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Mini Review Article

A Mini Review of Serotonin and Its Receptors

Mohammadreza Zarindast[1], Mohammad Nasehi[1], Mohammadjavad Hoseinpourfard[*1,2]

Abstract

Serotonin is one of the most important Neurotransmitter and made up of aminoacids. Including L-tryptophan, only the L-isomer is used in protein synthesis and can pass across the blood-brain. Serotonin concentration in organisms is among the lowest of all amino acids and it has relatively low tissue. In this paper a brief review has done pertaining to history of serotonin, and potential cognitive aspects including CNS and PNS modulation of serotonin. Major focus of paper is to review subtypes of serotonin receptors. It's gathered up-to-date information about other pharmacologic agents such as agonist and antagonist of serotonin.

1. Cognitive Neuroscience Department, Institute of Cognitive Sciences Studies, Tehran, Iran
2. Health Management Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

***Corresponding Author**
Mohammadjavad Hoseinpourfard, Health Management Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
E-mail: hpf.javad@gmail.com

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Introduction

What is the serotonin?

Serotonin or 5-hydroxytryptamine (5-HT) is a neurotransmitter. Serotonin is primarily found in the gastrointestinal (GI) tract, platelets, and in the central nervous system (CNS) of animals and in all bilateral animals [1]. It is popularly thought to be a contributor to feelings of well-being and happiness [2].

Where is serotonin in the human body?

Serotonin Pathway

Where does serotonin produce and release?

Serotonin is secreted by nuclei that originate in the median raphe of the brain stem and project to many brain and spinal cord areas, especially to the dorsal horns of the spinal cord and to the hypothalamus [3].

Serotonin secreted from the enterochromaffin cells eventually finds its way out of tissues into the blood [3]. It is actively taken up by blood platelets which store it [3]. When the platelets bind to a clot, they disgorge serotonin, where it serves as a vasoconstrictor and helps to regulate hemostasis and blood clotting [4, 5]. Serotonin also performs like as a growth factor for some types of cells which may give it a role in wound healing [6].

Serotonin receptors

The 1987 edition of Psychopharmacology described only four populations of 5-HT receptors: 5-HT1A, 5-HT1B, 5-HT1C, and 5-HT2C. The 1995 edition appended the 5-HT2A to its report. After that the most of the currently known 5-HT receptor populations were identified in the recent years. The last several years have witnessed an extraordinary number of publications (about 3,000 per year) in the 5-HT area; studies have reported the cloning of several receptor populations previously known but not yet cloned (e.g., 5-HT4, and 5-HT5). Nowadays occur development of novel agonists and antagonists with greater subpopulation selectivity, additional molecular biological studies (e.g., site-directed mutagenesis), and additional pharmacological and clinical studies. Evidence continues to mount in support of important roles for 5-HT receptors in various neuropsychiatric disorders. Anxiety, depression, schizophrenia, migraine, and drug abuse are at the top of the list. 5-HT receptors may also play important roles in appetite control, aggression, sexual behavior, and cardiovascular disorders. As the list of 5-HT receptors grows, the number of serotonergic agents has also grown. Today, we have many more selective, or semi-selective, agents than ever before. Knowledge of amino acid sequence data has allowed the construction of hypothetical three-dimensional graphics models of various populations of 5-HT receptors. Once appropriate models have been identified, it may be possible to rationally design novel and highly-selective serotonergic agents [4]. Table1. Show this progressive.

Mechanisms: Function and Effects

Functions of serotonin

Serotonin acts as a both exciter and inhibitor pertaining to location and its tasks. (Table1) It is an inhibitor of pain by its pathways in the spinal cord, and an inhibitor action in the higher regions of the nervous system. It is believed to help control the mood of the person, perhaps even to cause sleep [3].

It seems that serotonin in hypothalamus release the Enkephaline so it intervenes in biological rewards [5, 6].
Serotonin is particularly associated with punishment, rather than reward-related processing, and that individual sensitivity to punishment-related information and tryptophan depletion varies with genotype [7].
It mediates gut movements and the animals' perceptions of resource availability [8].
In the simplest animals, resources are equivalent with food, but in advanced animals, such as arthropods and vertebrates, resources also can mean social dominance. In response to the perceived abundance or scarcity of resources, an animal's growth, reproduction or mood may be elevated or lowered [9].
Serotonin contributes in many functions include the regulation of mood, appetite, and sleep [10].
Serotonin also has some cognitive functions, including memory and learning [6]. (see also Table1)

The Serotonin Affective Agents: Its agonists and antagonists

The combination of ondansetron (a 5-HT3 antagonist) and naltrexone (a mu opioid antagonist) appears to act synergistically at improving the drinking outcomes of early onset alcoholics (EOA) [11].
As ondansetron, a 5-HT3 receptor antagonist and modulator of cortico-mesolimbic dopamine function, has been shown to reduce some of the rewarding effects of d-amphetamine in animal and human laboratory studies [12].
the prototypic 5-HT3 receptor antagonist, ondansetron does not produce acute psychoactive effects when infused at doses of up to 40 mg and has no rewarding effects with this regime [13].
The propensity for naltrexone (a mu opioid antagonist) to reduce alcohol's rewarding effects and drinking in humans is greatest in individuals with high familial loading. Predicated on the added knowledge that 5-HT3 receptors may themselves mediate alcohol reward via activation of the endogenous opioid system [14].
Some study try to test whether the inhibition of serotonin neural activity by the local application of the 5-HT (1A) receptor agonist 8-hydroxy-2-(di-n-propylamino) tetralin in the dorsal raphe nucleus impairs rats' tolerance for delayed rewards. Most of them emphasize that the activity of serotonin neurons in the midbrain dorsal raphe nucleus increased when a task is doing that required to wait for delayed rewards. Although the causal relationship between serotonin neural activity and the tolerance for the delayed reward has remained unclear yet [15].
Agonists and Antagonists of serotonin
Fluvoxamine is a very potent SSRI compound and 5-HT3 antagonist as well as. On the other hand, depression has a high rate of co-occurrence with alcoholism and SSRIs are very potent antidepressant compounds, justifying the use of such agents in alcoholic subjects. Design: Subjects were recruited from the inpatients units and psychiatric outpatient department of the Jebel Psychiatric Hospital.[16].
Citalopram also decreased neural responses to the aversive stimuli conditions in key "punishment" areas such as the lateral orbitofrontal cortex. Reboxetine produced a similar, although weaker effect [17].

Selective agonists

5-HT1A agonists

Azapirones such as buspirone, gepirone, and tandospirone are 5-HT1A agonists marketed primarily as anxiolytics, but also recently as antidepressants [18].

5-HT1B agonists

Triptans such as sumatriptan, rizatriptan, and naratriptan are 5-HT1B receptor agonists that are used to abort migraine and cluster headache attacks [18].

5-HT1D agonists

Triptans are agonists at the 5-HT1D receptor which contributes to their antimigraine effect caused by vasoconstriction of blood vessels in the brain [18].

5-HT1F agonists

LY-334,370 was a selective 5-HT1F agonist that was being developed by Eli Lilly and Company for the treatment of migraine and cluster headaches. Development was halted however due to toxicity detected in animal test subjects. Lasmiditan has successfully completed Phase II clinical trials in early 2010 [18].

5-HT2A agonists

Psychedelic drugs like LSD, mescaline, and 2C-B, act as 5-HT2A agonists. Their action at this receptor is responsible for their "psychedelic" effects. Some of these drugs act as agonists for other 5HT receptor subtypes. Not all 5-HT2A agonists are psychoactive [19].

5-HT2C agonists

Lorcaserin is a thermogenic and anorectic weight-loss drug which acts as a selective 5-HT2C agonist [18].

5-HT4 agonists

Cisapride and Tegaserod are 5-HT4 partial receptor agonist that were used to treat disorders of gastrointestinal motility. Prucalopride is a highly selective 5-HT4 receptor agonist that can be used to treat certain disorders of gastrointestinal motility. Other 5-HT4 agonists have shown potential to be nootropic type drugs via promoting acetylcholine release.

5-HT7 agonists

AS-19 (drug) is a 5-HT7 receptor agonist that has been used only in research.
Nonselective agonist
Fenfluramine is a serotonin agonist [20].
Psilocin and DMT are serotonin analogs found in certain plants or mushrooms.

Antagonists

5-HT3 antagonists

Ondansetron, a 5-HT3 receptor antagonist and modulator of cortico-mesolimbic dopamine function [12].
Serotonin selective reuptake inhibitors (SSRIs) working in alcoholism, are at least antagonists of 5-HT3 receptor [16].
Fluvoxamine is a very potent SSRI compound and 5-HT3 antagonist as well as [16].

Conclusion

Many kinds of research have done in serotonin through the recent decades but it has seen a behavioral studies by fMRI can be interpreted evidence from neuroimaging of serotonin effects. It can represented by differential activation in serotonergic brain pathway and acceleration of reaction times. This can help to understand cognitive effects of

serotonin and the potential aspects in cognitive neuroscience.

In the present overview, we will focus on the composition and mechanism of serotonin. Unfortunately, length restrictions preclude a discussion of many important papers and issues in the field, and we apologize for the many omissions I am bound to commit. Despite significant progress, much about serotonin remains unknown, and we will at the end of each section briefly discuss open questions and major challenges.

Table1. Serotonin Receptors: What, Where and How

What		**Where**	**How**		
Type	Subtype(year)	Pathway	Potential	Function	Mechanism
5-HT$_1$	A (1987) B (1992) D (1991) F (1992) E (1993)	Blood Vessels CNS	Inhibitory	Addiction(21-23) Aggression(24) Anxiety(25-30) Appetite(31) Autoreceptor Blood Pressure(32, 33) Cardiovascular Function(34) Emesis(35) Heart Rate(32, 33) Impulsivity(36) Learning(37) Locomotion(38) Memory(37, 39) Mood(28, 40) Nausea(35) Nociception(41) Penile Erection(42) Pupil Dilation(43) Respiration(44) Sexual Behavior(45) Sleep(46) Sociability(47) Thermoregulation(48) Vasoconstriction(49)	Decreasing cellular levels of cAMP.
5-HT$_2$	A (1988) B (1992) C (1988)	Blood Vessels CNS GI Tract Platelets PNS Smooth Muscle	Excitatory	Addiction(potentially modulating)(50) Anxiety(51-56) Appetite(57) Cardiovascular Function Cognition GI Motility(58, 59) Imagination Learning Locomotion Memory Mood[55][56] Penile Erection(60, 61) Perception Sexual Behavior(62) Sleep(63, 64) Thermoregulation(65) Vasoconstriction(66)	Increasing cellular levels of IP_3 and DAG.
5-HT$_3$	A (1993) B (1993) C (1993) D (1993) E (1993)	CNS GI Tract PNS	Excitatory	Addiction Anxiety Emesis GI Motility Learning(67) Memory(67) Nausea	Depolarizing plasma membrane.
5-HT$_4$	UNIQUE(1995)	CNS GI Tract PNS	Excitatory	Anxiety(68, 69) Appetite[(70, 71) GI Motility Learning(72, 73) Memory(72-74) Mood(75, 76) Respiration(44, 77)	Increasing cellular levels of cAMP.

What		Where	How		
5-HT$_5$	A (1994) B (1993)	CNS	Inhibitory	Autoreceptor Locomotion(78) Sleep(79)	Decreasing cellular levels of cAMP.
5-HT$_6$	UNIQUE(1993)	CNS	Excitatory	Anxiety(80, 81) Cognition(82) Learning(83) Memory(83) Mood(81, 84)	Increasing cellular levels of cAMP.
5-HT$_7$	UNIQUE(1993)	Blood Vessels CNS GI Tract	Excitatory	Anxiety(85, 86) Autoreceptor Memory(87, 88) Mood(85, 86) Respiration(89, 90) Sleep(85, 89, 90) Thermoregulation Vasoconstriction	Increasing cellular levels of cAMP.

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