Ray Peat's Newsletter

'As the true method of knowledge is experiment, the true faculty of knowing must be the faculty which experiences.'
William Blake

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Nitric oxide, aging, and adaptation--the Procrustean adaptogen

The 1998 Nobel Prize in Physiology or Medicine was awarded for "discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system." It had previously been called the "endothelium-dependent relaxing factor." Those descriptions have strongly influenced the way people think about it. "Signal" implies purpose and control, "relaxing blood vessels" implies protection against hypertension. If we called nitric oxide "an anti-respiratory pro-inflammatory substance produced mostly by stressed cells," we would be very cautious about medical techniques to increase its production. Many people are now thinking about it in this way.

In the early 1990s, it was recognized that nitric oxide was a central factor in the shock state, and that inhibiting its formation could alleviate the shock state. The state of shock was often called "circulatory failure," from excessive vasodilation, so it was easy to see a role for the vasodilator nitric oxide in circulatory collapse; however, in most cases the real problem in shock was the failure of cellular respiration.

If inadequate circulation were the problem, oxygen-deprived tissues would cause the venous blood to be blue and free of oxygen, but in fact the venous blood in shock is likely to be bright red, showing that no oxygen was extracted by the tissues. Only an extremely small minority of publications on the physiology of nitric oxide are concerned with the fact that it inhibits mitochondrial use of oxygen for energy production in various ways, including by blocking the respiratory enzyme cytochrome C oxidase.

When I was studying estrogen's anti-fertility effects on the uterus, I noticed that the metabolic changes it produced were similar to those caused by a vitamin E deficiency or PUFA excess, by ionizing radiation, by oxygen deprivation, or by aging. All of these conditions involved interference with, or decreased activity of, the crucial respiratory enzyme, cytochrome C oxidase.

When Hans Selye was studying the biological effects of the steroids, he described the effect of a large dose of estrogen as similar to the shock phase of the stress reaction. He observed that body temperature and blood pressure were momentarily lowered in this first reaction to stress; these are both effects of nitric oxide. Later, other people observed that estrogen was produced by any tissue under stress.

After nitric oxide production was found to be stimulated by estrogen, in the early 1990s, there was an opportunity for a major advance in the understanding of stress physiology, but the estrogen-centered medical culture saw the need to describe nitric oxide as a well regulated, relaxing, signal substance involved in all of estrogen's notorious protective effects. The remarkable fact that both estrogen and nitric oxide are produced by practically any injury has seldom been mentioned, and their closely related effects on energy metabolism have been generally ignored.

I interpreted estrogen's role in reproduction and cell proliferation in terms of an idea that was discussed by Otto Warburg and others. In this view, multiplication is the basic, simplest function of any cell, and it is supported by inefficient non-oxidative metabolism, while the differentiation of cells to form part of a stable multicellular organism requires the highly efficient oxidative

production of metabolic energy. A substance such as estrogen is able to interrupt oxidative metabolism to initiate reproduction of the organism, or to stimulate tissue repair, in response to a local injury. Oxygen deprivation, ionizing radiation, and other stresses increase the formation of estrogen, and estrogen facilitates the multiplication of cells by shifting the metabolism to glycolysis, producing energy from glucose without using oxygen.

One of the anti-respiratory substances produced by estrogen is carbon monoxide (Tschugguel, et al., 2001). Another inhibitor of mitochondrial oxidation, hydrogen sulfide, is also increased by estrogen (Lechuga, et al., 2015).

The stresses of a harsh environment that make early reproduction advantageous, or that require accelerated tissue renewal, also favor epigenetic adaptations that reduce energy demands. It has been known for about 50 years that starvation during pregnancy reduces not only the metabolic capacity of the first generation, but of several following generations. For a species, this transgenerational effect is analogous to hibernation or estivation in an individual, reducing metabolic needs to match the diminished environmental resources.

When estrogen increases in the fall before hibernation, while progesterone is low, conception is prevented. Estrogen's increase of nitric oxide and/or hydrogen sulfide is adaptive for a hibernating animal, reducing its body temperature and metabolic rate (Gonzalez Nicolini, et al., 1998; Revsbech, et al., 2014; Li, et al., 2012).

The metabolic quiescence of the major organs in shock ("multiple organ failure") has been compared (Azevedo, 2010) to the state of hibernation. I have previously described some of the ways that the degenerative diseases resemble a mild kind of progressive shock or hibernation of tissues or organs.

In all of these conditions of stress adaptation, "epigenetic" modifications of DNA are involved, with nitric oxide participating, with estrogen and other hormones, in methylation of DNA and modification of histones, and a variety of other biochemical "lingering modifications." While those chromosomal effects of nitric oxide are just starting to be investigated, I think the outlines of its role in shaping the organism are now visible.

In the embryo and fetus, not much nitric oxide synthase, NOS, can be detected, but around the time of birth more of it appears, and it increases until around adolescence. During young adulthood, the level of nitric oxide in the body seems to be unrelated to aging, but then, after about the age of 40-50, it begins an increase that continues until old age.

The cells of the heart in the fetus multiply rapidly until birth, and then, as cell proliferation stops, they grow in size. The number of cells of the brain reaches a maximum several weeks before birth, and then many of them die, while the brain continues to enlarge as individual cells grow larger. Continuing into adulthood, nitric oxide serves to control nerve cell proliferation. In some other embryonic tissues (retina and testicle), nitric oxide is known to decrease cell proliferation; for example in the retina, adding nitric oxide to tissue culture decreased cell proliferation by about 70% (Magalhães, et al., 2006). In women with growth restricted, small-for-gestational-age fetuses, the nitric oxide content of blood platelets is above normal. In this study, the toxic peroxynitrite was also increased, arguing for the view that nitric oxide was a cause of the growth restriction, rather than a compensation for some other causative factor (Nanetti, et al., 2008).

An abundant supply of sugar is necessary to support fetal growth, especially for the brain with its high metabolic rate, and nitric oxide blocks the ability to use sugar, but it slows metabolism, so it could serve to adjust the size of developing organs, to allow survival when fuel is less abundant. Besides adjusting the relative size of organs, the fact that nitric oxide increases the activity of DNA methyltransferase indicates that it is contributing to the epigenetic methylation of DNA that shapes life-long, and transgenerational, inclinations.

From birth to adolescence, as the tissues are differentiating and maturing, and NOS is increasing, there is a steady decrease in the metabolic rate. In the process of cellular differentiation, new genes are being expressed in the developing tissues, with progressive demethylation of various sections of DNA, but at the same time, as the individual is adapting to the particular stresses of a unique environment, there may be need for new

methylations appropriate for that environment. The unique individual's "phenotype" is made up of functional systems that have established an equilibrium of internal and external resources.

Since the metabolic rate must be in balance with the availability of fuel, the thyroid hormone, which directly activates the respiratory enzymes, is especially important. Just as it wouldn't be possible for an animal to hibernate in a hyperthyroid state, a basic mechanism for dealing with stress in non-hibernators is to lower the production of thyroid hormone. Nitric oxide blocks the formation of thyroid hormone in response to thyroid stimulating hormone (Bazzara, et al., 2007). Oxygen deprivation (Giusti, et al., 2008) and hypothyroidism (Franco, et al., 2006) block energy production by increasing NOS in the mitochondria.

Although a primitive adaptive mechanism such as nitric oxide can be useful for a species, it can be harmful for individuals. When hypoxia is combined with nitric oxide, nerve cells are more likely to die than when exposed to either alone (Jekabsone, et al., 2007; Mander, et al., 2005). One of the enzymes inhibited by nitric oxide is pyruvate dehydrogenase (Klimaszewska-Lata, et al., 2015, Szutowicz, et al., 2014, Abe 1999), required for the oxidation of glucose, so that a diabetes-like state is created by nitric oxide damage, forcing the use of fatty acids instead of glucose for fuel. At least in some situations, some brain cells can be protected from hypoxia by an increased supply of glucose (Kelleher, et al., 1993).

The shift of metabolic fuel from glucose to fat causes the oxidation state of the organism to shift to the reduced side, away from the oxidized state which favors stable differentiated functioning. With aging, and during stress, animals' metabolism shifts toward reduction, with a higher ratio of lactate to pyruvate, of NADH to NAD, of ascorbate to dehydroascorbate, etc., a state of "reductive stress." When a particular cell or tissue becomes highly reduced, nitrate and nitrite can be converted to nitric oxide, leading to a vicious circle of blocked glucose oxidation and a more reductive condition.

"Pseudo-hypoxia" is sometimes used to describe reductive strsss, since the reduction-oxidation balance of the cells is similar to that produced by hypoxia even when there is adequate oxygen present. When cells convert glucose to lactate even in the presence of oxygen, it's called "aerobic glycolysis," and this is the condition that Otto Warburg recognized as the basic feature of cancer. Nitric oxide, by blocking the oxidation of glucose, creates aerobic glycolysis. The amyloid protein that accumulates in Alzheimer's disease promotes aerobic glycolysis. Recent studies have discussed the importance of reductive stress for the development of Alzheimer's disease (Lloret, et al., 2016; Badía, et al., 2013).

When the oxidation of glucose is impaired, with fatty acids being oxidized for energy, there is usually a decrease in the overall metabolic rate, as well as a shift toward a more reductive biochemistry. At an extreme, the reductive energy derived from aerobic glycolysis can be consumed by the synthesis of fat, permitting glycolysis to proceed, and this can lead to cancer cells that oxidize fatty acids for energy, while converting glucose to fats and lactic acid.

With aging, as the metabolic rate decreases, the ratio of glucose to fatty acids oxidized also decreases, yet the abdominal fat increases. In unusually long lived people, these features were more like the younger adults, with higher oxygen consumption and carbon dioxide production, higher respiratory quotient, lower proportion of body fat and lower waist fat (Rizzo, et al., 2005). In postmenopausal women, a lower respiratory quotient is associated with a higher risk of breast cancer (Prentice, et al., 2013). High estrogen (increasing NO, interfering with glucose oxidation) lowers the respiratory quotient, so that observation isn't surprising.

Nitrate and nitrite, which are formed in the body when nitric oxide is oxidized, themselvess reduce the metabolic rate (Pawlak-Chaouch, et al., 2016). These are being found increasingly in food and water, where they are thought to contribute to hypothyroidism and cancer (Mitacek, et al., 2008; Wang, et al., 2015; Njeze, et al., 2014).

Some of the obvious changes of aging, such as loss of muscle (Martinez-Moreno, et al., 2007) and gain of fat (Bahadoran, et al., 2015) and decreased sensitivity to insulin (Ropelle, et al., 2013), are produced by increased nitric oxide. The age-related collagen deposition in arteriosclerotic arteries and in the corpora cavernosa of the penis is associated with increased production of nitric

oxide, but this is usually explained as a compensatory reaction, which helps to slow the progress of the fibrotic degeneration. A high level of NO in keloids, scars that grow with over-production of collagen, was explained in the same way, but experiments showed that adding nitric oxide accelerates the formation of collagen (Hsu, et al., 2007). Although inhalation of nitric oxide is used to treat lung disease, experiments show that NO is an important factor in the development of fibrosis in the lungs (Ekekezie, et al., 2000; Cameli, et al., 2014).

Beyond the general increase in nitric oxide synthesis with aging, there is considerable evidence of an association of nitric oxide with brain defects of Alzheimer's disease. For example, people with an abnormal lipoprotein, apoE4, are more likely to develop Alzheimer's disease, and that abnormal protein is known to cause increased production of NO (Brown, et al.,2002; Law, et al., 2003). Besides an increase of NO with aging, some studies have found that some endogenous inhibitors of nitric oxide synthesis decrease with aging (Abe, et al., 2001). Nitric oxide's ability to inhibit steroid synthesis is undoubtedly a factor in the decrease of neurosteroids in the aging brain.

The mutant short-lived senescence-accelerated mice have been studied for insights into Alzheimer's disease as well as general aging. Between the ages of 2 months and 12 months, the NOS activity in their hippocampus nearly doubles (Ali, et al., 2009).

Most of the arguments for using drugs to increase nitric oxide production are related to its ability to relax blood vessels and lower blood pressure. The use of nitroglycerine and other nitrates to relieve heart pains has been common for more than 100 years, and it seems obvious that its effect is the result of widening the arteries in the heart, but there are other possible interpretations. For example, by reducing the body's metabolic rate and oxygen consumption, the heart's work is reduced. Investigations between the 1930s and 1960s (Geumei, et al., 1969) found that nitrite constricts the liver's vascular system, reducing the return of blood to the heart, directly reducing the heart's pumping action.

Nitric oxide has an action on the heart that isn't directly related to the blood vessels. When the parasympathetic nerves act on the heart, slowing and weakening its contractions, they are releasing nitric oxide, which reduces the heart's oxygen consumption as well as its energy production. The effects of nitric oxide on the heart resemble those produced by shock, and those that occur during heart failure, namely, a weakening of both contraction and relaxation (Kalk, et al., 2008; Jessup, et al., 2011; D'Annuzio, et al., 2012), and a loss of, or inversion of, the "staircase" effect, in which force of contraction normally increases with frequency of contraction.

Stimulation of the parasympathetic nerves to the heart can cause a vascular spasm, resulting in heart pain. The parasympathetic nervous system is more active during the night, and this kind of "variant angina" usually happens at night, rather than during exercise. I suspect that this can be explained in terms of the aerobic glycolysis and pseudohypoxia created by nitric oxide. The impairment of relaxation of the heart by NO is analogous to the rigor or contraction that occurs in smooth muscle during deprivation of oxygen and/or glucose. Ordinarily, parasympathetic nerves produce relaxation, but in a situation of prolonged or inescapable stress, intensified parasympathetic action and accumulation of nitric oxide, the state of reductive stress, pseudohypoxia, probably leads to the vascular spasms of angina pains, transient ischemic attacks in the brain, and worse.

There are other situations in which nitric oxide has an excitatory effect. For example, it's associated with brain arousal, waking, and rapid eye movement (REM) sleep (Mariño and Cudeiro, 2006). The amount of nitric oxide in the exhaled breath rises during the night, with the peak around 7 AM (Mattes, et al., 2002). It interacts closely with the orexin peptides, which stimulate appetite and wakefulness and increase blood pressure and heart rate, and an excess of NO can increase blood pressure and accelerate the heart beat (Kimura, et al., 2005). Its excitatory effects apparently include increasing the release of acetylcholine in the brain (Leonard and Lydic, 1997).

During aging and many stress-induced conditions, it can be therapeutic to use substances that block our energy-limiting systems, to permit restoration of full energy production. Excessive

estrogen, nitric oxide, prostaglandins, and parasympathetic nerve activity commonly occur simultaneously, and it happens that a substance which inhibits one of those will often inhibit the others.

Some of the most important anti-nitric oxide defenses are progesterone, vitamin E, vitamin K, vitamin A, niacinamide, coffee, aspirin, and foods containing flavonoids, terpenoids, polyphenols, and sterols. Grass-fed milk contains a variety of polyphenols. Citrus fruits, many tropical fruits (e.g., guavas, longans, and lychees), and cooked mushrooms are good sources of apigenin, naringenin and related chemicals.

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