

Oxidative Stress and Nrf2 Activation in Dogs

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By Lee Seward, DVM



Happy elderly canine

Oxidative Stress is a fact of life. Or, perhaps we should say, it is a fact of death. Every living organism that uses oxygen in its metabolic processes to create energy has some degree of Oxidative Stress (OS). Life cannot exist without the ability to create and use energy to drive cellular and physiological functions. But OS is a major contributor to the normal aging process. (1)

Oxidative Stress & The Normal Aging Process

Oxidative Stress occurs when free radicals, (charged molecules created by metabolic processes and oxidation used to create energy), accumulate in the body's cells at rates exceeding the body's ability to neutralize them. These charged molecules are attracted to the opposite charge in cellular structures in order to become neutral, and balanced. In so doing they may pull off parts of these structures, such as DNA, altering or damaging their function

and even creating more free radicals. Thus oxidative stress, also known as free radical damage, is associated with what we know as aging. *This is as true in dogs as it is in humans.* (1)
(2)

There are several strategies that different life forms use to deal with OS. Some have short life cycles, essentially doing nothing and allowing OS to take its toll. Others have lower metabolic rates to slow the building of oxidative stress. In mammals metabolic rates are related to size, the larger the animal the slower the metabolic rate. Obviously, this may not be the case within a species. Elephants may live longer than dogs but Chihuahuas live longer than Great Danes.

And others may intake nutrients that use the Nrf2 pathway to activate certain gene expression to produce powerful antioxidant enzymes within the cells themselves. Animals may use combinations of these strategies. (3) The latter strategy is called Nutrigenomics, using nutrition, food, and supplements, to activate specific genes for beneficial results.

I often hear the comment that dogs have seven times the oxidative stress of humans. This may come from the observation that certain breeds have a lifespan of roughly one-seventh that of humans. While the statement is an oversimplification, it does make the point that dogs are exposed in many ways well beyond what we humans experience, to things that we know increase OS. (4)

Free radicals and the resulting OS are not just the byproduct of metabolism but also created from exposure to ionizing radiation, solar radiation, electromagnetic radiation, toxic and physical insults, and physiologic stress.

Dogs are, in many cases, more exposed to these free radical generators than humans.

Dogs have an increased metabolic rate compared to humans and even though we may not realize it, most dogs are athletes and therefore subject to increased oxidative stress.

Our canine pals chase a ball or frisbee, play tug-of-war, and walk or run by our side for prolonged times. They pull sleds, herd livestock, guide or serve the disabled, and retrieve or find things including injured people. Happ, our Chiweenie, can go up and down our stairs, chasing his toys, with the best of human athletes.

They live with us and are exposed to the same electromagnetic radiation and household products, cleaners, sprays, fumes, etc, as us. They get X-rays and are treated with pharmaceuticals. They often spend prolonged periods outside exposed to **solar radiation, power line electromagnetic radiation, and cold and heat stress**. They are exposed to all the **chemical, industrial and agricultural pollution that we are but with greater intensity**. In addition to being outside more than most of us, they do not have protective clothing and are

not bathed as frequently as us. Therefore the chemicals and pollutants they may come into contact with have a better chance of being absorbed.

Their paws, which can absorb things on contact, are also unprotected. Dogs explore their environment with their noses, sticking them into all sorts of places and are scavengers sampling or eating all sorts of things they come across.

Dogs are subject to parasites, fleas, ticks, mites, lice, heartworms, and intestinal and other worms, plus we administer a plethora of toxic agents to treat, prevent or control these assaults.

All these characteristics of dogs and their surroundings lead to exposure of industrial chemicals, volatile organic solvents, sulfur dioxide, dioxins, etc., herbicides, dicamba, glyphosate, etc., pesticides, synthetic pyrethroids, organophosphates, etc., there are thousands of these toxic agents in the air and especially that settle to or near the ground. Many of these agents have been shown to increase OS or directly cause cellular damage and all are suspect.(4)

Even the most cared for urban dogs, due to their scavenger nature may ingest things that are to some degree toxic, e.g., household or personal use products. More importantly, they and all pet dogs are largely dependent on their guardians for food. Many of the foods commercially available, even if nutritionally sound, contain ingredients that can increase OS or have some degree of toxicity. This may be due to processing, such as high temperatures altering certain proteins or the addition of dyes or preservatives. Even the so-called boutique diets and raw diets are not free of concern as they do not receive much if any regulatory scrutiny and may not be produced with appropriate care or oversight.

The good news is that dogs have been shown to have the same cellular ability as humans to manage oxidative stress by way of Nrf2 activation. (2)(3)

Nrf2 is a protein inside our and the dogs' cells that is released by certain interactions and proceeds to interact with an area of the DNA (genome) called the survival genes which then produce antioxidant enzymes, superoxide dismutase, catalase, and glutathione being primary. These self-produced antioxidants have a massive advantage over ingested antioxidants in foods or supplements such as vitamins C and E or Beta Carotene. Further many of the over 500 genes that are activated by Nrf2 have cytoprotective functions by detoxification and elimination of toxic chemicals, toxic metals, and cellular trash. And to add icing to the cake some of these genes produce major changes to support a healthy inflammation response. (4)

After reviewing the results of their own studies as well as those of another scientist Dr. Kaitlyn Lewis and her collaborators at the University of Texas Health Science Center in San Antonio have hypothesized that this (Nrf2) signaling pathway plays a critical role in determining healthy aging in species and that this pathway may indeed be the master

regulator of the normal aging process and that the data support the hypothesis that Nrf2 directly plays a role in the determination of both healthy longevity and quality of life. (3) Drs Pall and Levine at Washington State University after reviewing all the scientific information available on the Nrf2 pathway concluded that Nrf2 is not a magic bullet but is likely to be of great importance in health promotion, particularly in those regularly exposed to toxic chemicals and that raising Nrf2 is likely to be the most important health-promoting approach into the foreseeable future and that we may be on the verge of new literature on health effects of Nrf2 which may well become the most extraordinary health breakthrough in history. (4) Interestingly the vast majority of studies reviewed in these papers were done in animals therefore these findings are at least as applicable to dogs as they are to humans.

The bad news is that the functioning of the Nrf2 activation pathway declines with age leading to an accumulation of free radical damage or OS. Again Drs Pall and Levine at Washington State University found that most of us are currently deficient in Nrf2-raising nutrients. This leads to normal aging and ultimately death. I believe the same is true in dogs. (5)

So what can we do about it? I have already mentioned many of the factors that lead to OS in dogs. Perhaps we can Biohack our dogs. Biohacking is taking control of their biology to achieve a benefit. By providing exercise, good food, high-quality water, protection from the elements, and a secure pack, (family), we can reduce physiological stress, maintain a proper weight and condition and reduce exposure to toxic insult. While this may help slow the increase in OS we cannot stop the overwhelming exposure to all the things which increase OS in Dogs.

One of the most powerful ways to Biohack our dogs and reduce OS is through Nutrigenomics.

There are close to 30,000 animal model studies on OS and close to 2,000 animal model studies on Nrf2 activation in the National Institute of Health Library (pubmed.gov) which show that the cellular mechanisms in animals including dogs are the same as they are for humans. (1)(3)

Research on Protandim, a nutritional supplement has proven to reduce oxidative stress in humans by 40% in 30 days and even more over longer periods of time. This decrease is achieved because Protandim activates the Nrf2 pathway. The result of activating this pathway is an increase in the cellular antioxidant enzymes called superoxide dismutase, catalase, and glutathione. (1)(5) In this case humans served as a great animal model for dogs! Opposed to a large amount of information available about nutrition and Nrf2 in humans, there is little information pertaining to animal diets and Nrf2. In a canine field study, Pertandim, a pet variation of this formulation containing the exact same ingredients along with -----, increased antioxidant enzymes and resulted in a decrease in the markers for oxidative stress The dogs also showed improvements in mobility and cognitive function. (7)

The benefits of reducing OS and Nrf2 activation have been validated by an almost 20-year-long study conducted under the auspices of the National Institute on Aging part of the National Institute of Health. A mouse model was used to test a variety of pharmaceuticals and natural compounds to see if they had an impact on longevity and Healthspan. Healthspan is the period we remain in good health as we age. The only natural product to significantly increase longevity and Healthspan in the mice being studied was the same herbal combination mentioned earlier, which gave the male mice a 7% increase in median lifespan. (8) This study is additional evidence to support the nutrigenomic theory that using nutrition, food, and supplements can activate specific genes for beneficial health results (“biohacking”).

All we have learned about the role Nrf2 plays in reducing OS, eliminating toxins from cells, and promoting a healthy inflammation response leads me to paraphrase Drs Pall and Levine in summarizing: Nrf2 may well become the most extraordinary breakthrough in the history of Canine health.

Bibliography

1. Hybertson, B.M., et al., Oxidative stress in health and disease: the therapeutic potential of Nrf2 activation. *Mol Aspects Med*, 2011. 32(4- 6): p. 234-46.
2. McMichael, M.A., Oxidative stress, antioxidants, and assessment of oxidative stress in dogs and cats. *JAVMA*, 2007. 231(5): p714-20.
3. Lewis, K.N., et al., Nrf2, a guardian of healthspan and gatekeeper of species longevity. *Integrative and Comparative Biology*, 2010. 50(5): p829-43.
4. Pall, M.L. and Levine, S., Nrf2, a master regulator of detoxification and also antioxidant, anti-inflammatory, and other cytoprotective mechanisms, is raised by health-promoting factors. *Acta Physiologica Sinica*, 2015. 67(1): p1-18.
5. Laflamme, D.P., Companion Animal Symposium: Obesity in dogs and cats: what’s wrong with being fat? *Jr of Animal Science*, 2012. 90(5): p1653-62.
6. Nelson, S.K., et al., The induction of human superoxide dismutase and catalase in vivo. *Free Radic Biol Med*, 2006. 40(2): p. 341-7.
7. Talbott, S., et al., Antioxidant and behavioral effects of canine health supplement in dogs. *The FASEB (Federation of Societies for Experimental Biology) Jr*, 2015. 29(1S): A922.12.
8. Strong, R. ET al., Longer lifespan in male mice treated with a weakly estrogen is agonist, an antioxidant, an alpha glycosides inhibitor or an Nrf2-inducer. *Aging Cell*, 2016. 15(5): p789-982.

