# Serotonin function and mechanism of antidepressant action



Neurotransmitters are chemicals located and released in the brain to allow an impulse from one nerve cell to pass to another nerve cell.

There are approximately 50 neurotransmitters identified. There are billions of nerve cells located in the brain, which do not directly touch each other. Nerve cells communicate messages by secreting neurotransmitters. Neurotransmitters can excite or inhibit neurons (nerve cells). Some common neurotransmitters are acetylcholine, norepinephrine, dopamine, serotonin and gamma aminobutyric acid (GABA).

Serotonin is a monoamine neurotransmitter. It is synthesized, from the amino acid L-tryptophan, in brain neurons and stored in vesicles. Serotonin is found in three main areas of the body: the intestinal wall; large constricted blood vessels; and the central nervous system. The most widely studied effects have been those on the central nervous system. The functions of serotonin are numerous and appear to involve control of appetite, sleep, memory and learning, temperature regulation, mood, behavior (including sexual and hallucinogenic behavior), cardiovascular function, muscle contraction, endocrine regulation, and depression. 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.

Serotonin is an inhibitory neurotransmitter which complements excitatory sympathetic systems like adrenaline and dopamine in the Central Nervous System. The physiological activity of serotonin starts from the brainstem in groups of brain cells called Raphe nucleus. Serotonin brain cells then spread

Page 3

to various regions of the central nervous system by branching out throughout the brain.

## History

In 1935, Italian Vittorio Erspamer showed that an extract from enterochromaffin cells made intestines contract. Some believed it contained adrenaline, but two years later Erspamer was able to show that it was a previously unknown amine, which he named enteramine.[4] In 1948, Maurice M. Rapport, Arda Green, and Irvine Page of the Cleveland Clinic discovered a vasoconstrictor substance in blood serum, and since it was a serum agent affecting vascular tone, they named it serotonin. In 1952 it was shown that enteramine was the same substance as serotonin, and as the broad range of physiological roles were elucidated, the abbreviation 5HT of the proper chemical name 5-hydroxytryptamine became the preferred name in the pharmacological field.

## Mechanism of action

The activity of serotonin arises in the brainstem from clusters of neurons known as the raphe nucleus. From the brain, serotonin neurons extend to virtually all parts of the central nervous system making the branching of the serotonin network the most expansive neurochemical system in the brain. The importance of this network becomes apparent when considering each serotonin neuron exerts an influence over as many as 500, 000 target neurons. Due to the widespread distribution of serotonin in the nervous system, it is not surprising that this neurotransmitter can be linked to many types of behavior. Of the chemical neurotransmitter substances, serotonin is perhaps the most implicated in the treatment of various disorders, including anxiety, depression, obsessive-compulsive disorder, schizophrenia, stroke, obesity, pain, hypertension, vascular disorders, migraine, and nausea. A major factor in the understanding of the role of 5-HT in these disorders is the recent rapid advance made in understanding the physiological role of various serotonin receptor subtypes. There are at least four populations of receptors for serotonin: 5-HT1, 5-HT2, 5-HT3, and 5-HT4. The physiological function of each receptor subtype has not been established and is currently the subject of intensive investigation.

## Effects as a neurotransmitter

Most neurotransmitters are released from tiny synaptic terminal buttons at the ends of nerve cells, but serotonin appears to be different. It is instead released freely from serotonergic varicosities into the general neuronal space, diffusing over a much larger area to activate the 5-HT receptors of nearby neurons. This reuptake can be disrupted by agents like MDMA, cocaine, tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs).

The overall action of serotonin is very complex and not entirely understood.

## **Peripheral effects**

• Cardiovascular action

The cardiovascular effects of serotonin are complex. They are variable depending on the dose injected, experimental conditions, animal species and vascular state.

• Action on vessels:

Serotonin induces either a vasoconstriction by 5-HT2 effect, in particular of renal vessels, or a vasodilation. Serotonin constricts veins and seems to induce venous thromboses and promotes platelet aggregating effect. It increases capillary permeability.

• Action on heart:

Serotonin has a positive chronotropic action by 5-HT4 receptor stimulation and could take part in the genesis of certain rhythm disorders. It has a positive inotropic effect.

• Action on blood pressure:

It is complex, according to experimental conditions, serotonin gives either hypotension, or hypertension, or no modification.

• Action on smooth muscles

Serotonin induces contractions of intestine, bronchi and uterus.

• Digestive effects:

Serotonin increases intestinal motility, probably by stimulation of 5-HT4 and 5-HT3 receptors: in human beings, injected by intravenous route, it increases duodenum and small intestine motility. This effect explains diarrhea observed in patients with carcinoid syndrome.

• Bronchial effects:

Serotonin has a bronchoconstrictive action and a serotonin aerosol induces dyspnea (difficult or labored respiration).

• Uterus effect:

Serotonin induces contractions of the uterus.

• Other actions

Researchers have also found evidence that serotonin may play a role in regulating milk production in the breast, and that a defect within the serotonin network may be one underlying cause of SIDS (sudden infant death syndrome).

• Central effects

Serotonin is involved in the regulation of sleep, mood (antidepressant action), temperature, appetite (appetite suppressant effect).

Overstimulation of 5-HT2 receptors could induce productive and negative symptoms of psychotic disorders. LSD or lysergide, agonist of 5-HT2 receptors and also of D1 and D2 dopaminergic receptors, has hallucinogenic properties.

Serotonin, thanks to its various types of presynaptic and postsynaptic receptors, modulates the activity of other transmitters. It plays a determining part in adaptation.

## Effects of Excess or Low Serotonin

Serotonin is involved in allergic and inflammatory symptoms and in certain diseases:

• Carcinoid syndrome:

The carcinoid syndrome is caused by metastatic tumors of enterochromaffin cells of the digestive tract which secrete various compounds, in particular a great quantity of serotonin. It is characterized by diarrhea, flushes (accesses of cutaneous vasodilation followed by a vasoconstriction), dyspnea and sometimes a damage to cardiac valves. The biological diagnosis of these tumors is based on the increase in serotonin concentration in blood and on the excretion of abnormal amounts of 5-hydroxy-indolacetic acid, 5-HIAA, in urines.

• Migraine:

Migraine is a disease characterized by repeated accesses of headache in which vasomotor phenomena and serotonin play a determining part. In the first prodromic phase, there is a vasoconstriction, and in the second painful phase, a vasodilation. This vasodilation is reduced by vasoconstrictive drugs.

• Myocardial ischemia:

Serotonin released from platelets seems to worsen the myocardial ischemia by vasoconstriction.

Hallucinations occur due to increased levels of Serotonin.

• Generalized anxiety disorder

People with generalized anxiety disorder (GAD) experience excessive worry that causes problems at work and in the maintenance of daily responsibilities. Evidence suggests that GAD involves several neurotransmitter systems in the brain, including norepinephrine and serotonin. Deficiencies or excessive intake of certain dietary minerals and vitamins can disrupt the level of serotonin, causing disruptions in the production or reuptake processes surrounding serotonin.

## Several drugs that affect the serotonin system

Several classes of drugs target the 5-HT system, including some antidepressants, antipsychotics, anxiolytics, antiemetics, and antimigraine drugs, as well as the psychedelic drugs and empathogens.

When Serotonin is low, certain problems with concentration and attention can be experienced. People become scatterbrained and poorly organized. It takes longer to do things because of poor planning. When Serotonin is moderately low, the following symptoms and behaviours have been observed:

- Chronic fatigue. Despite sleeping extra hours and naps, fatigue remains. There is a sense of being " worn out"
- Sleep disturbance.
- Appetite disturbance is present, usually in two types. There is a loss of appetite and subsequent weight loss or a craving for sweets and carbohydrates when the brain is trying to make more Serotonin.
- Total loss of sexual interest is present. In fact, there is loss of interest in everything, including those activities and interests that have been enjoyed in the past.
- Social withdrawal is common not answering the phone, rarely leaving the house/apartment, stop calling friends and family, and withdrawal from social events.

- Emotional sadness and frequent crying spells are common.
- Self-esteem and self-confidence are low.
- Body sensations, due to Serotonin's role as a body regulator, include hot flushes and temperature changes, headaches, and stomach distress.

## **Clinical Depression**

This is perhaps the most common mental health problem encountered in practice. One in four adults will experience clinical depression within their lifetime. Serotonin acts as an important "feel-good" neurotransmitter, sending signals that an individual is relaxed and happy. In the absence of serotonin, patients feel sad and unwell and may even experience fear, anxiety and physical discomfort. serotonin acts as an important "feel-good" neurotransmitter, sending signals that an individual is relaxed and happy. In the absence of serotonin, patients feel sad and unwell and may even experience fear, anxiety and physical discomfort.

Treatment for depression, as might be expected, involves increasing levels of Serotonin in the brain. Since the mid-eighties, medications have been available that attempt to specifically target and increase Serotonin. Known as Selective Serotonin Reuptake Inhibitors (SSRI's), these medications such as Prozac, Zoloft, and Paxil are felt to work by making more Serotonin available in the brain.

Like all neurotransmitters, we can have too much Serotonin.

Page 10

#### **Obsessive-Compulsive Disorder**

The American Academy of Family Physicians explains that one of the disorders categorized as a serotonin deficiency-related illness is obsessivecompulsive disorder. In this psychiatric condition, patients feel obsessed with certain issues, like cleanliness or order, and are therefore compelled to engage in what they perceive as related behaviors, including rigorous and repetitive cleaning or hand washing. Researchers have determined that low levels of serotonin in the brain are responsible for many cases of obsessivecompulsive disorder, and physicians prescribe pharmaceuticals that help increase brain levels of serotonin. These drugs help reduce or relieve symptoms entirely, allowing individuals with obsessive-compulsive disorder to live normal lives.

#### Serotonin Syndrome

While elevated levels of Serotonin produce a sense of well-being, bliss, and " oneness with the universe" too much Serotonin can produce a lifethreatening condition known as Serotonin Syndrome (SS). Likely to occur by accident by combining two Serotonin-increasing medications or substances. These are some of its symptoms:

- Cognitive mental confusion, hypomania, agitation, headache, coma
- Autonomic shivering, sweating, fever, hypertension, tachycardia, nausea, diarrhea
- Somatic myoclonus/clonus (muscle twitching), hyperreflexia, tremor

 Emergency medical treatment is required, utilizing medications that neutralize or block the action of Serotonin as the treatment for Serotonin Syndrome (SS).

## **Discontinuation syndrome**

Antidepressants such as SSRIs have some dependence producing effects, most notably a withdrawal syndrome. Their dependence producing properties (depending on the antidepressant) may not be as significant as other psychotropic drugs such as benzodiazepines, however, withdrawal symptoms nonetheless may be quite severe and even debilitating. SSRIs have little abuse potential, but discontinuation can produce disturbing withdrawal symptoms that may not be able to be distinguished from a reoccurrence of the original illness:

- Sexual side effects
- Cardiac side effects
- Suicide risk
- Post SSRI sexual dysfunction
- Aggression
- Permanent nuerophysiological changes
- Persistent pulmonary hypertension
- Bleeding tendencies

# **Applications of Serotonin**

# SSRIs

Selective serotonin reuptake inhibitors (SSRIs) are commonly used as first-

# line therapy to treat mood disorders due to their demonstrated efficacy,

safety, and tolerability profiles. SSRIs may play an intricate role in treating hormone-mediated disorders that disturb the guality of life for women. Selected uses of SSRIs, specifically in the treatment of hot flashes, premenstrual dysphoric disorder, and postpartum depression, are explored in this article. Data from several studies support the use of SSRIs in these conditions, and therefore, these agents have the potential to significantly improve mood, cognitive function, physical symptoms, and social functioning in patients with these disorders. In addition, SSRIs may prove to be viable alternatives to current therapies that may be contraindicated, poorly tolerated, or lack efficacy in patients with these disorders.

## **Post Traumatic Stress Syndrome**

PTSD is an anxiety disorder affecting individuals who have been exposed to a disastrous event, which may have threatened their lives or included witnessing tragic harm being afflicted. This disorder is most often related to individuals who have experienced combat. Patients are treated with an SSRI-Selective Serotonin Receptacle Inhibitors that have a calming effect on the body. The result for the patient is a calming effect on the body and reduction in the feeling of anxiety and aggression.

#### Fibromyalagia

Fibromyalgia is a disorder characterized by widespread pain of the muscles and tendons accompanied by varied tender points all over the body and general fatigue. Fibromyalgia affects more women than men and occurs in 2 percent of the population in the United States. As serotonin is a pain-fighting hormone, it is frequently used to treat fibromyalgia. Many medical

professionals agree fibromyalgia is caused by low levels of serotonin. Besides taking supplements, serotonin can be taken from natural sources of tryptophan. Tryptophan is an amino acid that aids in the body's production of serotonin and is found in soy, turkey, chicken, halibut, beans and cheddar cheese.

## **General Stress**

Serotonin's mood regulating neurotransmitters help alleviate stress in sufferers. People suffering from chronic stress benefit from supplementing their regular diet with serotonin, or tryptophan to increase its production. In some cases, using lavender can induce feelings of calm and happiness. Known as a feel good hormone, serotonin is actually lowered by high levels of stress and therefore must be added back.

Ways to increase serotonin levels: Eat healthy

- Free Range Turkey Tryptophan is an essential amino acid that is present, in different amounts, in all protein foods. This amino acid is the building block for the neurotransmitter serotonin.
- 2. Flaxseed/ Flaxseed oil As well as being great for fat loss, flaxseeds are great foods that raise serotonin levels because they contain both tryptophan and high levels of omega 3 fatty acids. 60 percent of the brain is made of structural fats, and omega 3 fatty acids make up a large proportion of brain nerve cells.
- 3. Wild Fish and Sea food = Fatty fish like wild salmon, sardines and herring are rich in oils containing the essential fats EPA and DHA. Both

of these long chain fats have been shown in trials both to smooth the mood swings of bipolar disorder and to ease regular depression.

- 4. Whey protein = Whey protein has gained a greater and greater reputation as a super-food over recent years. Whey has been shown to regulate appetite, improve insulin sensitivity and blood sugar levels, bolster the immune system and has been shown to be the ideal protein source to use around workout time.
- 5. Bananas
- 6. High quality Eggs
- 7. Sour Cherries
- 8. Free Range Beef
- 9. Dark Chocolate Cocoa is well known to increase serotonin levels in the brain the trick is not to eat so much that you crash a few hours later. Similarly most chocolate is clearly high in sugar and will spike blood sugar levels causing serotonin levels to plummet when your blood sugar crashes.