Ray Peat's Newsletter

The problems are solved, not by giving new information, but by arranging what we have known long since. L. Wittgenstein

 Raymond Peat P.O. Box 5764 Eugene OR 97405 **Q-2 2022**

Aging, Energy, Progesterone

In 1935 when Clive McKay's group began its study of caloric restriction and life-span extension, the "rate of living" theory of aging dominated thinking. In repeated studies, McKay made it clear that it was only the amount of energy metabolized, rather than the absence of particular substances, that accounted for longer life when the total energy of the diet was restricted. In a common version of the rate of living theory, it was oxidative damage necessarily produced by the respiring mitochondria that produced the "wear and tear" of living. From the beginning of the 20th century, a popular idea was that the accumulation of an inert or toxic "metaplasm" in cells in proportion to their metabolic rate accounted for the aging process. The accumulation of "age pigment," lipofuscin, in proportion to the presence of polyunsaturated fats, heavy metals, and oxygen tends to support the idea of aging as accumulation of metabolic waste—and to challenge the idea that energy-metabolism itself causes aging. The essential amino acids were among the nutrients causing lipofuscin to accumulate.

If metabolizing "pure energy" is the cause of aging, all of the substances known to contribute to the formation of metaplasm or lipofuscin are irrelevant, so the composition of food can't affect the rate of aging.

The rate of living theory was gradually being proven wrong in a variety of ways, as animals with a higher metabolic rate turned out to generally live longer than those with a lower metabolic rate, but it has become entrenched in the nutritional doctrines of the caloric restriction life-extension culture, and has blended into the durable sugar-phobic culture, in which excess sugar is seen as the major factor in the development of diabetes, cancer, heart disease, and and nerve degeneration, including dementia. In recent years, many studies have shown protective effects of diets with a lower ratio of protein to carbohydrate.

Biochemically, the closest cells can come to metabolizing pure energy (the basic cause of aging according to the rate of living theory) is when they are responding to the ATP delivered by glucose (Chaudhari and Kipreos, 2018), defined as a high Respiratory Quotient, as opposed to the lower ratio when fat or amino acids are oxidized for energy. As the rate of living theory has taken over, with "logical" arguments, the actual measurement of oxygen consumption and CO2 production has been discouraged, and replaced by new technologies that estimate them without direct measurement—for example, the doubly labeled water isotope method and the proprietary Agilent "Seahorse XF Analyzer" technology. To the extent that physiological measurements are important for science and

understanding health and sickness, the recent trends in measurement and explanation are catastrophic.

Has "evolution" increased the efficiency of respiratory energy production, and is energetic efficiency of energy production a good thing? Within the rate of living theory of aging, those are common opinions. A maximum of fat storage on a minimum of food consumption is an example of high efficiency. The highly "wasteful" inefficient energy metabolism of "uncoupled" mitochondria improves adaptability to the environments, and extends longevity.

In some fields, the need to hide failures of a belief system has produced very bad results. "In altitude studies, for example, it is generally accepted that mitochondrial volume density in human skeletal muscle diminishes with chronic high altitude exposure" (Jacobs, et al., 2018), but this result was caused by failure to account for the catabolic effects of the mountain environment, and the real effect of altitude hypoxia itself is the opposite, viz., mass skeletal muscle mitochondrial volume density increases in response to high altitude exposure.

This particular feature of high altitude physiology is very important for understanding the life-prolonging effect of living at high altitude. Aging corresponds closely to the decline of tissue mitochondrial mass, and things that preserve or restore mitochondria can preserve or restore tissue metabolism.

When investigating the effects of a lower ratio of protein to carbohydrate, it has been found that certain amino acids account for most of the protective effects of reducing dietary protein, especially methionine and tryptophan. This accounts for the main protective effects of gelatin in the diet, since this protein is deficient in methionine, cysteine, and tryptophan, the main anti-metabolic amino acids.

There is a threshold effect in exposure to the harmful amino acids, and this involves a very sensitive system for detecting their concentration, apparently involving the actin filament network throughout the body. Above the threshold concentration, methionine activates mTOR. Increased mTOR shortens life-span and increases the processes of aging. Increased fat in the diet increases mTOR, adding to the effects of amino acids. Several substances block the increase of mTOR, including the citrus flavonoid nobiletin, aspirin, and progesterone. Nobiletin preserves mitochondrial glucose metabolism, while protecting against the anti-metabolic effects of fat (Nohara, et al., 2019).

The way these regulators of energy and aging interact is holistic, and it's necessary to understand that organisms make generalizations about their problems. Things that inhibit mTOR will increase adaptation and organization with expansion of the time horizon, while things that activate it (methionine, estrogen, radiation) will accelerate cell growth and inflammation and activate terminal processes. Progesterone and estrogen relate to the degree of mTOR activity through the body as a whole, not just through a series of receptor intermediates.

A high RQ, oxidizing mostly glucose, is so harmful, according to present metabolic consensus, that it would seem logical to emphasize the importance of the simple old BMR studies, measuring CO2 produced and oxygen consumed, but these have been abandoned in favor of complex new techniques, which replace measurements with estimates of those quantities (doubly labeled water isotope measurement, and the proprietary "Seahorse" apparatus). I suspect that the weight of the simple facts of oxygen consumption was so disruptive to the newer methods of treating hypothyroidism that they eliminated the use of the tests, instead of finding real justification for their practices. Oxygen consumption is no longer understood in the medical culture to be the basis for the physiological effects of thyroid hormone.

The high energy represented by the ATP produced by oxidation of glucose is obviously essential for maintaining the essential features of life, and it is the system suppressed in an organized way by activation of mTOR, resulting from imbalances in the available nutrients. Progesterone's roles in this energy system have been seen to be crucial in pregnancy, and in protection against stress and degeneration, but its official categorization as a sex hormone has blocked insight into its real central functions.

For about 50 years, a dogmatic view of hormones has been that they act through nuclear receptors to activate the genes that explain their functions. Two such receptors, PRA and PRB, were identified, but failed to explain any of progesterone's important effects. In 2013 (Dai, et al.), a group looked for a protein that binds to progesterone and to the mitochondria, but not to DNA, and found that such a protein seems ubiquitous, and that binding progesterone causes it to hyperpolarize the mitochondria, increasing their energy production, and to prevent the decrease in size of the mitochondria that would otherwise occur with aging and loss of energy production.

Progesterone has been known to act protectively against catabolic stress hormones, the estrogenic, inflammatory, shock and autoimmune processes, pro-aging systems, including the mTOR system, but its direct structural and metabolic actions on the mitochondria will probably help to explain the nature of the age-accelerating effects of ionizing radiation, endotoxins and lipofuscins.

Progesterone, acting on the physical structure of the cell exactly where "pure energy" supports the living state and its functions, has become a new reference point for judging the conditions of the organism.

REFERENCES

J Gerontol A Biol Sci Med Sci. 2007 Apr;62(4):352-60. **Dietary protein restriction decreases oxidative protein damage, peroxidizability index, and mitochondrial complex I content in rat liver.** Victoria Ayala , Alba Naudí, Alberto Sanz, Pilar Caro, Manuel Portero-Otin, Gustavo Barja, Reinald Pamplona.

Caloric restriction (CR) decreases oxidative damage, which contributes to the slowing of aging rate. It is not known if such decreases are due to calories themselves or specific dietary components. In this work, the ingestion of proteins of Wistar rats was decreased by 40% below that of controls. After 7 weeks, the liver of the protein-restricted (PR) animals showed decreases in oxidative protein damage, degree of membrane unsaturation, and mitochondrial complex I content. The results and previous information suggest that the decrease in the rate of aging induced by PR can be due in part to decreases in mitochondrial reactive oxygen species production and DNA and protein oxidative modification, increases in fatty acid components more resistant to oxidative damage, and decreased expression of complex I, analogously to what occurs during CR. Recent studies suggest that those benefits of PR could be caused, in turn, by the lowered methionine intake of that dietary manipulation.

A Truncated Progesterone Receptor (PR-M) Localizes to the Mitochondrion and Controls Cellular Respiration.

Qunsheng Dai, Anish A. Shah, Rachana V. Garde, Bryan A. Yonish, Li Zhang, Neil A. Medvitz, Sara E. Miller, Elizabeth L. Hansen, Carrie N. Dunn, and Thomas M. Price.

Oncogene. 2016 Jul 7; 35(27): 3535–3543. mTORC1 directly phosphorylates and activates ER upon estrogen stimulation. A Alayev, R S Salamon, S M

Berger, N S Schwartz, R Cuesta, R B Snyder, and M K Holz.

Eur J Immunol. 2012 Oct;42(10):2683-96. Progesterone suppresses the mTOR pathway and promotes generation of induced regulatory T cells with increased stability. **Jee H Lee, John P Lydon, Chang H Kim.**

Eur J Immunol. 2012 Oct;42(10):2683-96. Progesterone suppresses the mTOR pathway and promotes generation of induced regulatory T cells with increased stability. Jee H Lee, John P Lydon, Chang H Kim.

Bioessays. 2018 Aug;40(8):e1800005. **The Energy Maintenance Theory of Aging: Maintaining Energy Metabolism to Allow Longevity.** Snehal N Chaudhari, Edward T Kipreos.

Fused, elongated mitochondria are more efficient in generating ATP than fragmented mitochondria. In diverse C. elegans longevity pathways, increased levels of fused mitochondria are associated with lifespan extension. Blocking mitochondrial fusion in these animals abolishes their extended longevity. The long-lived C. elegans vhl-1 mutant is an exception that does not have increased fused mitochondria, and is not dependent on fusion for longevity. Loss of mammalian VHL upregulates alternate energy generating pathways. This suggests that mitochondrial fusion facilitates longevity in C. elegans by increasing energy metabolism. In diverse animals, ATP levels broadly decreases with age. **Substantial evidence supports the theory that increasing or maintaining energy metabolism promotes the survival of older animals. Increased ATP levels in older animals allow energy-intensive repair and homeostatic mechanisms such as proteostasis that act to prevent cellular aging. These observations support the emerging paradigm that maintaining energy metabolism promotes the survival of older animals.**

Rejuvenation Res. 2009 Dec;12(6):421-34. Forty percent methionine restriction **decreases mitochondrial oxygen radical production and leak at complex I during forward electron flow and lowers oxidative damage to proteins and mitochondrial DNA in rat kidney and brain mitochondria.** Caro P, Gomez J, Sanchez I, Naudi A, Ayala V, López-Torres M, Pamplona R, Barja G.

Mol Endocrinol. 2013 May; 27(5): 741–753. **A Truncated Progesterone Receptor (PR-M) Localizes to the Mitochondrion and Controls Cellular Respiration.** Qunsheng Dai, Anish A. Shah, Rachana V. Garde, Bryan A. Yonish, Li Zhang, Neil A. Medvitz, Sara E. Miller, Elizabeth L. Hansen, Carrie N. Dunn, and Thomas M. Price.

Biochim Biophys Acta. 2006 May-Jun; 1757(5-6):496-508.Mitochondrial oxidative stress, aging and caloric restriction: the protein and methionine connection. Pamplona R, Barja G.

J Bioenerg Biomembr. 2004 Dec; 36(6): 545-52. Protein restriction without strong caloric restriction decreases mitochondrial oxygen radical production and oxidative DNA damage in rat liver. Sanz A, Caro P, Barja G.

FASEB J. 2006 Jun;20(8):1064-73. Methionine restriction decreases mitochondrial oxygen radical generation and leak as well as oxidative damage to mitochondrial DNA and proteins. Sanz A, Caro P, Ayala V, Portero-Otin M, Pamplona R, Barja G.

Exp Gerontol. 2013 Oct;48(10):1030-42. Regulation of longevity and oxidative stress by nutritional interventions: role of methionine restriction. Sanchez-Roman I, Barja G. J Endocrinol. 2015 Jul;226(1):R17-28. **Macronutrients and caloric intake in health and longevity.** Samantha M Solon-Biet, Sarah J Mitchell, Rafael de Cabo, David Raubenheimer, David G Le Couteur, Stephen J Simpson.

Aging Cell. 2018 Aug; 17(4): e12796. Role of dietary amino acid balance in diet restriction mediated lifespan extension, renoprotection, and muscle weakness in aged mice. Shohei Yoshida, 1 , [Link] Kosuke Yamahara, 1 , 2 , [Link] Shinji Kume,corresponding author 1 Daisuke Koya, 3 Mako Yasuda Yamahara, 1 , 2 Naoko Takeda, 1 Norihisa Osawa, 1 Masami Chin Kanasaki, 1 Yusuke Adachi, 4 Kenji Nagao, 4 Hiroshi Maegawa, 1 and Shin ichi Araki corresponding author

Gelatin in Nutrition and Medicine, N. B. Gotthoffer, Grayslake Gelatin Co., Grayslake, Illinois, 1945.

J Physiol. 2016 Mar 1; 594(5): 1151–1166. Twenty eight days of exposure to 3454 m increases mitochondrial volume density in human skeletal muscle. Robert A. Jacobs, Anne Kristine Meinild Lundby, Simone Fenk, Saskia Gehrig, 1 Christoph Siebenmann, 1 , 4 Daniela Flück, 1 Niels Kirk, 1 Matthias P. Hilty, 5 and Carsten Lundby corresponding author 1

Key points

It is generally accepted that mitochondrial volume density in human skeletal muscle diminishes with chronic high altitude exposure.

All data supporting this concept were collected during mountaineering expeditions, which are associated with the confounding effects of whole body negative energy balance.

Here we examine the effect of 28 days of exposure to 3454 m on skeletal muscle mitochondrial volume density in a setting where whole body weight, whole body composition, leg lean mass, skeletal muscle fibre area and maximal power output were preserved.

Our results demonstrate that total skeletal muscle mitochondrial volume density increases in response to high altitude exposure secondary to a preferential increase in intermyofibrillar mitochondrial populations.

This study provides direct evidence contradicting the notion that high altitude exposure diminishes skeletal muscle mitochondrial volume density, highlighting an inconsistent understanding of the role of hypoxia on skeletal muscle mitochondria.

Nature Communications volume 10, Article number: 3923 (2019). **Nobiletin fortifies mitochondrial respiration in skeletal muscle to promote healthy aging against metabolic challenge.** Kazunari Nohara, Venkata Mallampalli, Travis Nemkov, Marvin Wirianto, Jiah Yang, Youqiong Ye, Yuxiang Sun, Leng Han, Karyn A. Esser, Eugenia Mileykovskaya, Angelo D'Alessandro, Carla B. Green, Joseph S. Takahashi, William Dowhan, Seung-Hee Yoo & Zheng Chen.

Ann N Y Acad Sci. 2016 Jan; 1363: 116–124. Methionine restriction and lifespan control. Byung Cheon Lee, Alaattin Kaya, and Vadim N. Gladyshev.

Nature Communications volume 10, Article number: 3923 (2019). **Nobiletin fortifies mitochondrial respiration in skeletal muscle to promote healthy aging against metabolic challenge.** Kazunari Nohara, Venkata Mallampalli, Travis Nemkov, Marvin Wirianto, Jiah Yang, Youqiong Ye, Yuxiang Sun, Leng Han, Karyn A. Esser, Eugenia Mileykovskaya, Angelo D'Alessandro, Carla B. Green, Joseph S. Takahashi, William Dowhan, Seung-Hee Yoo & Zheng Chen.

Metabolism Volume 59, Issue 7, July 2010, Pages 1000-1011. Metabolism. Methionine restriction effects on mitochondrial biogenesis and **aerobic capacity in white adipose tissue, liver, and skeletal muscle of F344 rats.** Carmen E.Perrone Dwight A.L .Mattocks Maureen Jarvis-Morar Jason D.Plummer Norman Orentreich.

J. Biogerontology. 2012: 399-411. **Effects of aging and methionine restriction applied at old age on ROS generation and oxidative damage in rat liver mitochondria.** I.

Sanchez-Roman, Alexia Gomez Irene Perez. Carlota Sanchez Henar Suarez Alba Naud · Mariona Jove· Monica Lopez-Torres Reinald Pamplona Gustavo Barja. Courtney M. Peterson, Darcy L. Johannsen, Eric Ravussin,

Aktuelle Gerontologie, 01 Oct 1977, 7(10):535-538. **Long-term tryptophan restriction and aging in the rat.** Segall P.

J Aging Res. 2012;2012:194821. Skeletal muscle mitochondria and aging: a review. Courtney M Peterson, Darcy L Johannsen, Eric Ravussin Courtney M. Peterson, Darcy L. Johannsen, Eric Ravussin, "Skeletal Muscle Mitochondria and Aging: A Review",Courtney M. Peterson,1 Darcy L. Johannsen, and Eric Ravussin. **Aging is characterized by a progressive loss of muscle mass and muscle strength. Declines in skeletal muscle mitochondria are thought to play a primary role in this process. Mitochondria are the** major producers of reactive oxygen species, which damage DNA, proteins, and lipids if not rapidly quenched. Animal and human studies typically show that skeletal muscle mitochondria are altered with aging, including increased mutations in mitochondrial DNA, decreased activity of some mitochondrial enzymes, altered respiration with reduced maximal capacity at least in sedentary individuals, **and reduced total mitochondrial content with increased morphological changes. However, there has been much controversy over measurements of mitochondrial energy production, which may largely be explained by differences in approach and by whether physical activity is controlled for. <u>These changes may in turn alter mitochondrial dynamics, such as fusion and fission rates, and mitochondrially induced apoptosis, which may also lead to net muscle fiber loss and age-related sarcopenia.</u> Fortunately, strategies such as exercise and caloric restriction that reduce oxidative damage also improve mitochondrial function. While these strategies may not completely prevent the primary effects of aging, they may help to attenuate the rate of decline.**

Experimental Gerontology. Volume 48, Issue 10, October 2013, Pages 1030-1042. Regulation of longevity and oxidative stress by nutritional interventions: Role of methionine restriction. I. Sanchez-Roman, Gustavo Barja.

J Endocrinol. 2015 Jul;226(1): R17-28 Macronutrients and caloric intake in health and longevity. Samantha M Solon-Biet , Sarah J Mitchell, Rafael de Cabo, David Raubenheimer, David G Le Couteur, Stephen J Simpson. Both lifespan and healthspan are influenced by nutrition, with nutritional interventions proving to be robust across a wide range of species. However, the relationship between nutrition, health and aging is still not fully understood. Caloric restriction is the most studied dietary intervention known to extend life in many organisms, but recently the balance of macronutrients has been shown to play a critical role. In this review, we discuss the current understanding regarding the impact of calories and macronutrient balance in mammalian health and longevity, and highlight the key nutrient-sensing pathways that mediate the effects of nutrition on health and aging.

Aging Cell. 2018 Aug; 17(4): e12796. Role of dietary amino acid balance in diet restriction mediated lifespan extension, renoprotection, and muscle weakness in aged mice, Shohei Yoshida,, Kosuke Yamahara, Shinji Kume,corresponding author Daisuke Koya, Mako Yasuda Yamahara, Naoko Takeda, Norihisa Osawa, Masami Chin Kanasaki, Yusuke Adachi, Kenji Nagao, Hiroshi Maegawa, and Shinichi Araki.

****