

Ray Peat's Newsletter

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

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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.

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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.

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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.**

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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.

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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. 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. 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.

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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.

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