



Official Research Journal of
the American Society of
Exercise Physiologists

ISSN 1097-9751

JEPonline

Heart-Type Fatty Acid Binding Proteins as Markers of Myocardium and Skeletal Muscle Injury: A Review

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ABSTRACT

Morozov VI, Kalinski MI, Sakuta GA, Carnes AJ. Fatty Acid-Binding Proteins (FABPs) as Markers of Myocardium and Skeletal Muscle Injury: A Review. **JEP**online 2013;16(5):77-89. The characteristics, properties, and functions of fatty acid-binding proteins (FABPs) are reviewed. FABPs are small cytoplasmic proteins with molecular mass 15 kDa and broad ligand specificity. The long-chain fatty acids (LCFA) are important FABP ligands with great importance in the energy metabolism of the cell. Heart-type (H-FABP) works in myocardium and skeletal muscle, providing fatty acid transport to the working muscles. The acute myocardial infarction (AMI) results in elevated H-FABP blood concentration, which may have diagnostic use in patients with cardiac events and in cardiac intervention. This marker may also have predictive value for the assessment of AMI consequences. Exercise results in the release of muscle H-FABP into the blood and its measurement may be useful for assessing exercise-induced skeletal muscle injury. Determination of myoglobin concentration and calculation of the myoglobin/H-FABP ratio may help to differentiate between myocardium and skeletal muscle injury. Endurance training is accompanied by elevation of LCFA transporters in the myocyte membrane, providing enhanced capacity for myocyte fatty acid uptake. Methods of H-FABP analysis are also discussed.

Key Words: FABP, Myocardium, AMI, Exercise

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INTRODUCTION

Fatty acid-binding proteins (FABPs) are important cellular proteins associated with hydrophobic ligands and are responsible for transportation of long-chain fatty acids (LCFAs) into the cell and trafficking them to cellular compartments. Their intracellular location, tissue specificity, and low molecular mass make FABPs convenient clinical markers for monitoring cellular damage. Hence, the measurement of heart-type (H-FABP) in a cardiac emergency may provide valuable data for the early diagnosis of AMI.

FABP CHARACTERISTICS, PROPERTIES, AND FUNCTIONS

FABPs form a subfamily of the intracellular lipid-binding protein (iLBP) family and are involved in reversible binding of hydrophobic ligands inside the cell and trafficking them to diverse cellular compartments. Among these are the peroxisomes, mitochondria, endoplasmic reticulum, and nucleus (46). FABPs are small cytoplasmic proteins with molecular mass 15 kDa and broad ligand specificity. The long-chain fatty acids (LCFAs) are major ligands of FABPs with great importance to the energy metabolism of the cell. Heart-type fatty acid-binding protein (H-FABP) works in myocardium and skeletal muscle, providing fatty acid (FA) transportation to the working muscles (21,22,31). The LCFAs are the most important energetic substrate during prolonged exercise of low-to-moderate intensity (38). The source of LCFAs for contracting muscles is adipose tissue, where LCFAs are produced during lipolysis and supplied to the muscles from the microvascular compartment. LCFAs can passively diffuse across cell membrane, although recent data demonstrate that some cellular proteins are involved in LCFA uptake and intracellular transport (38). These membrane-associated proteins (fatty acid translocase – FAT/CD36, plasmalemmal-located fatty acid binding protein – FABPpm, and fatty acid transport protein – FATP) and cytoplasmic fatty acid-binding proteins (FABPs) transport FAs from the plasmalemma to the intracellular sites of conversion, such as the mitochondrial outer membrane (59).

The appearance of FABPs in the circulation can accompany injury to the liver – L-FABP (gene *FABP1*), myocardium and skeletal muscle – H-FABP (*FABP3*), kidney – H-FABP and L-FABP co-expressed, intestine – I-FABP (*FABP2*) and L-FABP co-expressed, brain – B-FABP (*FABP7*) and H-FABP co-expressed, adipocyte – A-FABP (*FABP4*), epidermal – E-FABP (*FABP5*), ileal – II-FABP (*FABP6*), myelin – M-FABP (*FABP8*) and testis – T-FABP (*FABP9*) (12,14,38,39,41,46,60). Nine genes encoding FABPs have been identified in humans, and a new candidate gene, *FABP12*, has

also been reported (47). It is also believed that FABPs are involved in the signaling mechanisms of the cell: L-FABP can enter nuclei, bind to nuclear receptors (PPAR α , HNF4 α , CRABP-2), and activate the transcription of genes involved in fatty acid and glucose metabolism (44).

The ability of L-FABPs to bind with the peroxisome proliferator activated receptors (PPARs) involved in the maintenance of cellular homeostasis has been previously demonstrated (61). It has also been suggested that the delivery of ligands by L-FABPs to PPARs is integral to regulatory pathways that mediate xenobiotic responses and host protection in the small intestine and the liver, where L-FABPs are effectively expressed (61).

Epidermal FABP (E-FABP) knockout mice were normal in gross and histological examination, but produced more H-FABP (functional compensation) and showed basal transepidermal water loss in functional analyses of the skin (50). Disruption of the adipocyte *FABP* gene markedly reduced basal and isoproterenol-stimulated lipolysis and increased adipocyte FA levels compared to wild type mice (7). Transgenic mice overexpressing the *FABP5* gene encoding E-FABP in adipocytes demonstrated a significant increase in adipocyte FABP levels due to a 10-fold increase in the E-FABP concentration (24). There were no differences in body weight, serum free FA or fat pad mass between wild-type and *FABP5* transgenic mice, while basal and isoproterenol-stimulated lipolysis increased in adipocytes of transgenic mice, suggesting a positive association between lipolysis and the total level of FABP (24).

Cytosolic extracts from H-/ heart and skeletal muscle and from L-/ liver demonstrated significantly decreased binding of LCFAs (5). The uptake, oxidation, and esterification LCFAs were reduced in H-/ heart and muscle and in L-/ liver. Compensatory mechanisms developed in H-/ mice include a redistribution of muscle mitochondria as well as increased cardiac and skeletal muscle glucose uptake and hepatic ketogenesis (5). Using *FABP5*-deficient mice, Sugawara et al. (50) have shown that this gene is involved in the regulation of sebaceous gland activity through modulation of cellular lipid signaling and/or metabolism (50).

All FABPs have similar tertiary structures, which include a 10-stranded antiparallel β -barrel and an N-terminal helix-turn-helix motif (49). These proteins are thought to be important for dietary lipid assimilation in the intestine, hepatic lipid targeting to catabolic and anabolic pathways, regulation of lipid storage and lipid-mediated gene expression in adipose tissue and macrophages, FA targeting to β -oxidation pathways in muscle, and maintenance of phospholipid membranes in neural tissues (49).

FABPs are thought, along with mitochondria-produced reactive oxygen species, to be involved in the development of metabolically triggered inflammation (metaflammation) - a low grade, chronic inflammatory state associated with obesity and related diseases (17). The development of pharmacological agents aimed at FABPs may be a prospective approach for tissue- and cell-type-specific control of lipid signaling pathways and inflammatory responses, as well metabolic regulation in obesity, diabetes, and atherosclerosis (16).

Therefore, FABPs function as tissue specific lipid chaperones and play important roles in the cell's fuel balance and in lipid-mediated biological processes through the regulation of different lipid signals. Moreover, these proteins might serve as prospective biomarkers for some pathologies and as targets for medication.

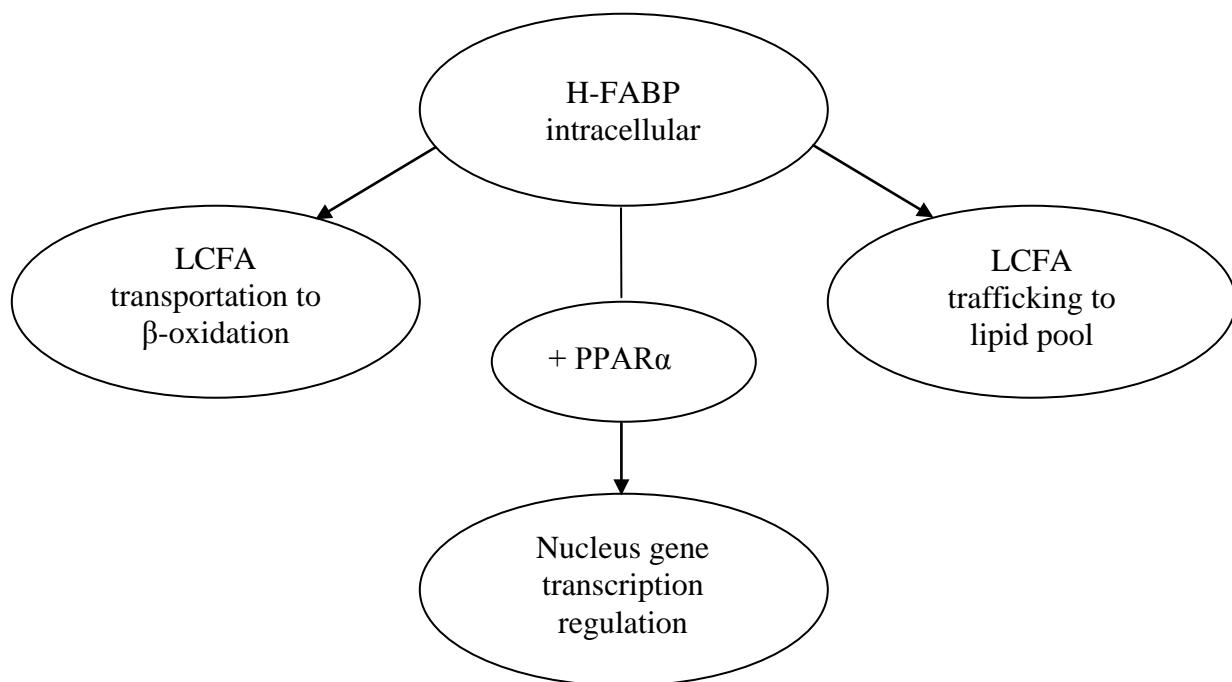


Figure 1. H-FABP Functions.

FABPs AND MYOCARDIUM DAMAGE

According to Loria et al. (30), about 25% of emergency department patients with acute coronary syndrome (ACS) have an atypical clinical presentation and an absence of electrocardiogram (ECG) alterations. These patients may be valuable in the evaluation of serum or plasma levels of injury biomarkers. Classic cardiac markers (myoglobin, CK-MB, troponins) have certain disadvantages. Animal and human data demonstrate that plasma and urinary H-HABP may be a useful marker for the early detection of myocardial injury and for the assessment of infarct size (19,47). However, renal function assessment should be done for the estimation of infarct size using serial plasma H-FABP or myoglobin concentrations. In patients with a mean creatinine concentration above the upper reference limit due to slower clearance from plasma, infarct size was overestimated in 20-25% of patients (62). The use of individually estimated clearance rates can provide more accurate values of infarct size within 24 hrs after the first symptoms (11). Normally, FABP presents in low concentration in the blood, but its concentration increases as early as 1.5 to 3 hrs after the onset of symptoms of infarction, peaks around 6 hrs, and returns to baseline values within 12 to 24 hrs (2,4). Patients with unstable angina showed high positive values of H-FABP while these values were low in normal coronary patients having chest pain (53).

H-FABP concentration in the ventricles (0.46 mg/g wet weight and 1.5% of the cytoplasmic protein in the left ventricle) was higher than in the atrial (0.25 mg/g wet weight and 0.7% of the cytoplasmic protein in the left atrium) (56). Tested skeletal muscles, except for those of the diaphragm, contained little H-FABP, the kidneys contained less than 1/10 of H-FABP found in the heart, and negligible amounts were found in the liver and small intestine. The heart and skeletal muscles' H-FABP distribution was comparable to the CK-MB activity distribution, but was inverse to the distribution of

myoglobin. As such, determination of the plasma myoglobin/H-FABP ratio could provide valuable diagnostic information in AMI patients (56). When comparing the efficacy of H-FABP and myoglobin for the early diagnosis of acute myocardial infarction (AMI) (within 6 hrs of the onset of chest pain), Ishii et al. (26) concluded that H-FABP is a more sensitive and specific marker and that the ratio of markers does not have an obvious advantage. A high efficacy of H-FABP was also demonstrated in patients with ST segment elevation myocardial infarction (52). Based on data from a study comparing H-FABP, myoglobin, and CK-MB as the early markers for AMI, Okamoto et al. (35) found H-FABP to be the best early marker. Its sensitivity, specificity, diagnostic efficacy, and accuracy for patients with chest pain within 3 hrs and/or 6 hrs after the onset of symptoms were comparable to those for patients within 12 hrs after symptoms.

Azzazy et al. (4) propose H-FABP as a useful marker not only for detecting cardiac injury in acute coronary syndrome (ACS), but also for predicting recurrent cardiac events in acute coronary syndromes and in congestive heart failure patients, while free FA increase may be associated with myocardial ischemia. Moreover, serum H-FABP may be a potential independent predictor of cardiac events within 6 months of patient admission and its predictive capacity is higher than cTnT in the early hours of ACS (3,27). Within the first 3 to 6 hrs after the onset of chest pain, H-FABP was more sensitive than the other markers (troponin I and CK-MB) in patients with suspected acute myocardial infarction (AMI), and it was an independent predictor of outcome within 6 months (18). When H-FABP was compared with the other markers in relation to myocardial necrosis in patients with acute chest pain, H-FABP appeared to contribute to early detection of myocardial damage and TnT was most likely to correlate with scintigraphic data, suggesting that these markers may complement each other (34).

However, some authors have contested the clinical value of H-FABP and myoglobin in patients with chest pain on admission (1). H- and L-FABP located in the distal and the proximal tubular cells of the kidney, respectively, have been shown to be useful markers for detection of renal injury (39). In some cases, urinary FABP level monitoring may be useful: after kidney transplantation, urinary L-FABP concentration correlated directly with both peritubular capillary blood flow and the ischemic time of the transplanted kidney (55). Wunderlich et al. (64) found early (peak at 2 to 3 hrs) but prolonged (>120 hrs) release of B-FABP and H-FABP in acute ischaemic stroke and suggested that these FABPs, especially H-FABP, may play a role as rapid markers of brain damage. Early H-FABP concentrations have been associated with the severity of the neurological deficit and the functional outcome following a stroke. High H-FABP release was also associated with large cerebral infarction on computer tomography (64).

H-FABP has also been considered as a useful marker in cardiac intervention. Plasma and urinary H-FABP may be early and sensitive markers for diagnosis of myocardial injury in patients undergoing cardiac surgery (23). Elective electrical cardioversion of atrial fibrillation (AF) did not lead to a significant change in the serum H-FABP level, which indicated an absence of myocardial necrosis during cardioversion (42). However, Mazovets et al. (33) showed that in most patients with AF and atrial flutter, H-FABP levels after direct current cardioversion correlated with total delivered energy. The authors failed to demonstrate an elevation of cTnI and suggested skeletal muscle injury to be a source of FABP increase. Patients with AMI who underwent successful reperfusion and had no evidence of reocclusion within the first 120 min demonstrated significant elevation in serum myoglobin and H-FABP levels at 15 min (36).

Malik et al. (32) compared the efficiency of H-FABP and CK-MB analysis for the assessment of myocardial injury in on-pump versus off-pump coronary artery bypass grafting. The total release of H-FABP and CK-MB was higher in the on-pump than in the off-pump group. H-FABP levels peaked as

early as 1 hr after declamping (on-pump group) or 2 hrs after the last distal anastomosis (off-pump group); whereas, CK-MB peaked only at 4 hrs after declamping (on-pump group) or 24 hrs after the last distal anastomosis (off-pump group). H-FABP also proved to be a more rapid marker of perioperative myocardial damage than CK-MB, and an effective predictor of the requirement for intensive monitoring for postoperative myocardial infarction (23,32). H-FABP, along with myoglobin, may also be useful in the noninvasive detection of reperfusion after thrombolysis (13,26).

Thus, AMI results in an early increase in H-FABP blood levels that may be used for diagnosis in patients with heart events and in cardiac intervention. Kidney function should be assessed as a possible cause of H-FABP elevation. Moreover, this marker may also have predictive value for the assessment of AMI consequences.

FABPs AND EXERCISE-INDUCED SKELETAL MUSCLE INJURY

FABP has been proposed as a marker of muscle injury (22,37,48). H-FABP is the dominant FABP type in skeletal muscles, but A-FABP is also expressed in this tissue (15). Interestingly, A-FABP and its mRNA were significantly more expressed in endurance trained subjects (15). This may be a result of both subject selection and muscle adaptation to endurance exercise. H-FABP is important in supporting muscle contraction – H-/- mice demonstrated decreased exercise tolerance (5). Endurance training (8 wks of swimming) and/or fish oil supplementation (omega-3-enriched diet) resulted in different effects on cytoplasmic FABP (FABP(c)) content in rat skeletal muscles and heart (10). Training caused a 30% increase in FABP(c) content in the extensor digitorum longus (EDL) and in the gastrocnemius associated with enhanced oxidative capacity (increased citrate synthase activity), while these effects were absent in the soleus and in the heart. Supplementation induced a large increase in the FABP(c) content in EDL (300%), gastrocnemius (250%), soleus (50%), and heart (15%). Furthermore, an additive effect of exercise and diet was found in the EDL. Increased FABP(c) in muscles and heart is presumably linked to increased FA flux in cell (10).

Exercise leads to the elevation of fatty acid transportation through myocyte membranes, and the effects of acute exercise and physical training on the expression and translocation of the various LCFA transporters in skeletal muscle tissue have been reviewed (38,40). Running rats (120 min at 20 m·min⁻¹) and cycling humans (120 min at 60% VO₂ max) showed an increase in plasma membrane FAT/CD36 (fatty acid translocase) and FABPpm (40 kD) content associated with increased palmitate uptake (6). In addition, 6 wks of interval exercise training increased FAT/CD36 and FABPpm content in whole muscle, FABPpm in the sarcolemma, and FAT/CD36 in the mitochondrial membranes of human skeletal muscle (51). FABPpm content was 43-226% higher in rat red muscles compared to white muscles, and was increased by 55% in red muscles after endurance training. FABPpm content was also positively correlated with succinate dehydrogenase activity (54). Interestingly, blood glucose increased in wild-type and H-FABP (+/-) mice during exercise; whereas, H-FABP(-/-) mice showed hypoglycemia associated with increased glucose utilization, especially in the heart and soleus (45). Three weeks of one-legged endurance training increased FABPpm content by 150% in muscle, but no change was observed in untrained control muscle (29). The parallel elevation of citrate synthase activity was also observed in the trained muscle.

Acute exercise induced a larger increase in FABP (70 to 362%) than in CK (24 to 156%) in a group of junior rowers during 5 wks of training (57). When the chronic effect of exercise was studied, baseline FABP level was independent of previous training; whereas, the baseline CK level was dependent on the training that took place during 1 day before and on the combined training of the previous 2 days.

These results suggest that FABP and CK could be used to monitor acute exercise and chronic exercise, respectively (57).

After eccentric exercise induced muscle injury, plasma FABP and Mb increase and decrease more rapidly than CK, indicating that both FABP and Mb are more useful than CK for the early detection of such injuries and the monitoring of injury during repeated exercise bouts (48).

Thus, exercise results in the release of muscle H-FABP into the blood and its measurement may be useful in the assessment of exercise-induced skeletal muscle injury. Determination of myoglobin concentration and the myoglobin/H-FABP ratio may provide a means of evaluating the contribution of the myocardium to these markers of muscle injury. Endurance training is accompanied by increased LCFA transporters in the myocyte membrane, which allows for increased uptake of these FA by myocytes.

FABP ANALYSIS

Wodzig et al. (63) reported on immunoenzyme analysis (IEA) for FABP detection in human plasma. The displacement immunoassay for FABP measurement has also been proposed (9,28,58). An inverse set-up was used in this system: enzyme labeled monoclonal antibodies were associated with an immobilized antigen and then displaced by an analyte of the sample during analysis. This immunoassay enables the analysis of a broad range of FABP concentrations (2-2000 microg·L⁻¹) (28). As a standard for immunoassays, recombinant human H-FABP has been suggested (42). To discriminate myocardium and skeletal muscle damage, parallel determination of myoglobin and the calculation of Mb/H-FABP ratio have been proposed. The ratio is significantly higher in the case of skeletal muscle damage (20-70) compared to myocardium damage (4.5) (60). Similar values of the Mb/H-FABP ratio (8-57 vs. <6) have also been reported (12). The biological basis for the application of the Mb/H-FABP ratio is a similarity in H-FABP and myoglobin release from the tissues, while myoglobin concentration is significantly higher in skeletal muscles (4,48). An H-FABP test system is available from Randox Laboratories Limited (UK). The assay is based on a latex enhanced immunoturbidimetric testing process that is suitable for H-FABP measurement in serum and plasma. The declared range of H-FABP measurement is 0.747-120 ng·ml⁻¹.

SUMMARY

FABPs are important intracellular proteins associated with hydrophobic ligands, which are responsible for LCFA transportation into the cell and trafficking them to diverse cellular compartments. Their intracellular location, tissue specificity, and low molecular mass make FABPs convenient clinical markers for monitoring cellular damage. H-FABP measurement in emergency cardiac patients may provide valuable data for early AMI diagnosis. Because exercise results in the release of muscle H-FABP into the blood, H-FABP determination may be useful in the assessment of exercise-induced skeletal muscle injury. Determination of myoglobin concentration and the myoglobin/H-FABP ratio can help to differentiate between myocardium and skeletal muscle injury. Endurance training increases expression of LCFA transporters in the myocyte membrane, increasing myocyte FA uptake.

FOUNDING STATEMENT

This work was supported by Russian Foundation for Basic Research, grant 13-04-00509.

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