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The subcellular compartmentation of fatty acid transporters is regulated differently by insulin and by AICAR

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Abstract Cellular fatty acid uptake is facilitated by a number of fatty acid transporters, FAT/CD36, FABPpm and FATP1. It had been presumed that FABPpm, was confined to the plasma membrane and was not regulated. Here, we demonstrate for the first time that FABPpm and FATP1 are also present in intracellular depots in cardiac myocytes. While we confirmed previous work that insulin and AICAR each induced the translocation of FAT/CD36 from an intracellular depot to the PM, only AICAR, but not insulin, induced the translocation of FABPpm. Moreover, neither insulin nor AICAR induced the translocation of FATP1. Importantly, the increased plasmalemmal content of these LCFA transporters was associated with a concomitant increase in the initial rate of palmitate uptake into cardiac myocytes. Specifically, the insulin-stimulated increase in the rate of palmitate uptake (+60%) paralleled the insulin-stimulated increase in plasmalemmal FAT/CD36 (+34%). Similarly, the greater AICAR-stimulated increase in the rate of palmitate uptake (+90%) paralleled the AICAR-induced increase in both plasmalemmal proteins (FAT/CD36 (+40%) + FABPpm (+36%)). Inhibition of palmitate uptake with the specific FAT/CD36 inhibitor SSO indicated that FABPpm interacts with FAT/CD36 at the plasma membrane to facilitate the uptake of palmitate. In conclusion, (1) there appears to be tissue-specific sensitivity to insulin-induced FATP1 translocation, as it has been shown elsewhere that insulin induces FATP1 translocation in 3T3-L1 adipocytes, and (2) clearly, the subcellular distribution of FABPpm, as well as FAT/CD36, is acutely regulated in cardiac myocytes, although FABPpm and FAT/CD36 do not necessarily respond identically to the same stimuli.

Keywords: Fatty acid transport; Translocation; FABPpm; FATP1; FAT/CD36

1. Introduction

Long chain fatty acids (LCFAs) are a principal source of energy for many tissues including the heart, which receives approximately 70% of its energy from LCFA oxidation [1]. While LCFAs are known to be taken up by cells through passive diffusion [2], other recent evidence has shown that LCFA transport could be facilitated via a highly regulated, protein-mediated mechanism [3–5] involving at least one or more LCFA binding proteins, including fatty acid translocase (FAT/CD36) [6,7], fatty acid transport proteins FATP1–6 [8–10], and plasma membrane associated fatty acid binding protein (FABPpm) [11–13].

Recently, it was shown that FAT/CD36 and FATP1 are involved in the acute regulation of LCFA uptake. In heart and skeletal muscle, contraction [14,15] and insulin [16,17] are able to increase LCFA transport as a consequence of the translocation of FAT/CD36 from an intracellular pool(s) to the plasma membrane. Similarly, insulin-induced translocation of FATP1 stimulates LCFA uptake into 3T3 L1 adipocytes [18]. These increased rates of LCFA transport are associated with increased rates of LCFA oxidation and esterification during contractile activity and insulin stimulation, respectively [15,17,19].

FABPpm is also a participant in trans-sarcolemmal LCFA transport in skeletal muscles [11,13]. FABPpm is identical to mitochondrial aspartate aminotransferase (mAspAT), which binds to the inner mitochondrial membrane, and is associated with the α-ketoglutarate dehydrogenase complex [20–22]. Transfecting 3T3 fibroblasts with mAspAT-cDNA induced the expression of plasmalemmal FABPpm, which resulted in saturable rates of LCFA transport [12]. It has been assumed that plasmalemmal FABPpm is not regulated acutely to promote the trans-membrane transport of LCFAs. However, this assumption may not be valid. We [23] have shown that plasmalemmal FABPpm can be increased while the total cellular content of FABPpm was not altered, suggesting the presence of a recruitable intracellular FABPpm pool. Recent studies, using immunogold labelling of FABPpm, indicate that in some tissues, but not all, FABPpm is also present in intra-cellular sites other than mitochondria [24]. These observations begin to suggest strongly that this LCFA transporter could be present in an intracellular depot from which it could be induced to translocate to the plasma membrane. But to date there is no evidence that (a) FABPpm can be recruited to the plasma membrane and whether (b) its translocation to the plasma membrane will increase the rate of fatty acid acid uptake. Therefore, we examined in cardiac myocytes (i) whether there is an intracellular depot of FABPpm, and (ii) whether FABPpm can be translocated from this intracellular depots to the plasma membrane (a) by insulin stimulation or (b) by AMP-kinase activation (AICAR stimulation), since these stimuli induce the translocation of FAT/CD36 [15–17]. In addition, (iii) we also examined

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the subcellular localization of FATP1 and the effects of insulin and AICAR on its subcellular redistribution. This was undertaken since insulin induces the translocation of FATP1 in 3T3 L1 adipocytes, but there is no certainty that this protein is similarly regulated in the heart. Importantly, we also determined (iv) whether the insulin-induced or AICAR-induced translocation of one or more of these LCFA transporters stimulated the rates of palmitate uptake.

2. Materials and methods

2.1. Materials

FAT/CD36 and FABPpm were detected using the MO25 antibody [25] and FABPpm antisera [26], respectively. The MCT-1 antibody was a gift (Dr H. Hatta, University of Tokyo). Cox-4, FATP-1 and secondary antibodies were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). [1-^{14}C]Palmitate was purchased from Amersham Life Science (Little Chalfont, UK). BSA (fraction V, essentially FA free (confirmed in separate analyses)) and phloretin were obtained from Sigma–Aldrich (St. Louis, MO). Collagenase type II was purchased from Worthington (Lakewood, NJ, USA). Insulin (Humulin-R) was purchased from Eli-Lilly, Toronto, ON. The cell-permeant adenosine analog 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR) was obtained from Toronto Research Chemicals Inc., North York, ON, Canada. All other chemicals were obtained from Sigma-Aldrich (St. Louis, MO). Sulfo-*N*-succinimidyl oleate (SSO) is routinely synthesized in our laboratory [15]. Male Wistar rats (250–300 g) were bred on site and maintained at 20 °C on a reverse light–dark cycle in approved animal holding facilities. They had unrestricted access to food and water. This study was approved by the committee on animal care at the University of Guelph.

2.2. Methods

Cardiac myocytes were isolated from adult rats as we have described in detail elsewhere [15,16]. Subsequently, cardiac myocytes were incubated (37 °C) for 30 min with or without additions of AICAR (2 mM) or insulin (10 nM). For all the experiments $\geqslant$ 80% of the cardiac myocytes were structurally intact. We examined the effects of AICAR and insulin on the total myocyte content of FAT/CD36, FABPpm, FATP-1, and MCT1 in crude membranes, as well as on the subcellular compartmentation of these proteins using Western blotting as we have described elsewhere [15,16].

To detect the subcellular distribution of fatty acid transporters, plasma membranes (PM) and low density microsomes (LDM) were isolated from cardiac myocytes as we have previously described [15,16]. Signals obtained by Western blotting were quantified by densitometry (SynGene, ChemiGenius2, Perkin Elmer, ON).

To examine the effects of AICAR (2 mM), insulin (10 nM) and SSO (0.4 mM) on the initial rates of palmitate uptake by cardiac myocytes we used the procedures that we have previously described [15,16]. Briefly, cardiac myocytes were incubated for 30 min with either insulin or AICAR and during the last 3 min of the incubation a [1-^{14}C]-palmitate-BSA complex was added (final palmitate concentration 100 μM, palmitate/BSA ratio of 0.3). In the studies in which SSO was used to inhibit palmitate uptake, cardiac myocytes were pre-incubated with this inhibitor for 15 min, after which the cells were washed twice. In all treatments, palmitate uptake was stopped by adding an ice-cold stop solution (KHB buffer supplemented with 0.1% BSA (w/v), 1 mM $CaCl_2$ and 0.2 mM phloretin). Subsequently, cells were washed twice with the stop solution at 60 × *g* for 2 min. The final pellet was assayed for radioactivity.

All data are expressed as means ± S.E.M. We used a *t* test to determine the statistical significance, which was set at $P \leqslant 0.05$.

3. Results

3.1. Identification of intracellular FABPpm, FATP-1 and FAT/CD36 depots in cardiac myocytes

Because we have recently shown that FAT/CD36 is present in mitochondria [27,28], and it is well known that FABPpm (also known as aspartate aminotransferase) is present in mitochondria [21,22], it was important to determine that the LDM and PM fractions were not contaminated with mitochondria. For these purposes we used MCT1 and Cox-4. MCT1 is known to be confined to the PM and mitochondria, while it is not present in LDM [29–31]. In the present study, we confirmed that MCT1 was present only in the PM fraction, not in the LDM fraction (Fig. 1). The absence of COX-4 in the LDM and PM fractions (Fig. 1) confirms that the fractions were not contaminated with mitochondria. Thus, our fractionation procedures successfully provided distinct PM and LDM fractions that were not contaminated with each other, nor with mitochondria. We also confirmed our previous work [15,16] that FAT/CD36 is present in the PM and LDM fractions. In addition, we show for the first time, that in cardiac myocytes FABPpm and FATP-1 are present not only in the PM, but also in the LDM fractions (Figs. 1 and 2C and G).

3.2. Effects of insulin and AICAR on fatty acid transporters (FAT/CD36, FABPpm, FATP-1)

The 30 min insulin and AICAR treatment did not alter the protein expression of the LCFA transporters, FAT/CD36, FABPpm, and FATP-1, nor the monocarboxylate transporter MCT1 (Fig. 2A–H, $P > 0.05$).

3.2.1. Insulin. Insulin failed to induce the redistribution of FABPpm as well as FATP-1 from the LDM to the PM (Fig. 2B and C, $P > 0.05$). As expected, insulin had no effect on MCT1, which is not present in the LDM (Fig. 2D). We confirmed our [16] previous observation that insulin induced the translocation of FAT/CD36 from the LDM (−32%, $P < 0.05$) to the PM (+34%, $P < 0.05$) in cardiac myocytes (Fig. 2A).

3.2.2. AICAR. In marked contrast to the failure of insulin signaling to translocate FABPpm, AICAR induced the translocation of FABPpm from the LDM (−27%, $P < 0.05$)

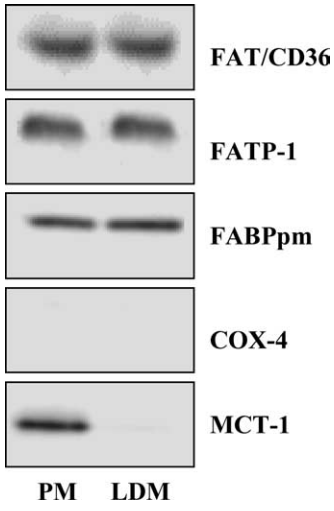

Fig. 1. Presence of FAT/CD36, FATP-1, FABPpm, Cox-4 and MCT1 in plasma membranes (PM) and low density membranes (LDM) prepared from cardiac myocytes. MCT-1 and Cox-4 were not detected in low density microsomes (LDM). In plasma membranes (PM) Cox-4 was not detected. Data are representative of five independent determinations (means ± S.E.M.).

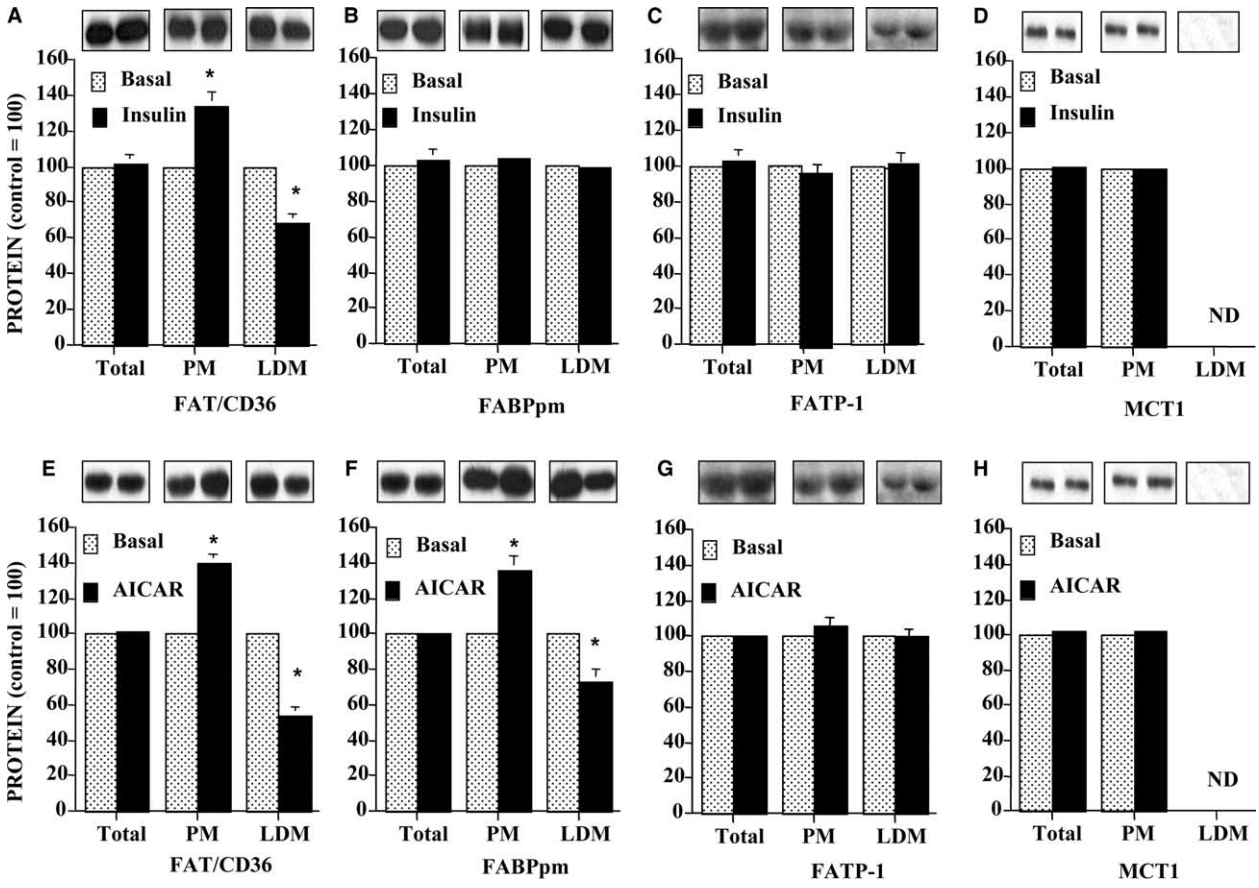

Fig. 2. Effects of insulin (10 nM, 30 min) and AICAR (2 mM, 30 min) on FAT/CD36, FABPpm, FATP-1 and MCT1 protein expression in cardiac myocytes (Total) and plasma membranes (PM), and low density microsomes (LDM). Data are based on five independent determinations for each treatment (means ± S.E.M.). ND: not detected. $^{*}P < 0.05$, insulin or AICAR vs basal.

to the PM (+36%, $P < 0.05$) (Fig. 2F). But, AICAR had no effect on FATP-1 redistribution (Fig. 2G), and as expected did not affect MCT1 at the PM (Fig. 2H). Previously, we [15] had shown that oligomycin activated AMPK and induced the translocation of FAT/CD36. In the present study, AICAR, the well-known activator of AMPK, induced an increase in FAT/CD36 at the PM (+40%, $P < 0.05$) and a concomitant FAT/CD36 reduction in the LDM (−36%, $P < 0.05$) (Fig. 2E).

3.2.3. Functional consequences of insulin- and AICAR-induced translocation of LCFA transporters on the initial rates of LCFA uptake. Incubations with insulin (10 nM), that increased plasmalemmal FAT/CD36 (+34%) but not plasmalemmal FABPpm, stimulated the initial rates of palmitate uptake (+60%, $P < 0.05$, Fig. 3). Incubation with AICAR (2 mM), which increased the plasmalemmal content of both FAT/CD36 (+40%) and FABPpm (+36%), also stimulated the initial rates of palmitate uptake (+90%, $P < 0.05$, Fig. 3). Interestingly, the increase in AICAR-stimulated rates of palmitate uptake (+90%) was significantly greater than the insulin-induced increase in palmitate uptake (+60%, $P < 0.05$, Fig. 3). Blocking of FAT/CD36 with the inhibitor SSO reduced the initial rates of palmitate uptake to similar rates in all conditions examined (Fig. 3), independent of the insulin- or AICAR-induced increase in palmitate uptake.

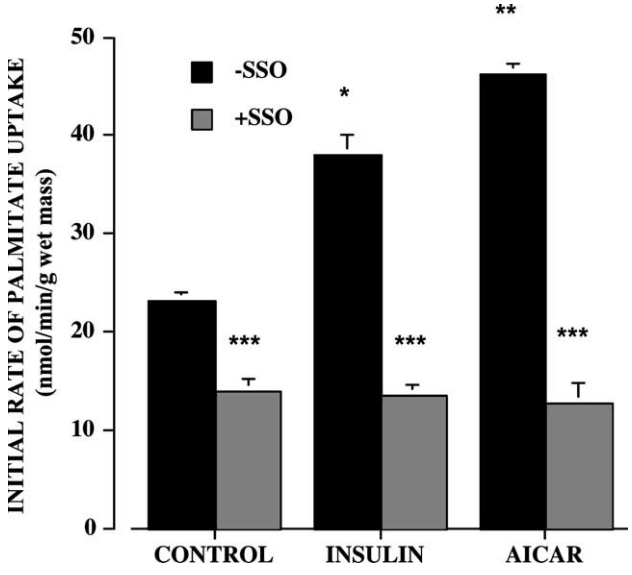

Fig. 3. Effects of insulin (10 nM, 30 min), AICAR (2 mM, 30 min) and SSO (0.4 mM) on the initial rates of palmitate uptake by cardiac myocytes. Data are based on five independent determinations for each treatment (means ± S.E.M.). $^{*}P < 0.05$, insulin vs control $^{**}P < 0.05$, AICAR vs control and insulin ***SSO vs control, insulin or AICAR.

4. Discussion

In the present study, we have a number of novel observations. We demonstrate for the first time in cardiac myocytes (a) that FABPpm and FATP-1 are present in LDM depots, (b) that FABPpm can be translocated to the plasma membrane when stimulated by AICAR, but not by insulin, and (c) that FATP-1 redistribution is not altered either by insulin or by AICAR. Importantly, (d) the increase in the initial rates of palmitate uptake induced by insulin (+60%) and by AICAR (+90%) parallels the increase in the insulin-induced plasmalemmal FAT/CD36 (+34%), and the sum of the AICAR-induced increase in plasmalemmal FAT/CD36 (+40%) and plasmalemmal FABPpm (+36%). This study has now also confirmed our [15,16] previous observations that either AMPK activation or insulin can induce the translocation of FAT/CD36 to the plasma membrane in cardiac myocytes.

The increase in the plasmalemmal content of FABPpm, induced by AICAR, was not attributable to the increased expression of this protein. We [16] have previously shown that our fractionation procedures permit us to detect insulin-induced GLUT4 translocation in cardiac myocytes. Moreover, the PM and LDM fractions were free of mitochondrial contamination, and the LDM fraction was not contaminated with the plasma membrane. Thus, we have carefully established that FABPpm and FATP-1 are present in an intracellular depot, as well as at the PM. We had previously established a similar subcellular distribution for FAT/CD36 [15,16].

4.1. FABPpm translocation from intracellular pool(s) to the plasma membranes

As far as we are aware, there is no information in the literature, concerning the redistribution of FABPpm from an endosomal pool to the plasma membrane. Interestingly, our previous studies had suggested that this protein could be relocated to the plasma membrane [23]. Specifically, in hearts of obese Zucker rats there was an increase in LCFA transport, which was associated with an increase in plasmalemmal FABPpm, as well as plasmalemal FAT/CD36, while the expression of these proteins was not altered [23].

In the present study, only AICAR induced the translocation of FABPpm from LDM to the PM. This responsiveness to AICAR, but not to insulin, contrasts markedly with the insulin- and AICAR-induced translocation of FAT/CD36 [15,16]. Since AICAR is well known to activate AMP-kinase [15], it is tempting to speculate that FABPpm is recruited to the PM at times when there is a requirement for an enhanced rate of LCFA oxidation, which may assist, in an unknown manner, with the targeting of LCFAs to the mitochondria. This is currently under investigation.

The LDM FABPpm depots are not only found in cardiac myocytes. We have also determined that such a pool also exists in skeletal muscle (Chabowski and Bonen, unpublished data). Whether the intracellular depot of FABPpm in skeletal muscle is also uniquely sensitive to AICAR but not to insulin remains to be established.

4.2. Insulin or AICAR fail to induce FATP1 translocation in cardiac myocytes

Both insulin and AICAR failed to translocate FATP-1 from intracellular depots to the plasma membranes. These results are in marked contrast with studies in which insulin-treated 3T3-L1 adipocytes showed rapid redistribution of FATP-1 to the plasma membranes [18]. The non-recruitability of FATP1, suggests that in cardiac myocytes this LCFA transporter is stored in an intracellular membrane compartment that is different from recycling endosomes. It was also shown recently that FATP1 concentrations in the heart are far less than FATP6 concentrations [32], suggesting perhaps, that in the heart FATP1 likely has a minor role in transporting LCFAs [32]. This may be a reason why this protein is not induced to translocate in the heart. Alternatively, other stimuli may induce the translocation of this protein in the heart. Since the effects of insulin on FATP1 differ in adipose tissue and the heart, it will be important to ascertain whether FATP1 can be induced to translocate in other tissues such as skeletal muscle, where it is more predominatly expressed than other FATP isoforms [8–10].

4.3. FAT/CD36 translocation from intracellular pool(s) to the plasma membranes

Our present results are in agreement with our recent work showing that insulin [16,17], and AICAR [15] or muscle contraction [14] induce the translocation of FAT/CD36 from LDM to PM in skeletal muscles [14,17] and in the heart [15,16]. The effects of insulin and contraction on LCFA uptake are additive in skeletal muscle [19] and in cardiac myocytes [15]. This implies that there may be different intracellular pools of the FAT/CD36, which are sensitive to insulin- and contraction-mediated signals. Evidence for distinct insulin and contraction recruitable LDM depots has been shown for GLUT4 [33].

4.4. Effects of insulin and AICAR on LCFA uptake by cardiac myocytes

An important aspect of our study was to establish whether the AICAR- and insulin-induced translocation of the LCFA transporters resulted in changes in the initial rates of LCFA uptake by cardiac myocytes. We observed that the changes in the initial rates of LCFA uptake were closely correlated with changes in plasmalemmal LCFA transporters. For example, when insulin induced the translocation of only FAT/CD36 to the PM (+34%), there was a concomitant increase in LCFA uptake (+60%). However, this increase in the initial rate of palmitate uptake was far greater (+90%), when AICAR induced the translocation of both plasmalemmal FAT/CD36 (+40%) and FABPpm (+36%) to the PM, compared to when only FAT/CD36 was induced to translocate. Thus, our study indicates that altered rates of fatty acid uptake are strongly associated with concomitant changes in the subcellular translocation of LCFA transporters from the LDM to the PM.

It is not possible to ascertain conclusively from our study whether the increased plasmalemmal FABPpm acts independently, or acts in concert with FAT/CD36, to increase LCFA uptake. However, the data strongly indicate that FABPpm and FAT/CD36 interact with each other, as there appears to be additional gain of function when both FAT/CD36 and FABPpm are induced to translocate to the plasma membrane, compared to when only FAT/CD36 is translocated to the plasma membrane. These observations alone do not establish whether these 2 proteins act independently to facilitate palmitate uptake. However, FAT/CD36 inhibition with SSO

lowered the rates of palmitate uptake, either when FAT/CD36 alone was translocated to the plasma membrane, or when both FAT/CD36 and FABPpm were translocated to the plasma membrane. This is the strongest evidence to date that at the functional level these two proteins interact at the plasma membrane to facilitate the uptake of palmitate, and concurs with previous speculations about their mode of action [34,35]. We recognize that another fatty acid transporter, FATP-6, could also be involved in promoting insulin and/or AICAR stimulated uptake of palmitate in the heart since this protein has recently been shown to be more abundant in heart than FATP1. However, in the absence of any measurements of FATP6 we cannot speculate about its role in palmitate uptake in cardiac myocytes.

5. Conclusions

We have provided several novel observations; (1) the discovery of FABPpm and FATP-1 in cardiac myocytes LDM depot(s), (2) the ability to induce the redistribution of FABPpm from the LDM to the PM by AICAR, but not by insulin, and (3) the translocation of the LCFA transporters to the PM increases the initial rates of LCFA uptake into cardiac myocytes in proportion to the two fatty acid transporters (FAT/CD36 and FABPpm) at the plasma membrane.

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