increases cyclically every 90–120 min during the interdigestive fasting period to generate short intervals of strong peristaltic contractions from the stomach toward the duodenum and the small intestine. This pattern of peristaltic contractions is known as the phase III contraction of the migrating motor complex (8, 10). Most of the research regarding the role of motilin has focused on understanding the mechanisms underlying the motot-stimulating (prokinetic) properties of this peptide in the GI tract. This was further propelled by the observations that motilin could accelerate gastric emptying in patients with diabetic gastroparesis with important therapeutic applications for this peptide (5, 9, 11). The major interest has been to develop motilin agonists for the treatment of hypomobility disorders of the GI tract. In this context, very little is currently known about potential effects of motilin beyond its role in the regulation of GI tract motility. The article in this issue by Miegueu et al. (7) provides novel and compelling evidence that motilin, although apparently discrepant with the fact that the mRNA expression of GPR38 in subcutaneous human adipose tissue correlated positively with the homeostasis model assessment of insulin resistance (HOMA-IR) (7).

Most findings of Miegueu et al. (7) were obtained using murine and rat adipocytes, two species in which the genes coding for motilin and its receptors have been reported to exist only as pseudogenes (1, 4), therefore considered natural motilin knockouts (3). The study by Miegueu et al. provides an alternative view on this issue, since not only 3T3-L1 but also isolated primary rat adipocytes elicited functional responses to motilin. Furthermore, the concentration-dependent 125I-motilin binding profile and motilin-induced FA incorporation in 3T3-L1 adipocytes were inhibited by GPR38 and the growth hormone secretagogue receptor (GHSR) antagonists MB10 and [d-lys3]-GRP6, respectively (7). Thus, providing evidence that both the GPR38 and the ghrelin receptors mediate the lipogenic effects of motilin in adipocytes. These findings open up the possibility of exploring whole body and tissue-specific effects of motilin and of its synthetic agonists/antagonists utilizing rodents as models. This could quickly advance the understanding of the potential metabolic effects of motilin on various organs and tissues as well as to assess the broader physiological implications of using motilin as a prokinetic drug target for the treatment of hypomobility disorders of the GI tract.

The work by Miegueu et al. raises several important questions that need to be addressed. It is crucial that future experiments clearly identify signaling mechanisms by which motilin induces adipogenic effects. This could also provide insight into the potential cross-talk of motilin with other major hormones (i.e., insulin, ghrelin, catecholamines, and glucocorticoids) that regulate WAT metabolism and whole body energy homeosta-

MOTILIN IS A 22 AMINO ACID PEPTIDE present predominantly in endocrine cells of the duodenal mucosa, although it can also be found in the myenteric plexus and the thyroid gland, as well as in the brain, with the highest concentration detected in the hypothalamus (3). The orphan G protein-coupled receptor (GPR38) has been identified as the human motilin receptor, which is mainly found in the gastrointestinal (GI) tract in a species-dependent manner (3). Motilin is well known for its GI motor-stimulating properties. Its plasma concentration increases cyclically every 90–120 min during the interdigestive fasting period to generate short intervals of strong peristaltic contractions from the stomach toward the duodenum and the small intestine. This pattern of peristaltic contractions is known as the phase III contraction of the migrating motor complex (8, 10). Most of the research regarding the role of motilin has focused on understanding the mechanisms underlying the motot-stimulating (prokinetic) properties of this peptide in the GI tract. This was further propelled by the observations that motilin could accelerate gastric emptying in patients with diabetic gastroparesis with important therapeutic applications for this peptide (5, 9, 11). The major interest has been to develop motilin agonists for the treatment of hypomobility disorders of the GI tract. In this context, very little is currently known about potential effects of motilin beyond its role in the regulation of GI tract motility. The article in this issue by Miegueu et al. (7) provides novel and compelling evidence that motilin, although apparently discrepant with the fact that the mRNA expression of GPR38 in subcutaneous human adipose tissue correlated positively with the homeostasis model assessment of insulin resistance (HOMA-IR) (7).

Most findings of Miegueu et al. (7) were obtained using murine and rat adipocytes, two species in which the genes coding for motilin and its receptors have been reported to exist only as pseudogenes (1, 4), therefore considered natural motilin knockouts (3). The study by Miegueu et al. provides an alternative view on this issue, since not only 3T3-L1 but also isolated primary rat adipocytes elicited functional responses to motilin. Furthermore, the concentration-dependent 125I-motilin binding profile and motilin-induced FA incorporation in 3T3-L1 adipocytes were inhibited by GPR38 and the growth hormone secretagogue receptor (GHSR) antagonists MB10 and [d-lys3]-GRP6, respectively (7). Thus, providing evidence that both the GPR38 and the ghrelin receptors mediate the lipogenic effects of motilin in adipocytes. These findings open up the possibility of exploring whole body and tissue-specific effects of motilin and of its synthetic agonists/antagonists utilizing rodents as models. This could quickly advance the understanding of the potential metabolic effects of motilin on various organs and tissues as well as to assess the broader physiological implications of using motilin as a prokinetic drug target for the treatment of hypomobility disorders of the GI tract.

The work by Miegueu et al. raises several important questions that need to be addressed. It is crucial that future experiments clearly identify signaling mechanisms by which motilin induces adipogenic effects. This could also provide insight into the potential cross-talk of motilin with other major hormones (i.e., insulin, ghrelin, catecholamines, and glucocorticoids) that regulate WAT metabolism and whole body energy homeosta-
sis. The use of wortmannin prevented motilin-induced FA uptake (7), indicating that the adipogenic effects of motilin are, at least in part, mediated by the PI 3-kinase signaling pathway. It would also be important to determine whether differences exist between acute and chronic effects of motilin on glucose and FA metabolism in the WAT. The acute effect of this peptide on adipocyte metabolism may not significantly alter WAT function; however, the chronic therapeutic use of motilin or of a mimetic as a prokinetic drug may induce important effects on whole body glucose and lipid metabolism. It is intriguing to think that under physiological conditions motilin is released during the interdigestive fasting period (8, 10), a time when a lipogenic response would seem unlikely to occur. This raises the possibility that motilin could have a modulatory effect on WAT metabolism through the interaction with other counterregulatory hormones that also regulate FA release and esterification in adipocytes. Last, it will also be important to assess whether these lipogenic effects of motilin are reproduced in human adipocytes. This is of particular interest since GPR38 mRNA expression in human adipose tissue correlated positively with the HOMA-IR and negatively with adiponectin mRNA expression (7). These and other important questions should be the subject of further work in this area. The findings reported by Miegueu et al. present novel opportunities to further our understanding of how gut peptides control GI function and also regulate glucose and lipid metabolism in WAT.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES