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Review

Fatty Acid Binding Protein 4 (FABP4) and the Body Lipid Balance

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The FABP4 protein, present predominantly in adipocytes and macrophages, is responsible for the uptake and storage of fatty acids in the adipose tissue. By regulating expression of the genes responsible for lipid metabolism, it is crucial for the proper functioning of metabolic processes and maintenance of the body's energy balance. Currently, the FABP4 protein is considered to be one of the key proteins associated with metabolic disorders of the body. FABP4 plays a key role in regulating insulin sensitivity, inflammation processes, development of coronary atherosclerosis and lipid metabolism. Increasing evidence indicates that pharmacological agents that modify FABP4 function may offer therapeutic opportunities for metabolic syndrome.

Key words: FABP4, fatty acid, metabolism, adipose tissue.

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Fatty acid binding protein 4 (FABP4), otherwise referred to as adipocyte fatty acid binding protein (A-FABP), is a FABP protein isoform primarily found in adipocytes and macrophages (MATARESE & BERNLOHR 1988; FU *et al.* 2000). Proteins of the FABP family are intracellular proteins primarily responsible for binding and transport of fatty acids as well as preventing cellular damage due to excessive accumulation of amphipathic fatty acid molecules (MISHKIN *et al.* 1972; OCKNER *et al.* 1972). Thus far, nine isoforms of these proteins have been identified. Their names come from the locations where they were identified, or the organ or tissue where they occur at the highest concentrations. FABPs are proteins with a molecular weight of about 14-15 kDa, sharing moderate amino acid sequence similarity of 20-70% (HERTZEL & BERNLOHR 2000; STORCH & THUMSER 2000). Depending on the tissue, they represent 1-5% of all proteins dissolved in the cytosol. Higher concentrations of FABP isoforms have been observed in tissues with high levels of fatty acids serving as main substrates in lipid synthesis (HAUNERLAND & SPENER 2004). The basic function of all FABPs is binding of long chain fatty acids or ligands close to them. However, each member of the FABP family differs in ligand specificity or its binding mechanism (HANHOFF *et al.* 2002). Transfer of fatty acids from most FABP isomers to membranes occurs during active coupled transport (protein-membrane interactions), although fatty acids transfer from L-FABP4 (Liver Fatty Acid Binding Protein) to membranes is consistent with the diffusion mechanism. (THUMSER & STORCH 2000; STORCH *et al.* 2002). FABP – through accumulation of fatty acids in the cytosol (FABP increases fatty acids absorption into the cell) - provides substrates for enzymes that catalyze lipid metabolism. (WEISIGER 1996). Proteins of the FABP family such as B-FABP (Brain Fatty Acid Binding Protein), H-FABP (Heart Fatty Acid Binding Protein) and L-FABP are involved in the regulation of cell growth and differentiation processes (STORCH & THUMSER 2008). In the case of L-FABP these regulations are possible via binding of mitogens or carcinogenic factors – prostaglandin A and J, non-

genotoxic (amphipathic carboxylates, tetrazole acetophenones) and genotoxic (2-acetylaminofluoren, aminoazo dyes) carcinogens (KHAN & SOROF 1994; SOROF 1994).

The *FABP4* gene

The location of the gene on the chromosome varies from species to species. In man, it is located on chromosome 8, in sheep on chromosome 9, while in cattle and chicken the gene *FABP4* is located on chromosomes 14 and 2, respectively.

Use of a diet rich in long chain fatty acids results in increased expression of *FABP4* (AMRI *et al.* 1991; DISTEL *et al.* 1992; HERTZEL & BERNLOHR 1998). Intensified *FABP4* gene expression is also observed in response to prolonged exposure of adipocytes to high lipid concentrations (VEERKAMP & VAN MOERKERK 1993). During adipocyte differentiation, the concentration of FABP4 in cells increases (HERTZEL & BERNLOHR 1998). In the presence of fatty acids, mioblasts may be differentiated into adipocytes. A consequence of such transformation is an immediate, dramatic increase in *FABP4* expression (GRIMALDI *et al.* 1997; TAYLOR-JONES *et al.* 2002). It has been demonstrated that *FABP4* expression is higher in obese patients than lean individuals. Also *FABP4* gene expression was significantly higher in subcutaneous adipose tissue than visceral adipose tissue of obese subjects (FISHER *et al.* 2001; DROLET *et al.* 2008). On the other hand, increased body fat in morbidly obese individuals is associated with decreased expression of all genes involved in lipid metabolism in the visceral and subcutaneous fat tissue (CLEMENTE-POSTIGO *et al.* 2011). The described changes in gene expression associated with adipose tissue metabolism may indicate an abnormal effect of adipose tissue, which can lead to metabolic abnormalities. Under normal conditions, excess energy is stored at the expense of increasing adipose tissue. In the case of obesity as a result of continuous energy surplus, lipid storage capacity by adipose tissue may be exceeded. Adipose tissue, which makes it possible to react to this excess, can reduce the expression of genes involved in lipid metabolism (CLEMENTE-POSTIGO *et al.* 2011).

Transcription factors such as PPARα, -β, -γ, which are activated by fatty acids or other hydrophobic ligands, are responsible for stimulation of *FABP4* gene expression (TONTONOZ *et al.* 1994; DESVERGNE & WAHLI 1999; TAN *et al.* 2002). PPARγ stimulates differentiation of adipocytes: there is a PPARγ binding sequence in the *FABP4* promoter region (GREGOIRE *et al.* 1998). It was experimentally shown that with increased fatty acid concentration - the direct ligand binding to receptors, PPARγ activates *FABP4* gene expression in a concentration-dependent manner (FORMAN *et al.* 1997).

Mutations in the human *FABP4* gene are primarily associated with obesity and insulin sensitivity (DAMCOTT *et al*. 2004). Genetic variability in the human *FABP4* region can also be used to predict the risk of breast cancer in women (WANG *et al.* 2014).

In farm animals, all identified polymorphisms of the *FABP4* gene *locus* were associated with production characteristics and meat quality, principally with the adipose tissue level and composition (MERCADÉ *et al.* 2006; XU *et al.* 2011; IBRAHIM *et al.* 2014). In sheep, research conducted by YAN *et al.* (2012, 2014) on segregation of *FABP4* gene alleles revealed the presence of recombinant phenomena in the meiosis process.

Variability of the protein encoded by *FABP4* was also analyzed in terms of the effect on milk yield and changes in fat content in bovine milk (ZHOU *et al.* 2015). In addition, an SNP (single nucleotide polymorphism) has been identified in the *FABP4* gene; it is responsible for increasing resistance to sheep wool defects, i.e. so-called fleece rot (SMITH *et al*. 2010).

The FABP4 protein

FABP4 is a protein composed of 128-132 amino acids with a molecular weight of 14-15 kDa (ZIMMERMAN & VEERKAMP 2002). The protein structure is made up of two β-sheets, each consisting of 10 hydrogen-bonded β-strands. Between the β-sheet structures, a cavity filled with water forms; about 50% of amino acids on the surface of this cavity are polar. This is the fatty acid binding site. The carboxyl group within the structure is surrounded by amino acid residues of two arginins and tyrosines. The N-terminus of the protein contains a structure consisting of two α-helices and one loop, which probably by means of conformational changes of the protein is responsible for allowing the fatty acid to enter and attach in the cavity between the β-sheet structures, as well as to exit the cavity (HERTZEL & BERNLOHR 2000).

Functions

The main and basic functions of the adipocyte fatty acid binding protein are the uptake and intracellular storage of fatty acids. This protein is also responsible for stimulating expression of genes responsible for a number of metabolic processes, as well as cell proliferation and differentiation (ZIMMERMAN & VEERKAMP 2002).

Role of FABP4 in fatty acid transformations

The FABP4 protein after binding to oleic acid in the presence of a phosphorylated form of hormone-sensitive lipase (HSL) stimulates the ac-

tivity of this enzyme (STORCH & MCDERMOTT 2009). In contrast, insufficient levels of this protein lead to a decrease in the export of lipids from adipocytes (COE *et al.* 1999), due to inhibition of lipolysis which is catalyzed by HSL (SHEN *et al*. 1999; JENKINS-KRUCHTEN *et al.* 2003).

Mice with impaired *FABP4*$^{-/-}$ protein synthesis (*FABP4* gene knockout) did not show significant morphological changes. The animals developed normally, were healthy and had adipocytes of a correct structure. The *FABP4*$^{-/-}$ mice when placed on a diet rich in fats gained weight similarly to those of the wild genotype, but did not show elevated levels of triglycerides in the plasma and of insulin in the serum. In addition, obese *FABP4*$^{-/-}$ mice were characterized by lower plasma glucose and cholesterol concentrations than the control group. Moreover, insulin and glucose tolerance were maintained in the *FABP4* gene knockout mice, while obese animals with the *FABP4*$^{+/+}$ wild genotype were insulin resistant and diabetic (HOTAMISLIGIL *et al.* 1996).

The link between the FABP4 protein and onset of atherosclerosis in obese or diabetic animals has been studied. To prove the existence of this relationship, MAKOWSKI *et al.* (2001) used two genetic models (*FABP4*$^{-/-}$ and *ApoE*$^{-/-}$ knockouts) of mice with inoperative genes that had developed atherosclerotic lesions regardless of obesity or elevated insulin and glucose levels. The offspring of these mice with *FABP4*$^{+/+}$/*ApoE*$^{-/-}$ and *FABP4*$^{-/-}$/*ApoE*$^{-/-}$ genotypes did not show any difference in glucose, cholesterol and triglyceride concentrations, or in insulin sensitivity. In the aortas of the double knockout mice, a significantly lower level of development of atherosclerotic changes compared to animals with normal expression of the *FABP4* gene was observed. This indicates that indeed FABP4 levels are associated with the risk of atherosclerosis (MAKOWSKI *et al.* 2001).

Transplantation of bone marrow from the *FABP4*$^{-/-}$/*ApoE*$^{-/-}$ mice into animals with the *FABP*$^{+/+}$/*ApoE*$^{-/-}$ genotype allowed to obtain a mixed model where *FABP4* was expressed exclusively in adipocytes, and was not present in bone marrow macrophages. Lack of the FABP4 protein in macrophages did not affect glucose and lipid levels, but decreased atherosclerotic changes by about 50% (MAKOWSKI *et al*. 2001). Similar effects have also been observed in animals with severe hypercholesterolemia (BOORD *et al*. 2002). The results of these studies confirm the significant role of FABP4 in the onset of the metabolic syndrome via expression of this protein in adipocytes, and vascular damage through FABP4 expression in macrophages (HAUNERLAND & SPENER 2004). FABP4 secreted in the macrophages is responsible for regulating atherosclerotic lesions, cholesterol transport as well as anti-inflammatory action as it controls two major signaling pathways of these processes: PPARγ-LXRα-ABCA1 and IKK-NFκB pathways (MAKOWSKI *et al.* 2005). The findings presented by FURUHASHI *et al.* (2016) support the hypothesis that FABP4 locally produced by epicardial/perivascular adipocytes and macrophages localized in the artery are significantly related to the development of coronary atherosclerosis (FURUHASHI *et al.* 2016).

YANG *et al.* (2011) used the RNA interference (RNAi) technique to obtain mice with the *FABP4* gene knockout. The purpose of their studies was to evaluate the effect of the reduced form of protein encoded by this gene on body weight control, glucose concentration and lipid balance in mice with diet-induced obesity. The researchers have shown that lack of the FABP4 protein is associated with increased body weight, as well as an increase in body fat without changes in glucose concentration or lipid homeostasis (YANG *et al.* 2011). Studies on FABP4 and MAL1 (the latter gene also belonging to the FABP family) double knockout mice have shown that these animals were resistant to diet-induced obesity and demonstrated high insulin resistance. It was found to be associated with an increase in insulin receptor activity, as well as a drastic decrease in activity of the *SCD1* gene in the liver (MAEDA *et al.* 2005). CAO *et al.* (2006) further supplemented these studies by using a cross between *FAB4*$^{-/-}$/*mal*$^{-/-}$ mice with *ob/ob* mice (leptin-deficient mice model). Weakened leptin activity leads to improved insulin sensitivity and decreased body weight, and has also been shown to protect against hepatic steatosis (CAO *et al.* 2006). Other studies have indicated FABP4 as an adipokine connected with hepatic glucose production, suggesting that FABP4 could be useful as an effective therapeutic strategy for diabetes or other metabolic disease (CAO *et al.* 2013).

Inhibition of FABP4 activity is directly linked to the decrease in synthesis of foam cells forming atherosclerotic plaques, induced by the presence of very low density lipoproteins (VLDLs). It is therefore posited that inhibition of development of atherosclerosis in humans can be achieved by decreasing expression of the *FABP4* gene (BOß *et al.* 2015). Research is underway to develop drugs targeted at diabetic and atherosclerotic patients and based on FABP4 inhibitors (CAI *et al.* 2015).

It is well known that the PPAR-gamma protein and gene are associated with changes in expression of the *FABP4* gene. In contrast, FABP4 is responsible for an increase in PPARγ activity by transporting its ligands to the nucleus and activating the expression of its genes (TAN *et al.* 2002; AYERS *et al.* 2007). However, there are also publications that contradict these findings by reporting the reverse function of FABP4, which seems to be associated with PPARγ ligand degradation (HELLEDIE

et al. 2002). Recent studies have shown that FABP4 is certainly responsible for binding of PPARγ, at the same time inducing its ubiquitination and degradation (GHKOLNIK-SHKOLNIK *et al.* 2014).

The FABP4 protein can be used to monitor rapid changes in body weight in weight loss process as a biomarker. It has been shown that the levels of fatty acid binding proteins in the adipocytes (ENGL *et al.* 2008) significantly increased in patients during weight loss. An elevated concentration of this protein in the plasma is present in people suffering from the metabolic syndrome. The level of FABP4 in the serum depends also on age and gender, dyslipidemia and blood pressure. In addition, concentration of this protein is directly proportional to the number of metabolic syndrome symptoms diagnosed in a patient (XU *et al.* 2006). Higher – compared to healthy subjects – levels of the FABP4 protein have also been reported in people suffering from non-alcoholic fatty liver disease and type 2 diabetes (KOH *et al.* 2009). In obese individuals, elevated FABP4 levels and local expression of the protein encoding gene in the pericardial fatty tissue are linked to an increased risk of cardiac dysfunction. The above is probably the result of the inhibitory effect of this protein on calcium-ion dependent cardiomyocyte contractions (LAMOUNIER-ZEPTER *et al.* 2009).

High levels of FABP4 in young men are associated with an increased risk of coronary artery disease (DOI *et al.* 2011). BOORD *et al.* (2002) and FURUHASHI *et al.* (2007) demonstrated the pathogenic function of this protein in cardiovascular diseases. GIRONA *et al.* (2013) showed that FABP4 has a direct effect on migration and proliferation of the coronary artery smooth muscle. This protein induces activity of the active forms of nuclear transcription factors c-jun and c-myc regulated by the Mitogen-Activated Protein Kinase (MAPK) pathway. At the same time, FABP4 induces increased expression of genes responsible for cell cycle regulation and cell migration (GIRONA *et al.* 2013).

Furthermore, FABP4 is a key factor in the interaction between adipocytes and ovarian cancer cells, as it stimulates metastasis and is involved in the energy supply for tumor cells (NIEMAN *et al.* 2011; NIEMAN *et al.* 2013). Strong *FABP4* gene overexpression was also observed in tumor cells in obese mice, what was confirmed later for human prostate cancer. It has been pointed out that interactions between FABP4 and PPARγ might lead to increased aggression (metastasis) of this tumor (HERROON *et al.* 2013).

Considering the functions of the fatty acid binding protein 4 in the human body, and especially its involvement in metabolic disorders, it can be assumed that development of drugs inhibiting or completely neutralizing this protein in the future will help in overcoming such conditions as cardiovascular disease, asthma or various types of metastasising cancers (FURUHASHI *et al*. 2014).

Role of FABP4 in shaping fat content and quality of animal origin products

Measurement of expression of genes encoding proteins responsible for synthesis of triglycerides and fatty acids, including FABP4, may serve in ruminants to determine the intramuscular fat level of a selected group of animals (GUO *et al.* 2014). Expression of this gene influences the quality of meat of farmed animals (MICHAL *et al.* 2006). The fatty acid binding protein 4 thus plays an important role in the regulation of animal fat deposition and impacts the quality of animal origin products such as meat and milk (MERCADÉ *et al*. 2006; MICHAL *et al.* 2006; ZHOU *et al.* 2015).

Summary

Intracellular protein transporting fatty acids produced as a result of expression of the fatty acid binding protein 4 gene is one of the most common proteins in mature adipocytes. As it is responsible for the uptake and storage of intra-cellular fatty acids, regulation of gene expression as well as proliferation and differentiation of cells, FABP4 plays a key role in regulating insulin sensitivity, inflammation processes and lipid metabolism. Because of its role in the body, the *FABP4* gene and its protein product seem particularly interesting in light of increasingly widespread obesity – a 21st century epidemic.

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