Pathophysiology of serotonin receptors in psychiatric disorders

Essay

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Introduction

Serotonin is a monoamine neurotransmitter. It is extensively found in the gastrointestinal tract, and about 80 to 90 % of the human body's total serotonin is located in the enterochromaffin cells of the gut, where it is regulates intestinal movements. The remainder is synthesized in serotonergic neurons in the central nervous system mainly raphe nucleus , where it has various functions, including control of appetite, mood and anger. Serotonin is found not only in humans and animals, but also in fungi and plants, including fruits and vegetables. (**Berger et al; 2009**).

Serotonin was originally discovered in the late 1940s. Isolated and named in 1948, serotonin was initially identified as a vasoconstrictor substance in blood serum – hence serotonin, **a serum agent affecting vascular tone**. This agent was later chemically identified as 5-hydroxytryptamine (5-HT) by **Rapport,1948** and as the broad range of physiological roles were elucidated, 5-HT became the preferred name in the pharmacological field (**Rapport et al; 1948**).

Distribution of 5-HT receptors in the human brain may be imaged with the positron emission tomography (PET) using the radioligand [11 C]WAY- 100,635.

Labeled with tritium, WAY-100,635 may also be used in autoradiography. (**Price et al ; 2002**).

The pathway for the synthesis of serotonin is from tryptophan. In humans serotonin is synthesized from the amino acid L-tryptophan by a short metabolic pathway consisting of two enzymes: tryptophan hydroxylase (TPH) and amino acid decarboxylase (DDC). TPH has been shown to exist in two forms: TPH1; found in several tissues, and TPH2; which is found in brain. Serotonin taken orally does not pass into the serotonergic pathways of the central nervous system because it does not cross the blood-brain barrier. However, tryptophan and its metabolite 5-hydroxytryptophan (5-HTP), from which serotonin is synthesized, can cross the blood-brain barrier. These agents are available as dietary supplements and may be effective serotonergic agents. The product of serotonin breakdown is 5-Hydroxyindoleacetic acid (5 HIAA) , which is excreted in the urine.(**Walther et al; 2003**).

The neurons of the raphe nuclei are the principal source of 5-HT release in the brain.The raphe nuclei are neurons grouped into about nine pairs and distributed along the entire length of the brainstem centered around the reticular formation . Axons from the neurons of the raphe

nuclei form a neurotransmitter system, reaching large areas of the brain. Axons of neurons in the caudal raphe nuclei terminate in the following locations: Deep cerebellar nuclei, Cerebellar cortex , Spinal cord On the other hand, axons of neurons in the rostral raphe nuclei terminate in Thalamus ,Striatum ,Hypothalamus ,Nucleus accumbens ,Neocortex ,Cingulate gyrus ,Cingulum , Hippocampus and Amygdala. Thus, activation of this serotonin system has effects on large areas of the brain. (**Frazer and Hensler, 1999**).

The serotonin (5-hydroxytryptamine, 5-HT) receptors are a group of G protein-coupled receptors (GPCRs) and ligand-gated ion channels (LGICs) found in the central and peripheral nervous system. They mediate both excitatory and inhibitory neurotransmission. The serotonin receptors are activated by the neurotransmitter serotonin, which acts as their endogenous ligand. The serotonin receptors modulate the release of many neurotransmitters, including glutamate, GABA, dopamine, epinephrine/norepinephrine, and acetylcholine, as well as many hormones, including oxytocin, prolactin, vasopressin, cortisol, corticosterone, corticotropin, and substance P, among others. The serotonin receptors influence various

biological and neurological processes such as aggression, anxiety, appetite, cognition, learning, memory, mood, nausea, sleep, and thermoregulation. The serotonin receptors are the target of a variety of pharmaceutical and illicit drugs, including many antidepressants, antipsychotics, anorectics, antiemetics, gastroprokinetic agents, hallucinogens, and entactogens. (**Nichols and Nichols 2008**).

Different types of serotonin receptors include two groups; Excitatory group : as 5- HT2 which is protein coupled, Increasing cellular levels of IP 3 and DAG; 5-HT3 Ligand-gated Na + and K + cation channel, Depolarizing plasma membrane; 5-HT4 , 5-HT6 and 5-HT7 each of them protein coupled, Increasing cellular levels of cAMP. Inhibitory group :as 5- HT1 and 5- HT5 each of them protein coupled, Decreasing cellular levels of cAMP. Within these general classes of serotonin receptors a number of specific types (subtypes) are characterized : 5-HT1 subtypes (a,b,d,e,f) ; 5-HT2 subtypes (a,b,c) ; 5-HT3 subtypes (a,b); 5-HT5 subtypes (a,b). **(Wesolowska,2002).**

For example,5-HT1a receptors that exist in cerebral cortex, hippocampus, raphe nucelus and basal ganglia, triggers the inhibition of norepinephrine release in locus

coeruleus, increase dopamine release in the medial prefrontal cortex and hippocampus, impair cognition, learning and memory by inhibiting ACH release, it is also involved in decreasing aggression and food intake , increased impulsivity ,facilitation of sexual behavior and prolongation of REM sleep. **(Müller et al ;2007).** Agonists of 5-HT1a receptor like buspirone are effective in relieving anxiety and depression ,On the other, hand . Antagonists as lecozotan are used in treatments of Alzheimer's disease. **(Bantick et al ; 2005).**

5-HT2c receptors which exist in scattered areas of CNS and choroid plexus , cause anxiety ,depression and compulsive behaviors , also mediate the release of dopamine in response to many drugs as amphetamine. Agonists of 5-HT2c lead to hypolocomotor effect and anorexic behavior, yet ,5-HT2c antagonists increase food consumption. It is responsible for many side effects caused by SSRI medications. **(Esposito, 2006).**

5-HT3 receptors that exist in cortical limbic areas , peripheral ganglia and nerves (superior cervical ganglion and vagus nerve) and substantia gelatinosa of the spinal cord, facilitate the release of substance P, ACh and DA,

modulate nociceptive mechanism, also induce emesis and anxiety. Thus, 5-HT3 receptor antagonists used as anxiolytic , antidepressant and antiemetic. **(Rang, 2003).**

5-HT5a receptors are found in raphe nuclei, suprachiasmatic nucleus (SCN),cerebral cortex and hippocampus ,they regulate intracellular Ca^{2+} mobilization,control of circadian rhythms, mood and cognitive function ,5-HT5a receptor-selective ligands as Valerenic acid could be used in treatment of schizophrenia and unipolar depression. **(Thomas, 2006).**

It worth mentioning , Serotonin acts as a growth factor and although brain serotonin is not essential for viability, its ablation causes impairments such as growth retardation;50% mortality in the first four weeks of postnatal life, and effects on various physiological and behavioral pathway. **(Alenina et al; 2009).**

Chapter 1
Serotonin

Serotonin or 5-Hydroxytryptamine (5-HT) is a monoamine neurotransmitter. Biochemically derived from tryptophan, and primarily found in the gastrointestinal (GI) tract, platelets, and in the central nervous system (CNS) of humans and animals. Approximately 80 % of the human body's total serotonin is located in the enterochromaffin cells in the gut, where it is used to regulate intestinal movements however selective serotonin reuptake inhibitors (SSRI) has GIT side effects **(Berger et al, 2009).** Serotonin is not only found in animals but also in fungi and plants **(Kang et al, 2009).**

During human embryonic development, serotonin is one of the first neurotransmitters to appear, with detectable CNS neurons by 5 weeks of gestation **(Sundstrom et al, 1993)**.

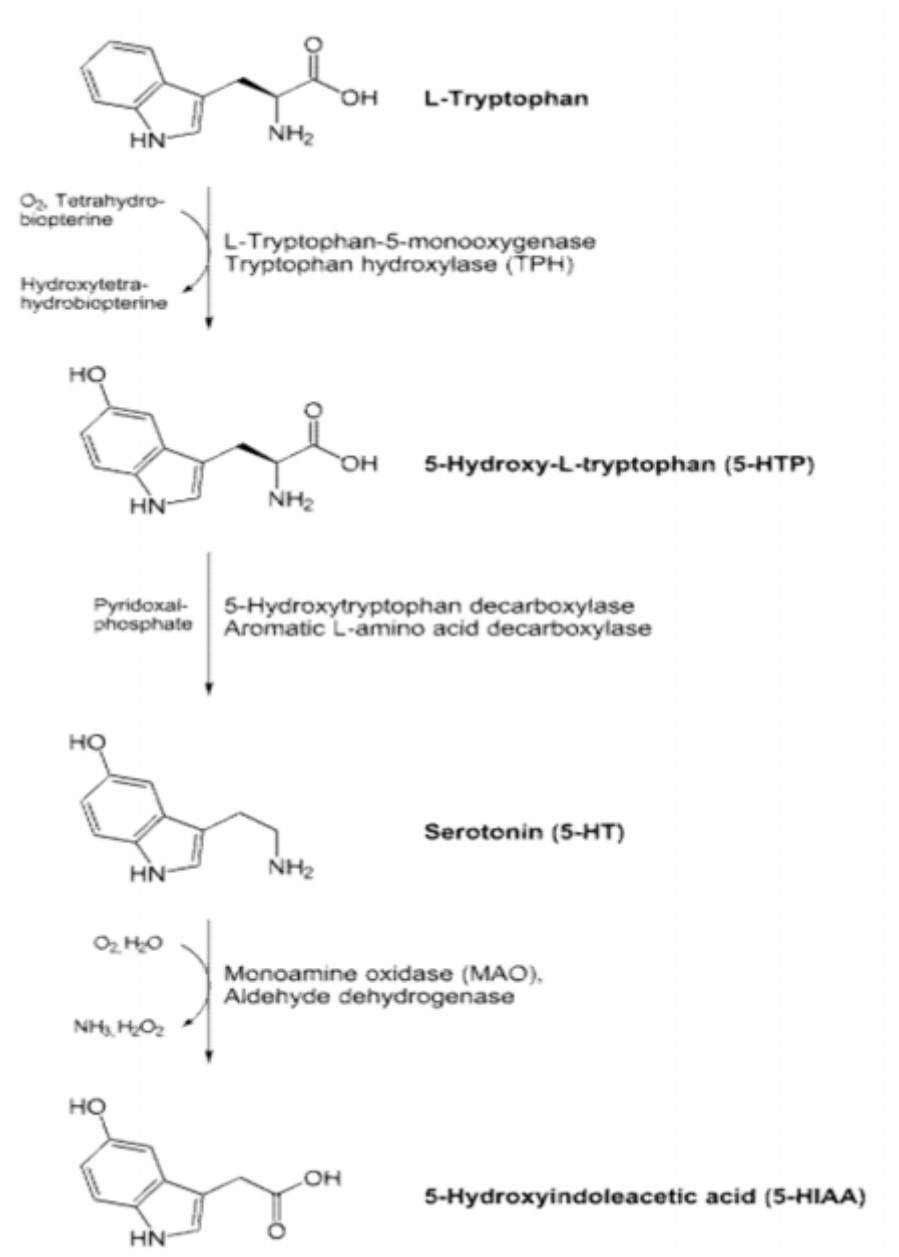
An important role for serotonin is also a trophic factor during development , it has been found in neural crest cells ,heart and in CNS development **(Gustafsson et al, 2005).**

Biosynthesis of serotonin

In humans, serotonin is synthesized from the amino acid L-tryptophan by a short metabolic pathway consisting of two enzymes: tryptophan hydroxylase (TPH) and amino acid decarboxylase (DDC). The TPH-mediated reaction is the rate-limiting step in the pathway(as showen in fig.**1**) .TPH has been shown to exist in two forms: TPH1, found in several tissues, and TPH2, which is a brain-specific isoform **.** There is evidence that genetic polymorphisms in both these subtypes influence susceptibility to anxiety and depression in humans **(Walther et al, 2003).**

Figure (1)

Synthesis of serotonin from tryptophan **(Walther et al, 2003)**



The two molecules involved in regulating levels of serotonin in the brain are the serotonin transporter (5HTT) which transports serotonin from the extracellular space, and monoamine oxidase A (MAOA), the key enzyme responsible for degrading serotonin **(Newman et al, 2005).**

The serotonin transporter (5-HTT) gene regulates serotonin which found in a very low amounts in people diagnosed with depression compared to other people. Serotonin helps in the modulation of **anger**, **appetite**, **sexuality**, **sleep and mood**. People with depression often have impaired 5-HTT genes. There are two forms of the 5-HTT gene and everyone has the two form , There is a long form of 5-HTT and a short form of 5-HTT. Research shows that people with both 5-HTT genes being the long form are less likely to become depressed while people with one short and one long or two short forms are more likely to develop depression **(Walther et al, 2003).**

Serotonin has been shown to be an important factor in regulating the neuro-development of brain regions critical for emotional processing. In animal models, dysregulation of serotonin during these early neuro-developmental stages have revealed behavioural outcomes

with important parallels to human neuropsychiatric disorders **(Niklas and Oreland, 2010).**

In the sense that genetic factors regulating serotonin levels result in developmental alterations to specific neurocircuits involved in emotional processing, causing different responses to external stimuli, which has been observed to have an effect on serotonergic neurotransmission, further affecting on-going neuronal development. Future studies on the causal mechanisms behind the role of serotonin during brain development will hopefully provide knowledge, not only of how the neurocircuits involved in emotional processing work, but also give an improved understanding of the biological aetiology for neuropsychiatric disorders. **(Caspi et al, 2002).**

Synthesis

The neurons of the raphe nuclei are the principal source of 5-HT release in the brain.The raphe nuclei are neurons grouped into about nine pairs and distributed along the entire length of the brainstem centered around the reticular formation . Axons from the neurons of the raphe nuclei form a neurotransmitter system, reaching large

areas of the brain. Axons of neurons in the caudal raphe nuclei terminate in the following locations: **deep cerebellar nuclei , Cerebellar cortex and Spinal cord** On the other hand, axons of neurons in the rostral raphe nuclei terminate in **Thalamus ,Striatum ,Hypothalamus ,Nucleus accumbens ,Neocortex ,Cingulate gyrus,Cingulum , Hippocampus and Amygdala**. Thus, activation of this serotonin system has effects on large areas of the brain (**Frazer and Hensler, 1999).**

Metabolism

Serotonergic action is terminated primarily via uptake of 5-HT from the synapse. This is through the specific monoamine transporter for 5-HT, SERT, on the presynaptic neuron. Various agents can inhibit 5-HT reuptake including Methylenedioxymethamphetamine (MDMA) or (ecstasy), amphetamine, cocaine, dextromethorphan (an antitussive), tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Interestingly, also there is a newly discovered monoamine transporter, known as plasma monoamine transporter (PMAT), may account for "a significant percentage of 5-HT clearance" **(Caspi et al, 2003).**