ARTICLE

Serotonin: Effects in disease, aging and inflammation

Interpreting medical publications requires some skills that aren't needed for understanding more strictly scientific reports, because medical writing often takes into account the fact that physicians spend most of their time interacting with the public, rather than studying. The public's understanding of medicine is shaped by "public relations," by the introduction of words and concepts that frame the argument. (The linguist George Lakoff summarized the essence of public relations by observing that people reject facts that are outside their view of reality, their mental framework.) Television and public schools now frame the worldview of the affluent cultures, according to the needs of the ruling powers. Long before specific prescription drugs could be advertised directly to consumers, the medical and pharmaceutical industries were creating a favorable frame for their products.

Many years ago, public relations experts used expensive opinion polls to judge the effectiveness of their efforts, but now there is a convenient way to see how the general public is thinking: Wikipedia, the internet encyclopedia. The success of corporate advertising can be seen in their recent article on serotonin, which says "It is a well-known contributor to feelings of well-being; therefore it is also known as a 'happiness hormone' despite not being a hormone."

The culture that has happy and unhappy hormones was a culture in which each hormone had a receptor, a substance in a cell which, when its ligand was bound to it, made the cell do something. Although that culture still has influence in the 21st century, discoveries made between 1940 and 1970 showed that those mechanical ideas of receptors didn't reflect biological reality. Albert Szent-Gyorgi and the Pullmans showed that the electronic qualities of molecules determined their functions, and Szent-Gyorgyi showed that the state of the cell, tissue, and organism governed the effect of hormones and drugs. In the 1960s, substances with very different biological effects, such as acetylcholine and adrenaline, were shown to be selectively bound to the same cellular site in some cells. It was primarily the drug industry that created and sustained the specific receptor doctrine. That doctrine suited the recognition of their public relations- marketing experts, that successful advertising had to be directed at the sixth-grade educational level. The ideas of bioelectronics and context-sensitive molecules, like morphogenetic fields, were just too complicated to sell well.

Although metaphorical thinking can be creative and productive, metaphors mustn't be taken literally. The identification of multiple types of receptor for a given natural substance involves the use of different substances as metaphors or similes for the natural substance. That type of pharmacology is slowly being replaced by an attempt to understand state-dependent sensitivities. The energetic state of a cell, and of the whole organism, determines the meaning of events and conditions, such as the presence of the "regulatory substances."

The receptor culture can be tentatively disregarded when thinking about the history of serotonin. In the 1930s Vittorio Erspamer identified an amine in the intestine, that caused the intestine to contract. Then a group in England extracted an amine from serum that caused blood vessels to contract, and identified its chemical nature. Later, Erspamer showed that the intestinal amine and the vascular amine were chemically the same. The English group who had identified the substance by extracting tons of beef blood, wanted to find sensitive ways to assay it for further studies, and in 1951 they gave a sample to a pharmacologist, John Gaddum, who tested its effects on tissues including blood vessels and rat uteruses.

Gaddum tested the serotonin in combination with a variety of other drugs, including ergot derivatives, that he knew acted on smooth muscles, and very soon observed that LSD blocked the effects of serotonin. Since he knew that LSD produced mental effects (Sandoz had distributed samples of it to researchers in 1947), he reasoned that the brain might also contain serotonin, and by 1952 was able to demonstrate that it does contain small amounts of it. A couple of years later he suggested "that the mental effects of lysergic acid diethylamide are due to interference with the normal action of this HT [5- hydroxytryptamine, serotonin]." At the Rockefeller Institute in New York, Woolley and Shaw also saw the antagonistic effects on smooth muscle, and drew similar conclusions about the brain. Erspamer (Renic. sc. farmital. 1, 1, 1954) showed that LSD was a highly effective antagonist against the antidiuresis caused by serotonin (enteramine).

Around the same time, in the early 1950s, several people recognized that the symptoms produced by administering an excess of serotonin were similar to those experienced by people with intestinal tumors called argentaffinomas or carcinoid tumors, which are usually in the small intestine or appendix. The normal intestine contains about 95% of the serotonin in the body (and the brain normally contains only about 1%), and in the normal person only about 1% of the dietary tryptophan is converted to serotonin. But in an advanced case of carcinoid, 60% of the tryptophan can be turned into serotonin. Especially if the tumor has invaded the liver, the serotonin won't be destroyed by the liver in the usual way, and will circulate in the bloodstream at high levels, producing symptoms of flushing, sweating (sometimes dark-colored), diarrhea (serotonin stimulates small intestine smooth muscle, but inhibits the large [Bennett & Whitney, 1966]), nausea, anxiety, reduced urination, muscle and joint pains, and, in late stages, very often cardiovascular disease (especially inflammation, fibroma and calcification of the valves in the right side of the heart) and aggressive behavior (Russo, et al., 2004) and psychosis.

Testing Gaddum's idea of antagonism between LSD and serotonin in humans, Montanari and Tonini found that intramuscular injections of serotonin antagonized the psychological effects of LSD. Other drugs, especially other ergot derivatives, were more successful than LSD in blocking the effects of serotonin (Dubach and Gsell, 1962). There have been suggestions that pregnancy hormones could control serotonin excess (McCullough and Myers, 1965). Since estrogen promotes serotonin, progesterone is likely to be the protective factor (Donner & Handa, 2009; Hiroi, et al., 2006; Berman, et al., 2006; Bethea, et al., 2000).

More recently (Spigset, et al., 2004), it was found that LSD binding to a presumed serotonin receptor was low in carcinoid patients, supporting

the idea of antagonism between the substances, but in the older studies symptoms, rather than competition for binding to certain proteins, were the focus of attention. The effects produced by injections and oral doses of synthetic serotonin, and of substances that block the synthesis of serotonin, were studied in both animals and humans. When a symptom such as clotting, flushing, or diarrhea is produced by serotonin itself, or prevented by a blocker of serotonin synthesis, "receptors" aren't an issue.

Aldous Huxley was one of the first people to think about the general biological meaning of drugs such as LSD. Referring to the ideas of Henri Bergson and William Blake, he suggested that the brain usually acts as a filter, or "reducing valve," to make us disregard most of the information we are receiving through our senses, and that the psychedelic drugs temporarily remove the filter, or open the sensory reducing valve. Bergson had suggested that the filter was a practical measure needed to allow us to focus on practical survival needs; Blake had suggested that the doors of perception were kept closed for cultural reasons.

Some recent reviews have discussed the evidence supporting the serotonin system as primarily inhibitory and protective (Anne Frederickson, 1998, Neil Goodman, 2002). Goodman describes the serotonergic system as one of our "diffuse neuroregulatory systems," and suggests that drugs such as LSD weaken its inhibitory, filtering effect. (Jacobs, 1983, 1987: by changes in the effects of serotonin in the brain, produced by things that affect its synthesis, release, catabolism, or receptor action.) LSD depresses the rate of firing of serotonergic nerves in the raphe nuclei (Trulson and Jacobs, 1979) causing arousal similar to stimulation of the reticular formation, as if by facilitating sensory input into the reticular formation (Bowman and Rand, 1980).

In European culture, some people--e.g., Plato, Descarte, Locke, Eccles, probably even B.F. Skinner--have believed that mind and body are essentially different things (analogous to computer hardware and its programs), while another tradition--Blake, Lamarck, Darwin, C.L. Morgan, Pavlov, Reich, C.R. Cloninger, for example--has emphasized the continuity of consciousness and character with the body.

Understanding the authoritarian personality has been an important issue in the 20th century. Wilhelm Reich used some old ideas about the nervous system that were current near the beginning of the century, and Cloninger (1995) and others (Netter, et al., 1996, Ruegg, et al., 1997, Gerra, 2000), toward the end of the century, were able to incorporate the newer information about the serotonergic-dopaminergic antagonisms. In this newer view, high serotonin production causes behavioral inhibition and harm avoidance, which are traits of the authoritarian personality, while anti-authorians tend to have "novelty seeking" personalities, with high dopamine and low serotonin functions.

In the 1960s, experimenters put electrodes into a chicken's optic nerve, and when the chicken saw a checkerboard pattern, they could measure a patterned electrical activity in the nerve. Without the light stimulating the retina, the nerve was quiet. But when they gave the chicken LSD or similar chemicals, they recorded patterned electrical activity in the nerve, in the absence of external stimulation. Around the same time, other experimenters showed that retinal fatigue quickly desensitized the retina, preventing the transmission of impulses to the brain, except when the light pattern corresponded to something familiar, showing that impulses from the brain are always involved in renewing, in patterned

ways, the sensitivity of the retina.

The latter experiment shows that everyone's perception involves an outward-directed activity of the brain, and the experiments using the chemical stimulants suggested that the intensity of the outward- directed action can vary.

The inhibitory serotonergic "harm avoidance" system, and the opposing excitatory activating "novelty seeking" systems are constantly being influenced by many factors, including nutrition, hormones, environmental challenges and opportunities, social interactions, seasons, and the rhythm of night and day alternation.

Several kinds of research are now showing that the effects of the environment on the serotonergic system and its antagonists can influence every aspect of health, not just the personality.

For example, there have been suggestions that early life isolation of an animal can affect its serotonergic activity and increase its anxiety, aggression, or susceptibility to stress (Malick and Barnett, 1976, Malick, 1979, dos Santos, et al, 2010), and these effects are associated with increased risk of becoming depressed, and developing organic problems. Animals kept in darkness (or with blurring lenses) become nearsighted, as the eyeball grows longer under the influence of increased serotonin, and the eyes are protected against myopia by serotonin antagonists (George, et al., 2005). The incidence of myopia is increasing, at least in countries with industrialized economies, and is more common in females.

Migraine headaches are also increasing in incidence. By the end of the 1950s, it was widely accepted that migraine headaches and associated symptoms including nausea and visual disturbances were caused by an excess of serotonin, and antiserotonin drugs of various types were being used for treatment. In one of the early studies of the use of LSD in psychotherapy, some of the patients noticed that their chronic headaches had stopped. Cluster headaches have also responded well to LSD and similar drugs (Sewell, et al., 2006).

Women have migraines more often than men do, and they tend to occur in association with ovulation or menstruation. Estrogen inhibits monoamino oxidase, MAO, especially the A form that is most active in detoxifying serotonin, and it increases the enzymes that control the rate of serotonin synthesis. During serotonin excess, the veins and capillaries of the pia mater are engorged with blood, while circulation to the brain generally is depressed. Visual symptoms are probably produced by contriction of arterioles, while the pain is associated with engorged veins. Progesterone activates the MAO-A, and has other antiserotonin effects on blood vessels and nerves.

Recently (Shansky, et al., 2010; Figueiredo, et al., 2007), females have been found to be more susceptible to stress, and to have reduced uptake of serotonin (prolonging its effects), which increases glucocorticoids and ACTH. Kendler, et al. (2005) have found that people with reduced serotonin uptake are more susceptible to stress-induced depression.

The increase of inhibitory serotonin with stress and depression is probably biologically related to the role of serotonin in hibernation, which is an extreme example of "harm avoidance" by withdrawal. A diet high in polyunsaturated fat increases the tendency to go into hibernation, probably by increasing the brain's uptake of tryptophan.

When this is combined with an increasingly cold environment, the form of MAO that removes serotonin decreases its activity, while the form that removes norepinephrine increases its activity. The metabolite of serotonin, 5-HIAA, decreases, as the effect of serotonin increases.

In experiments to investigate the mechanism of hibernation, animals were injected with serotonin, at different environmental temperatures. In a cool environment, the serotonin caused their temperature to fall, by decreasing their heat production, and increasing their loss of heat (by causing vasodilation in the skin, "flushing"). In a hot environment, serotonin can cause the animal's temperature to rise.

Serotonin can reduce the production of energy by inhibiting mitochondrial respiratory enzymes (Medvedev, 1990, 1991), and by reduction of oxygen delivery to tissues by vasoconstriction. It also appears to interfere with the use of glucose (de Leiva, et al., 1978, Moore, et al., 2004).

The brains of people with Alzheimer's disease have a decreased ability to metabolize glucose, and high cortisol contributes to the altered glucose metabolism, and to the destruction of nerve cells. People with Cloninger's "harm avoidance" personality trait, which is closely associated with serotonin (Hansenne, et al., 1999), are more likely to develop dementia (Clément, et al., 2010). These observations are consistent with the stress-susceptibility of people with high serotonin exposure, and to the effects of cortisol on nerves and glucose-derived energy production.

Researchers in Brasil have suggested that the serotonergic system facilitates conditioned fear, while inhibiting the fight or flight reaction, and that this can protectively limit the stress response (Graeff, et al., 1996). "5HT systems reduce the impact of impending or actual aversive events. Anticipation of an aversive event is associated with anxiety and this motivates avoidance behaviour" (Deakin, 1990). In a stressful situation, the serotonergic nerves can prevent ulcers. In other contexts, though, increased serotonin can cause ulcers.

The protective, defensive reactions involving serotonin's blocking of certain types of reaction to ordinary stresses, are similar to the effects of serotonin in hibernation and in Alzheimer's disease (Mamelak, 1997; Heininger, 2000; Perry, et al., 2002). In those extreme conditions, serotonin reduces energy expenditure, eliminating all brain functions except those needed for simple survival. These parallels suggest that improving energy production, for example by providing ketones as an alternative energy source, while reducing the stress hormones, might be able to replace the defensive reactions with restorative adaptive nerve processes, preventing or reversing Alzheimer's disease.

One of the factors promoting excess cortisol production is intestinal irritation, causing absorption of endotoxin and serotonin. Fermentable fibers (including pectins and fructooligosaccharides) support the formation of bacterial toxins, and can cause animals to become anxious and aggressive. Fed to horses, some types of fiber increase the amount of serotonin circulating in the blood. Grains, beans, and other seeds contain fermentable fibers that can promote intestinal irritation.

The liver has several ways to detoxify endotoxin and serotonin, but these can fail as a result of poor nutrition and hypothyroidism.

The lung can bind and destroy any excess serotonin that reaches it. A lack of carbon dioxide makes platelets release their stored serotonin, and it probably has the same effect in the lung endothelial cells. Without being able to bind the serotonin, the enzyme (indoleamine 2,3-dioxygenase) would be unable to destroy it.

An excess of tryptophan in the diet, especially with deficiencies of other nutrients, can combine with inflammation to increase serotonin. Polyunsaturated fatty acids promote the absorption of tryptophan by the brain, and its conversion to serotonin. (A "deficiency" of polyunsaturated fat decreases the expression of the enzyme that synthesizes serotonin [McNamara, et al., 2009).

Some fruits, including bananas, pineapples, and tomatoes, contain enough serotonin to produce physiological effects in susceptible people.

Besides avoiding foods containing fermentable fibers and starches that resist quick digestion, eating fibrous foods that contain antibacterial chemicals, such as bamboo shoots or raw carrots, helps to reduce endotoxin and serotonin. Activated charcoal can absorb many toxins, including bacterial endotoxin, so it is likely to reduce serotonin absorption from the intestine. Since it can also bind or destroy vitamins, it should be used only intermittently. Frolkis, et al. (1989, 1984) found that it extended median and average lifespan of rats, beginning in old age (28 months) by 43% and 34%, respectively, when given in large quantities (equivalent to about a cup per day for humans) for ten days of each month.

The amino acid theanine, found in tea, has been reported to decrease the amount of serotonin in the brain, probably by decreasing its synthesis and increasing its degradation.

This seems to be the opposite of the processes in hibernation. Progesterone, thyroid, and niacinamide (not nicotinic acid or inositol hexanicotinate) are other safe substances that help to reduce serotonin formation, and/or accelerate its elimination. (Niacinamide seems to increase serotonin uptake.)

To provide usable energy to the over-stressed brain (and heart), R.L. Veech has advocated the use of ketones, but the pure chemicals are expensive to make. An easily available and inexpensive source of ketones (in the form of ketoacids, which can be converted to amino acids if they aren't needed for energy) is the juice extracted (with a centrifugal juicer) from raw potatoes, which also contains proteins and other nutrients. The juice can be scrambled like eggs, and is usually tolerated even by very debilitated people.

Hypothyroidism is a very common cause of increased serotonin (e.g., Henley, et al., 1998), and if the thyroid hormone is supplemented until symptoms are resolved, it's likely that the serotonin will have been normalized.

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