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Biomedical Significance of Tryptamine: A Review

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Abstract

Tryptamine the important psychotropic drug having indole ring has wider biological and pharmaceutical significance. The focus is to see the relevant and recent achievements as neurotransmitter and neuromodulator, vasoconstrictor and vasodilator, antimicrobial and antibacterial, antioxidant and antifungal agents. Tryptamine and its natural and synthetic derivative have been reported for the variety of biological significance in the above mentioned area. This review covers all these aspects in a comprehensive way.

Keywords: Tryptamine; Neurotransmitter; Neuromodulator; Psychotropic drug

Introduction

Tryptamine, a monoamine alkaloid containing an indole ring structure is derived by the decarboxylation of amino acid tryptophan [1]. The indole ring is the important nucleus of many complex natural products having importance in drug discovery and a variety of naturally occurring, synthetic and semi-synthetic drugs are based on tryptamine skeleton. Tryptamine is found in fungi, plants and animals [2]. Tryptamine structural distinction is in approximation to the neurotransmitter serotonin and as hallucinogens and well-known drugs in these classes are DMT etc. Its importance as the neurotransmitter, neuromodulator and as psychedelic drugs is well known because of its presence in mammalian brain in trace amount approximately 3.5 mol/g [3, 4].

Tryptamine analogues produced by its synthetic modification play a vital role in human life due to the introduction of biologically active functionalities in its nucleus which may cause alterations of the physical and mental status of human brain. A variety of neuroactive compounds ranging from toxic substances to anti-migraine drugs, such as sumatriptan, rizatriptan and zolmitriptan are produced by substitutions on the indole ring at C-2 and nitrogen of its side chain [5]. For producing psychotropic phenomena, a trace amount of tryptamine is required due to its intoxications and fatalities for several reasons.

Biomedical Significance of Tryptamine

Plants containing tryptamine

In plants tryptamine in trace amount acts as a promising stage to the plant hormone indole-3-acetic acid in one biosynthetic pathway. Many Acacia species contains the list of psychoactive alkaloids and among one of these is tryptamine present in elevated level. Tryptamine derivative DMT (N, N-dimethyltryptamine) (I) is the active constituent for the hallucinogenic effect of brew known as the "vine of the souls" i.e Ayahuasca [6, 7].

Traditionally this drink is used in indigenous amazonian tribes in religious ceremonies as well for therapeutic purposes in northern South America for the effective treatment of abuse disorders and some physical maladies [8]. Ayahuasca, the most common tea with the considerable amount of DMT have ethnomedicine applications and many other plants are also the source of DMT [9]. The most common hallucinogenic fungi contains derivatives of tryptamine are the "magic mushrooms" which belongs to Psilocybecubens species comprising psilocybin (4-phosphoryloxy-N, N-dimethyltryptamine) (XI) and psilocin (4-hydroxy-N, N-dimethyltryptamine) (X) have well-known psychotropic effects [6]. Psilocybin and psilocin have (lysergic acid diethylamide) LSD-like properties and produce changes in perception and behavior [10].

Tryptamine Derivatives and Their Biomedical Significance

Natural derivative

There is the good number of naturally occurring tryptamines occurring in plants, animals. Serotonin the important neurotransmitter increases serotonergic activity of human brain and melatonin a hormone concerned to maintain the sleep-wake cycles are important natural derivative of tryptamine. Serotonin (5-hydroxytryptamine, 5-HT) (II), the important signaling hormones involved in central nervous system regulation and harmonization of many processes such as temperature regulation, memory, sleep, cognition and behavior etc. [11]. Melatonin (N-acetyl-5-methoxytrypatmine) (III), rhythm and regulates diverse physiological processes through the secretion of pineal gland and this pineal-produced melatonin acts mostly as an endocrine substance. A number of functions of extrapineal-derived melatonin as endocrine, autocrine or paracrine substance as well as regulation of many G1 function such as proliferation of epithelium, water and ion transport, acid secretion, motility and immune system [12].

Synthetic derivative

The design and synthesis of highly selective sumatriptan (IV), [13] drug has resulted through the study and classification of 5-

hydroxytryptamine receptors for migraine treatment. Similarly ondansetron (VII) [14] and alosetron (VIII) [15] synthesized through these studies for nausea and vomiting suppression caused by cancer chemotherapy and radiotherapy and for irritable bowel syndrome treatment respectively [16].

The tryptamine derivative α-methyltryptamine (V) has multidimensional functions (Table 1) such as antidepressant, powerful psychedelic drug, stimulant and monoamine oxidase inhibitor etc. Similarly, it's N, N-Dimethyltryptamine (I) analogue preparation by ancient and modern South American cultures as a hallucinogenic indole alkaloid that occurs naturally in a variety of plants [17]. Securinine (TPS) derived tryptamine (IX) derivative belongs to Euphorbiaceae family has found antioxidant along with mito and cytoprotective activities [18].

Halogen derivatives

In the field of radiopharmaceuticals production for nuclear medicine and positron emission topography (PET), the introduction of 18F, 79Br, 81Br and 131I by replacement of hydrogen had played a vital role in enhancing the biological significance of tryptamine [19].

Through investigation of halogen metabolism, the potential radiopharmaceutical 18F-tryptamine is the subject of essential research in nuclear medicine because of its promising effect in Parkinson, Alzheimer and Schizophrenia diseases for abnormal brain stress monitoring [20].

Tryptamine as neurotransmitter

The studies shows that enzymatic decarboxylation of amino acids leads to alkaloids such as L-ADDC enzyme found in serum of various animals and humans is an effective catalyst for tryptamine production as well as pyridoxal phosphate (PLP) distributed in mammalian tissues responsible for the production of serotinine and melatonin [21]. The regional distribution in both striatum and hypothalamus of 5-hydroxytryptamine a well-known neurotransmitter helps in regulation of alcoholism in humans as well as mood, sleep and anxiety in mammals [22]. The renowned 5-HT biogenic amine as neurotransmitter to regulate human CNS such as mood-anxiety, aggressiveness, impulsivity, cognition, feeding behaviours and body temperature also contribute in modulation of peripheral activities such as in the gut function, the immune and inflammatory responses, blood stem cells differentiation and hemodynamic functions [23].

The alteration of 5-HT transmission has resulted in autism and cognitive deficit, mood-affective disorders [24], obesity and other syndromes with peripheral symptoms such as chronic fatigue syndrome and irritable bowel syndrome (IBS) etc. [25]. The scavenging properties of circadian regulators, N-acetyl-5-HT (NAS) and melatonin (MLT) is due to indoleamines in 5-HT moiety and through "kynurenine shunt" a number of molecules produce in vertebrates and humans, are involved in inflammation, excitatory neurotransmission, immune response and many other functions [26].

Tryptamine as neuromodulator

Neuromodulator function to attenuate or amplify information at synaptic junctions transferred by neurotransmitter and central effects of 5HT can be modified by tryptamine in both positive and negative direction. Similarly in mammalian CNS, tryptamine and its derivatives such as dimethyltryptamine so-called "trace amines" act as neuromodulator [27]. Neuropsychiatric manifestations arises due to the disturbance in synthesis and metabolism of tryptamine and urinary output of tryptamine is correlated with increasing severity of psychosis as Schizophrenic, Parkinsonion and depressed patients has disturbed urinary output of tryptamine [28].

Tryptamine as vasoconstrictor

Tryptamine, a trace indirect sympathomimetic amine and subtype of vascular 5-HT like receptors are not consistently dispersed over cardiovascular system [29]. By vasoconstriction, tryptamine enhances blood pressure because of noradrenaline discharge from sympathetic neurons [30]. Tryptamine correlate with 5-HT receptors due to its structural resemblance [30], produced vasoconstrictor responses in mmole range as in rabbit, narrowing of aorta occur due to undeviating in cooperation of 5-HT receptors and α-adrenoceptors [31]. Sumatriptan, unique receptor agonist similar to 5-HT also generate vasoconstrictor responses, however these responses are limited to definite blood vessels *in vitro* and restricted to the cerebral vascular beds *in vivo* [32]. As compared to the blood and urine the concentration of tryptamine is higher in human brain and its level goes up after tryptamine rich food is taken in diet [33]. Vasocostrictor responses induced by tryptamine can be terminating by 5-HT2A receptor antagonists, ritanserin and ketanserin [34].

Tryptamine as vasodilator

A tryptamine analogue 5-CT (5-Carboxamidotryptamine) (VI) has a powerful vasodilator effect *in vivo* and vitro studies due to its undeviating act on vascular smooth muscle [35]. However in specific vascular beds, 5-CT has been revealed to generate vasoconstrictor responses [36]. In diverse vascular regions of a variety of species, such as dogs [37] rabbit, pig, [38] monkey [39] and neonatal porcine vena cava [40]. 5-HT7 receptors have been revealed to intercede vasodilatation [41]. Increase of perfusion pressure through phenylephrine infusion results in a marked vasodilator response when tryptamine was tested in the presence of ritanserin in mesenteric vascular beds [42]. The trace amines i.e tyramine and β-PEA (β-phenylethylamine) show vasodilator response under perfusion pressure similar to tryptamine due to the activation of TAARs (trace amine-associated receptors) and this affect is eliminated by the action of L-NAME (NG-nitro-L-arginine methyl ester) [30].

Discussion

Antimicrobial, anti-oxidant and antibacterial activity of tryptamine

Hetrocyclic compound have a lot of importance in the field of pharmaceuticals and industries. Tryptamine derivatives show [43-48] significant properties such as anti-oxidant, anti-inflammatory [47], antibacterial activity [48]. Tryptamines have an indole ring structure and antimicrobial activity is due to presence of pyrrolidine ring [44]. According to Chinese academy of science shanghai, anti-viral activity against hepatitis B virus shown by series of tryptamine derivatives. Many tryptamine derivatives show antimicrobial and antibacterial activities especially tryptamine based sulfonamide-compounds (XII) widely used as antibacterial and antimicrobial agents [45].

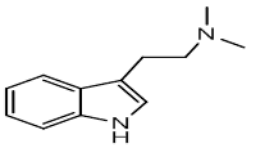
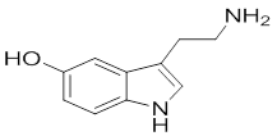
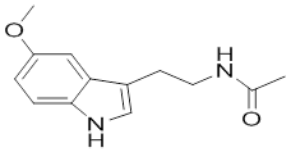
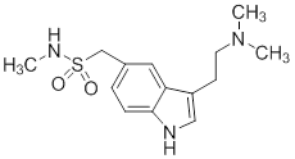
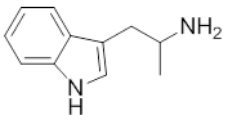
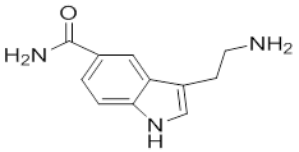
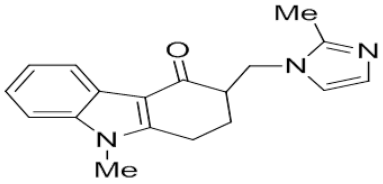
Moreover, doubly phenylated tryptamine also shows anti-microbial activity [46]. Reactive oxygen species (ROS) production can also cause a range of chronic health troubles such as cancer, ageing, Parkinson's

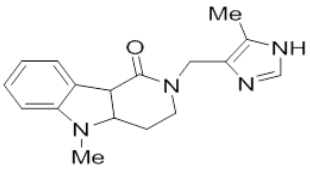
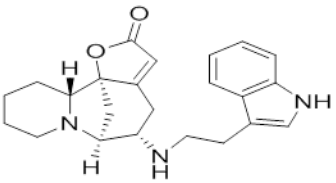
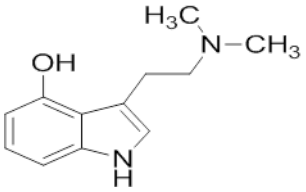
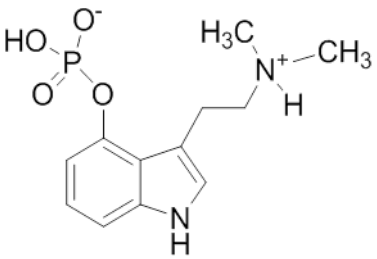
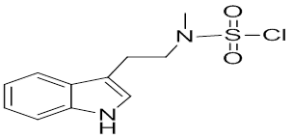
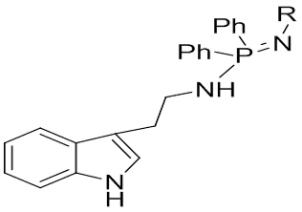
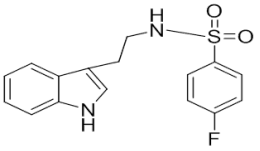
disease and Alzheimer's disease [49]. Production of ROS is regularized by natural anti-oxidants. Synthesis of a series of novel phosphorylated derivatives of tryptamine (XIII) by Staudinger reaction show antioxidant properties because of presence of nitro, chlorine and aldehyde as functional groups in hetero cyclic rings, these compound acts as good antioxidants [50].

Epilepsy is one of the most common diseases of the nervous system. In the pathogenesis of epilepsy oxidative stress plays a significant role [51]. A new tryptamine derivative of securinine (TPS) (IX) has antioxidant as well as cytoprotective activities [52]. TPS is a secondary metabolite of a plant from the Euphorbiaceae family, which act as antioxidant.

Antifungal activity

Tryptamine derivative exhibited potential antibacterial and antifungal activities by using fungal strain of *Aspergillus Niger* Such as N-(2-(1H-Indol-3-yl)ethyl)-4-fluorobenzenesulfonamide (XIV), N-(2-(1H-Indol-3-yl)ethyl)-4-nitrobenzenesulfonamide (XV) and N-(2-(1H-Indol-3-yl)ethyl)-4-chloro-3-nitrobenzenesulfonamide (XVI) showed prevention of growth of tested microorganisms exhibited potent antimicrobial activity (Table 1). These sulfonamide derivatives have been widely used for bacterial, protozoal and fungal infections and in safe therapeutic dosage ranges are among first effective chemotherapeutic agent [53].

Name of compound	Structure	Biomedical significance
DMT (N, N-dimethyltryptamine) (I)		A powerful psychedelic compound Known as "vine of the souls".
Serotonin (5-hydroxytryptamine, 5-HT) (II)		neurotransmitter and signalling hormones in CNS
Melatonin (N-acetyl-5-methoxytrypatmine) (III)		Control of diurnal rhythm of various physiological functions
Sumatriptan (IV)		For migraine treatment
α-methyltryptamine (V)		Antidepressant, stimulant, psychedelic drug, monoamine oxidase inhibitor etc.
5-CT (5-Carboxamidotryptamine) (VI)		Vasodilator and vasoconstictor effect.
Ondansetron (VII)		Nausea and vomiting suppression caused by cancer chemotherapy and radiotherapy

Alosetron (VIII)		For the treatment of irritable bowel syndrome
Tryptamine derivative of securinine (TPS).(IX)		Show antioxidant and cytoprotective activities.
Psilocin (4-hydroxy-N,N-dimethyltryptamine) (X)		Well-known psychotropic effects, LSD-like properties and produce changes in perception and behaviour.
Psilocybin (4-phosphoryloxy-N, N-dimethyltryptamine) (XI)		Well-known psychotropic effects, LSD-like properties and produce changes in perception and behaviour.
Tryptamine based sulfonamide-compound (XII)		Used as antibacterial and antimicrobial agents.
Phosphorylated derivative of tryptamine (XIII)		Antioxidant activity.
N-(2-(1H-Indol-3-yl)ethyl)-4-fluorobenzenesulfonamide (XIV)		Antifungal activity.

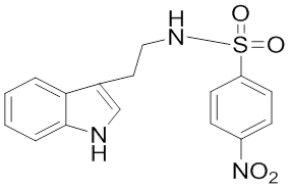
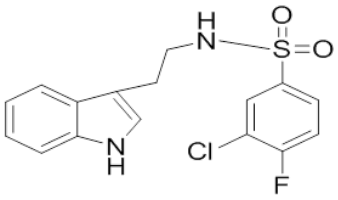
N-(2-(1H-Indol-3-yl)ethyl)-4-nitrobenzenesulfonamide (XV)		Antifungal activity.
N-(2-(1H-Indol-3-yl)ethyl)-3-chloro-4-fluorobenzenesulfonamide		Antifungal activity.

Table 1: Biomedical significance of tryptamine derivatives.

Toxicity of tryptamine

Tryptamines and phenelthylamines are used for psychological and medicinal purpose (licit use) and illicit use for frivolous purposes (illicit use). Although tryptamine plays several important functions but it has toxic effect also. According to Nichols, because of lack of affinity for the relevant receptors and targets, the tryptamine group are usually doubtful to "cause death-dealing changes in cardio-vascular, renal or hepatic function", but the use of α-methyl tryptamine/α-methoxy tryptamine (AMT) or 5-MeO-AMT('foxy') lead with US fatalities. However the potency of tryptamine enhanced when methoxyl group is attached in tryptamine ring at position 5. Disturbance in behaviour may also lead due to hallucinogenic effects of tryptamines, so patient face life-threatening situations. Severe cardiac failure may also occur due to over dose of this drug.

Conclusion

Trypytamine a mono amine alkaloid is present in fungi, plants and animals is important heterocyclic compound in drug discovery studies. Among potential naturally occurring products this is considered important type of molecule which is also present in mammalian brain in trace amount. Tryptamine plays important biomedical role as neurotransmitter and neuromodulator, vasoconstrictor and vasodilator, antimicrobial and antibacterial, antioxidant and antifungal agents. Its modification at different position leads to many compounds of pharmacological importance. Large numbers of research are currently in progress on tryptamine and its derivatives. This paper reviews the current status and the recent studies of biologically active tryptamine and its derivatives and this will promote various research activities in growing this field.

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