Chronic Leptin Administration Decreases Fatty Acid Uptake and Fatty Acid Transporters in Rat Skeletal Muscle*

Gregory R. Steinberg‡‡, David J. Dyck‡, Jorges Calles-Escandón§, Narendra N. Tandon¶, Joost J. F. P. Luiken***‡‡, Jan F. C. Glatz§§, and Arend Bonen††

From the ‡Department of Human Biology and Nutritional Sciences, University of Guelph, Ontario N1G 2W1, Canada, *Glaxo SmithKline, Miami, Florida 33134, the †Thrombosis Research Laboratory, Otisuka Maryland Research Institute, Rockville, Maryland 20850, the §Department of Physiology, Maastricht University, 6200 MD Maastricht, The Netherlands, and the §§Department of Kinesiology, University of Waterloo, Waterloo, Ontario N2L 3G1, Canada

Chronic leptin administration reduces triacylglycerol content in skeletal muscle. We hypothesized that chronic leptin treatment, within physiologic limits, would reduce the fatty acid uptake capacity of red and white skeletal muscle due to a reduction in transport protein expression (fatty acid translocase (FAT/CD36) and plasma membrane-associated fatty acid-binding protein (FABPpm)) at the plasma membrane. Female Sprague-Dawley rats were infused for 2 weeks with leptin (0.5 mg/kg/day) using subcutaneously implanted miniosmotic pumps. Control and pair-fed animals received saline-filled implants. Leptin levels were significantly elevated (∼4-fold; \( p < 0.001 \)) in treated animals, whereas pair-fed treated animals had reduced serum leptin levels (approximately ∼2-fold; \( p < 0.01 \)) relative to controls. Palmitate transport rates into giant sarcolemmal vesicles were reduced following leptin treatment in both red (∼45%) and white (∼84%) skeletal muscle compared with control and pair-fed animals \( ( p < 0.05) \). Leptin treatment reduced FAT mRNA (red, ∼70%; white, ∼48%, \( p < 0.01 \)) and FAT/CD36 protein expression (red, ∼32%; \( p < 0.05 \)) in whole muscle homogenates, whereas FABPpm mRNA and protein expression were unaltered. However, in leptin-treated animals plasma membrane fractions of both FAT/CD36 and FABPpm protein expression were significantly reduced in red (∼28 and −34%, respectively) and white (∼44 and −50%, respectively) muscles \( ( p < 0.05) \). Across all experimental treatments and muscles, palmitate uptake by giant sarcolemmal vesicles was highly correlated with the plasma membrane FAT/CD36 protein \( ( r = 0.88, p < 0.01 \) and plasma membrane FABPpm protein \( ( r = 0.94, p < 0.01 \) ). These studies provide the first evidence that protein-mediated long chain fatty acid transport is subject to long term regulation by leptin.

The development of obesity and insulin resistance in both humans and rodents is associated with abnormalities in lipid metabolism, involving impaired fatty acid oxidation and increased storage as intramuscular triacylglycerol (1, 2). Whereas the association of insulin resistance with increased concentrations of intramuscular triacylglycerol is well recognized (1–3), the underlying mechanisms are unknown. In ob/ob mice, the absence of leptin results in a phenotype characterized by obesity and insulin resistance, and treatment with recombinant leptin results in a rapid reduction in body adiposity and the restoration of insulin sensitivity (4). In skeletal muscle, an essential tissue responsible for regulating whole body lipid and glucose metabolism, leptin has been shown to increase fatty acid oxidation and intramuscular triacylglycerol hydrolysis acutely (<1 h) (5–7) while decreasing fatty acid esterification (5).

The effects of chronic (>7 days) leptin treatment on skeletal muscle fatty acid uptake have not been examined. Several studies have demonstrated that chronic leptin treatment in lean and diabetic rats as well as ob/ob mice leads to reduced body mass and results in significant reductions in circulating insulin, independent of reduced food intake (8–10), suggesting an improved insulin sensitivity. Chronic hyperleptinemia has also been shown to increase glucose uptake in skeletal muscle (3, 8). However, this is not due to increased GLUT-4 expression, suggesting that leptin may be altering the transporter’s intrinsic activity and/or translocation to the sarcolemma (9). Another possible mechanism for improved insulin sensitivity may be the decrease of intramuscular triacylglycerols observed in red skeletal muscle following leptin treatment (3), since intramuscular triacylglycerol accumulation is correlated with insulin resistance (1–3, 11). Thus, it is important to understand the mechanisms by which chronic leptin treatment alters intramuscular triacylglycerol concentrations. A possible mechanism contributing to the insulin-induced reductions in intramuscular triacylglycerols may occur at the level of fatty acid transport into the muscle cell.

Fatty acids traverse the plasma membrane via passive diffusion and a protein-mediated mechanism (12). Several proteins have been shown to facilitate fatty acid transport, including the fatty acid translocase (FAT/CD36) and plasma membrane-associated fatty acid-binding protein (FABPpm) (12). While fatty acid transport protein 1 (FATP1) was initially thought to be a fatty acid transporter (13), recent studies have...

* This work was supported by grants from the Canadian Institutes of Health Research (to A. B.) and the Natural Sciences and Engineering Research Council of Canada (to D. J. D. and A. B.) and by Netherlands Heart Foundation Grant DH98.012 (to J. F. C. G. and J. J. F. P. L.). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

†† A Dekker postdoctoral fellow of the Netherlands Heart Foundation.

‡‡ A Dekker postdoctoral fellow of the Netherlands Heart Foundation.

§ Recipient of a Natural Sciences and Engineering Research Council postgraduate scholarship.

To whom correspondence should be addressed: Dept. of Kinesiology, University of Waterloo, Waterloo, Ontario N2L 3G1, Canada. Tel.: 519-888-1211 (ext. 5214); Fax: 519-746-6776; E-mail: abonen@healthy.uwaterloo.ca.
shown that FATP1 is a very long chain fatty acyl-CoA synthetase (14). The cytosolic, 15-kDa fatty acid-binding protein (FABPc) is also an important feature of the fatty acid transport system, since it acts as a fatty acid sink once fatty acids have crossed the plasma membrane (12).

In muscle, FABPc is present in great excess and therefore does not limit fatty acid uptake (12). However, increasing the expression of FAT/CD36 in skeletal muscle increases fatty acid transport and oxidation (15), whereas in FAT/CD36 null mice the uptake of fatty acids is reduced (16). Other mechanisms besides altered FAT/CD36 expression can also regulate fatty acid transport. In contracting muscles, FAT/CD36 is translocated, within minutes, from an intracellular pool to the plasma membrane, resulting in an increased rate of fatty acid transport (17). Thus, skeletal muscle fatty acid transport can be affected in a number of ways, by altering the expression of FAT/CD36 and/or relocating this protein to the plasma membrane.

A link between leptin-induced reductions in intramuscular triacylglycerol depots and improved insulin sensitivity in skeletal muscle may be the reduced uptake of fatty acids into the muscle cell. Fatty acids are known to induce insulin resistance in muscle (18), and limiting their entry into the muscle cell may be expected to reduce fatty acids available for esterification, thereby improving insulin sensitivity. We therefore hypothesized that chronic leptin treatment can lead to a reduced rate of fatty acid transport into muscle due to reductions in skeletal muscle fatty acid transporters, FAT/CD36 and FABPpm. We have examined the effects of chronic hyperleptinemia (2 weeks) on fatty acid transport, the expression of fatty acid transporters (FAT/CD36 and FABPpm), and their localization in the plasma membrane. The present studies have shown that leptin treatment (2 weeks) repressed FAT/CD36 expression in muscle and reduced plasma membrane FAT/CD36 and FABPpm, which resulted in a reduced fatty acid transport across the sarcolemmal membrane.

**EXPERIMENTAL PROCEDURES**

**Animals**—Female Sprague-Dawley rats (247.6 ± 2.6 g) were randomly assigned to one of three groups (ad libitum fed saline-treated (control), pair-fed saline-treated (pair-fed), or leptin-treated (n = 8 per group)). In anesthetized (halothane) animals, miniosmotic pumps (2ML2; Durect Corp., Cupertino, CA) were implanted subcutaneously, with leptin (Amgen, Thousand Oaks, CA). A leptin dosage of 0.5 mg/kg/day was used, since this dosage was previously demonstrated to induce moderate hyperleptinemia (10, 19). Animals, assigned to individual cages, were kept on a 12 h/12 h light/dark cycle. Water was freely accessible for all groups. Food intake was ad libitum for both the control and leptin-treated animals, whereas pair-fed treated animals were fed the same amount of chow as the leptin-treated animals consumed. Body mass was monitored weekly over the 2-week treatment period. The committees on animal care at the Universities of Waterloo and Guelph approved all procedures.

**Blood and Tissue Sampling**—Blood samples were collected at the completion of treatment (2 weeks) via cardiac puncture after exsion of red and white skeletal muscle. Samples were taken in the fed state between 0000 and 1100 to eliminate diurnal variability. Serum leptin and insulin concentrations were assayed in duplicate using radioimmunoassay kits (Linco, St. Charles, MO) specific for rat leptin and insulin. Fatty acids were assayed using a Wako NEFA kit (Wako Chemical, Richmond, VA). Serum glucose levels were determined fluorometrically (20). Soleus muscle intramuscular triacylglycerol content was determined on freeze-dried samples, which were dissected free of all visible connective tissue and blood, as previously outlined (21).

**Giant Sarcolemmal Vesicles**—Vesicles from red (vastus intermedius, red vastus lateralis, red gastrocnemius, red tibialis anterior) and white muscles (plantaris, white vastus lateralis, white gastrocnemius, white tibialis anterior) were prepared as we have described in detail previously (12). Vesicles were immediately used for transport experiments. In addition, some of the vesicles were placed in a blood cell counting chamber and were photographed under a phase-contrast microscope to determine vesicle size and density. Remaining vesicles were stored at −80°C for determinations of plasma membrane FAT/CD36 and FABPpm.

**Fatty Acid Transport**—Palmitate uptake has been shown to be linear for up to 25 s in vesicles from red and white muscles, due in part to the large intravesicular sink of FABPc, which is present in great excess in giant vesicles derived from red and white muscles (12). The content of FABPc in muscles was determined by sandwich-type enzyme-linked immunosorbent assay as previously described (12). In the present experiments, palmitate (15 μM) uptake by giant sarcolemmal vesicles (80 μg of protein) was determined over a 15-s period, as we have previously described in detail (12).

**Western and Northern Blotting**—The putative fatty acid transporters FAT/CD36 and FABPpm were measured in muscle homogenates as well as in plasma membranes of giant sarcolemmal vesicles. To detect FAT/CD36 and FABPpm, we used antibodies and procedures that have been described previously (12, 15, 17, 20). Messenger RNA for FAT and FABPpm were measured in red and white vastus muscle using procedures previously described (24).

**RESULTS**

**Body Composition and Food Intake**—Food intakes were significantly reduced in leptin-treated animals (−33%; p < 0.01) compared with ad libitum fed controls (Fig. 1A). In pair-fed treated animals, food intake was matched with leptin-treated animals. Over the 2-week treatment period, food intake was constant in all groups. Body mass was reduced in both leptin and pair-fed treated animals (−12.5%; p < 0.05) compared with controls following 2 weeks of treatment (Fig. 1B).

**Circulating Concentrations of Leptin, Insulin, Glucose, and Fatty Acids**—Chronic leptin treatment increased circulating leptin (8.75 ± 0.75 ng/ml) compared with control (1.72 ± 0.30 ng/ml) and pair-fed animals (0.5 ± 0.10 ng/ml) (p < 0.05). In contrast, leptin treatment reduced circulating insulin (0.20 ± 0.05 ng/ml) and fatty acids (0.18 ± 0.40 mm) compared with control (insulin, 1.30 ± 0.04 ng/ml; FA, 0.35 ± 0.05 mm) and pair-fed animals (insulin, 1.17 ± 0.30 ng/ml; fatty acids, 0.18 ± 0.10 mm) (p < 0.05). Glucose concentration did not differ among the three groups of animals (5.05–5.20 mm) (p > 0.05).

**Intramuscular Triacylglycerols**—Intramuscular triacylglycerols (Fig. 2) in soleus muscle was significantly reduced in leptin-treated animals, relative to control (−41%; p = 0.03) and pair-fed animals (−33%; p = 0.05). Intramuscular triacylglycerols of pair-fed animals was not significantly different from controls.

**FAT/CD36 and FABPpm mRNA and Protein Expression**—With leptin treatment, FAT mRNA abundance was significantly reduced in both red (−70%; p < 0.001) and white (−48%; p < 0.05) muscles (Fig. 3A), while FABPpm mRNA abundance was unchanged (Fig. 3B). We measured the protein expression of FAT/CD36 and FABPpm in both red and white muscle homogenates (intracellular plus plasma membrane pools) as well as in plasma membrane only fractions derived from giant sarcolemmal vesicles. Chronic leptin treatment reduced FAT/CD36 protein in red (−32%; p < 0.01) and white muscle homogenates (−15%; p > 0.05) (Fig. 4A). FABPpm protein in both red and white muscle homogenates was unchanged with leptin treatment (Fig. 4B). Plasma membrane FAT/CD36 (Fig. 5A) and FABPpm (Fig. 5B) were significantly reduced following leptin treatment in both red and white muscles (FAT/CD36: red −49%, white −57%; FABPpm: red −26%, white −43%; p < 0.05).

**Palmitate Transport in Giant Sarcolemmal Vesicles**—To determine whether leptin affected fatty acid transport in muscle giant sarcolemmal vesicles obtained from red and white skeletal muscle were used. We have previously characterized fatty acid transport in red and white muscle (12). The giant vesicles from both red and white muscle were spherical in appearance and averaged 13.8 ± 0.05 μm (n = 120) in diameter, and vesicle size was similar in all groups (p > 0.05). As previously demonstrated (12), red muscle contained a greater sink for incorpo-
rated palmitate due to an elevated FABPc content (red, 1.53 ± 0.25 mg/g, wet weight; white, 0.23 ± 0.05 mg/g, wet weight; \( p < 0.001 \)). There was no difference in FABPc content among treatments. As we have demonstrated previously (12), palmitate uptake was greater in red versus white skeletal muscle (\( 58\% \), \( p < 0.001 \); Fig. 6). Palmitate uptake was significantly reduced in leptin-treated versus control animals in both red and white skeletal muscle (~33 and −46%, respectively; \( p < 0.05 \); Fig. 6) but was not different between pair-fed and control animals.

**DISCUSSION**

The movement of fatty acids across the sarcolemma involves the fatty acid transporters FAT/CD36 (25, 26) and FABPpm (27) and is the first step in the regulation of fatty acid metabolism. Recent studies in our laboratory (12, 23, 24) and others (28, 29) have demonstrated that fatty acid transporter expression is regulated by the metabolic demand of skeletal muscle (23), obesity (28, 29), and diabetes (29). These latter studies (28, 29) suggest that there may be hormonal regulation of fatty acid transporter expression, resulting in altered rates of plasma membrane fatty acid transport. Leptin may be one of the endocrine signals regulating fatty acid transporter expression, and skeletal muscle may be an important target for leptin. This tissue is important for regulating fatty acid homeostasis because of its mass (40% of body weight) and highly variable metabolic rate.

In isolated muscles, the acute (≤60 min) effects of leptin include an increased rate of fatty acid oxidation and a concomitantly reduced rate of esterification (5–7). Prolonged hyperleptinemia (6–14 days) reduces muscle triacylglycerol depots (30), an effect that may be achieved, in part, by reducing the protein mediated uptake of fatty acids into the myocyte. Therefore, we have investigated the effects of chronically (14 days) elevated circulating leptin levels on fatty acid transporter expression.
and localization in red and white rat skeletal muscle as well as on fatty acid transport into giant sarcolemmal vesicles derived from these two types of muscle. Several novel findings are reported in this study. Leptin treatment reduced FAT mRNA abundance and the expression of FAT/CD36 protein, while FABPpm mRNA and protein expression were not altered; however, both of the fatty acid transport proteins, FAT/CD36 and FABPpm, located at the plasma membrane were reduced, which resulted in a reduced rate of fatty acid transport into red and white skeletal muscle giant sarcolemmal vesicles. These effects were not observed in pair-fed animals that lost the same body weight as the leptin-treated animals.

Importantly, the chronic (2 weeks) effects of leptin on fatty acid uptake and transporters are not comparable with studies in which isolated muscles have been acutely exposed to leptin (5–7). In those studies, leptin did not alter fatty acid uptake; rather, leptin repartitioned the fatty acids taken up toward oxidation and away from esterification (5–7).

In this study, we induced moderate levels of hyperleptinemia (~4-fold increase), a level that is similar to that obtained following 2 weeks of high fat feeding in rodents (5). This physiologic increase in leptin reduced intramuscular triacylglycerol depots and circulating insulin and fatty acids, while not altering circulating glucose concentrations. These results parallel studies in which pharmacological levels of leptin have been administered (8, 30–33). Since the serum insulin concentrations were already quite low in the control animals, it seems unlikely that a retarded rate of insulin-stimulated fatty acid esterification, rather than the increased leptin concentrations, accounted for the reduction in the intramuscular triacylglycerol depots. The reduction in circulating fatty acids is probably due to a selective depletion of the labile visceral adipose stores

![FIG. 4. Muscle homogenate protein expression of FAT/CD36 (A) and FABPpm (B) in red and white gastrocnemius muscle following a 2-week treatment period. Control, ad libitum fed, sedentary animals; Pairfed, pair-fed sedentary animals (pair feeding occurred with leptin-treated animals); Leptin, continuous leptin infusion for 2 weeks; a, significantly different from control; b, significantly different from pair-fed; c, significantly different from red.](http://www.jbc.org/)

![FIG. 5. Plasma membrane protein expression of FAT/CD36 (A) and FABPpm (B) in red and white gastrocnemius muscle following a two-week treatment period. Control, ad libitum fed, sedentary animals; Pairfed, pair-fed sedentary animals (pair feeding occurred with leptin-treated animals); Leptin, continuous leptin infusion for 2 weeks. a, significantly different from control; b, significantly different from pair-fed; c, significantly different from red.](http://www.jbc.org/)

![FIG. 6. Fatty acid transport into giant sarcolemmal vesicles derived from red and white gastrocnemius muscle following a 2-week treatment period. Control, ad libitum fed, sedentary animals; Pairfed, pair-fed sedentary animals (pair feeding occurred with leptin-treated animals); Leptin, continuous leptin infusion for 2 weeks. a, significantly different from control; b, significantly different from pair-fed; c, significantly different from red.](http://www.jbc.org/)
The reduced serum insulin and unaltered glucose concentrations indicated that insulin sensitivity was improved, an observation that has previously been observed following chronic leptin treatment (3, 8, 19, 31, 32). This improved insulin sensitivity is probably due to the reductions in muscle triacylglycerol depots, since the relationship between elevated intramuscular triacylglycerol depots and impaired insulin sensitivity is well established in rodents (3, 11) and humans (1, 2), although the underlying mechanism(s) are unknown. It has been suggested that intramuscular triacylglycerol depots may reduce insulin sensitivity by impairing the insulin-signaling pathway (37, 38). Since fatty acid transport in the leptin-treated animals was reduced, this may also contribute to reducing the intramuscular triacylglycerol depots and in this manner contribute to the improved insulin sensitivity observed in leptin-treated animals.

The giant sarcolemmal vesicle preparation used in our studies allows for a true measurement of FA transport, independent of metabolism (12). Unlike other preparations that have been used to measure FA transport, such as hepatocytes, cardiomyocytes, and adipocytes (28, 29), giant sarcolemmal vesicles provide many advantages. We (12) have shown that, in giant sarcolemmal vesicles, (a) initial rates of FA uptake can be determined; (b) giant vesicles contain FABPs in excess, which provides for a large intravesicular fatty acid sink; (c) all of the palmitate taken up by the vesicles is fully recovered as unesterified palmitate (i.e. none of the palmitate taken up is esterified, oxidized, or associated with the plasma membrane); and (d) vesicles are 100% oriented right side out. Therefore, the giant sarcolemmal vesicle preparation used in the present study provides an appropriate model with which to examine leptin’s effects on FA transport in skeletal muscle.

In the present study, we observed that chronic leptin treatment reduces palmitate transport into giant sarcosomal vesicles. This reduction was associated with concomitant reductions in plasma membrane FAT/CD36 and FABPpm proteins. Previously, we have shown that fatty acid uptake in heart and skeletal muscle is highly correlated with the fatty acid transporters, FAT/CD36 and FABPpm, but not FATP1, located at the plasma membrane (12, 39). This correlation between these plasma membrane fatty acid transporters and fatty acid transport was confirmed in the present studies (Fig. 7). It is believed that FABPpm and FAT/CD36 may interact with each other to facilitate fatty acid uptake across the sarcolemma (12), but the specific role of each transporter has not been completely elucidated. It is known that both proteins are critical for mediating fatty acid transport in skeletal muscle, because blocking of either transporter results in significantly reduced rates of fatty acid uptake (39). While chronic leptin treatment led to significant reductions in both FAT/CD36 and FABPpm protein in the plasma membrane of skeletal muscle, the mechanisms by which these reductions occurred were different for the two transport proteins.

The regulation of expression of FAT/CD36 and FABPpm has been examined in only a few studies. At the level of their mRNAs, one or both of these transporters are altered in some but not all models of genetic obesity and diabetes, and this seems to depend also on the tissue being examined (26–29). Altering the metabolic demands of the muscle by chronic muscle contraction for 7 days (23) has been demonstrated to increase the expression of FAT/CD36 and fatty acid transport rates in skeletal muscle. In the present experiments, leptin decreased both the FAT mRNA abundance and the expression of FAT/CD36 protein in red and white skeletal muscles, suggesting that prolonged exposure to leptin reduced the transcription of FAT. Contrary to the effects on FAT/CD36, leptin

---

2 J. J. F. P. Luiken, unpublished data.
did not alter the FABPpm mRNA abundance or its protein product. Thus, in muscle, leptin alters the expression of FAT/CD36, but not FABPpm.

Our studies demonstrate clearly that whether or not the expression of the fatty acid transport proteins are altered, fatty acid transport can be lowered due to a reduction in plasmalemmal FAT/CD36 and FABPpm. We (17) have recently shown that FAT/CD36 is located both at the plasma membrane and in an intracellular (endosomal) depot. Muscle contraction causes a translocation of the FAT/CD36 transporter from endosomal compartments to the plasma membrane within 5 min of the onset of stimulation, leading to an increase in fatty acid transport rates (17). Thus, the plasmalemmal localization of FAT/CD36 can be regulated independently of the total available pool, analogous to the regulation of GLUT-4. However, in the present study, the leptin-induced reductions in plasmalemmal FAT/CD36 would seem to be attributable to the reduced expression of this protein and not its intracellular redistribution.

In contrast, the leptin-induced reductions in plasmalemmal FABPpm cannot be explained by reductions in the total pool of this transporter, since the total FABPpm availability was not affected by leptin treatment. This suggests that the localization of FABPpm in the plasma membrane is also an important means to regulate fatty acid uptake. The selective reduction in plasma membrane FABPpm in the face of unaltered total quantities of muscle FABPpm protein content suggests that there may therefore also be an intracellular pool of FABPpm. Indeed, we now have preliminary evidence for this suggestion.

Dietary and genetic models of rodent obesity and diabetes are characterized by either a lack of leptin (ob/ob mice) (40), or leptin receptor defects (db/db mice and obese Zucker (fa/fa) rat) (41, 42). In skeletal muscles of obese Zucker (fa/fa) rat, FAT/CD36, but not FABPpm.

Acknowledgments—We acknowledge the excellent technical assistance of Yoga Arumugam and Lisa Code.

REFERENCES

1. Phillips, D. I., Caddy, S., Hsu, Y., Fielding, K. N., Bornthwick, A. C., and Taylor, R. (1996) Metabolism 45, 847–850
2. Pan, D. A., Lillyjo, A. D., Kriketos, M. R., Baur, L. A., Bogardus, A. B., Jenkins, A. B., and Storlien, L. H. (1997) J. Clin. Invest. 98, 983–987
3. Buehtner, R., Newgard, C. B., Rhodes, C. J., and O’Doherty, R. M. (2000) Am. J. Physiol. 278, E563–E569
4. Pellemounter, M. A., Cullen, M. J., Baker, B. M., Hecht, R., Winter, D., Boone, T., and Collins, F. (1995) Science 269, 540–543
5. Steinberg, G. R., and Dyck, D. J. (2000) Am. J. Physiol. 279, E1374–E1382
6. Musico, D. M., Dohn, G. L., Fiedorek, F. T. J., Tapscott, E. B., and Coleman, R. A. (1997) Diabetes 46, 1360–1363
7. Musico, D. M., Dohn, G. L., Tapscott, E. B., and Coleman, R. A. (1999) Am. J. Physiol. 276, E913–E921
8. Chinoosokwong, N., Wang, J.-L., and Shi, Z.-Q. (1999) Diabetes 48, 1407–1492
9. Wang, J.-L., Chinoosokwong, N., Scully, S., Qi, M., and Shi, Z.-Q. (1999) Endocrinology 140, 2117–2124
10. Harris, R. B., Zhou, J., Redmann, S. M., Smagin, G. N., Smith, S. R., Rodgers, E., and Zachwieja, J. J. (1998) Endocrinology 139, 8–13
11. Storlien, L. H., Jenkins, A. B., Chisholm, D. J., Pascoe, W. S., Kheusi, S., and Kraegen, E. W. (1991) Diabetes 40, 280–289
12. Bonen, A., Luiken, J. F. P., Liu, S., Dyck, D. J., Kiens, B., Kristiansen, S., Tordi, L., van der Vusse, G. J., and Glatz, J. (1999) Am. J. Physiol. 275, E471–E478
13. Schaffer, J. E., and Lodish, H. F. (1994) Cell 78, 427–436
14. Coo, N. R., Smith, A. J., Freychet, B. I., Watkinson, P. A., and Bernholt, D. A. (1999) J. Biol. Chem. 274, 36300–36304
15. Ibrahimi, A., Bonen, A., Blake, W. D., Hajir, L., Xi, X., Zhong, K., Cameron, R., and Abumrad, N. A. (1999) J. Biol. Chem. 274, 20761–20766
16. Febbraio, M., Abumrad, N. A., Hajir, D. P., Sharma, K., Cheng, W., Pearce, S. F. A., and Silverstein, R. L. (1999) J. Biol. Chem. 274, 19095–19062
17. Bonen, A., Luiken, J. F. P., Arumugam, Y., Glatz, J., and Tandon, N. N. (2000) J. Biol. Chem. 275, 14501–14508

A. Bonen, J. F. P. Luiken, and J. F. C. Glatz, unpublished data.
18. Boden, G. (1996) Diabetes Care 19, 394–395
19. Barrilà, N., Wang, J., Massion, D., Vuguin, P., Hawkins, M., and Rossetti, L. (1997) J. Clin. Invest. 100, 3105–3110
20. Bergmeyer, H. U., Bernt, E., Schmidt, F., and Stork, H. (1974) in Methods of Enzymatic Analysis (Bergmeyer, H. U., ed) Vol. III, pp. 1196–1201, Academic Press, Inc., New York
21. Frayn, K. N., and Maycock, P. F. (1980) J. Lipid Res. 21, 139–144
22. McCullagh, K. J. A., O’Brien, M., and Bonen, A. (1996) Mol. Cell. Biochem. 156, 51–57
23. Bonen, A., Dyck, D. J., Ibrahimii, A., and Abumurad, N. A. (1999) Am. J. Physiol. 276, E642–E649
24. Dyck, D. J., Miskovic, D., Code, L., Luiken, J. J. F. P., and Bonen, A. (2000) Am. J. Physiol. 278, E778–E875
25. Abumurad, N. A., El-Maghrabi, M. R., Amri, E.-Z., Lopez, E., and Grimaldi, P. (1993) J. Biol. Chem. 268, 17665–17668
26. Berk, P. D., Zhou, S.-L., Kiang, C.-L., Stump, D. D., Bradbury, M. W., and Isola, L. M. (1997) J. Biol. Chem. 272, 8830–8835
27. Zhou, S. L., Stump, D., Sorrentino, D., Potter, B. J., and Berk, P. D. (1992) J. Biol. Chem. 267, 14456–14461
28. Mononen, R. A., Fuller, J., Moser, A. H., Smith, P. J., Grunfeld, C., and Feingold, K. R. (1999) Diabetes 48, 121–127
29. Berk, P. D., Zhou, S.-L., Kiang, C.-L., Stump, D. D., Pan, X., and Bradbury, M. W. (1999) J. Biol. Chem. 274, 28626–28631
30. Shimabukuro, M., Koyama, G. Chen, M.-Y. Wang, F., Trieu, Y. Lee, C. B. Newgard, and R. H. Unger. (1997) Proc. Natl. Acad. Sci. U. S. A. 94, 4637–4641
31. Yaspelkis, B. B., Davis, J. R., Saberi, M., Smith, T. L., Rozental, A., Singh, M., Fernandez, V., Trevino, B., Chinookoswong, N., Wang, J., Shi, Z.-Q., and Levin, N. (2001) Am. J. Physiol. 280, E130–E142
32. Barzilia, N., She, L., Liu, L., Wang, J., Hu, M., Vuguin, P., and Rossetti, L. (1999) Am. J. Physiol. 277, E291–E298
33. Pelsers, M. L., Luitgerink, J. T., van Nieuwenhoven, F. A., Tandon, N. N., van der Vasse, G. J., Arends, J. W., Hogenboom, H. R., and Glaz, J. F. C. (1999) Biochem. J. 337, 407–414
34. Luiken, J. J. F. P., Azumugam, Y., Dyck, D. J., Bell, R. C., Pelsers, M. L., Turcotte, L. P., Tandon, N. N., Glaz, J. F. C., and Bonen, A. (2001) J. Biol. Chem. 276, 40567–40573
35. Luiken, J. J. F. P., Turcotte, L. P., and Bonen, A. (1999) J. Biol. Chem. 274, 2516–2322
36. Han, D.-H., Hansen, P. A., Host, H. H., and Holloszy, J. O. (1997) Diabetes 46, 1761–1767
37. Kim, J. K., Wi, J. K., and Young, J. H. (1996) Diabetes 45, 651–658
38. Luiken, J. J. F. P., Turcotte, L. P., and Bonen, A. (1999) J. Lipid Res. 40, 1007–1016
39. Zhang, Y, Proenza, R., Maffei, M., Barone, M., Leopold, L., and Friedman, J. M. (1994) Nature 372, 442–443
40. Tartaglia, L., Dembski, M., Weng, X., Deng, N., Culpess, J., Devos, R., Richards, G. J., Campfield, L. A., Clark, F. T., Deeds, J., Muri, C., Sanker, S., Moriarty, A., Moore, K. J., Smutko, J. S., Mays, G. G., Woolf, E. A., Monroe, C. A., and Tepper, R. I. (1995) Cell 83, 1263–1271
41. Chua, S. C., Jr., Chung, W. K., Wu-Peng, X., Zhang, Y., Liu, S. M., Tartaglia, L., and Leibel, R. L. (1996) Science 271, 994–996
42. Somekura, J.-A., Veerkamp, J. H., Turcotte, L. P., and Kelley, D. E. (1999) FASEB J. 13, 2051–2060
43. Unger, R. H., Zhou, Y. T., and Orci, L. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 2327–2332
44. Coburn, C. T., Knapp Jr, F. F., Febbraio, M., Beets, A. L., Silverstein, R. L., and Abumrad, N. A. (2000) J. Biol. Chem. 275, 32523–32529
45. Megeney, L. A., Neufier, P. D., Dehm, G. L., Tan, M. H., Blewett, C. A., Elder, G. C. B., and Bonen, A. (1993) Am. J. Physiol. 264, E583–E593
46. Megeney, L. A., Michel, R. N., Boudreau, C. S., Fernandez, P. K., Prasad, M., Tan, M. H., and Bonen, A. (1995) Am. J. Physiol. 269, R1148–R1153
47. McCullagh, K. J. A., and Bonen, A. (1995) Am. J. Physiol. 269, R884–R888
48. Wilson, M. C., Jackson, V. N., Hedle, C., Price, N. T., Pilegaard, H., Juel, C., Bonen, A., Montgomery, L., Hutter, O. F., and Halestrap, A. P. (1998) J. Biol. Chem. 273, 15920–15926
Chronic Leptin Administration Decreases Fatty Acid Uptake and Fatty Acid Transporters in Rat Skeletal Muscle
Gregory R. Steinberg, David J. Dyck, Jorges Calles-Escandon, Narendra N. Tandon, Joost J. F. P. Luiken, Jan F. C. Glatz and Arend Bonen

J. Biol. Chem. 2002. 277:8854-8860.
doi: 10.1074/jbc.M107683200 originally published online November 29, 2001

Access the most updated version of this article at doi: 10.1074/jbc.M107683200

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 49 references, 26 of which can be accessed free at http://www.jbc.org/content/277/11/8854.full.html#ref-list-1