Ray Peat's Newsletter

The people have no voice because they have no information . . . **Gore Vidal**

Serotonin: Energy, Degeneration, and Aging

Serotonin is often called a "neurotransmitter," and considered to act on "receptors" to "transmit information," which may be "processed" the way computers process digital information. I think it's more useful to think of it in terms of fields and formative processes that shape the way the organism uses energy to adapt to stresses and possibilities. It is involved in the energetic and structural changes that occur during stress and adaptation. Getting rid of the misleading abstractions makes it easier to see some simple patterns that exist throughout the organism.

The dominant and misleading abstractions surrounding serotonin have distracted attention from its fundamental role in energy management, stress, and adaptation.

The receptor doctrine is part of an ideological attitude toward life, an attitude that would like things to be clearly definable and uncomplicated. The fact that "hormones" and "neurotransmitters" can crucially interact with things that aren't their "receptors" has usually been disregarded, if not denied. The professionalization of science in the last 150 years has created a culture in which authoritative assertions can be accepted for decades without any supportive evidence at all. The practice of "estrogen therapy" for prostate cancer, from the 1940s to the 1990s, is an example. Statements about serotonin in the medical journals and mass media and on the internet are another example.

The development of physics, beginning with calculations of the trajectory of cannonballs and the production of heat in boring cannons, has been guided by militarism. The development of genetics had ulterior motives, from Darwin's assertion of the hereditary superiority of English people, plants, and animals, and Mendel's denial of the mutability of traits, through Konrad Lorenz's explanation of the need to exterminate inferior races. Medicine has been transformed by the influence of the pharmaceutical industry, including the popular understanding of serotonin that has been created by that industry.

These three traditions—physics, genetics, and medicine—have interacted in ways that reinforce themes that favor the industries' vested interests, and that eliminate themes that would harm their interests. For example, the major journals of "health physics" considering the biological effects of radiation are controlled by the nuclear industry, and have concentrated on heritable changes in DNA, rather than bystander and epigenetic effects, genetic stability, and behavioral and physiological changes. The situations in which the effects of ionizing radiation, estrogens, and polyunsaturated fats synergize have been shunned. The food and drug industries have found common interests in promoting the biological value of increased polyunsaturated fats, estrogens, and serotonin. Each of these has been featured in huge marketing campaigns. When studies of the biological role of one of these substances reveals its close biochemical interactions with one or both of the others, this is usually treated as though it confirms the importance of

the study, because of the halo of cultural associations around each of them.

The ideology of "receptors" has allowed medicine to disregard the physical chemistry of biological molecules interacting with cells.

When serotonin was found to decrease when people adapted to living at high altitude, the natural response within the culture, where the "SSRI antidepressants" are said to stop depression by increasing serotonin, was to assume that lower serotonin would mean greater depression at high altitude. This led to studies finding that the suicide rate in Colorado is high, and the mass media spread the idea widely, that the lower serotonin at higher altitude causes depression, leading to suicide. There are high altitude places (Ecuador, Mexico, Colombia) with very low suicide rates, and low altitude places (Lithuania, Bangladesh, South Korea) with high suicide rates. Economics, health, and religion strongly affect the rate of suicide, but there is no industry spending billions of dollars advertising those effects.

The serotonin advertising culture allows major medical journals and internet medical websites to say that serotonin is higher in the daytime than during the night, and higher in the summer than in winter, despite evidence from a great range of species (e.g., Poncet, et al., 1993; Piccione, et al, 2005; Curzon and Filippini, 1996; Prosser, 2003), showing that serotonin peaks during darkness, even in nocturnally active rats and mice. Serotonin is the precursor for melatonin, which is important for adapting to darkness by promoting sleep to reduce stress. **Mood is generally higher in the daytime (along with mental and physical abilities), so the advertising culture has to claim, despite the facts, that serotonin, the happy hormone, is higher in the daytime.**

Thinking about the events that lead to serotonin's synthesis will clarify its place in the organism's adaptive stress response system. Increased free tryptophan in the blood is the main factor determining the production of serotonin in the brain, and free fatty acids, produced by stress, cause bound tryptophan to be released from albumin in the blood. Hypoglycemia, resulting from many kinds of stress, leads to an increase of free fatty acids in the blood. Almost everyone in the US has heard the claim that sugar's ability to cause relaxation and sleepiness is because it causes tryptophan to enter the brain, **but in fact it is hypoglycemia, which causes irritability and anxiety, that increases the brain's uptake of tryptophan** (Yehuda and Meyer, 1984; Montilla, et al., 1988; Danguir, et al., 1984; Heyes, et al., 1990).

The synthesis of serotonin in the brain depends on the activity of the enzyme, tryptophan hydroxylase, TPH, and this enzyme is activated by excitation of the cell, with increased intracellular calcium and reduced glutathione (GSH), and inactivated by oxidation of glutathione. Stress consumes glucose and oxygen, creating a relative hypoglycemia and hypoxia, and both of these are associated with reductive stress, increasing the formation of serotonin.

The cultural script that aging is caused by "oxidative stress" is being increasingly questioned, with the recognition of a reductive cellular state as a common factor in shock, stress, and degeneration.

The amount of serotonin in the brain at a particular time is influenced by a variety of things that affect the balance between its synthesis and its sequestration or degradation. The so-called serotonin transporter binds and holds serotonin, reducing its interactions with other cell components, and the enzyme monoamine oxidase, MAO, degrades serotonin, turning it into the inactive 5-HIAA. Many other factors besides its concentration affect serotonin's effect on the brain, for example, the amount of dopamine. **Serotonin activates the stress hormones, and the cortisol produced as a result can have the protective effect of inhibiting the enzyme that makes serotonin, as well as activating the MAO that removes it** (Clark and Russo, 1997; Ou, et al., 2006; Popova, et al., 1989). **Estrogen increases serotonin synthesis, decreases its binding, and inhibits its degradation** (Smith, et al., 2004).

The ideology of "receptors" has allowed medicine to disregard the physical chemistry of biological molecules interacting with cells. When a substance in the brain, 5-hydroxytryptamine, was discovered in 1953 to be identical to the previously known enteramine, which causes the intestine to contract, and a vasoconstrictor substance in the blood named serotonin, with about 20 times more of the substance being made outside of the brain, the idea of a compartmentalization by a blood-brain barrier allowed the strict "neurotransmitter" understanding of serotonin's functions to develop.

There has been almost no interest in testing the reality of a blood-brain barrier for serotonin. In one test, para-chlorophenylalanine (PCPA), which blocks the synthesis of serotonin throughout the body by inhibiting TPH, was given to animals, and then serotonin was injected into the brain; the blood level of serotonin was quickly increased, showing free passage from the brain into the blood. The amount of serotonin in the urine, blood, and brain have been shown to be very closely associated (Audhya, et al., 2012). Although serotonin is much more water soluble than tryptophan, the positive charge of its ionized amino group can form a link with the negative charge of a phosphate group (Peters, et al., 2013) in cellular phospholipids, such as lecithin, allowing the pair to be very mobile in the lipophilic cytoplasm. Since even large molecules such as proteins can cross the so-called barrier, it shouldn't be surprising that hormones and "neurotransmitters" cross it, according to physical principles such as solubility.

Although its name, "serotonin," is based on the fact that it constricts blood vessels, it also increases their leakiness. Both of these actions contribute to its role in fatigue and inflammation, and to the therapeutic effects of serotonin antagonists in a variety of problems including arthritis (Cloutier, et al., 2012) and traumatic brain injury (Okiyama, et al., 1996, Vannemreddy, et al., 2006). Stressful exercise, increasing serotonin, decreases the brain's ability to exclude harmful substances, including small particles (Feng, et al., 1996).

When large amounts of serotonin are released into the serum by endotoxin, the amount of serotonin in the brain isn't necessarily increased. Endotoxin induces a tryptophan degrading enzyme, IDO, in the brain, producing substances that can be pro-inflammatory and immunosuppressive, and this can reduce the amount of tryptophan available to make serotonin. Because of this, the depression caused by endotoxin inflammation can be associated with decreased serotonin production in the brain.

One of the implications of the bi-directional movement of serotonin across the blood-brain "barrier" would be that events in the intestine, where most serotonin is produced, in the blood where it's transported, and in the lung, where much of it is detoxified, will affect the brain. Toxins produced by intestinal bacteria cause serotonin to be released into the bloodstream, and if the platelets aren't able to keep it tightly bound until the lungs can eliminate it, some of it will reach the brain, where it will interfere with sleep and other brain functions.

Hypoxia or hypoglycemia causes platelets to release serotonin during stress. This situation, in which it is the serotonin that isn't in the platelets that does the harm, has caused a huge amount of confusion.

Although the liver has a much larger capacity than the lungs for detoxifying serotonin, the lungs detoxify several times as much of the circulating serotonin as the liver does. The reason for this is that in the high oxygen environment of the lungs, carbon dioxide is lost from the blood, and carbon dioxide is needed for retention of serotonin by the platelets. With the loss of CO2, the platelets release their serotonin very quickly, to be immediately detoxified by the local MAO. If something (such as smoking, or very high oxygen concentration, or a hormonal imbalance) inhibits the activity of MAO, the high local activity of serotonin can cause lung edema, decreased blood oxygenation, lung fibrosis and pulmonary arterial hypertension. Estrogen is an important inhibitor of MAO in the vascular endothelium; progesterone has the opposite effect, increasing the activity of MAO (Youdim, et al., 1989).

When the lungs fail to detoxify the serotonin released from platelets in the presence of a high level of oxygen, a sample of blood taken from a vein will show a depletion of serotonin in the

platelets, and an increase in the plasma. This situation of an increase in plasma serotonin with decreased platelet serotonin exists in people with pulmonary hypertension (Hervé, et al., 1995; Kéreveur, et al., 2000), and a variety of other degenerative conditions, including heart failure (Ahmed and Nussbaum, 1981). Energy deprivation, for example caused by hypoglycemia or hypoxia, causes platelets to release serotonin during stress. This situation, in which it is the serotonin that isn't in the platelets that does the harm, has caused a huge amount of confusion.

The beneficial effects of negatively ionized air on health and mood have been recognized for several decades. Beginning in the 1960s (Krueger and Smith, 1960), several investigators have found that breathing negatively ionized air accelerates the degradation of serotonin in the lungs. When the oxygen molecule carries an extra electron, it can function as the superoxide radical ion (Goldstein, et al., 1992), and this form of active oxygen oxidizes serotonin (Wrona and Dryhurst, 1998; Peña-Silva, et al., 2009); it is thought to be an intermediary in the action of MAO.

The ideology around stress physiology, falsifying the meaning of serotonin, estrogen, unsaturated fats, sugar, lactate, carbon dioxide, and various other biological molecules, has hidden the simple remedies for most of the inflammatory and degenerative diseases.

The enzyme that degrades superoxide, superoxide dismutase (SOD), is sold as a health food supplement, following the cultural script that aging is caused by "oxidative stress," and that antioxidants are protective. That view is being increasingly questioned, with the recognition of a reductive cellular state as a common factor in shock, stress, and degeneration. A large excess of SOD occurs in Down's syndrome, and is associated with their decreased longevity. When an increase of SOD is produced in cultured cells and in mice and worms, similar harmful effects—accelerated aging—are seen (Nabarra, et al., 1996; Feaster, et al., 1977; Groner, et al., 1990, 1994; Tamarkina, et al., 1997). Serotonin is one of the factors that can increase the formation of SOD (Stralin and Maryland, 2001).

The physical problems (sexual dysfunction, gynecomastia, osteoporosis, glaucoma, cancer, dementia, pulmonary hypertension) that can result from a chronic excess of serotonin are now widely recognized, but the idea of serotonin as a "happy hormone" persists, helping to sell the SSRI, with about 40 million people in the US currently using them. The known effects of increased serotonin on mood and behavior aren't at all consistent with the SSRI marketing idea, so as they become better known insurance companies might begin to discourage their use.

The SSRI drugs inhibit the binding of serotonin to the "serotonin transporter," increasing the effects of serotonin. Mice have been altered to knock-out the gene that makes that transporter. These mice have elevated basal serotonin and increased aggression (Pang, et al., 2012). They more easily become depressed by stress (Wellman, et al., 2007), are more anxious and less exploratory (Carroll, et al., 2007), the cortex of their brain is thinner (Altamura, et al., 2007), their fear memory is enhanced (Lima, et al.,2019), and males are less active and tend to become obese without eating more (Uçeyler, et al., 2010).

Mice have also been altered to eliminate the genes that make both the peripheral and the brain tryptophan hydroxylase that makes serotonin. The double knock-out mice completely lacking serotonin were, surprisingly, "viable and normal in appearance" (Savelieva, et al, 2008), but they did differ in behavior and resistance to stress. They were less likely to die from sepsis and from toxin-induced lung fibrosis (Zhang, et al., 2018, 2017).

Since 2004, the FDA has required a warning that antidepressants can increase "suicidality," aggression, and other problems, and since then several studies have shown changes in the brains of people who have died by suicide, showing abnormally high levels of both serotonin and its breakdown product, 5-HIAA, increased amounts of TPH, the enzyme that makes it, and an increased number of the serotonergic cells that

secrete it (Bach, et al., 2014; Bach-Mizrachi, et al., 2006, 2008; Underwood, et al., 1999).

Several serotonin antagonist drugs are increasingly recognized as antidepressants, and also for treatment of chronic fatigue and insomnia, and many of the degenerative diseases, but since most of them are prescription drugs, their use won't be widespread as long as most doctors accept the myth. The ideology around stress physiology, falsifying the meaning of serotonin, estrogen, unsaturated fats, sugar, lactate, carbon dioxide, and various other biological molecules, has hidden the simple remedies for most of the inflammatory and degenerative diseases.

Avoiding prolonged fasting and stressful exercise that increase free fatty acids, and combining sugars with proteins to keep free fatty acids low, and using aspirin, niacinamide, or cyproheptadine to reduce the formation of free fatty acids by unavoidable stress, avoiding an excess of phosphate relative to calcium in the diet, having milk and other antistress foods at bedtime or during the night, and being in a brightly lighted environment during the day, with regular sunlight exposure, can minimize the harmful effects of excessive serotonin and reduce the inflammation, fibrosis, and atrophy associated with it.

A later newsletter will consider serotonin in relation to age related changes in metabolism, atrophy, fibrosis and cancer.

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