Chapter 10

Fatty Acids in Veterinary Medicine and Research

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Abstract

Fatty acid regulation is an essential process for all animals. A number of studies have shown that diet affects the levels/availability of fatty acids in the body but increasingly an evidence shows that disease states can alter the amounts within the body too. Fatty acid levels and availability have been altered by a number of diseases, disorders and reactions including inflammatory responses, heart disease and heart failure and wound repair. They are also essential during the growth and development stages of animals. The amount of research into the consequences of different fatty acid intake and levels in various disease states and during development has increased in both humans and animals. This review presents an overview of the research undertaken to date and highlights the importance, uses and benefits of understanding the roles of fatty acids in both the healthy animals and animals under differing disorders and diseases.

Keywords: heart disease, Inflammation, development, nutrition, cancer, pregnancy

1. Introduction to fatty acids

Fatty acids consist of a carboxylic acid with a hydrocarbon chain tail, the length of which varies between fatty acids, as does the presence or absence of double bonds between the carbon atoms and their location [1]. Some fatty acids are ingested in the diet whereas others are synthesized into other fatty acids by elongation and desaturation enzymes [2–4], see **Figures 1** and **2**. In mammals, fatty acids are obtained from the diet prior to metabolism or incorporation as components of cells [5–8]. *n*-6 polyunsaturated fatty acids (PUFAs) and *n*-3 PUFAs are the two major groups of fatty acids; the first is obtained from fats and oils, and the latter from

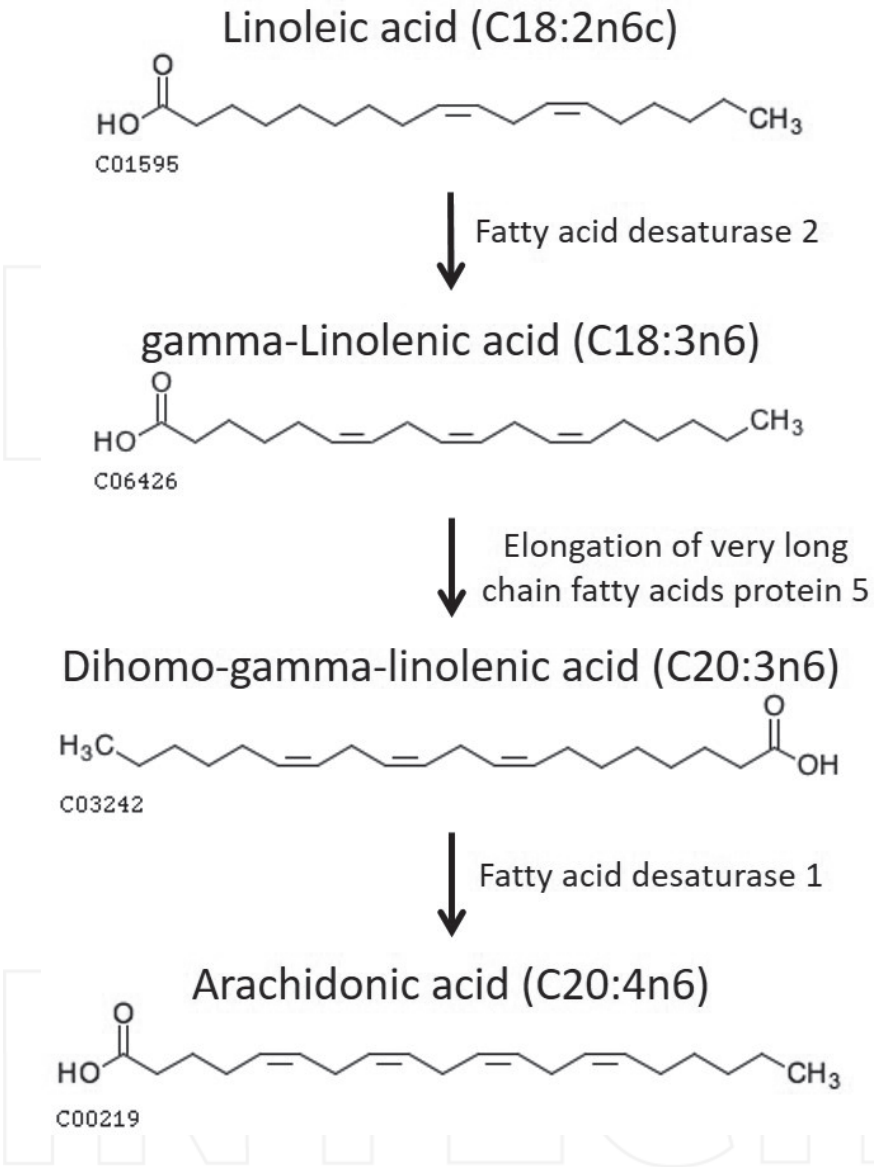

Figure 1. Schematic of linoleic and arachidonic acid biosynthetic pathway derived from KEGG pathway maps [2].

fish and seafood products [6]. It is essential that the precursors of both *n*-6 and *n*-3 PUFAs are extracted by mammals from their diet as they are not able to convert these fatty acids (FAs) between the two major pathways [9].

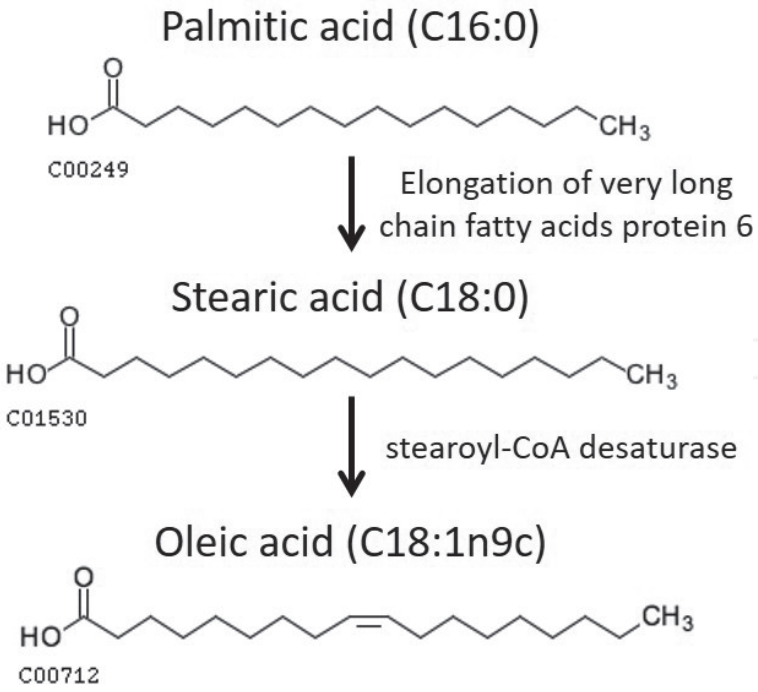

Figure 2. Schematic of palmitic and oleic acid biosynthesis pathway derived from KEGG pathway maps [2].

2. Inflammation, disease and the immune system

Fatty acids are crucial components of the immune system, providing the structural basis of all cell membranes, acting as signaling molecules, and providing a major substrate for energy production [1, 8, 10]. Many diseases involve inflammatory responses either as a reaction to disease or in the initiation of the disease process; although inflammation itself is not always detrimental, for instance, it is an important aspect of wound repair [11–14]. Elevated markers of inflammation are frequently detected in heart failure and cancers although this could be due to the response to disease, or the underlying cause of disease [15–19].

Fatty acid-derived eicosanoids are important contributors to the inflammatory response [13, 20, 21]. The *n*-6 PUFA arachidonic acid is a precursor of the most important pro-inflammatory eicosanoids, while the *n*-3 PUFA derivatives, eicosapentaenoic acid and docosahexaenoic acid metabolites are considered less inflammatory [20]. Arachidonic acid is released from cell membranes by phospholipase A_2 enzymes in response to pro-inflammatory stimuli [22–25]. Cyclooxygenase, lipoxygenase and cytochrome P450 enzymes then convert free arachidonic acid into eicosanoids [26–29]; however, these enzymes are rate limiting as they

similarly convert other fatty acids to their metabolites [20]. It has been suggested that if cyclooxygenase, lipoxygenase and cytochrome P450 enzymes are exposed to increased levels of *n*-3 fatty acids, the result is fewer arachidonic acid-derived eicosanoids [20, 30].

Due to the difference in the inflammatory response between fatty acid metabolites, it is hypothesized that the fatty acid profiles could differ between diseased and healthy individuals. Indeed, fatty acid profiles have been shown to be altered in blood and tissues in individuals with a range of conditions compared to unaffected individuals in both humans and dogs. These conditions include Crohn's disease, heart disease, skin disease and cancer [31–34], and are discussed in greater detail below.

2.1. The role of fatty acids in Crohns' disease

An interesting inflammatory response disorder is inflammatory bowel disease, including Crohn's disease. A number of animal studies, including guinea pigs and rats, have shown novel results in the adipocytes, lipid rafts and fatty acid-derived messenger molecules which indicated that aberrant fatty acid composition could play a role in Crohn's disease [35–38]. This research led directly into looking at the role of FAs in human cases of Crohns' disease, a disorder which is linked to both inflammation and the immune system. Perinodal adipose tissue (PAT) is a specialized adipose tissue depot which surrounds lymph nodes and acts in a paracrine manner—delivering specific FAs and adipokines directly to the node. Research has demonstrated that PAT associated with the lymph node is present in most animals and humans [39]. Crohn's disease is associated with altered mesenteric PAT FA content, suggesting impaired delivery of FAs to lymphocytes [40]. For many years, patients with Crohn's disease have been advised to take dietary fish oils that are rich in *n*-3 PUFAs, but interestingly patients have naturally (prior to taking supplements) presented with higher levels of *n*-3 PUFAs than observed in controls with concurrent deficiencies in arachidonic acid (20:4*n*-6) [41–43]. More recent evidence suggests that higher levels of *n*-6 PUFAs, including linoleic acid (18:2*n*-6) were most effective at relieving inflammatory symptoms [43]. The biosynthetic links between arachidonic acid (20:4*n*-6) and linoleic acid (18:2*n*-6) are shown in **Figure 1** and help to understand why an increased linoleic acid intake could reverse the decrease in arachidonic acids observed in patients. A number of animal species develop differing forms of inflammatory bowel disease, therefore understanding whether FAs are affected for the differing types of animals and differing breeds could help to indicate differing dietary or treatment requirements.

2.2. The role of fatty acids in cardiovascular function and disease

A number of links have been made between fatty acid levels and heart disease and heart failure. Human patients with significant left ventricular dilation have a larger percentage of oleic acid and a smaller percentage of arachidonic acid in their blood serum compared to patients with moderate left ventricular dilation [33]. It is also important to highlight that none of the patients involved in the study had a confirmed diagnosis, and although valve disease and coronary artery disease were excluded as the underlying cause of left ventricular dilation, infarction was not. Infarction may have skewed the fatty acid results due to the strong inflammatory nature of myocardial infarction [33, 44].

In cats with hypertrophic cardiomyopathy, differing levels of FAs were observed when compared to cats with no hypertrophic symptoms [45]. Hypertrophic cardiomyopathy cats had higher levels of docosahexaenoic acid, palmitic acid and total *n*-3 PUFAs and lower levels of linoleic acid. Differential levels of docosatetraenoic acid have been observed in canine myocardial tissue in dogs affected by dilated cardiomyopathy [46]. Mobile lipid content within the myocardium was significantly increased in a 24-hour coronary occlusion canine heart, not only throughout the body but also 'local' increases were observed around the heart with cardiac levels up to 10 times higher than the rest of the body [47–50]. It has been suggested that increased fatty acid levels alongside a decrease in creatine can lead to diastolic dysfunction, as observed in humans with diabetic cardiomyopathy [51, 52]. Despite the observations in dogs and humans, a study in rats showed increased fatty acids and decreased creatine but no associated diastolic dysfunction was observed [53]. With differing observations between species, more research is needed in order to understand the mechanisms and circumstances under which diastolic alteration occurs. Increased levels of palmitoleic acid have been associated with heart failure, higher levels of behenic acid and stearic acid have been associated with lower risk of developing atrial fibrillation, women with higher circulating pentadecanoic acid are less likely to have a myocardial infarction, hypertensive rats have higher circulating eicosedienoic acid and in renal patients higher circulating C20:5n3 is associated with good cardiac functional measures [54–60].

Although the fatty acids themselves play a key role in cardiovascular health and disease, other molecules within the fatty acid utilization cascades play important roles too. Heart-type fatty acid-binding protein (H-FABP) is expressed in cardiomyocytes and despite the name, it is also expressed in renal and skeletal muscle cells [61]. Heart-type fatty acid-binding protein (H-FABP) is used as a prognosis tool biomarker in human cardiac disease as it indicates myocardial stretch and injury in chronic heart failure even in children. Higher levels of H-FABP are associated with a poorer long-term outcome in both adults and children [61–65]. Although little work has been carried out in other species, this is an area of research which has potential, in addition to investigating whether H-FABP levels are raised prior to infarction and/or heart disease. A rat model has shown that H-FABP is increased following cardiac injury [66]. It also enables detection via a number of differing methods including EIA, ELISA, fully automated latex-agglutination assay and qualitative lateral-flow assay microparticle enhanced immunoassay [61].

External factors such as diet and surgery can play large roles in fatty acid composition and cardiovascular health. A study looking at differing feeding regimes in obese rats in comparison with lean rats showed that *n*-3 acyl chains, unsaturated and polyunsaturated fatty acids, were all significantly higher in *obese* rats than in the *lean* ones [53]. What was also interesting was the fact that mild, short-term diet changes (food intake was restricted by 20% for two weeks) did not alter the cardiac fatty acid profiles. The obese mice also showed symptoms of early stage obese cardiomyopathy; although interestingly the symptoms of this started to improve upon calorie restriction, an important finding as it showed that mild calorie restriction can be of benefit under these circumstances. Fatty acids are not only an important indicator of heart disease in animals, but also important in situations such as surgery. Increased free fatty acid levels also have been noted in response to heart surgery in pigs especially when heparin is co-administered [67]. In the surgery cases, it was found that the young patients were more affected than older patients and the levels were more likely to rise if cyanosis and prolonged ischemia were present.

Although most of the work into cardiovascular health has concentrated on disease and disorders, a number of suggestions for healthy levels have been put forward as ways of preventing disease. There is some evidence that higher levels of circulating arachidic acid are associated with lower risk of atrial fibrillation and diabetes [57, 68]. Another example is docosahexaenoic acid (*n*-3 PUFA) which has been implicated as having beneficial effects in a wide range of diseases including heart disease and neurological dysfunction [55, 69].

2.3. Fatty acids and skin disease

There are two main ways in which differing fatty acid profiles contribute to skin disease—as part of inflammation and affecting membrane fluidity. These are not mutually exclusive and it is possible that fatty acids are affecting the development of skin disease via both. People with atopic eczema have been shown to have a different fatty acid profile in their skin than people without atopic eczema. In particular, they have shorter fatty acids within their skin than unaffected individuals. This difference is suggested to lead to impaired skin barrier [70]. Atopic eczema is an inflammatory disease and thus processes of inflammation as discussed earlier will be active in the disease process [71]. As with other cases where a difference in fatty acid profiles has been established between individuals with disease and healthy individuals, it is not clear whether the fatty acid change causes the disease or is a response to disease, or possibly both, but it is a potential novel treatment route. Similar to people with atopic eczema, pruritic dogs have been shown to have a different fatty acid profile compared to dogs with healthy skin [72]. More recently, dogs with atopic dermatitis whose diets were supplemented with *n*-3 PUFA improved significantly more than those given the placebo [73]. As with human skin disease, it is not clear as to how this works, but it is an additional treatment option and area for further research.

2.4. Cancer associations with fatty acids

Cancer is the result of aberrant cellular processes. Many genes and proteins are differentially expressed in tumor tissue compared to nontumor tissue [74–77]. Thus, it is intuitive that fatty acid profiles are likely to be altered in tumors compared to nontumor tissue and this has indeed been demonstrated in breast and prostate cancer [78, 79].

There have been studies showing that differential dietary intake of fatty acids can either reduce or increase risk of disease, including cancer. A meta-analysis of studies relating breast cancer risk with *n*-3 PUFA intake showed that overall increasing *n*-3 PUFA intake reduced the risk of developing breast cancer [78]. In transgenic mice in which males develop prostate cancer, *n*-3 PUFA intake from marine sources suppressed tumorigenesis [80]. This is also the case in people where there is reduced risk of developing prostate cancer with increased intake of marine *n*-3 PUFAs [81–83]. Longer chain *n*-3 PUFAs from non-marine sources, however, are associated with an increased risk of prostate cancer [79, 82, 83].

While ultimately work is required in whole organisms, cell lines are a valuable starting point for research. Of particular note in relation to veterinary medicine and fatty acids are two studies on canine tumor cell lines. The first is that of canine lymphoma cell lines; in this study, stearidonic acid was shown to sensitize cells to anticancer drugs, even when the cells

were previously resistant to drugs [84]. The second study utilized fatty acids themselves as antitumor agents. In this study, a specific fatty acid, *trans*-10, *cis*-12 conjugated linoleic acid, was shown to inhibit cell growth and induce apoptosis in canine osteosarcoma cell lines and canine lipomas [85, 86].

3. The effects of fatty acids on fertility and during pregnancy and development

Many animal and human studies have established that restriction of a range of nutrients within the maternal diet throughout pregnancy results in offspring that are programmed to be at increased risk of later hypertension and metabolic disease including diabetes and obesity [87–90]. This theory has become known as the "developmental origins of health and disease" (DOHaD) hypothesis. Fatty acid intake has been shown to have effects even before pregnancy as severe undernutrition of specific fatty acids has resulted in low reproductive rates in males and females. For example, in male cats, a linoleic deficient diet results in tubular degeneration of the testes and low fertility rates, and in females, the litters were not viable [91, 92].

Other studies have shown birth defects in offspring from females fed on low fatty acid diets but it also showed that arachidonate was a key contributor to viable offspring [93, 94]. In contrast, excess macronutrient intake has been implicated in the incidence of the metabolic syndrome is emerging in a number of rodent [95–97] and sheep studies [98]. Studies linking maternal over-nutrition to adverse offspring health in later life are conspicuously lacking, despite a huge effort in understanding the influence of maternal nutrition and its link to obesity. A number of rodent studies have established that a high-fat maternal diet leads to impaired offspring glucose and lipid metabolism [95–97, 99], but the influence of increasing other dietary components has not been investigated, perhaps due to the assumption that a high-fat or "junk food" diet is more prevalent in the western world. Rodent studies of increased fat intake during pregnancy are often associated with an overall decrease in food intake which limits their usefulness [97]. The timing of a nutritional insult is also important in determining the outcome for offspring, differential results have been observed in studies investigating early or late gestational nutritional insults in both animal [100, 101] and human studies [102]. As well as a high-fat diet increasing adipocyte and ectopic lipid accumulation, it may also decrease glycogen deposition in skeletal muscle. Increased plasma free fatty acids impair insulin-stimulated glucose disposal, including glycogenesis and glucose uptake—resulting in reduced skeletal muscle glycogen content [103]. Type-2 diabetes in humans is associated with a reduction in glycogen synthase and tissue glycogen [104], it is unknown whether a sub-optimal maternal diet will result in similar changes in offspring. Recent work has demonstrated that there are physiological [105–107] and emerging molecular differences between pigs with low, normal or high birth weights [108–111]. Extensive physiological examinations of low and high birth weight pigs, at 12 months of age showed that low birth weight pigs had increased fat depth and glucose intolerance and insulin resistance [105]. Also of interest is that, peroxisome proliferator-activated receptor (PPAR)α expression in skeletal muscle is positively correlated to birth weight in these pigs [110]. In younger pigs (7 or 14 days of postnatal age) designated low, normal or high to birth weight, molecular differences have been observed in adipose

tissue and skeletal muscle genes known to regulate lipid metabolism including uncoupling proteins (UCPs), PPARα and γ, fatty acid-binding protein (FABP) 3 and 4 and the glucocorticoid receptor (GR) [108, 109, 111].

The role of PPARs is not just restricted to animals subjected to over-nutrition. Studies of maternal low protein diets in rats have demonstrated that post-weaning, offspring had significantly increased hepatic PPARα expression due to decreased methylation as a result of differences in overall dietary fat intake [112]. PPARs are a nuclear hormone receptor family that have attracted much interest due to their involvement in adipogenesis, lipid metabolism, insulin sensitivity, inflammation and blood pressure [113]. PPARγ regulates transcription of genes involved in lipid metabolism by binding to responsive elements in the promoters of respective genes. This transcription regulation stimulates fatty acid storage in adipose tissue by increasing the storage capacity and the quantity of fatty acids that enter adipocytes and also plays a key role in adipocyte differentiation, promoting the formation of mature lipid-laden adipocytes [114]. The activities of PPARγ are regulated by fatty acids (which are thought to be the endogenous ligands) [115]. PPARγ is often referred to as the "genetic sensor" for fat and a number of dietary studies have demonstrated an increase following high-fat feeding [116, 117], which may provide benefits to the animal by protecting against lipotoxic species [117]. PPARα also acts as a ligand-activated transcription factor and is expressed in tissues which have a high rate of fatty acid catabolism such as skeletal muscle and liver. The fibrate group of drugs has long been utilized as a synthetic ligand for PPARα, but endogenous ligands are still under investigation. Long-chain fatty acyl-CoAs and saturated fatty acids however are known to activate PPARα at micromolar ranges [118]. PPARα has a key role in stimulating lipid oxidation pathways to prevent storage of fats as well as increasing insulin sensitivity and glucose tolerance. The expression of PPARs may represent one of the molecular factors driving excess tissue lipid uptake, storage and production in animals that experienced a sub-optimal environment in utero, in particular low birth weight offspring; ectopic lipid storage, especially intramyocellular, is associated with glucose intolerance and type-2 diabetes [104, 119].

The regulation of fatty acids is also an important factor during the lactation period. A number of studies have shown that the relative fatty acid content of milk differs depending on the species. Donkeys have milk more similar to humans than cows, with lower levels of saturated fats and higher essential fatty acids than cows, more akin to humans [120, 121]. Milk, from humans, dog, and guinea pig are mostly comprised from long-chain fatty acids (48–54 acyl carbon atoms), cow, sheep, and goat, have more short-chain acids (28–54 acyl carbon atoms) and horses tended to have medium-chain fatty acids (26–54 carbon atoms range) [122]. Maternal diet can also have an impact on the fatty acid contents of her milk. This has been shown in many species from mice and sheep to humans [123–125]; the pregnancy status of the mother also vastly changes milk fatty acid composition [126]. These are important factors when assessing whether the mother is receiving an appropriate diet, assessing whether she is pregnant or not and whether milk replacement formulae contain the appropriate levels of fatty acids.

4. Fatty acid-binding proteins and lipid modulation

Fatty acids are now recognized as crucial components of cellular signaling cascades, in particular, those regulating lipid metabolism, as described above with PPARs. Research into fatty acids as signaling molecules is in its infancy, but it is well known that fatty acids are ligands for transcription factors. Fatty acids are carried through tissue membranes and in the cytosol by chaperones known as fatty acid-binding proteins (FABPs), of which there are a number of tissue-specific isoforms [127]. Knock-out mice not expressing the adipocyte-specific FABP4 exhibited protection from the metabolic effects (e.g. insulin resistance and hypercholesterolaemia) of a high-fat diet, suggesting FABP4 modulates a number of components of the metabolic syndrome [127]. In skeletal muscle, a fat-rich diet increases the expression of the cytosolic and plasma membrane specific FABP [128].

Insulin resistance is characterized by a decrease in the enzymes and proteins involved in lipid oxidation [129]. Lipogenesis and adipogenesis are modulated by the enzymes acetyl-CoA carboxylase 1 and 2 (ACC1 and ACC2, respectively) and AMP-activated protein kinase (AMPK); both enzymes are potential drug targets to treat obesity and the metabolic syndrome and AMPK has been suggested as a target for metformin [130, 131]. Briefly, ACC1 controls fatty acid biosynthesis and ACC2 controls fatty acid oxidation. ACC1 catalyses the conversion of acetyl-COA to malonyl-CoA, therefore modulating the rate limiting step of long-chain fatty acid biosynthesis in adipose tissue. ACC2 is expressed in skeletal muscle, where the product malonyl-CoA inhibits fatty acid oxidation. The AMPKα subunit is activated during periods of metabolic stress (e.g. increased AMP/ATP ratio) by phosphorylation and inhibits the activity of ACC1 and 2, thus promoting fatty acid oxidation, glucose uptake and inhibits lipid synthesis [132] and thereby reducing ectopic lipid storage. An isocaloric high-fat diet has been shown to inhibit AMPK in rats [133]. Despite great potential for modulation by maternal diet, there are few DOHAD studies of ACC and AMPK expression; however, early studies of an obese pregnant ewe model have shown decreased AMPK signaling in fetal offspring muscle [98].

5. Future fatty acid research and medicine

Although artificially induced disease often only replicates a small aspect of disease and does not reflect the typically longer time scales involved in natural disease progression in both humans and animals [134, 135], these studies can be valuable when compared to naturally occurring diseases in order to understand mechanisms and development. All of the 'natural population' studies discussed in this chapter may have their own caveats too. Differences in diet, age, sex and even pre-clinical symptoms and diagnosis can all affect the results observed in both disease and fatty acid states. This chapter has concentrated on development, cardiovascular disease, cancer and immunity but differing fatty acids have been implicated or associated with in a number of diseases and disorders ranging from human, rodent and canine epilepsy through to canine ADHD and reproductive ability [92, 136, 137].

Fatty acid profiling has important potential applications as a diagnosis tool across the species, especially in cases where pre-clinical symptoms are difficult to observe. Although it is not always necessarily known if differences in fatty acid profiles are contributing to the initiation of disease or are a response to disease processes, these differences could be drug targets [26, 138–140]. In addition, there are genes that contribute to fatty acid profile composition and if a particular part of the pathway is shown to be different in individuals with disease compared to healthy individuals, these could be likely genes for candidate gene studies in the future [141, 142]. The scientific methodologies available for looking at lipid levels have also progressed over the years; just one example is the use of proton magnetic resonance spectroscopy of protons (H-MRS) to assess cardiac lipids in a non-invasive manner [52]. This is a valuable tool for animal health and welfare, and there are additional uses in looking at metabolism and fatty acids. Much of the present work involves looking at genes and lipid levels of animals intended for the meat industry. An example is the evidence that differing polymorphisms in genes can result in differing meat quality traits. This includes fatty acid synthase (FASN) which was found to correlate with meat weight loss during the first salting of dry-cured ham production [143], meat quality including marbling in cattle [144] and playing a role in the mammary gland and milk in goats and cattle [145, 146], in addition to many other roles. Differing H-FABP polymorphisms/expression levels have also been related to growth rate and size of beef cattle and chickens and could therefore provide useful markers for breeding [147, 148].

Research into the links between fatty acids and differing developmental stages and disease states is increasing in both humans and animals and provides the potential for innovative diagnostic and treatments tools.

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