Proceedings of the Nutrition Society (2004), **63**, 239–244 DOI:10.1079/PNS2004332

The 12th Conference of the International Research Group on the Biochemistry of Exercise was held at Maastricht University, Maastricht, The Netherlands on 13–16 July 2003

Symposium 2: The fatty acid transporters of skeletal muscle

Studies of plasma membrane fatty acid-binding protein and other lipid-binding proteins in human skeletal muscle

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The first putative fatty acid transporter identified was plasma membrane fatty acid-binding protein ($FABP_{pm}$). Later it was demonstrated that this protein is identical to the mitochondrial isoform of the enzyme aspartate aminotransferase. In recent years data from several cell types have emerged, indicating that $FABP_{pm}$ plays a role in the transport of long-chain saturated and unsaturated fatty acids. In the limited number of studies in human skeletal muscle it has been demonstrated that dietary composition and exercise training can influence the content of $FABP_{pm}$. Ingestion of a fat-rich diet induces an increase in $FABP_{pm}$ protein content in human skeletal muscle in contrast to the decrease seen during consumption of a carbohydrate-rich diet. A similar effect of a fat-rich diet is also observed for cytosolic fatty acid-binding protein and fatty acid translocase/CD36 protein expression. Exercise training up regulates $FABP_{pm}$ protein content in skeletal muscle, but only in male subjects; no significant differences were observed in muscle $FABP_{pm}$ content in a cross-sectional study of female volunteers of varying training status, even though muscle $FABP_{pm}$ content did not depend on gender in the untrained state. A higher utilization of plasma long-chain fatty acids during exercise in males compared with females could explain the gender-dependent influence of exercise training on $FABP_{pm}$. The mechanisms involved in the regulation of the function and expression of $FABP_{pm}$ protein remain to be clarified.

Diet: Gender: Exercise: Training: Lipid-binding proteins

In recent years data have been obtained suggesting that fatty acid-binding proteins participate in the transport of long-chain fatty acids (LCFA) in different tissues (Bonen *et al*. 1998*a*,*b*; Abumrad *et al*. 1999). Among these proteins are particularly: (1) plasma membrane fatty acid-binding protein ($FABP_{pm}$), an approximately 43 kDa protein located peripherally on the plasma membrane; (2) fatty acid translocase (FAT)/CD36, an 88 kDa integral membrane glycoprotein, with two predicted transmembrane domains, which is identical to glycoprotein IV or CD36 of human blood platelets and leucocytes (Abumrad *et al*. 1993); (3) fatty acid transport protein, a 63 kDa integral protein with six predicted transmembrane domains (Schaffer & Lodish, 1994; Hirsch *et al*. 1998; Bonen *et al*. 1999). Furthermore, two proteins are responsible for the transport of LCFA and long-chain acyl-CoA esters in the aqueous cytoplasm: the 14–15 kDa cytosolic fatty acid-binding protein ($FABP_c$; Glatz *et al*. 1993; Glatz & Storch, 2001) and the 10 kDa acyl-CoA-binding protein (Mogensen *et al*. 1987; Faergeman & Knudsen, 1997).

$FABP_{pm}$ was isolated in 1985 from highly-purified rat liver plasma membranes by high-affinity chromatography (Stremmel *et al*. 1985) and was the first putative fatty acid transporter identified. Binding studies indicated that the protein had a high affinity for LCFA, and antibodies raised against the protein confirmed its location on the plasma

Abbreviations: $FABP_c$, cytosolic fatty acid-binding protein; $FABP_{pm}$, plasma membrane fatty acid-binding protein; FAT, fatty acid translocase; LCFA, long-chain fatty acids; mAspAT, mitochondrial isoform of aspartate aminotransferase.

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membrane (Stremmel *et al*. 1985; Stump *et al*. 1993). A role for $FABP_{pm}$ in the transport of long-chain saturated and unsaturated fatty acids has been suggested from the use of antibodies against $FABP_{pm}$, which leads to inhibition of LCFA uptake in various cell types and of transport of LCFA into giant vesicles of skeletal muscle in rats in a dose-dependent manner (Schwieterman *et al*. 1988; Sorrentino *et al*. 1988; Stremmel, 1988; Zhou *et al*. 1992; Bonen *et al*. 1998*b*; Turcotte, 1999). However, elucidation of the role of $FABP_{pm}$ in LCFA transport was challenged by the finding that $FABP_{pm}$ is identical to the mitochondrial isoform of the enzyme aspartate aminotransferase (mAspAT; Stremmel *et al*. 1985; Berk *et al*. 1990; Stump *et al*. 1993; Bradbury & Berk, 2000). A role for mAspAT/$FABP_{pm}$ in fatty acid binding was suggested by molecular-modelling studies of the crystal structure of mAspAT that have identified a pocket, within the larger domain of the enzyme, that is of sufficient size to accommodate the typical LCFA (Berk & Stump, 1999). Whether this pocket serves as a fatty acid-binding site remains to be elucidated. Recently, a study using a polyclonal antibody against rat mAspAT in immunogold electron microscopy of rat tissue sections has shown a strong labelling of mitochondria in several cell types (Cechetto *et al*. 2002). Labelling was also observed in other locations, such as endothelial cell surfaces, and it was concluded from these observations that mAspAT/$FABP_{pm}$ is both a mitochondrial enzyme and a plasma membrane protein (Cechetto *et al*. 2002).

Influence of diet on plasma membrane fatty acid-binding protein, fatty acid translocase/CD36 and cytosolic fatty acid-binding protein

As both the membrane-associated ($FABP_{pm}$, FAT/CD36, fatty acid transport protein) and cytoplasmic ($FABP_c$, acyl-CoA-binding protein) lipid-binding proteins are involved in the lipid metabolism of the cell, interventions leading to changes in lipid metabolism may also induce altered regulation of these proteins. Dietary manipulation is one such intervention, but there is little information in the literature on the effects of diet and dietary composition on the different lipid-binding proteins. Available information is mainly on the cytoplasmic $FABP_c$. Moreover, most data have been derived from rat studies in which animals were fed a fat-rich diet, mainly composed of saturated fatty acids (Coe & Bernlohr, 1998). Collectively, these data have shown that $FABP_c$ in heart and skeletal muscle does not respond to an increase in dietary fatty acids (Coe & Bernlohr, 1998; Storch & Thumser, 2000). In contrast, a recent study in rat heart and skeletal muscle has shown that ingestion of a diet rich in *n*-3 fatty acids markedly increases $FABP_c$ content (Clavel *et al*. 2002), suggesting that the length and extent of saturation of the C chain of the fatty acids are important for the regulation of $FABP_c$.

To evaluate the influence of dietary composition in human skeletal muscle a group of healthy non-obese young male subjects aged 30–40 years was studied. The subjects were randomly assigned to two groups, with one group consuming a fat-rich diet and the other group consuming a carbohydrate-rich diet for 4 weeks. During the intervention period the subjects kept their physical activity habits unchanged and all subjects followed well-controlled experimental diets. The nutrient composition (% energy) of the experimental diets was carbohydrate 65, protein 15 and fat 20 for the carbohydrate-rich diet and carbohydrate 21, protein 17 and fat 62 for the fat-rich diet. The fat ingested in the fat-rich diet had a high content of *n*-3 fatty acids and *n*-6 fatty acids, as described previously (Helge *et al*. 1996, 1998). Ingestion of the carbohydrate-rich diet for 4 weeks did not influence the $FABP_c$ protein content in *m. vastus lateralis*, whereas ingestion of the fat-rich diet induced a significant increase in $FABP_c$ content ($P<0{\cdot}05$; Fig. 1(c)). It has been suggested that FAT/CD36 and $FABP_c$ cooperate in the uptake of LCFA in cardiac and skeletal muscle (Luiken *et al*. 1999). Interestingly, in the dietary intervention study a similar change was observed in $FABP_c$ and FAT/CD36; an increase in FAT/CD36 protein content in *m. vastus lateralis* was seen during the fat-rich diet whereas no change was obtained during the carbohydrate-rich diet (Fig. 1(b)). Similar findings for the effect of diet on FAT/CD36 have emerged from the study by Cameron-Smith *et al*. (2003), in which the dietary intervention period was only 5 d. In the present diet study an increase in the content of $FABP_{pm}$ was also observed after 4 weeks, but only when the fat-rich diet was consumed. In fact, when the carbohydrate-rich diet was consumed a decrease in $FABP_{pm}$ content in *m. vastus lateralis* was obtained (Fig. 1(a)). There was no response in skeletal muscle $FABP_{pm}$ content to 1 week of dietary intervention. This finding is supported by the results of a recent study (Cameron-Smith *et al*. 2003) in which well-trained male subjects ingested either a carbohydrate-rich diet (70–75% energy as carbohydrate and <15% energy as fat) or a fat-rich diet (>65% energy as fat and <20% energy as carbohydrate) for 5 d; no change in the protein content of $FABP_{pm}$ in skeletal muscle was detected.

In summary, these data show that $FABP_{pm}$ expression requires a long-term (>1 week) dietary change for adaptations to take place in human skeletal muscle and that the adaptations to a fat-rich diet and a carbohydrate-rich diet occur in opposite directions. The data also indicate that the FAT/CD36 protein content of human skeletal muscle is increased by ingestion of a fat-rich diet for 5 d and that the long-term (4 weeks) increase in FAT/CD36 is paralleled by an increase in $FABP_c$ protein content.

Influence of exercise training on plasma membrane fatty acid-binding protein

It is well known that exercise training induces an increased capacity for lipid oxidation in skeletal muscle (Kiens *et al*. 1993). Only limited information is available on the influence of exercise training on the different lipid-binding proteins in skeletal muscle. Data from rats have revealed a 55% higher $FABP_{pm}$ protein content in red muscle of trained rats compared with untrained rats (Turcotte *et al*. 1999). The higher $FABP_{pm}$ protein content was associated with a higher palmitate uptake in the trained rats at rest

https://doi.org/10.1079/PNS2004332 Published online by Cambridge University Press

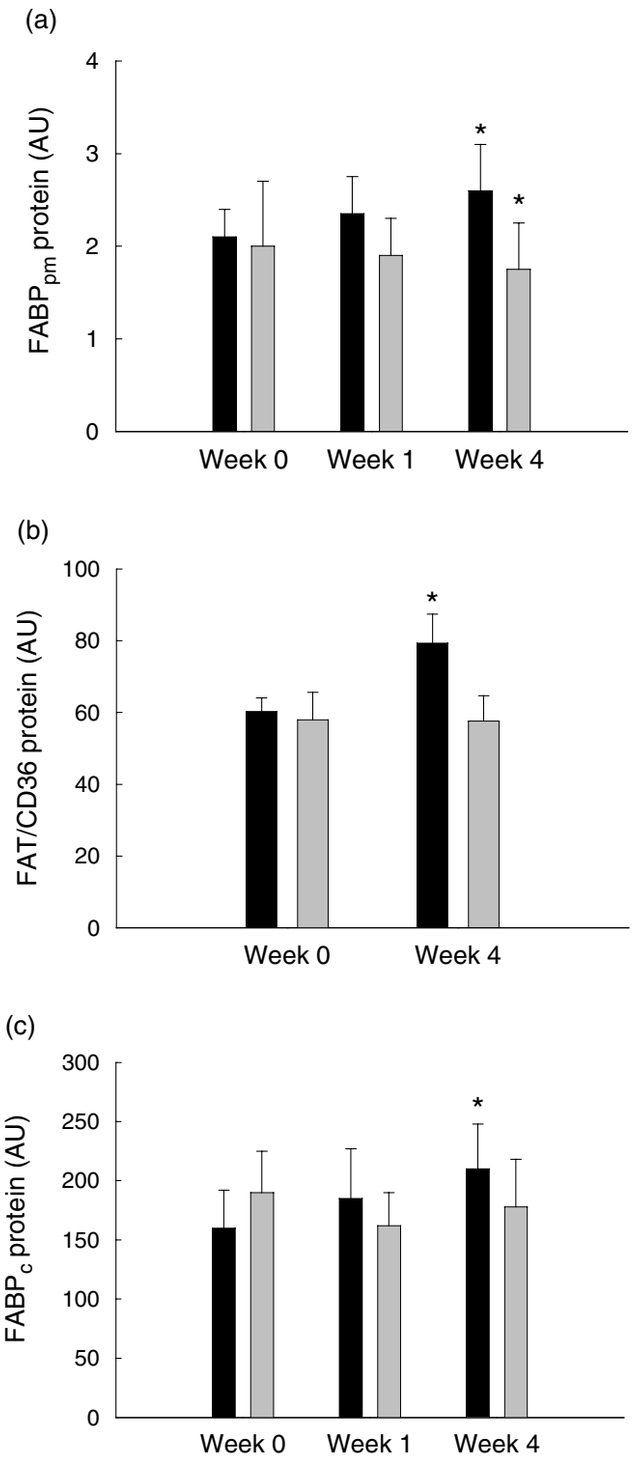

Fig. 1. Content of lipid-binding proteins in *m. vastus lateralis* of human volunteers before, during, and after ingestion of a fat-rich diet (■) or a carbohydrate-rich diet (□) for 4 weeks. (a) Plasma membrane fatty acid-binding protein ($FABP_{pm}$); (b) fatty acid translocase (FAT)/CD36; (c) cytosolic fatty acid-binding protein ($FAPB_c$). AU, arbitrary units. Values are means with their standard errors represented by vertical bars. Mean values were significantly different from those at 0 weeks on the corresponding diet: $^*P<0{\cdot}05$.

(48%), and during exercise both uptake and oxidation of palmitate were higher (57%) in the trained rats compared with the untrained rats (Turcotte *et al*. 1999). The authors suggested that the enhanced content of $FABP_{pm}$ could partly explain the training-induced increase in LCFA oxidation (Turcotte *et al*. 1999). Similarly, in healthy non-obese male volunteers 3 weeks of exercise training with knee extensors of one leg resulted in an increase in $FABP_{pm}$ protein content whereas no changes were observed in the contralateral untrained leg (Kiens *et al*. 1997). These findings in human skeletal muscle were supported by a recent cross-sectional study (B Kiens, C Roepstorff, JFC Glatz, A Bonen, P Schjerling, J Knudsen and JN Nielsen, unpublished results), which showed that the $FABP_{pm}$ protein content of *m. vastus lateralis* was significantly higher ($P<0{\cdot}05$) in a group of endurance-trained male volunteers who had been exercise training for several years, compared with an untrained male group. In contrast to these findings, the $FABP_{pm}$ protein content in *m. vastus lateralis* measured in female volunteers, who were matched to the male subjects according to peak V_{O_2}/kg lean body mass and training history, was similar in the untrained and the endurance-trained female groups and not significantly different from that for untrained males (B Kiens, C Roepstorff, JFC Glatz, A Bonen, P Schjerling, J Knudsen and JN Nielsen, unpublished results). Furthermore, no effect of training status was observed in skeletal muscle FAT/CD36 or $FABP_c$ content in either males or females (B Kiens, C Roepstorff, JFC Glatz, A Bonen, P Schjerling, J Knudsen and JN Nielsen, unpublished results). The fact that training induced up-regulation of $FABP_{pm}$ protein content was seen only in male subjects could explain, or could be explained by, the gender-related difference in utilization of the different lipid sources during exercise. Recent findings (C Roepstorff and B Kiens, unpublished results) provide support for such a notion. Untrained males (*n* 7) and females (*n* 7) as well as endurance-trained males (*n* 7) and females (*n* 7) exercised on a bicycle ergometer at the same relative work load (60% peak V_{O_2}) for 90 min. [^{13}C]palmitate was infused intravenously and arterial blood samples were obtained at rest and during exercise. Quantification of the rate of disappearance and oxidation of systemic plasma fatty acid was performed as described elsewhere (Roepstorff *et al*. 2002). The data demonstrated that during exercise the rate of disappearance of systemic plasma fatty acid was not significantly different for the untrained (26·6 (SE 4·8) μmol/kg lean body mass per min) and endurance-trained (19·1 (SE 3·1) μmol/kg lean body mass per min) female volunteers (C Roepstorff and B Kiens, unpublished results), which parallels the observation of no difference in $FABP_{pm}$ protein content in skeletal muscle between the two groups (B Kiens, C Roepstorff, JFC Glatz, A Bonen, P Schjerling, J Knudsen and JN Nielsen, unpublished results). In contrast, a significantly higher ($P<0{\cdot}05$) rate of disappearance of plasma fatty acid was observed during exercise in the endurance-trained male subjects (21·1 (SE 4·9) μmol/kg lean body mass per min) compared with the untrained male subjects (11·2 (SE 2·9) μmol/kg lean body mass per min) (C Roepstorff and B Kiens, unpublished results). These two groups also differed

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significantly ($P<0{\cdot}05$) in their skeletal muscle content of $FABP_{pm}$ (B Kiens, C Roepstorff, JFC Glatz, A Bonen, P Schjerling, J Knudsen and JN Nielsen, unpublished results). These data suggest that the greater reliance on plasma LCFA as an energy substrate during exercise in endurance-trained males compared with untrained males stimulates the up-regulation of the $FABP_{pm}$ protein in skeletal muscle. Alternatively, the higher $FABP_{pm}$ in endurance-trained males compared with untrained males may induce the greater reliance during exercise on blood-borne fatty acids in endurance-trained males than in untrained males.

Regulation of lipid-binding proteins

It may be hypothesized as to why dietary interventions but not exercise training can lead to such marked overall responses in the expression of lipid-binding proteins as those illustrated earlier. When a fat-rich diet is consumed, the expression of several lipid-binding proteins is up-regulated. In addition, consumption of a fat-rich diet also enhances the β-oxidative enzyme capacity of skeletal muscle (Helge & Kiens, 1997). Despite an increased β-oxidative capacity after consumption of a fat-rich diet, the LCFA taken up by muscle cells are obviously not all metabolized, as re-esterification to triacylglycerol in the muscle cell has been reported under such circumstances (Kiens *et al*. 1987; Helge *et al*. 2001). It has been suggested that the excess delivery and uptake of plasma LCFA in skeletal muscle as compared with the oxidation rate of LCFA, which is the case during consumption of a fat-rich diet, will lead to the accumulation of cellular fatty acids that are then available to stimulate up-regulation of transcription of the different lipid-binding proteins. In contrast, when exercise induces an increase in plasma LCFA concentration and uptake into muscle, this increase is paralleled by an increased lipid oxidation rate in the mitochondria as a result of enhanced energy demand. Under these circumstances accumulation of cellular fatty acids may not take place and, hence, no up-regulation of the lipid-binding proteins will occur. One exception is $FABP_{pm}$, as exercise training induces an increase in $FABP_{pm}$ content in skeletal muscle, but in males only. A possible explanation of this gender-related effect of exercise training on $FABP_{pm}$ could be the larger dependence on plasma lipids during exercise in males than in females. Females, in contrast, rely to some extent on other lipid sources during exercise, such as intramuscular triacylglycerols (Roepstorff *et al*. 2002; Steffensen *et al*. 2002).

The mechanism associated with the up-regulation of lipid-binding proteins by training and diet has not been fully elucidated, particularly in relation to $FABP_{pm}$, and certainly not in skeletal muscle. Recent studies in other tissues have indicated that LCFA act as modulators of gene expression (Grimaldi *et al*. 1999), and have suggested that the effects of LCFA are mediated by activation of the PPAR. The findings indicate that fatty acids of different chain length and extent of saturation interact with PPAR (Xu *et al*. 1999). After activation by LCFA, the PPAR/retinoid X receptor heterodimer is able to bind to the peroxisome proliferator response element found in a large number of genes encoding for proteins involved in lipid metabolism, such as FAT/CD36 (Van Bilsen *et al*. 2002) and $FABP_c$ (Besnard *et al*. 2002).

Interestingly, recent data on hepatocytes have shown that the liver isoform of $FABP_c$ induces the fatty acid transfer to the nuclear receptors through direct protein–protein interaction with PPARα and PPARγ, indicating that $FABP_c$ exerts an active role in gene regulation (Wolfrum *et al*. 2001). However, studies on the effects of specific PPAR activators on mRNA levels of FAT/CD36 and mAspAT/$FABP_{pm}$ in liver of mice suggest that expression of only FAT/CD36 mRNA, but not mAspAT/$FABP_{pm}$ mRNA, is under the control of PPARα (Motojima *et al*. 1998).

Conclusion

$FABP_{pm}$ has not been as well studied in rodent models or in man as other fatty acid transporters such as FAT/CD36 and $FABP_c$. The available evidence indicates that $FABP_{pm}$ protein is identical to mAspAT. The protein has been shown to be located in the mitochondria in several tissues, including skeletal muscle, and also in other sites, including the endothelial cell surface. The fatty acid content of the diet is involved in modulating $FABP_{pm}$ protein expression in human skeletal muscle, whereas exercise training only seems to influence the $FABP_{pm}$ protein content in males, as no effect of training status has been observed in females.

Acknowledgements

We thank Professors Arend Bonen, Jan F.C. Glatz and Lorraine Turcotte for kindly donating antibodies. We acknowledge the skilled technical assistance of Irene Bech Nielsen. The Danish National Research Foundation Grant 504-12 and The Danish Sports Research Council supported the studies.

References

Abumrad N, Coburn C & Ibrahimi A (1999) Membrane proteins implicated in long-chain fatty acid uptake by mammalian cells: CD36, FATP and FABPm. *Biochimica et Biophysica Acta* **1441**, 4–13.

Abumrad NA, el Maghrabi MR, Amri EZ, Lopez E & Grimaldi PA (1993) Cloning of a rat adipocyte membrane protein implicated in binding or transport of long-chain fatty acids that is induced during preadipocyte differentiation. Homology with human CD36. *Journal of Biological Chemistry* **268**, 17665–17668.

Berk PD & Stump DD (1999) Mechanisms of cellular uptake of long chain free fatty acids. *Molecular and Cellular Biochemistry* **192**, 17–31.

Berk PD, Wada H, Horio Y, Potter BJ, Sorrentino D, Zhou SL, Isola LM, Stump D, Kiang CL & Thung S (1990) Plasma membrane fatty acid-binding protein and mitochondrial glutamic-oxaloacetic transaminase of rat liver are related. *Proceedings of the National Academy of Sciences USA* **87**, 3484–3488.

Besnard P, Niot I, Poirier H, Clement L & Bernard A (2002) New insights into the fatty acid-binding protein (FABP) family in the small intestine. *Molecular and Cellular Biochemistry* **239**, 139–147.

Bonen A, Dyck DJ & Luiken JJ (1998*a*) Skeletal muscle fatty acid transport and transporters. *Advances in Experimental Medicine and Biology* **441**, 193–205.

Bonen A, Luiken JJ, Liu S, Dyck DJ, Kiens B, Kristiansen S, Turcotte LP, van der Vusse GJ & Glatz JF (1998*b*) Palmitate transport and fatty acid transporters in red and white muscles. *American Journal of Physiology* **275**, E471–E478.

Bonen A, Miskovic D & Kiens B (1999) Fatty acid transporters (FABPpm, FAT, FATP) in human muscle. *Canadian Journal of Applied Physiology* **24**, 515–523.

Bradbury MW & Berk PD (2000) Mitochondrial aspartate aminotransferase: direction of a single protein with two distinct functions to two subcellular sites does not require alternative splicing of the mRNA. *Biochemical Journal* **345**, 423–427.

Cameron-Smith D, Burke LM, Angus DJ, Tunstall RJ, Cox GR, Bonen A, Hawley JA & Hargreaves M (2003) A short-term, high-fat diet up-regulates lipid metabolism and gene expression in human skeletal muscle. *American Journal of Clinical Nutrition* **77**, 313–318.

Cechetto JD, Sadacharan SK, Berk PD & Gupta RS (2002) Immunogold localization of mitochondrial aspartate aminotransferase in mitochondria and on the cell surface in normal rat tissues. *Histology and Histopathology* **17**, 353–364.

Clavel S, Farout L, Briand M, Briand Y & Jouanel P (2002) Effect of endurance training and/or fish oil supplemented diet on cytoplasmic fatty acid binding protein in rat skeletal muscles and heart. *European Journal of Applied Physiology* **87**, 193–201.

Coe NR & Bernlohr DA (1998) Physiological properties and functions of intracellular fatty acid-binding proteins. *Biochimica et Biophysica Acta* **1391**, 287–306.

Faergeman NJ & Knudsen J (1997) Role of long-chain fatty acyl-CoA esters in the regulation of metabolism and in cell signalling. *Biochemical Journal* **323**, 1–12.

Glatz JF & Storch J (2001) Unravelling the significance of cellular fatty acid-binding proteins. *Current Opinion in Lipidology* **12**, 267–274.

Glatz JF, Vork MM, Cistola DP & van der Vusse GJ (1993) Cytoplasmic fatty acid binding protein: significance for intracellular transport of fatty acids and putative role on signal transduction pathways. *Prostaglandins, Leukotrienes and Essential Fatty Acids* **48**, 33–41.

Grimaldi PA, Teboul L, Gaillard D, Armengod AV & Amri EZ (1999) Long chain fatty acids as modulators of gene transcription in preadipose cells. *Molecular and Cellular Biochemistry* **192**, 63–68.

Helge JW & Kiens B (1997) Muscle enzyme activity in humans: role of substrate availability and training. *American Journal of Physiology* **272**, R1620–R1624.

Helge JW, Richter EA & Kiens B (1996) Interaction of training and diet on metabolism and endurance during exercise in man. *Journal of Physiology (London)* **492**, 293–306.

Helge JW, Watt PW, Richter EA, Rennie MJ & Kiens B (2001) Fat utilization during exercise: adaptation to a fat-rich diet increases utilization of plasma fatty acids and very low density lipoprotein-triacylglycerol in humans. *Journal of Physiology (London)* **537**, 1009–1020.

Helge JW, Wulff B & Kiens B (1998) Impact of a fat-rich diet on endurance in man: role of the dietary period. *Medicine and Science in Sports and Exercise* **30**, 456–461.

Hirsch D, Stahl A & Lodish HF (1998) A family of fatty acid transporters conserved from mycobacterium to man. *Proceedings of the National Academy of Sciences USA* **95**, 8625–8629.

Kiens B, Essen-Gustavsson B, Christensen NJ & Saltin B (1993) Skeletal muscle substrate utilization during submaximal exercise in man: effect of endurance training. *Journal of Physiology (London)* **469**, 459–478.

Kiens B, Essen-Gustavsson B, Gad P & Lithell H (1987) Lipoprotein lipase activity and intramuscular triglyceride stores after long-term high-fat and high-carbohydrate diets in physically trained men. *Clinical Physiology* **7**, 1–9.

Kiens B, Kristiansen S, Jensen P, Richter EA & Turcotte LP (1997) Membrane associated fatty acid binding protein (FABPpm) in human skeletal muscle is increased by endurance training. *Biochemical and Biophysical Research Communications* **231**, 463–465.

Luiken JJ, Turcotte LP & Bonen A (1999) Protein-mediated palmitate uptake and expression of fatty acid transport proteins in heart giant vesicles. *Journal of Lipid Research* **40**, 1007–1016.

Mogensen IB, Schulenberg H, Hansen HO, Spener F & Knudsen J (1987) A novel acyl-CoA-binding protein from bovine liver. Effect on fatty acid synthesis. *Biochemical Journal* **241**, 189–192.

Motojima K, Passilly P, Peters JM, Gonzalez FJ & Latruffe N (1998) Expression of putative fatty acid transporter genes are regulated by peroxisome proliferator-activated receptor alpha and gamma activators in a tissue- and inducer-specific manner. *Journal of Biological Chemistry* **273**, 16710–16714.

Roepstorff C, Steffensen CH, Madsen M, Stallknecht B, Kanstrup IL, Richter EA & Kiens B (2002) Gender differences in substrate utilization during submaximal exercise in endurance-trained subjects. *American Journal of Physiology* **282**, E435–E447.

Schaffer JE & Lodish HF (1994) Expression cloning and characterization of a novel adipocyte long chain fatty acid transport protein. *Cell* **79**, 427–436.

Schwieterman W, Sorrentino D, Potter BJ, Rand J, Kiang CL, Stump D & Berk PD (1988) Uptake of oleate by isolated rat adipocytes is mediated by a 40-kDa plasma membrane fatty acid binding protein closely related to that in liver and gut. *Proceedings of the National Academy of Sciences USA* **85**, 359–363.

Sorrentino D, Stump D, Robinson RB, White R, Kiang CL & Berk PD (1988) Oleate uptake by cardiac myocytes is carrier mediated and involves a 40-kD plasma membrane fatty acid binding protein similar to that in liver, adipose tissue, and gut. *Journal of Clinical Investigation* **82**, 928–935.

Steffensen CH, Roepstorff C, Madsen M & Kiens B (2002) Myocellular triacylglycerol breakdown in females but not in males during exercise. *American Journal of Physiology* **282**, E634–E642.

Storch J & Thumser AE (2000) The fatty acid transport function of fatty acid-binding proteins. *Biochimica et Biophysica Acta* **1486**, 28–44.

Stremmel W (1988) Uptake of fatty acids by jejunal mucosal cells is mediated by a fatty acid binding membrane protein. *Journal of Clinical Investigation* **82**, 2001–2010.

Stremmel W, Strohmeyer G, Borchard F, Kochwa S & Berk PD (1985) Isolation and partial characterization of a fatty acid binding protein in rat liver plasma membranes. *Proceedings of the National Academy of Sciences USA* **82**, 4–8.

Stump DD, Zhou SL & Berk PD (1993) Comparison of plasma membrane FABP and mitochondrial isoform of aspartate aminotransferase from rat liver. *American Journal of Physiology* **265**, G894–G902.

Turcotte LP (1999) Fatty acid binding proteins and muscle lipid metabolism in skeletal muscle. In *Biochemistry of Exercise*, vol. 5, pp. 201–215 [M Hargreaves, editor]. Champaign, IL: Human Kinetics.

Turcotte LP, Swenberger JR, Tucker MZ & Yee AJ (1999) Training-induced elevation in FABPPM is associated with increased palmitate use in contracting muscle. *Journal of Applied Physiology* **87**, 285–293.

Van Bilsen M, van der Vusse GJ, Gilde AJ, Lindhout M & Van der Lee KA (2002) Peroxisome proliferator-activated receptors: lipid binding proteins controlling gene expression. *Molecular and Cellular Biochemistry* **239**, 131–138.

Wolfrum C, Borrmann CM, Borchers T & Spener F (2001) Fatty acids and hypolipidemic drugs regulate peroxisome proliferator-activated receptors alpha- and gamma-mediated gene expression via liver fatty acid binding protein: a signaling path to the nucleus. *Proceedings of the National Academy of Sciences USA* **98**, 2323–2328.

Xu HE, Lambert MH, Montana VG, Parks DJ, Blanchard SG, Brown PJ, Sternbach DD, Lehmann JM, Wisely GB, Willson TM, Kliewer SA & Milburn MV (1999) Molecular recognition of fatty acids by peroxisome proliferator-activated receptors. *Molecular Cell* **3**, 397–403.

Zhou SL, Stump D, Sorrentino D, Potter BJ & Berk PD (1992) Adipocyte differentiation of 3T3-L1 cells involves augmented expression of a 43-kDa plasma membrane fatty acid-binding protein. *Journal of Biological Chemistry* **267**, 14456–14461.