Ray Peat's Newsletter

That which we must learn to do, we learn by doing. Aristotle

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Sugar, stress and the degenerative diseases

The physiology of sugar has been of great interest since the work of Claude Bernard in the 1850s and '60s, but its role in sickness and aging is still very controversial. To understand what sugar normally does, and what it can do, it's helpful to consider what happens when the amount of sugar in the blood is lower than normal—or lower than optimal.

In the 1940s, hypoglycemic shock was generally recognized as a dangerous effect of using insulin for diabetes, and "insulin shock" was a common treatment for psychiatric patients. During the first World War, intravenous glucose was recognized as a treatment for shock (Erlanger and Woodyatt, 1917). Around 1947, I was interested to see bottles of honey and instant tea on a shelf in a dentist's operating room; he said he used it for patients who seemed to be going into shock.

During the next 20 years, I had numerous opportunities to see the mental and physical effects of using sugar as an emergency treatment, for people and various animals, and occasional publications reported beneficial effects of supplementing glucose or fructose. However, around 1970, I began noticing that doctors were very reluctant to use intravenous glucose, even for people hospitalized for terminal cancer, or heart failure, stroke, or shock. In the 1970s I saw an article describing the successful treatment of septic shock with intravenous glucose, but a recent medical graduate told me that such an effect was impossible. Since then, medical hostility toward sugar has increased, and there are organizations lobbying governments to restrict the availability of foods and drinks with a high sugar content.

The availability of synthetic glucocorticoids starting in the 1950s provided alternatives to the therapeutic use of sucrose, glucose, and fructose, to "support glucose homeostasis," and around the same time pharmaceutical alternatives to insulin (phenformin, followed by metformin) became available, with new marketing campaigns to control "the sugar disease." It was during this same period that the cholesterol theory of heart disease became popular. While the "essential fatty acids" were sold to "lower cholesterol," the ability of sugar to increase cholesterol and triglycerides was publicized. A book by John Yudkin, in 1972, argued that sugar was the real cause of heart disease. **The popular science culture, informed by advertising, understood polyunsaturated fats to be good, sugar to be bad, and after a couple of generations, medicine reflected the popular culture.**

In this environment, it's possible to think about the basic involvement of stress and inflammation in the major diseases and degenerative aging processes, without thinking about the central involvement of glucose metabolism in stress and inflammation, except as a villain. The culture's identification of glucose as a harmful substance led to the

identification of a new disease, "gestational diabetes," and to a general lack of interest in the risks of gestational hypoglycemia.

The brain consumes about 60% of the body's glucose when a person is physically inactive, and because of its dependence on glucose, it's easily damaged by even short periods of hypoglycemia. Most of its energy is used for a constant restructuring process—it never stops its developmental processes, though their intensity decreases with age. When hypoglycemia occurs during gestation or in infancy, when metabolic intensity is greatest, the adaptations can lead to life-long problems.

The optimal blood sugar level during human pregnancy isn't known, but animal experiments have shown that a decrease in the mother's blood sugar can stop brain growth in the fetus. Stress, or an imbalance of hormones, can limit the mother's ability to provide glucose needed for the baby's brain growth. Experiments with developing chicken eggs showed that providing extra glucose (as an equivalent amino acid) can cause brain growth to continue at the stage when it is normally stopped by the limited amount of glucose available in an egg. Birds, such as crows and parrots, which hatch at an earlier stage of development, and receive an uninterrupted supply of nutrients, are much more intelligent than birds like chickens, that develop to a physically more mature self-reliant stage before hatching.

As soon as a baby is born, and stops receiving a constant supply of glucose from the placenta, the muscles begin using fat as their basic energy source, allowing the brain to use most of the glucose that's available, from glycogen stores and from the conversion of tissue protein to glucose, under the influence of the cortisol that rises during the process of being born.

This glucose-sparing system is essential for the adaptability of animals: Its sudden failure creates the "shock" state, and its gradual weakening leads to the various degenerative diseases.

During adaptation, the functional load is shifted to the system that is meeting the new challenge, and a variety of stimuli, from nerves and hormones, activate the cells of that responsive system, and resources, such as amino acids, can be moved from less active systems to support the new level of functioning. The organism has to focus its stimulating factors accurately, and the resources, including glucose stored in the tissues as glycogen, have to be adequate. If stimulation is too intense or too widespread, and if too much fat is mobilized relative to glucose, self-defeating processes can occur.

During aging, there is an increase in the percentage of polyunsaturated fats in the tissues. The unsaturated fatty acids increase activation of the pituitary and adrenal cortex, increasing the production of ACTH and the glucocorticoids (Widmaier, et al., 1995). This activation of ACTH follows the activation of nicotinergic cholinergic nerves (Nishizaki, et al., 1999) and the most important excitatory system in the brain, the NMDA receptor system, part of the glutamatergic system (Bazan, et al., 1995).

Stress increases the production of lactic acid in the brain, and lactic acid activates the NMDA system. Lactate is produced when a cell is in a reducing state (with a higher ratio of NADH to NAD+), relatively deprived of oxygen, and it can transfer the reductive condition to other cells, acting as a transmitter. The NMDA receptor (like many other regulatory proteins, e.g., COX, TLR, NOS, aromatase) is activated by reduction of its thiol groups. The reductive state, which activates this excitatory system, can be produced by an actual oxygen deficiency, but also by inhibiting mitochondrial function, creating a state of "pseudohypoxia."

I think this connection between lactate and the glutamatergic system that's involved in excitotoxicity provides an insight into the basic nature of stress. Stress exists to the degree that cells are shifted into a reductive, pseudohypoxic state, by an imbalance between stimulation and the rate of restorative oxidative metabolism.

Starvation and diabetes, in which glucose oxidation is limited, and amino acids and fatty acids are used for fuel, are pseudohypoxic states, forming lactic acid from both glucose and glutamine.

Hypoglycemia, besides causing unconsciousness and shock, can cause grand mal seizures, hypertension, vasospasm, and other excitatory processes, by leading to the release of glutamate and the activation of the NMDA system. This excitation creates reductive stress, resembling that in cancer cells, with the activation of the regulatory proteins, including HIF (the hypoxia inducible factor), that reinforce that state of inflammation and lactate production. Providing extra glucose can lower the HIF.

The reductive state, resulting from starvation or hypoglycemia, or an excess of lactate or fat, or oxygen deprivation, activates the release of glutamate, and the excitation produced by that can shut off mitochondrial oxidation, reinforcing the state of pseudohypoxia. Nitric oxide synthesis, activated by reductive stress, is a major factor in the suppression of mitochondrial oxidation.

In the excessively electron-rich intracellular environment, iron is activated, and a variety of enzymes directly reduce and activate oxygen (Korge, et al., 2015, 2016). These reactive oxidative molecules damage all kinds of cellular structure, including DNA, and lead to some of the stress-related events such as heart attacks and strokes. In patients hospitalized with subarachnoid hemorrhage, those with blood glucose below 80 mg. per 100 ml. had worse outcomes than those with higher levels (Naidech, et al. 2010). In patients with traumatic brain injury, those with lower glucose concentration in the brain didn't recover as well as those with higher levels (Vespa, et al., 2003). Animals are more likely to die from anaphylactic reactions to allergens when their blood sugar is lowered by insulin (Dhar, et al., 1967, Adamkiewicz, et al., 1964).

The heart is more susceptible to infarction during fasting than after a meal (Liepinsh, et al., 2014). A two day fast causes both diabetics' and normal people's glucose tolerance to deteriorate, and when diabetic men were put on a 75% carbohydrate diet their glucose tolerance was better than on a 44% carbohydrate diet (Anderson, 1977). The high carbohydrate diet improved the men's insulin sensitivity, and fasting, similar to a high fat diet, impairs insulin sensitivity.

When fats are oxidized instead of glucose, more oxygen is needed to produce the same amount of energy, and less carbon dioxide is produced. While lactic acid and a more reducing balance in cells activate the excitatory glutamatergic system, an increased concentration of carbon dioxide inhibits that system (Urenjak, et al., 1997). The glutamatergic/NMDA system is one of the activators of the nerves in the brain that regulate breathing, and it's probably through this system that lactate increases breathing, and tends to produce hyperventilation, lowering CO2 throughout the body. Carbon dioxide is both a product of, and an activator of, oxidative energy production, and with the loss of CO2 through hyperventilation, the NADH/NAD+ ratio increases, and oxidative energy production decreases.

In the hypoglycemic state, or when stress is blocking glucose oxidation, amino acids can be used in place of glucose, but in this process the amino group is removed as ammonia. The

brain can eliminate some ammonia by combining it with glutamate, to form glutamine (in a process that consumes some glucose), but when large amounts of the potentially toxic ammonia are formed, the liver normally converts it to urea, by combining it with carbon dioxide, but in the stress conditions, which increase the formation of ammonia, the availability of carbon dioxide decreases. Ammonia activates the NMDA system, with the potential of intensifying the stress processes.

Lithium has been used for many years to treat various mood disorders, including anxiety and depression, and it reduces activation of the NMDA system, possibly by binding ammonia. Lithium protects against the hyperphosphorylation of excitotoxicity, and supports the formation of glycogen, while generally improving glucose metabolism. Starvation produces the hyperphosphorylation that is characteristic of Alzheimer's disease. The biological changes associated with the shift of fuels from glucose to fatty acids and amino acids in stress, aging, and dementia, have been called "the deprivation syndrome" (Heininger, 2000, 2001).

All the tissues of a healthy fetus contain glycogen, corresponding to an abundant supply of glucose, relative to the level of stressful stimuli. Later, during independent life, the amount of glycogen in the tissues has a daily cycle, especially in the brain, where it decreases during the day, and is replenished during the night. When there isn't enough stored glycogen in the liver, muscles, and other tissues, to provide the brain's nocturnal glucose requirement, cortisol rises, breaking down tissue proteins to provide amino acids and glucose, but free fatty acids are also increased by this nocturnal stress. Some of these are taken up by the brain, and interchanged with the fatty acids liberated from the brain's structural lipids during the brain's intense nocturnal metabolism.

As the proportion of polyunsaturated fatty acids increases with aging, some arachidonic acid becomes incorporated into the brain, and, especially during the night, the highly unsaturated fatty acids amplify the excitatory processes, including the formation of prostaglandins and other inflammation-producing compounds. All of these processes interact, resulting in a progressive decrease of brain glycogen with aging, and a reduced ability of the brain to oxidize glucose.

Since the basic activating factor for these degenerative changes is a shift in the direction of pseudohypoxia or reductive stress, things that cause a redox shift in the opposite direction can slow or reverse these degenerative processes.

The use of lactate or beta-hydroxybutyrate as metabolic fuel shifts the balance in the reductive direction, the way ethanol metabolism does. Fuels that shift the balance in the protective, more oxidized, direction include fructose and acetoacetate. Several of the flavonoids of fruits and vegetables (rutin, naringenin, naringin, hesperetin, apigenin, fisetin, luteolin, quercetin, curcumin) have a catalytic prooxidant effect similar to that of vitamin C and aspirin.

The rise of cortisol during the night causes a tendency for a surge of blood pressure in the morning, and is probably the main factor in the increased frequency of heart attacks and strokes during the morning hours. Having a large part of the day's carbohydrate intake late in the day, or even during the night, can help to restore the brain's glycogen with less need for cortisol, and helps to reduce the nocturnal rise of free fatty acids, and their excitatory-inflammatory effects.

Other substances that protect against the effects of hypoglycemia or impaired glucose oxidation include progesterone, caffeine, certain anesthetics including xenon, niacinamide, agmatine, carbon dioxide, and

methylene blue. Since the excitatory NMDA receptors seem to be in cells of all types, including cancer, substances that correct systemic stress apparently can correct cellular stress by reducing their stimulation. Since starvation or glucose deprivation can create aerobic glycolysis in organismic shock and in isolated cells, it's likely that things that relieve shock will be able to correct cancer metabolism.

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