Compromised Hepatic Detoxification in Companion Animals and its Correction via Nutritional Supplementation and Modified Fasting

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Abstract
Dietary components play a crucial role in the health of companion animals, especially those exposed to elevated levels of toxins and free radicals. Investigation into animals' hepatic antioxidant and metabolite conjugation systems, and the metabolic processes that influence them, provides some understanding regarding the relationship of diet to disease prevention and treatment. A review of current literature and research publications suggests nutritional supplementation can be an effective treatment for animals suffering from increased oxidative stress and toxicity. The results of recent *in vivo* assessments, clinical trials, and observational studies show oral supplementation with vitamin E, selenium, glutathione, and taurine to be beneficial for both maintaining natural antioxidant systems and protecting against a number of degenerative diseases associated with free radical damage and toxin exposure. In many instances, it has been observed that the introduction of specific nutrients positively influences the health status, symptomatic presentation, and life span of animals whose natural detoxification systems are compromised.
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Introduction

Mammals adapt remarkably well to the demands of their environment. Nonetheless, concomitant with various exposures to increasingly diverse environments are the increased risks for cellular, tissue, and organ damage due to oxidative stress and contact with toxins. Over time, animals have developed a complex process for toxin metabolism and a system of antioxidant defense to combat the deleterious effects of exposure to toxic and reactive chemicals.

Hepatic metabolism and the subsequent excretion of toxins are the primary means of detoxification in the body. In conjunction with the liver's system of detoxification, the utilization of diet-derived antioxidants can be efficacious in helping to prevent oxidative damage. Both lines of defense are extremely important for maintaining optimal health and preventing disease states in humans and animals.[1]

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Notwithstanding its many capabilities, the natural detoxification process can be inadequate to fully cope with sustained exposure to toxins. If an animal's ability to effectively metabolize and expel toxins from the body is compromised – for example, due to enzymatic imbalance, physical or mental stress, or dietary excess or deficiency – and/or the production of reactive chemical species is increased, an accumulation of toxins in the body can result. The inability to eliminate an ever increasing concentration of poisons and/or waste products from the body may cause toxicity – a state implicated in the pathogenesis of many degenerative diseases, permanent organ damage, and cancer.[2]

The integrity of the physiological systems responsible for detoxification, cellular repair, and immune processes is dependent on the nutritional status of an organism.[3-4] Supporting adequate nutrition is integral to maintaining a functional and effective system of detoxification.

Fortunately, when the normal biological defense systems are ineffective and toxicity results, there are a number of effective treatment options. Methods for decreasing toxic substances in the body include modified fasting and administration of nutrients to prevent oxidative damage and increase the rate of toxin processing and elimination by the liver.

Toxins

Toxins include substances that enter into or are produced by the body that have a harmful effect on a living organism. Toxins are introduced into an organism in a variety of ways. For the purposes of this article environmental toxins are defined as industrial pollutants, pathogenic bacteria, phytochemicals, insecticides, certain prescription antibiotics and over-the-counter medications, and excesses of certain foods. Not all toxins present in the environment are innately harmful to an organism; some compounds, due to the body's normal metabolic processes, are broken down into reactive intermediates and rendered toxic.[5]

Toxin damage may be direct, via oxidation, for example; or it may be indirect, such as by inciting inflammation. In addition, toxins can interfere with normal intracellular communication, such as when hydrogen peroxide induces T-cell signals.[6] Another example is the interaction of the infectious organism *H. pylori* with gastric epithelial cells associated with tyrosine phosphorylation through protein tyrosine kinase. Tyrosine phosphorylation is necessary for the initiation of altered cellular communication.[7]

Internal sources of toxins include waste products produced by the body, substances produced during digestion (both intestinal and hepatic), by-products from the breakdown of natural substances (e.g., hormones), and bacterial endotoxins. Reactive oxygen species are generated during normal respiration of oxygen through the mitochondrial electron transport chain. Although they exist only a very short period of time because of their reactivity, free radical species are very destructive when they attack biologically important molecules such as proteins, lipids, carbohydrates, and nucleic acids (DNA and RNA). Toxins continue to generate free radicals during their time in the body, either in their original state or in a partially processed form.

Toxins are metabolized by the liver in two stages. Water-soluble toxins are primarily excreted in urine and, to a lesser extent, by the skin and lungs. Fat-soluble toxins are excreted in the bile, being transmitted to the small intestine and becoming part of the fecal matter. There may be some re-circulation of toxins by this latter route as they are reabsorbed from the intestines. When fat-soluble toxins exceed the liver's capacity to process and excrete them, they remain in circulation to be picked up and stored in body fat. If a body's fat stores are filled, or if there is abrupt weight loss with a decrease in available fat stores, the toxins continue to circulate in the blood, causing cellular damage throughout the body.

Mitochondria are damaged when toxin levels reach sufficiently high concentrations. Because mitochondrial DNA is separate from cellular DNA, and because, unlike cellular DNA, it lacks significant repair mechanisms,[8] mitochondrial damage is permanent.

All organisms are susceptible to the harmful effects of toxins and oxidative stress, no matter what state of health they may be in. Even a healthy animal not exposed to noxious substances will have some toxins present in the body (e.g., mercaptans, short-chain fatty acids, skatoles, indoles, ketone bodies). Free radical production occurs continuously in the body as a by-product of aerobic respiration and normal cellular function.[9]

The cumulative effects of oxidative stress and the bioaccumulation of toxins in the body have been implicated in a number of degenerative diseases, immune system dysfunction,[10] liver fibrosis and chronic hepatitis leading to cirrhosis,[11] an increased frequency of tumors,[12] heart disease,[9, 13] impaired motor coordination,[14] dementia, Parkinson-like symptoms,[5] and cancer.[2] Disease state and severity can vary from species to species and will depend on an individual animal's age, nutritional status, metabolic activity, and degree of toxicity.

Toxin Processing by the Liver

The first pathway for metabolism of nutrients, drugs, toxins, and other compounds is catalyzed by Phase I enzymes in the liver. This process involves the p450 system of cytochromes, comprised of mixed-function oxidative enzymes. In this phase, chemicals are broken down through oxidation, reduction, hydrolysis, hydration, and dehalogenation. The resulting Phase I metabolites include both harmless and potentially harmful products. When Phase I oxidation reactions fail to render metabolites as stable intermediates, free radicals are generated, an excess of which cause harm to cellular membranes and organ tissues. Once free radicals are produced, a chain reaction occurs wherein lipid peroxidation becomes self-perpetuating, generating more free radicals, and causing further harm.[15-17] This is seen, for example, where lipid peroxidation is implicated in the pathogenesis of chronic hepatitis and feline hepatic lipidosis. Metabolites resulting from Phase I detoxification can be as toxic as, or even worse than, the primary metabolite. For example, benzene is initially processed to an even more toxic phenol.

Table 1. Supplements to Enhance Phase I Enzyme Reactions

Riboflavin
Niacin
Pyridoxine
Folic acid
Vitamin B12
Glutathione
Bioflavonoids
Phospholipids
Branched chain amino acids

Metabolites rendered water-soluble by Phase I processing are excreted in the urine by the kidney. If they remain as reactive chemical species they undergo further processing by Phase II enzymes. If a metabolic bottleneck exists at this point – because of decreased Phase II enzymes, an increase in the amount or activity of Phase I enzymes, or an increase in toxins being processed – Phase I metabolites enter the bloodstream until being removed from circulation by storage in body fat. When fat stores are full, the metabolites remain in the bloodstream where they can

further damage body tissues. If liver and kidney functions are significantly impaired, the rate at which toxins are excreted is accordingly decreased, resulting in damage to organ tissues.

To process metabolites, Phase I enzymes use riboflavin, niacin, folic acid, cobalamin (vitamin B12), branched-chain amino acids (leucine, isoleucine, and valine), flavonoids, and phospholipids as co-factors (Table 1). These substances can be used to influence Phase I reactions whether or not deficiencies exist.[18, 19]

Antioxidants such as the endogenous antioxidants superoxide dismutase (SOD), coenzyme Q10 (CoQ10), and vitamin C, as well as supplemental sources such as pycnogenols, vitamin A, carotenes, bioflavonoids, vitamin E, and selenium protect against tissue damage from intermediate Phase I metabolites. The minerals copper, zinc, and manganese act as co-factors for SOD, and protective antioxidants from plant sources include thiols (from onions and cruciferous vegetables) and *Silybum marianum* (milk thistle).[1, 4, 9, 18, 19, 26] Several of these dietary components will be discussed in more detail later in the article.

Phase II enzymes act on the oxygenated metabolites of Phase I reactions to produce extremely hydrophilic compounds that are easily excreted.[2] Phase II reactions include conjugation, sulfation, glucuronidation, methylation, acetylation, and amino acid conjugation. Glutathione conjugation uses N-acetylcysteine, cysteine, and methionine; cystine is used for sulfation; and glucuronidation requires pantothenic acid (vitamin B5). Amino acids most commonly used for conjugation include glycine, taurine, glutamine, arginine, and ornithine. All of these substances can be supplemented to increase the rate of Phase II reactions.[1, 4, 9, 18, 19, 26] Maintenance of adequate glutathione levels in the body is crucial to efficiently processing toxins and preventing oxidative destruction of organ tissues.[17] Because glutathione levels become decreased from either physical or oxidative stress,[20] stress reduction is especially important during the detoxification process. It should be noted that a 24-hour water fast decreases glutathione levels in the liver by 50 percent, slowing Phase II processing of toxins.[20]

Phase III consists of further metabolism of glutathione conjugates. It is relatively unimportant in the production of a toxic reaction and is not discussed in this article.

Antioxidant System

Aerobic organisms have a remarkable system of innate antioxidants and enzymes that defend the body against oxidative damage and cellular toxicity. These antioxidant components work independently, cooperatively, and even synergistically to maintain the integrity of organ tissues.[17, 21]

There are three main categories of antioxidant molecules (Table 2). The first group contains preventive antioxidants, which reduce the formation of reactive oxygen species by decomposition of radical-producing compounds; sequestering metal ions (which can act as catalysts to peroxidation reactions); and by quenching free radicals. This group of antioxidants includes glutathione peroxidase, glutathione S-transferase, peroxidase, catalase, apoferritin, transferrin, lactoferrin, ceruloplasmin, carotenoids, and SOD.[16, 20]

The second category of antioxidants is comprised of free-radical scavenging molecules that inhibit chain initiation and suppress chain propagation by trapping a radical before it reaches its cellular target. Examples of antioxidants in this group include vitamins C and E, uric acid, albumin, thiols, bilirubin, CoQ10, and carotenoids.[1, 16, 20]

The third group involves nutrients and enzymes responsible for cellular repair and selective cleavage of peroxidized lipids from cellular membranes. This category contains phospholipids, proteolytic enzymes, proteinases, proteases, and peptidases.[16, 20]

Table 2. Endogenous Antioxidant/Enzyme Systems

Preventive Endogenous Antioxidants	Free Radical Scavengers	For Cellular Repair
Vitamin C	Glutathione peroxidase	Phospholipids
Carotenoids	Glutathione S-transferase	Proteolytic enzymes
Vitamin E	Peroxidase	Proteinases
Uric acid	Catalase	Proteases
Albumin	Apoferritin	Peptidases
Thiols	Transferrin	
Bilirubin	Lactoferrin	
CoQ10	Ceruloplasmin	
	Carotenoids	
	Superoxide dismutase	

Without this antioxidant defense system in place, mammals are very susceptible to disease. In fact, oxidative stress may progress to such an extent that it becomes lethal. This is demonstrated in experiments with transgenic mice which lack the ability to synthesize mitochondrial superoxide dismutase. These animals typically die soon after birth from lung damage, and those that survive suffer severe neurodegeneration.[22, 23] Similarly, mice that are bred lacking the Phase II enzyme glutathione peroxidase, while phenotypically normal, are hypersensitive to toxins which generate free radicals and have particularly vulnerable cardiac tissue.[24, 25]

Oxidative Stress and Chronic Toxicity

The susceptibility of an organism to oxidative damage is described as a function of the overall balance between the factors that exert oxidative stress and those that exhibit antioxidant potential. In situations where antioxidant potential is weakened or oxidative stress is increased, irreversible cell membrane damage can occur. Imbalances in levels of hepatic enzymes and/or inadequate nutritional status can cause the body's natural detoxification system to fail. Studies in humans have found that dietary influence on the normalization of Phase I p450 activity in relation to Phase II glycine conjugation increased the rate of detoxification and reduced symptomatic complaints.[26]

Table 3. Supplements that Protect the Body from Free Radicals Produced by Phase I Enzyme Reactions

Arginine
Carnitine
Cysteine
Cystine
Glucuronic acid
Glutamine
Glutathione
Glycine
Methionine
N-acetylcysteine
Ornithine
Taurine
Pantothenic acid
Riboflavin
Selenium
Sulfates
Superoxide dismutase
Copper
Zinc
Manganese
Vitamin A
Carotenoids
Vitamin C
Bioflavonoids
Pycnogenol
Vitamin E
Thiols (onions, crucifers)
Silybum marianum

If Phase I and Phase II enzyme levels are both high in the liver, the detoxification process occurs quickly. Conversely, if Phase I and Phase II enzyme levels are both low, the metabolism of toxins occurs slowly. If Phase I enzymes are low while Phase II enzymes are high, these animals will have systems that behave as if both enzyme system concentrations are low, since the Phase I enzymes are the limiting factor in the metabolic process.

In organisms where Phase I enzymes are high but Phase II enzymes are low, there is great risk of a toxic episode. This occurs when high levels of toxins are processed by Phase I, producing high levels of intermediate metabolites; but insufficient Phase II enzymes are available to complete metabolism. The greatly reduced processing of the excess Phase I intermediates results in a correspondingly higher level of these reactive metabolites accumulating in the bloodstream. Table 3 is a list of compounds that can neutralize those free radicals produced during Phase I detoxification. Compounds that have been shown to inhibit the activity of certain p450 enzymes include grapefruit,[27] procyanidolic oligomers extracted from grape seeds (*Vitis vinifera*),[28] and certain amphiphilic compounds such as oleic acid.[29] The site of free radical formation and bioaccumulation is important. Hydrophilic antioxidants such as vitamin C, though useful against aqueous toxins, cannot effectively scavenge free radicals within lipid membranes. Therefore, even a small number of radicals generated in the aqueous phase that penetrate the cellular membrane can induce a chain reaction that amplifies the damage.[22]

Species Specific Reactions to Enzyme Imbalances

Organisms within the same species have different levels of Phase I and Phase II enzymes; different species have even more pronounced differences.[30,31] Cats are relatively deficient in some Phase II enzymes, such as glutathione peroxidase,[32] and cannot suspend gluconeogenesis when fasting, due to the high activity of the rate-limiting enzymes of glucogenesis (pyruvate carboxylase, fructose-1, 6-bisphosphatase, and glucose-6-phosphatase).[33,34] Consequently, fasting or decreasing protein content in a cat's diet will not markedly decrease toxic by-products in the body

Table 4.
Supplements that Support Phase II Conjugation

N-acetylcysteine
Pantothenic acid
Taurine
Glycine
Sulfates
Catechins

associated with protein metabolism, and may in fact result in the cat being more prone to toxic injury.

Dogs and humans use the amino acid glycine as a major Phase II conjugate. The liver in both humans and dogs can synthesize taurine from cysteine as long as an adequate level of cysteine is in the diet; whereas, cats must have the primary amino acid taurine introduced from dietary sources. In addition, cats are not able to synthesize arginine, needed for the urea cycle, and will develop hyperammonemia without it.[35] The primary factors used by cats in the Phase II pathway are glucuronic acid and sulfate; however, cats have lower levels of glucuronic acid enzymes than dogs or humans. Therefore, cats are more likely to suffer from toxicity and should never be completely fasted. To do so invites the likelihood of developing hepatic lipidosis.[36] Table 4 summarizes nutrients necessary for Phase II detoxification.

The Role of Nutrition in Detoxification and Cellular Repair

It has been said the importance of the diet in the prevention of chemical-induced toxicity cannot be underestimated.[4] Likewise, the role of nutritional components in maintaining a proper balance of metabolic enzymes cannot be questioned. Supplementation with a select number of vitamins and trace elements can boost an organism's defenses against oxidative stress and aid in cellular detoxification.

Vitamin E

Due to its ability to quench free radicals by donating an electron, breaking the chain of radical propagation, and preventing the peroxidation of lipids within cellular membranes, vitamin E is one of the most significant dietary antioxidants. The role of vitamin E in protecting against peroxidation related to liver damage seems also to be related to its ability to decrease the basal expression of transforming growth factor β-1 (TGFβ-1), the best known pro-fibrogenic cytokine in the liver.[11]

Dietary antioxidant requirements (as in the case of vitamin E) are proportional to the amount of exercise an animal undertakes. Because exercise increases the demand for energy from mitochondria, the number of free radicals escaping the electron transport chain also increases.[37] Studies on the effects of strenuous physical activity performed in female albino rats showed a direct correlation between the level of exhaustive exercise and the concentration of lipid peroxides in pulmonary tissues. When the diets of these animals were supplemented with vitamin E and selenium (whose antioxidant properties and synergistic relationship to vitamin E are discussed later in the article) for a period of 12 weeks, the oxidative reactions and resultant lipid peroxidation were notably reduced in pulmonary tissues. This study concluded that dietary vitamin E is effective in combating exercise-induced oxidative stress.[38]

Also relevant is the fact that dogs normally have a higher rate of fat oxidation (having twice the rate of free fatty acid metabolism) both in exercise and resting states, than do humans. This suggests canines would be subject to a relatively high rate of free radical generation and potential for oxidative damage due to greater lipid peroxidation.[39] These metabolic characteristics further suggest canines would benefit from supplementation of their normal diet with additional vitamin E. The RDA for dogs is 50 IU vitamin E per kg food,

on a dry matter basis, which has been determined to be enough for maintenance for a young adult dog. It increases proportionally for pregnant and lactating dogs as their food intake increases. This translates to 35.4 IU per day for a 150-lb dog at rest, and increases to 175 IU per day for a heavily working dog eating the same food. Ironically, if a dog is given a food of higher caloric density, the intake of vitamin E is decreased, since it is calculated on a dry matter basis, not a caloric basis.

Increased needs during pregnancy are due to the increased risk of toxin damage and oxidative stress. Studies emphasize the importance of adequate dietary intake of vitamin E for maintaining reproductive health, and for preventing fetal resorption, degeneration of germ cells in male animals, and muscular dystrophy and liver necrosis in progeny. It has been speculated that vitamin E is important for normal reproduction because it protects the amniotic membrane against peroxidation.[20]

As an animal ages, the nutritional requirement for vitamin E increases. The long-term effects of oxidative stress threaten many organ systems in aged mammals and have been associated with several disease states. Although the free radical-based theory of aging is still under debate, the scientific community has reached a consensus regarding the cumulative damage of oxidative stress and its ramifications on the health and longevity of an animal. It has been shown that a lipid peroxidation-decreasing diet (low levels of polyunsaturated fats (PUFAs) and copper) along with antioxidant administration of vitamin E and selenium can increase the life expectancy of animals.[13]

Increased levels of dietary PUFAs can increase the PUFA content of cellular membranes. The incorporation of PUFAs into the cellular membrane bilayer allows for accelerated lipid peroxidation since the number of targets for oxidative reactions is increased. Vitamin E exhibits its antioxidant properties by quenching free radicals in the PUFAs of membrane phospholipids. To protect against cellular toxicity and tissue damage due to peroxidation, a ratio of 0.6:1 (vitamin E:PUFAs in mg/g) is recommended as a nutritional minimum for animals.[40] As the level of unsaturated fatty acids increases in an animal's diet, the amount of vitamin E supplementation should increase accordingly.[5, 41]

When an animal suffers from chronic inflammation, the surrounding tissues are exposed to high levels of superoxide radicals generated by the activity of phagocytic cells. While this phenomenon is responsible for preventing infection by invading micro-organisms, the consequence is increased oxidative damage. This is characteristic of diseases in humans such as rheumatoid arthritis, systemic lupus erythematosis, and psoriatic arthritis.[5] This factor should be taken into consideration when prescribing treatment for animals with repeated invasive surgeries or acute traumas (as in the case of Digger; see case study discussion later in the paper).

Vitamin E deficiency in dogs appears to impair the immune system and, in extreme states (especially when combined with insufficient selenium levels), can cause muscle weakness and degeneration, subcutaneous edema, anorexia, depression, dyspnea, and renal mineralization.[40] It has also been implicated in decreased reproductive performance, retinal degeneration, and the development of dermatological disorders. In cats, a condition called pansteatitis, which includes symptoms of lethargy, anorexia, depression, and fever, can occur when dietary levels of vitamin E fall too low.[41]

High dietary levels of vitamin E have not been associated with any deleterious effects, and there is no evidence that supplementation has caused hypervitaminosis or toxicity in animals. Doses of 1,000 IU/kg of food (the equivalent of 700 to 3,500 IU per day) have been set as a high end by AAFCO, the agency that sets the standards; although, there is no evidence of toxicity at twice that level.

Extremely high levels have been associated with prolonged clotting time – reversible by giving vitamin K; decreased storage of vitamin A – reversible by giving vitamin A; and decreased bone mineralization in growing animals – reversible by giving vitamin D. This is from competition with other fat-soluble vitamins for absorption, not from toxicity of vitamin E itself.

Selenium

Selenium, vitamin E's synergistic antioxidant partner, aids in detoxification by preventing peroxide formation, as well as acting as a catalyst for metabolic enzymes. It is considered an essential trace element for both humans and animals.[12, 41] It has been estimated that approximately 36 percent of selenium's activity is associated with selenium-dependent-glutathione peroxidase in the liver (based on the rat as a physiological model). Selenium plays an integral role in the synthesis of glutathione peroxidase, a key Phase II enzyme responsible for reducing hydroperoxides to harmless hydroxy acids.[20] This relationship may account for a major portion of the nutritional essentiality of selenium.[42] Selenium deficiency has been directly associated with the development of cancers, cardiovascular disease, and hepatic lesions.[12, 41] As with vitamin E, the dietary requirement for selenium is proportional to an animal's intake of polyunsaturated fatty acids, as well as the amount of strenuous physical exercise undertaken.[40, 42]

Glutathione

Glutathione (GSH) is important for reducing mammalian susceptibility to the effects of toxins. GSH is necessary for glutathione peroxidase and glutathione-S-transferase activity. It is a cysteine-containing tripeptide with reducing and nucleophilic properties, which allow it to aid in the neutralization of peroxides and conjugation with reactive chemical species.[43] This protective function is seen particularly in the lungs, intestines, kidney, and liver.

Glutathione is normally synthesized in mammalian cells from its constituent amino acids (glutamic acid, cysteine, and glycine). However, in certain physical states such as severe toxicity or oxidative stress, normal synthesis may be insufficient to maintain adequate intracellular GSH levels, which in turn leads to further GSH depletion. Diminished GSH concentrations cause a greater degree of toxicity as the body becomes less able to combat the effects of lipid peroxidation, thiol oxidation, and the alkylation of critical proteins.[44] A decline of intracellular GSH has been linked to functional deterioration associated with aging, neuronal death, and liver disease.[45-47]

High success rates in reducing toxicity in animals have been shown with oral GSH supplementation.[43] Glutathione can be absorbed through the gastrointestinal wall, where it is utilized by the intestinal epithelial cells, as well as transported to the cells of the lung, kidney, blood plasma, and other tissues to aid with chemical detoxification.[43] Based on animal data, oral doses of several grams can be taken without deleterious effects. Supplemental doses should be high enough to support detoxification of lipid peroxides and radical oxygen species, especially in situations where normal synthesis of glutathione may be compromised.

Taurine

Taurine is a sulfur-containing amino acid required for membrane stabilization and detoxification.[48, 49] In most mammals (excluding felines) taurine is synthesized endogenously from conversion of the essential amino acid methionine to cysteine, then to taurine. The antioxidant activities stem from taurine's ability to neutralize potent oxidizing substances such as hypochlorous acid, thus protecting the body from the toxic effects of chloride ions and aldehyde release. It should be noted that deficiencies in pyridoxine have been

shown to negatively affect taurine synthesis, which in turn decreases the efficacy of its protective properties.[48]

Oral administration of taurine has been shown to protect hepatocytes against toxins, such as carbon tetrachloride, that selectively attack liver tissues.[11, 50] Taurine is also thought to modify the underlying factors that influence an animal's susceptibility to toxins, as evidenced by its ability to prevent translocation and endotoxemic injury in the intestines of experimental animals.[49] Supplementation of taurine is particularly important for cats, since they cannot synthesize it. Deficiency studies in animals have shown that inadequate levels of taurine cause retinal dysfunction and, especially in developing animals, are associated with the development of cardiomyopathy.[49]

Additional Dietary Supplements

Several additional oral supplements have proven useful in detoxification treatments. A group of water-soluble vitamins, including ascorbic acid and the B vitamins, have important functions in protecting the body against toxicity and oxidative stress.

Thiamin acts as a coenzyme (cocarboxylase) in production of reducing equivalents for the metabolism of lipids and carbohydrates, and assists in the repair of damaged cellular membranes. Riboflavin also aids in a cell's ability to repair damaged molecules and is believed to be involved in the regulation of glutathione reductase activity. Cobalamin functions in the metabolism of certain fatty acids key to myelin formation and, as such, is thought to be involved with repair and/or replacement of molecules damaged through oxidative stress.[10]

Vitamin C acts as a reducing agent to maintain active sulfhydryl compounds, including GSH. It is also capable of scavenging free radicals, and has a synergistic relationship with vitamin E and GSH.[5]

Other supplements recently subjected to investigation for their antioxidant properties include SOD, CoQ10,[51] *Ginkgo biloba* and *Silybum marianum* . SOD possesses enzymatic activity that modifies reactive oxygen species, transforming them into the less reactive hydrogen peroxide.[16] CoQ10 is involved in the electron transport chain reaction where it protects mitochondrial membranes from peroxidative damage.[10] Ginkgo has been shown to possess a very strong scavenging action on free radicals by suppressing the production of reactive oxygen species, inhibiting the increase of lipid peroxidation metabolites, and preventing oxidative damage to mitochondria.[52-54] Silybum has also received attention for its ability to increase the intracellular concentration of glutathione in the liver and prevent cellular damage by toxins.[55] Although these antioxidant compounds hold promise for use in detoxification treatment, additional research should be undertaken before their benefit for various animal species is fully understood.

Therapeutic Detoxification

To therapeutically detoxify an animal, any commercial or homemade foods that may contain toxins (such as artificial colors or propylene glycol) or food allergens need to be removed from the diet. In sick animals, body fat breakdown must be minimized in order to delay entry of fat-stored toxins into the bloodstream. If the animal is overweight, it needs multiple detoxification sessions (e.g., one to three-day modified fasts with appropriate supplements, with gradual fat breakdown). Complete fasts should be avoided, and a modified fast should not last more than three days. This is especially critical in cats – enough protein must be given to prevent muscle breakdown without any excess to cause additional loads on the liver. Adequate supplements should be given to enhance Phase II metabolism without over-stimulating Phase I, and to prevent damage to mitochondria. If diarrhea is a symptom, replacement nutrients should be given to guard against toxin absorption and

dehydration. Commercially available rice protein-based products may be used. These typically include vitamins, minerals, antioxidants, and ingredients to aid in amino acid conjugation, sulfation, glucuronidation, methylation, and acetylation. These products can be used during a fast, proportional to the weight of the patient, and will result in better owner and patient compliance than relying on administration of long lists of supplements.

Cats require one-and-one-half tablespoons of lean ground meat daily per ten pounds ideal bodyweight. A dog needs a ratio of two tablespoons lean ground meat per cupful of white rice cooked in chicken broth, fed at the rate of one cup per ten pounds of bodyweight. If a dog is still hungry, more rice is allowable but not more meat.

Antioxidants, B vitamins, glutathione, vitamin E, selenium, and critical amino acids should be added to the diet to boost natural detoxification systems. Cats, in particular, should be supplemented with niacin, taurine, and arginine. In addition, cats need pre-formed vitamin A from an animal source, not carotenoids.

Case Study

An animal may show signs suggesting it is toxic (such as lethargy and decreased ability to heal), accompanied by a lack of abnormal results from conventional laboratory tests and a history suggestive of toxicity (laboratory tests exist for humans, but are not practical for animals). Animals with this type of history are good candidates for detoxification.

It is critical during the detoxification process to watch for signs of toxicity, such as nausea, vomiting, decreased appetite, or increased lethargy. Fasting should be stopped immediately at the appearance of any of these signs, and the patient should be force fed, if necessary. Otherwise, there is a risk of creating hepatic lipidosis in cats, and a toxic cascade in all animals, with an escalation of oxidative damage.

When a complete workup does not reveal any cause for lethargy, detoxification should be considered, as in the following case:

"Digger," a six-year-old male yellow Labrador used for field trials, was seen after his original veterinarian spent one year in search of a foxtail that worked its way from his left axilla to the perineal area. Digger had been on long-term antibiotic therapy using a rotation of most antibiotics available. He had undergone multiple surgeries, since successive attempts to remove the foxtail were unsuccessful and draining tracts kept returning. Surgery in the perineal area finally located the foxtail, which was removed. One month later, however, the draining tracts returned, at which time the owner sought different treatment. The owner complained Digger had no energy and lacked the endurance to complete a field trial competition without becoming exhausted.

Toxin sources were identified: long-term infection, multiple long-term antibiotic treatments, and multiple anesthetic procedures including pre-anesthetic medication. The lack of energy in light of the compromised immune system (evidenced by return of draining tracts after removal of the foxtail) led to a diagnosis of toxicity. Digger showed no sign of muscle wasting or neurological problems, so he was put on a relatively mild detoxification program.

Digger was placed on a regimen of a B-complex vitamin twice daily, 500 mg vitamin C twice daily, 400 IU vitamin E once daily, and 30 mg CoQ10 twice daily. He was placed on a modified fast consisting of three days of white rice cooked in chicken broth (which he ate until satiated) and a half-cup lean ground beef, followed by another three days of equal parts regular dog food and white rice, then back to his normal diet of high-quality dog food. He was taken off antibiotics and the draining tracts were ignored. He recovered his energy by the fourth day of the diet. Within a week the tracts dried up and had not returned four years later. The problem of lethargy recurred twice more, each time after Digger had gotten

into the garbage. In both instances, by following the same regimen of modified fast and antioxidant supplementation, Digger's energy returned to original levels.

Conclusion

Avoiding toxic compounds and elevated oxidative stress, and ingesting a diet rich in antioxidant compounds is a prudent means of preventing extreme states of toxicity and oxidative damage. However, it is not possible for aerobic animals in an environment full of pollutants to avoid toxins. When an animal's natural defense system is overloaded and its ability to break down and expel toxins is compromised, the best means of treatment is to remove as many potential toxins as possible and increase the availability of protective nutrients the body normally uses for detoxification.

Oral supplementation with vitamins and essential nutrients has been shown to have a dramatic effect on animal health and vitality, especially animals with high activity levels, deficiency disorders due to malnutrition, and/or chronic health problems. The antioxidant vitamins A, E, and C, as well as B vitamins, selenium, glutathione, and taurine have all proven beneficial in prevention and treatment of toxicity in humans and animals.

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