Serotonin: Origins, Roles, and Toxic Effects

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Through its imperative modulatory and regulatory role in supporting life, serotonin has heavily influenced a number of functions within the body since evolutionary beginnings. The discovery of this indolamine in the brain has led to much research in exploring its role within the synapse and receptors. The receptors themselves are associated with an array of phenomena and behaviours, which are also influenced by the locations in which the serotonergic projections innervate. The 5-HT_{1A},and 5-HT_{2A} receptors have primarily been the target of research, as they have been implicated in affecting psychological states such as empathy, anxiety, and depression; imperative life functions such as sleep and hunger; and basic psychological functions such as inhibition and control. Despite all the beneficial functions serotonin can contribute to, overstimulation of serotonin can lead to life threatening conditions such as serotonin syndrome. Dangerous but treatable if attended to in time, the syndrome provides a drastic example of how crucial serotonin's role is within the body. Given its impact in maintaining life, more research must be conducted to fill in the gaps of the current literature and to produce viable treatments for serotonin syndrome.

Keywords: serotonin, 5-HT_{1A}, 5-HT_{2A}, receptors, serotonin syndrome

Ancient and ubiquitous, the indolamine serotonin (also known as 5-hydroxytryptamine or 5-HT) has always been an asset for life, modulating and stimulating biological processes and functions (Turlejski, 1996). Appearing early in evolution, indolamines play a large role in the development and plasticity of cells (Turlejski, 1996). Serotonin holds an imperative role in fetal development of neuronal structures due to the ability of serotonergic fibers to modulate mitosis, dendritic elongation and spine appearance (Azmitia, 1999). Serotonergic fibers are innately very plastic in the mature brain, inducing regenerative sprouting responses on the serotonergic neuron when contacts with motoneurons are disrupted by damage of the spinal cord or forebrain (Azmitia, 1999). Serotonin specifically influences basic cell functions such as RNA synthesis, cAMP levels, mitosis, and cell and energy regeneration, making it imperative to sustaining and developing life (Turlejski, 1996). In researching the actions of the serotonin produced in the central nervous system, researchers are able to link neuroanatomical and neurophysiological bases to behaviours and phenomena such as empathy, clinical disorders, sleep, hunger, aggression, impulsivity, and more. This is imperative given the ubiquitous influence serotonin has on the body, driving the need for even more research to fill in the gaps of the current literature and to produce the most optimal treatments for these resulting afflictions.

Serotonin can act both peripherally and centrally within the nervous system. The literature has however focused primarily on the serotonin produced in the central nervous systems due to its role in affecting behaviour and psychological states (Turlejski, 1996). Serotonin was first discovered peripherally in the enterochromaffin cells of the gut of rabbits in the form of enteramine by Vittorio Erspamer in 1937, which was later identified as serotonin by Maurice Rapport, Arda Green, and Irvine Page in 1943 using blood from cows (Nichols & Nichols, 2008). A decade after this identification, Twarog and Page (1953) discovered serotonin's presence in the central nervous system by examining the brain tissue of dogs, rats, and rabbits. As a result of these efforts, a link between serotonin and lysergic acid diethylamide (LSD-25) was made, as a scaffold for the serotonin structure was found in the chemical structure of LSD (Nichols & Nichols, 2008). This was a significant finding, as it was one of the first neurochemical explanations for mental illness, as the serotonergic interferences brought upon by LSD alters the mind and causes 'mental disturbances' similar to those seen in a variety of psychiatric conditions (Nichols & Nichols, 2008). By linking the two, researchers were then prompted to produce the vast amount of research and literature on serotonin's role in the human brain seen today.

Though more than 90% of the serotonin in the body is located in the gut, research on the role of the gut in producing behavioural effects is currently in its infancy. It is only just recently that the brain-gut-microbiome axis has been implicated in psychological disorders (Ganci et al., 2019). Gut microbiota produced in the gastrointestinal tract contribute to the availability of peripheral serotonin precursors, which is then used in the synthesis of 5-HT in the central nervous system (Martin et al., 2018). By influencing the levels of serotonin throughout the body, various effects on behaviour and psychological effects can occur as a result (Martin et al., 2018). Clinical studies have also implicated gut probiotics with psychiatric symptoms such as obsessive-compulsive tendencies and increased scores on anxiety and depression measures, symptoms often associated with alteration in serotonin levels (Martin et al., 2018). These effects can all be attributed to the bidirectionality of serotonin's role in the peripheral and central nervous systems.

Chemically, serotonin is synthesized from the precursor indolamine, tryptophan; the structure itself involves tryptophan hydroxylase and aromatic amino acid decarboxylase (Azmitia, 2007). This comprises the base of serotonin, which is synthesized and released into the cell synapse to influence the cells involved, the receptors themselves, and ultimately behaviour (Azmitia, 2007). With 14 different receptor subtypes grouped into seven families, serotonin has the most receptor subtypes out of the classical neurotransmitters (Nichols & Nichols, 2008). The 5-HT_{1A} and 5-HT_{2A} receptors are the primary focus of research, as they are expressed in high concentrations within serotonin's neuroanatomical system and play

a large role in the psychological and behavioural phenomena discussed (Nichols & Nichols, 2008). The neuroanatomical system mentioned refers to the serotonergic projections of the raphe nuclei which vastly expand to the rest of the brain, impacting behaviour through its interactions with various brain structures (Hornung, 2003). The 5-HT_{1A} receptor is expressed in high concentrations within the amygdala, hypothalamus, hippocampus and septal area, while 5-HT_{2A} is expressed in high concentrations within the cortex, nucleus accumbens, and striatum (Nichols and Nichols, 2008). As these receptors are expressed in copious quantities in these specific anatomical regions, serotonin can produce varying behaviours and psychological phenomena depending on the location.

The Prefrontal Cortex, Aggression, and Impulsivity

The prefrontal cortex is implicated in acts of aggression and impulsivity due to its role in functions such as inhibition and control (Cetin et al., 2017). Serotonergic innervation due to projections of the dorsal raphe nucleus in the cortex influence these behaviours, as 60% of the glutamatergic and 25% of the GABAnergic neurons within the prefrontal cortex have 5-HT_{1A} or 5-HT_{2A} receptors (Santana et al., 2004). Research has associated 5-HT_{2A} in particular with these behaviours, showing that stimulation of these receptors increases dopamine release, regulating hyperactivity and thus increasing impulsivity seen in disorders like attention deficit hyperactivity disorder (ADHD) (O'Neill et al., 1999). Additionally, the presence of increased 5-HT_{2A} receptor concentration in the prefrontal cortex has been associated with impulsive aggression behaviours (Moeller et al., 1996). Autism, being associated with decreased ability to control actions and increased aggressive behaviour, is also implicated with tryptophan depletion (McDougle et al., 1996). In the study by McDougle et al. (1996), researchers found that an increase in behaviours associated with autism such as whirling around, hitting oneself, flapping arms, and more were worsened with depleted levels of tryptophan, which would result in decreased serotonin levels. The participants also reported feeling less calm and happy, and experienced increased anxiety, demonstrating the role of serotonin in influencing affect (Zmudzka et al., 2018).

Affect and Influences on Clinical Disorders

Serotonin plays a large role in the modulation of affect, feelings, emotions, or moods experienced in everyday life, as serotonergic projections deeply innervate structures involved with producing complex emotions such as the amygdala and the ventromedial prefrontal cortex (vmPFC) (Crockett et al., 2010; Jhangiani et al., 2014). Crockett et al., (2010) studied this relationship by enhancing the effects of serotonin in subjects using serotonin reuptake inhibitors (SSRIs) and measuring their emotional reactions to moral dilemmas (ultimatum games). These moral dilemmas were designed to elicit emotional responses, which previous research have linked to activity within the amygdala and vmPFC (Blair, 2008). Subjects given SSRIs and controls were instructed to pick between utilitarian outcomes (e.g. saving multiple lives) and aversive harmful actions (e.g. killing an innocent civilian). They found that enhanced aversiveness in harming others and thus prosocial behaviour can be promoted by serotonin.

As serotonin can modulate affect, it has also been implicated in clinical disorders such as anxiety and depression. Modulation of anxiety-like behaviour occurs as a result of serotonin's interaction with the 5-HT_{1A} receptors in the bed nucleus of the stria terminalis, which is a major output pathway of the amygdala (Zmudzka et al., 2018). Abnormalities such as decreased binding of 5-HT and short alleles of the 5-HTT gene on the human chromosome have been found to elicit symptoms of anxiety. The serotonin-transporter-linked polymorphism region (5-HTTLPR) genotype in particular is associated with increased trait anxiety and knocking out these genes in mice yield abnormal levels of anxiety behaviours (Hariri & Holmes, 2006; Holmes et al., 2003). Depression is also impacted by interactions with its 5-HT_{1A} receptors as well as its 5-HT_{2A} receptors, as both are utilized by antidepressants to aid in mitigating depressive symptoms (Celadaet al., 2004; Zmudzka et al., 2018). However, unlike anxiety, depression can be influenced

by serotonin action within the hippocampus as well. Depletion of 5-HT_{1A} receptors in the hippocampus can lead to a decrease in neurogenesis, which is associated with eliciting depressive symptoms (Zmudzka et al., 2018). Neurotrophins may play a role in this decrease, as Banerjee (2013) found that post-mortem individuals with major depressive disorder also showed decreased levels of neurotrophins, brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). Selective 5-HT_{2A} receptor antagonists were also found to block the expression of stress-induced down-regulation of BDNF in the hippocampi of rats, providing further evidence of this mediatory relationship between serotonin and neurotrophins in the hippocampus (Vaidya et al., 1999).

The Hypothalamus, Sleep, and Hunger

Neural activity at the hypothalamus is also modulated by serotonin and controls thermoregulation, hunger, sleep, and more. As a precursor to melatonin, serotonin interacts alongside melatonin, being released at varying points throughout the sleep cycle (Ursin, 2002). Animal research investigating 5-HT_{1A} receptor agonists found that a response of serotonergic neurons within the dorsal raphe nuclei, similar to the activity of these neurons during wakefulness, was elicited (Guzman-Marin et al., 2000). The projections of the raphe nuclei innervating the hypothalamus and the cortex allow for this action, as these structures play a large role in modulating arousal and attention (Guzman-Marin et al., 2000; Ursin, 2002). Narcolepsy is directly affected by serotonin's role in wakefulness, as animal research has revealed that during cataplexy, a symptom which causes sudden episodes of muscle tone loss, the raphe nuclei are active and releasing higher levels of serotonin than normal during REM sleep (Wu et al., 2003). Hunger is also a factor controlled by serotonergic control over the hypothalamus. Serotonin receptors are involved in hunger modulation, as 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C} agonists have been found to reduce food intake, while 5-HT_{2C} is the primary receptor for maintaining the homeostatic relationship between food intake and energy balance (Feijo, et al., 2010). The 5-HT_{2C} receptor is critical for mediation of serotonin's effect in the body's ingestive behaviours (Lam et al., 2008).

Serotonin Syndrome

As serotonin holds a heavy influence over many behaviours and phenomena, overactivation is dangerous and potentially life threatening. Serotonin syndrome is a condition occurring as a result of overactivation of 5-HT_{1A} and 5-HT_{2A} receptors (Boyer & Shannon, 2005). As the syndrome itself is defined as the presence of a toxic levels of serotonin in the brain, there is no singular diagnostic test for the condition; diagnosis must be conducted by a medical toxicologist (Boyer & Shannon, 2005). The condition is the consequence of excessive 5-HT agonism, affecting most if not all of the phenomena mentioned previously, impairing function of thermoregulation, mood, aggression, anxiety and depression levels, modulation of wakefulness, and more (Volpi-Abadie et al., 2013). This is due to the abundant axonal projections of the raphe nuclei, which innervate and modulate many structures of the brain in its role as the primary serotonin pathway (Volpi-Abadie et al., 2013). Symptoms range from mild to severe, depending on the level of serotonin present. Mild symptoms can consist of hypertension, tachycardia, tremor, and hyperreflexia, while moderate symptoms can consist of hyperthermia, pressured speech, mild agitation, and hypervigilance (Volpi-Abadie et al., 2013). Severe symptoms add to the symptoms of the previous severity levels with the possibility of experiencing delirium, seizures, renal failure, coma, or even death (Volpi-Abadie et al., 2013).

Approximately 75% of those diagnosed with the syndrome present symptoms within 24 hours of the initial use of medication, overdose, or change in dosage (Mason et al., 2000). Many psychopharmacological mechanisms are reported to cause the syndrome. Drug abuse, drug interactions with antidepressants like SSRIs or monoamine oxidase inhibitors (MAOIs), and more can cause mechanisms of serotonin syndrome like the inhibition of serotonin uptake, decreased serotonin synthesis, increased serotonin release, activation of serotonergic receptors, or possibly the inhibition of cytochrome P450 (CYP45), which would enable accumulation of

serotonergic drugs in the body due to decreased metabolism of drugs (Volpi-Abadie et al., 2013). The keys to managing the syndrome are to discontinue use of serotonergic agents, stabilizing and monitoring vital signs, providing oxygen, or sedating with benzodiazepines (Volpi-Abadie et al., 2013). If symptoms persist, the most effective treatment is to administer 5-HT_{2A} antagonist drugs (such as cyproheptadine and chlorpromazine), these interventions mitigate the more severe symptoms of the syndrome by blocking the activation of 5-HT_{2A} receptors (Nisijima et al., 2001).

As for research and diagnosis of serotonin syndrome, there are still gaps in the literature due to the nature of the syndrome itself. Due to the large variety of symptoms, variation in causes (which drugs, specifically) and the requirement of a toxicologist to diagnose, the true incidence of the syndrome is unknown (Werneke et al., 2016). Medical professionals who are less knowledgeable in the condition may put their patient in danger, as failure to diagnose can turn mild drug interactions into a deadly concoction (Werneke et al., 2016). Even those who are familiar with serotonin syndrome may overlook symptoms due to the lack of consensus on the existing criteria systems for diagnosis, or confuse the condition for neuroleptic malignant syndrome, which shares similar symptoms (Haberzettl, 2013; Werneke et al., 2016). A lack of standardized measures also exists within research, as scientists have found it difficult to model it consistently in animals (Haberzettl, 2013). Problems arise when looking at discriminability of symptoms since the animal symptoms differ across as well as within species (Haberzettl, 2013). The symptoms observed in a rodent will differ from another rodent and will differ even more compared to a human. Evaluation of a human model is only able to be made in case studies and by physician reports, and while animal models can assist in this research, the area still requires further research (Haberzettl, 2013).

Conclusion

Thanks to the discoveries in the mid-1990s by researchers examining cells, blood, and tissue, scientists today are able to further our understanding of serotonin and the implications of fluctuating levels or overdose. Through its role in the central and peripheral nervous system, serotonin influences a wide array of psychological and life-sustaining functions. The omniety of this indolamine, though helpful in modulating necessary functions such as affect, sleep, hunger, and aggression/impulsivity, can also cause severe symptoms when there is an overabundance. The recent research on the brain-gut-microbiome axis shows promise in contributing to the management and treatment of serotonin syndrome, as there is still much about this system that is currently unknown. Despite the current state of the field, the least researchers can do right now is to continue to expand the current knowledge on serotonin and elucidate where the projections of serotonin reach, what functions it affects and what treatments target the conditions resulting from high levels of serotonin while having the fewest side effects. Though a difficult task at a glance, much work and knowledge has been gathered since Erspamer in 1937, and given the advances in technology since then, it is most definitely within arm's reach.

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