

**Studies on effects of anti-oxidant astaxanthin
supplementation in healthy and obese dogs**

Summary

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In world population, 1.9 billion are diagnosed as overweight and 650 million are diagnosed as obesity, and obesity is world health problem. In recent years, overweight and obesity are frequently observed also in dogs and cats. Obesity and its related disorders such as diabetes mellitus and Cushing's syndrome become social problem in veterinary medicine. This thesis is constructed with 4 chapters. In chapter 1, pathophysiology and onset mechanism of obesity is reviewed. Inflammatory reaction caused by lipid metabolism disorders accompanying with obesity is called as lipotoxicity. The main cause of lipotoxicity is lipid peroxidation by over produced reactive oxygen species (ROS) in the process of fatty acid β -oxidation. Therefore, anti-oxidant substances reduce lipotoxicity in various tissues of animals. Effect of supplementation with astaxanthin (ASX) as vigorous anti-oxidant substance was investigated in healthy dog (Chapter 2) and obese dogs (Chapter 3). Moreover, effect ASX supplementation was investigated in dogs with diabetes mellitus and Cushing's syndrome.

1. Epidemiology of glucose and lipid metabolism disorders

Obesity is a risk factor to induce various metabolic disorders in both human and animals. Classification of obesity is done with body condition score (BCS) in dogs and cats, however there is not suitable method to classify simple obesity with excessive subcutaneous fat accumulation and obesity disease with excessive visceral fat as ectopic fat accumulation. Excess lipid as accumulated visceral fat induces proinflammatory reactions in various tissues. Adipocytes (fat cells) have two functions as energy storage organ and cytokine secretion organ. These cytokines are called as adipokines and show important functions to regulate various physical activities in animals. The most important factor for obesity to induce various metabolic disorders is remodeling of fat cells in accumulated visceral adipose tissues. Enlarged fat cells secrete various inflammatory cytokines (adipokines) such as non-esterified fatty acids (NEFA), M1 macrophages, which induce activation of NADPH oxidase and oxidative stress leading acceleration of obesity domino reaction consequently metabolic syndrome with insulin resistance, glucose intolerance, hypertension and lipid abnormality. From the above results, various preventive treatments targeting suppression of obesity onset are considered to be effective

to prolong lifespan of animals.

2. Effect of ASX supplementation on lipid metabolism in healthy dogs

Astaxanthin is generally known as vigorous anti-oxidant substance. As ASX shows suppressive lipid peroxidation function and singlet oxygen elimination function, ASX is used as a functional food in various fields, food industry and fish culture, etc. Oxidative stress with excess amount of ROS causes chronic inflammation in many tissues. The chain reaction by ROS is known as lipotoxicity and causes metabolic syndrome. Effect of ASX supplementation was investigated in healthy dogs with BCS3 (ideal body weight). ASX was orally supplemented at a dose of 0.3 mg/kg BW/day for 8 weeks. After the supplementation for 8 weeks, plasma triglyceride (TG) and malodialdehyde (MDA) concentrations and lactate dehydrogenase (LDH) activities decreased significantly. These results seem to clarify that ASX supplementation ameliorates liver function leading to improve lipid metabolism in dogs. Their body weight and BCS were not changed in healthy dogs after ASX supplementation. Anti-oxidative functions of ASX are effective to maintain health and prevent some metabolic disorders caused by ROS in dogs, so ASX is very useful functional food.

3. Effect of ASX supplementation in obese dogs

In obese condition, a series of chain reaction of chronic hepatic injury and oxidative stress caused by lipid peroxidation accelerate fat cell remodeling. ASX has stronger anti-oxidant activity, 200 to 500 times higher than that of vitamin E. As shown in Chapter 1, ASX supplementation can ameliorate lipid metabolism in liver of healthy dogs. In this chapter, effect of ASX supplementation is investigated in obese dogs with over BCS4. ASX was supplemented to 5 obese dogs with BCS 4 and 5 at a dose of 0.3mg/kg/day for 8 weeks. After the supplementation, plasma TG concentrations and alanine aminotransferase (AST) activities were decreased in all 5 dogs. Plasma LDH activities decreased in 4 of 5 dogs, and MDH concentrations decreased in 3 of 5 dogs. BW and BCS were not changed after the ASX supplementation. Decreased ALT activities suggest amelioration of injured liver by oxidative stress with excess amount of ROS.

Improvement of hepatic function leads reduced values of TG, LDH and MDA. Dogs reared in house prone to fall into unbalance of energy metabolism between intake and consumption of calories. ASX with high anti-oxidant activity are effective to maintain function of fat cells in obese dogs.

4. ASX supplementation in dogs with diabetes mellitus and Cushing's syndrome

ASX supplementation effect was investigated in dogs with diabetes mellitus and Cushing's syndrome. Each disorders were treated with appropriate procedure, respectively. Diabetic dog (Maltese, spayed, 11 years old) was maintained with appropriate insulin injection, and was supplemented with ASX at a dose of 0.68mg/kg/day. On 60 days after the supplementation, plasma ALT, γ -GTP, NEFA and MDA concentrations decreased significantly. Then ASX supplementation was discontinued and on 60 days after ASX cancellation plasma MDA concentrations elevated significantly and NEFA and γ -GTP values increased too in the diabetic dog. ASX supplementation is considered to be effective to ameliorate insulin resistance. Miniature Dachshund (spayed, 11 years old) with Cushing's syndrome showed overweight (BCS4). ASX was supplemented orally with this dog at a dose of 0.28mg/kg/day. On 30 days after the supplementation, plasma total cholesterol (TC), TG, ALT and NEFA values were not changed, however, on 120 days plasma TG and NEFA concentrations decreased.

As the above results, ASX supplementation may suppress lipid peroxidation in tissues, in particular in liver, and may improve liver function, which is effective to treat metabolic disorders such as diabetes mellitus and Cushing's syndrome in dogs. It is very important to ameliorate liver function by suppression of lipid peroxidation for prolongation of lifespan in obese dogs. Therefore, supplementation of anti-oxidant substance like ASX is very effective to prevent obesity and its related metabolic syndrome.