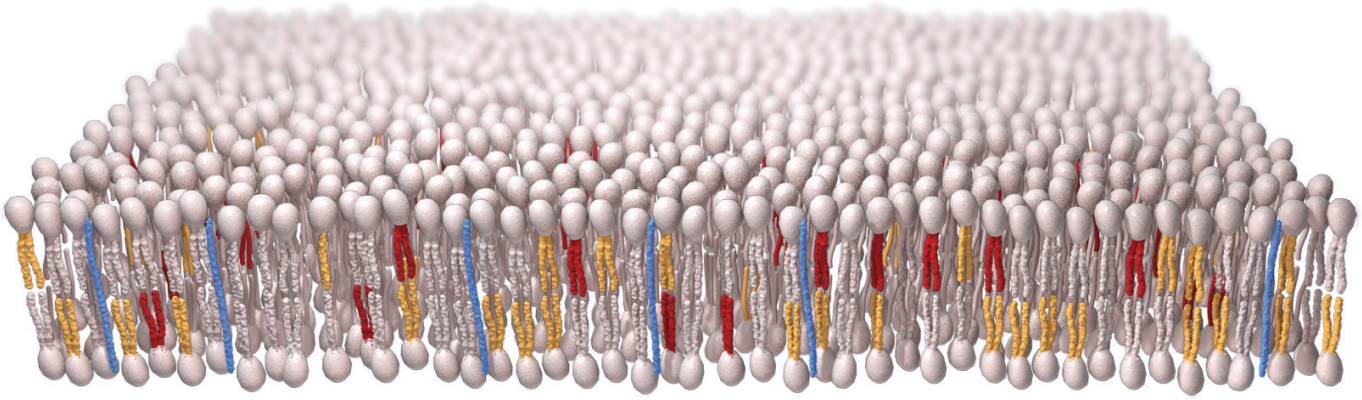
Nutrition and Cellular Function

Tara Hembrooke, PhD, MS



Twenty years ago, many people, including veterinarians, physicians and laypeople, considered the primary role of nutrition in humans and animals to be to support growth and provide the appropriate amount of nutrients needed for energy. And that is true. To a degree. Today, however, we know that nutrition plays additional critical roles in health, performance and overall functioning of the body. In fact, most of nutrition's effects occur "under the surface" in ways that are not always obvious to the naked eye. That is, until there is evidence of disease. Nutrition affects each and every living organism, and it starts at the cell.

To better understand the role of nutrition in cellular function, let us first consider the three primary areas of the cell:

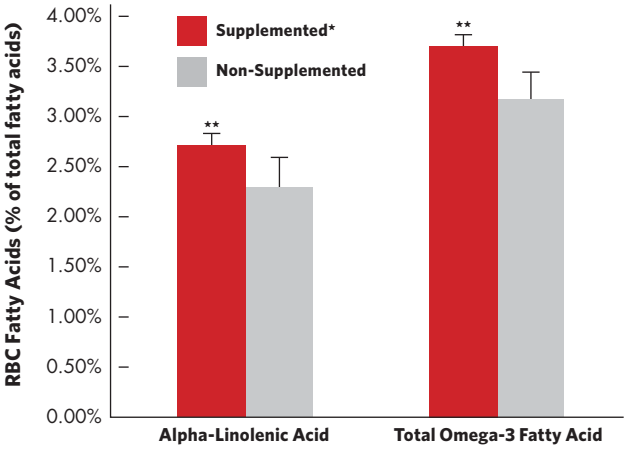
1. **Cell Membrane:** *outer portion composed of a lipid bilayer that encloses and protects the critical intracellular components, controls the inflow and outflow of various compounds, and orchestrates communication between cells.*
2. **Cytosolic Components:** *organelles (or "little organs") that have specialized functions within the cell.*
3. **Nucleus:** *organelle that acts as the "control center" of the cell by housing the cell's genetic material and controlling gene expression.*

Cell Membrane

Nearly all membranes consist of a double-layered lipid structure that interacts well with water on its external portions (i.e., the very outside of the cell and the layer lining the inside of the cell) and also interacts with non-polar substances within the membrane.[1] Although the cell membrane is impermeable to water-soluble molecules such as some proteins and ions, it interacts well with non-polar substances including certain vitamins and lipids. The composition of the cell membrane directly affects the cell's ability to function. Omega-3 fatty acids, when incorporated into the cell membrane, increase membrane fluidity due, in part, to their high number of unsaturated bonds. This fluidity enhances cell-to-cell communication by aiding the flow of electrical signals between cells,[1] which is crucial for brain and muscular function. Membrane fluidity influences cellular receptor function[2] and allows cells to respond appropriately to outside signals. Membrane fluidity also controls the transport of compounds into and out of the cell and can affect cell recognition through alterations in membrane proteins.[3] Omega-6 fatty acids tend to have fewer double bonds and promote less membrane fluidity than omega-3 fatty acids. For this reason, dietary modifications that increase the intake of omega-3 fatty acids at the expense of omega-6 fatty acids have often been recommended

in order to optimize cell health and function. In human medicine, a large body of research correlates membrane omega-3 fatty acid content (termed the "omega-3 index") with various disorders, including cardiovascular disease and diabetes.[4,5] Although no such research currently exists in the horse, it is conceivable that a membrane omega-3 index could also relate to various equine-related conditions. For this reason, dietary-induced alterations in equine red blood cell membrane fatty acid content should be a factor to consider in the horse. One such successful dietary modification has been the inclusion of a flax-based omega-3 supplement* which has been shown to effectively increase cell membrane content of omega-3 fatty acids over non-supplemented horses (Figure 1).

Figure 1. **Red Blood Cell Omega-3 Fatty Acids from Supplemented* vs Non-Supplemented Horses**



**Significantly greater than Non-Supplemented horses

In addition to improving cell membrane omega-3 content, supplementation with an omega-3 and micro-nutrient supplement* has been associated with lower levels of pro-inflammatory cytokines and a better oxidative stress marker profile in the horse. Some studies have shown improved metabolic status and enhanced measures of fertility in the horse, as well.

Fluidity is not the only factor affecting cell membrane integrity. Inflammation is traditionally considered a natural response to injury or insult and is required for tissue healing. However, when inflammation persists, the chemical mediators of inflammation result in cellular damage.[6,7] Unfortunately, this cellular insult invariably results in further release of inflammatory mediators, and the extent of the damage worsens. Therefore, managing inflammation is another key factor in cellular health, and once again omega-3 fatty acids play a key role in this area. Membrane-associated fatty acids are cleaved and utilized by cyclooxygenease (COX) and lipoxygenase (LOX) enzymes. When omega-6 fatty acids predominate as the substrate for these enzymes, the resultant metabolites have strong inflammatory activities. In contrast, the products of COX and LOX-metabolized omega-3 fatty acids have less potent inflammatory effects, and some, in fact, directly help resolve inflammation.[8] Anti-inflammatory benefits attributed to commercial flax-based supplements with additional micronutrients± include lower levels of the pro-inflammatory cytokines TNF-alpha, IFN-gamma, and IL-6 as well as higher levels of an anti-inflammatory cytokine termed IL-10. These changes in inflammatory measures were seen in both horses and dogs.

The unsaturated fatty acids present in cell membranes can increase the potential for oxidative damage due to the increased susceptibility of their double bonds to free radical attack.[9] As a result, these oxidized lipid membranes become "leaky"[10] and no longer provide an adequate barrier between the internal and external environments. Membrane-bound proteins invariably are damaged in this process, which can result in further disruption of cellular function.[11] This heightened risk for oxidative damage highlights the importance of protecting lipid membranes with antioxidants. Vitamin E is a potent, natural antioxidant with a primary function in the body of protecting lipids from oxidative damage. This dietary nutrient removes free radical intermediates and prevents the further propagation of radical formation. Although vitamin C doesn't directly interact with the cell membrane, it does scavenge oxygen radicals and can return the reduced form of vitamin E back to its active state. Therefore, vitamin C has an indirect effect on cell membrane

* Horses were supplemented with either Platinum Performance® Equine Wellness and Performance Formula or Platinum Performance® CJ Formula

± Platinum Performance Equine Wellness Formula and/or Canine Wellness + Antioxidant Formulas

integrity and function. Vitamin A/beta-carotene, alpha-lipoic acid, pterostilbene, co-enzyme Q10, and curcumin are other antioxidant compounds that provide protection against oxidative damage to cell membranes. The body also has a natural antioxidant enzymatic system consisting of superoxide dismutase, glutathione peroxidase, and catalase. These enzymes require copper, zinc, manganese, iron and selenium as cofactors for them to function appropriately,[12] therefore, certain dietary minerals also play an important role in an animal's defense against oxidative stress.

Cytosolic Components

The intracellular organelles have specific functions that are critical to the health and well-being of the cell. For example, mitochondria generate ATP and act as the "powerhouse" of the cell by supplying energy. Lysosomes engulf and degrade waste, food particles, and invading organisms as well as carry undigested material to the cell surface for removal. The endoplasmic reticulum synthesizes proteins that are then processed for secretion by the golgi apparatus. All of these organelles are comprised of membranes that are very similar to the cell membrane, and their health depends on the same factors that are important for the cell membrane. In addition, organelles rely on specific nutrients to perform their individualized functions.

Oxidative stress can significantly affect the structure and function of these intracellular organelles through alterations in membrane lipid and protein integrity. Therefore, maintaining adequate antioxidant status could directly impact intracellular activities. Mitochondria are a primary source of radical formation due their high rate of oxidative metabolism while producing ATP. This makes mitochondria particularly susceptible to oxidative damage,[14] which has been directly linked to impaired mitochondrial function.[15] The radicals released by mitochondria also can damage other structures inside the cell. For example, oxidative damage to the membranes that comprise lysosomes can result in the release of lysosome-enclosed enzymes that can damage the cell.[16] Under such conditions, the inability of the lysosomes to digest waste products can cause these toxic waste products to accumulate in the cell.[16]

Nucleus

The nucleus of the cell is where DNA is housed. It is this genetic material that controls protein production and, ultimately, overall functioning of the organism. Omega-3 fatty acids are natural activators for various transcription factors, such as PPARs and the retinoic X receptors.[2] Consequently, omega-3 fatty acids influence the rate and level of gene expression and, thus, the rate and level of protein production in the body. Omega-3 fatty acids also inhibit the activity of NF-kappa beta,[17] a transcription factor linked to a variety of pro-inflammatory activities. Similarly, inhibition of the sterol regulatory element-binding protein transcription factor by omega-3 fatty acids, DHA in particular, has a strong influence on lipid metabolism.[17] Vitamin A also plays a role in transcription and gene expression and is critical for cellular differentiation.[18] Similarly, vitamin D interacts with a specific receptor in the nucleus; in fact, more than 50 genes throughout the body are regulated by 1,25 dihydroxyvitamin D, the biological form of vitamin D.[19] Zinc is also important for gene expression and protein synthesis and is critical to proper DNA stabilization and function.[20]

The effects of oxidative stress and inflammation can be detected in the nucleus and, more specifically, in the DNA. Free radicals can mutate and damage DNA, and this is believed to be a precursor to many cancers and other diseases.[21] Inflammation has been linked to alterations in components of DNA configuration that result in epigenetic changes[22] which are modifications in gene expression. Because of the far-reaching and potentially hazardous effects of DNA derangement, any action that prevents oxidative stress and reduces inflammation at the level of the nucleus is critical. Thus, dietary modifications that incorporate the anti-inflammatory omega-3 fatty acids and antioxidant compounds are key steps to protecting cellular health and function by way of protecting DNA.

Summary

Clearly, specific dietary nutrients have a critical impact on cellular function. They play much larger roles in health and longevity than merely providing energy and supporting growth. Various dietary nutrients support cellular biochemical reactions, provide cellular structural integrity, and act as cell signaling molecules. Nutrition can also have a direct impact on inflammation and oxidative stress, which are key factors in dysfunction and disease due to their damaging effects at the cellular level. Nutrition isn't merely about food for the body. Most importantly, it is about nutrients for the cells.

Literature Cited

1. Robertson J. Membrane structure. *J Cell Biol* 1981;91:189s-204s.
2. Schmitz G, Ecker J. The opposing effects of n-3 and n-6 fatty acids. *Prog Lipid Res* 2008;47:147-155.
3. Singer S. Molecular interactions at the cell surface. *Prog Clin Biol Res* 1982;97:3-24.
4. Harris W. The omega-3 index: clinical utility for therapeutic intervention. *Curr Cardiol Rep* 2010;12:503-508.
5. Virtanen JK, Mursu J, Voutilainen S, et al. Serum Omega-3 Polyunsaturated Fatty Acids and Risk of Incident Type 2 Diabetes in Men: The Kuopio Ischemic Heart Disease Risk Factor Study. *Diabetes Care* 2014;37:189-196.
6. Edwards S. Tissue viability: understanding the mechanisms of injury and repair. *Nurs Stand* 2006;21:48-56.
7. Huang J, Wolk J, Gewitz M, et al. Progressive endothelial cell damage in an inflammatory model of pulmonary hypertension. *Exp Lung Res* 2010;36:57-66.
8. Calder P. Fatty acids and inflammation: The cutting edge between food and pharma. *Eur J Pharmacol* 2011;668:S50-58.
9. Catalá A. Lipid peroxidation modifies the picture of membranes from the "Fluid Mosaic Model" to the "Lipid Whisker Model". *Biochimie* 2011;[Epub ahead of print].
10. Wong-Ekkabut J, Xu Z, Triampo W, et al. Effect of Lipid Peroxidation on the Properties of Lipid Bilayers: A Molecular Dynamics Study. *Biophys J* 2007;93:4225-4236.
11. Wiseman H. Dietary influences on membrane function: importance in protection against oxidative damage and disease. *J Nutr Biochem* 1996;7:2-15.
12. Irshad M, Chaudhuri P. Oxidant-antioxidant system: role and significance in human body. *Indian J Exp Biol* 2002;40:1233-1239.
13. Richter C, Park J, Ames B. Normal oxidative damage to mitochondrial and nuclear DNA is extensive. *Proc Natl Acad Sci U S A* 1988;85:6465-6467.
14. Boveris A, Navarro A. Brain mitochondrial dysfunction in aging. *IUBMB Life* 2008;60:308-314.
15. Pivtoraiko V, Stone S, Roth K, et al. Oxidative stress and autophagy in the regulation of lysosome-dependent neuron death. *Antioxid Redox Signal* 2009;11:481-496.
16. Lo C, Chiu K, Fu M, et al. Fish oil decreases macrophage tumor necrosis factor gene transcription by altering the NF kappa B activity. *J Surg Res* 1999;82:216-221.
17. Jump DB, Botolin D, Wang Y, et al. Docosahexaenoic acid (DHA) and hepatic gene transcription. *Chemistry and Physics of Lipids* 2008;153:3-13.
18. Ross A, Gardner E. The function of vitamin A in cellular growth and differentiation, and its roles during pregnancy and lactation. *Adv Exp Med Biol* 1994;352:187-200.
19. Guyton K, Kensler T, Posner G. Vitamin D and vitamin D analogs as cancer chemopreventive agents. *Nutr Rev* 2003;61:227-238.
20. Wu F, Wu C. Zinc in DNA replication and transcription. *Annu Rev Nutr* 1987;7:251-272.
21. Khansari N, Shakiba Y, Mahmoudi M. Chronic inflammation and oxidative stress as a major cause of age-related diseases and cancer. *Recent Pat Inflamm Allergy Drug Discov* 2009;3:73-80.
22. Brigati C, Banelli B, di Vinci A, et al. Inflammation, HIF-1, and the epigenetics that follows. *Mediators Inflamm* 2010;2010.

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