5-Hydroxytryptamine Receptors

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1. 5-Hydroxytryptamine Receptors

5-Hydroxytryptamine (5-HT) receptors, also referred to as serotonin receptors, are a monoamine receptor molecule, activated by the neurotransmitter serotonin. These receptors are responsible for mediating both the inhibitory and excitatory synaptic transmission in CNS and PNS. And, depending on the nature and type of 5-HT receptors, they can function either as a G-protein coupled receptor or as a ligand gated ion channel receptor [1]. Considered one of the largest groups of receptors found in mammal, 5-HT receptors can be categorized into a family of six GPCRs, namely 5-HT1, 5-HT2, 5-HT4, 5-HT5, 5-HT6 and 5-HT7, and one ionotropic receptor, 5-HT3. Combined, 5-HT consists of 14 distinct serotonin receptor subtypes with distinguished structure and pharmacological activities [2]. Except for 5-HT3, an ionotropic receptor, the seven membrane GPCR-type of serotonin receptors can couple with G-proteins, for instance, Gαq/11, Gαi/o, or Gαs, to produce a nerve signal, and as such can be classified on the basis of their signaling mechanism. The 5-HT3 receptor is a ligand gated ion channel receptor that is permeable to cations such as Na^+, K^+ and Ca^{2+} for modulating the excitatory neurotransmission in CNS and PNS [3].

2. Specifics

5-HT1 receptors with subtypes 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, and 5-HT1F, and 5-HT5 receptors with subtypes 5-HT5A and 5-HT5B, bind with Gαi/o – protein to mediate neurotransmission, such as adenylyl cyclase inhibition and decreased cAMP levels [4]. 5-HT2 receptors, comprise of subunits 5-HT2A, 5-HT2B, and 5-HT2C, bind with Gαq/11, a protein that initiates the activation of phospholipase C (PLC) for hydrolyzing phosphatidylinositol bisphosphate with the generation of inositol trisphosphate 3 (IP3), mobilization of intracellular Ca^{2+}, influx of extracellular Ca^{2+} and activation of protein kinase C (PKC) [5]. Among the 5-HT2 receptor subtypes, 5-HT2A is well distributed in the CNS, primarily in the brain region responsible for cognitive and learning functions making them a novel target for therapeutic development to address AD and other neurodegenerative diseases [6].

Similarly, the remaining GPCR- type receptors, 5-HT4, 5-HT6, and 5-HT7 bind with Gαs-protein to mediate CNS excitatory neurotransmission. 5-HT4 and 5-HT7 are widely expressed in the central and peripheral CNS and are involved in modulating gastrointestinal functions and enhancing the cAMP production level [7]. Likewise, 5-HT6 is also highly abundant in nucleus accumbens, striatum, cerebral cortex, hippocampus and olfactory tubercle, and is involved in enhancing cAMP signaling and stimulating the adenylyl cycle. These receptors also have a key role in cognition and memory function, where the agonists and antagonists of 5-HT6 receptors are believed to ameliorate glutamatergic and cholinergic mediated learning and memory impairments [8]. 5-HT receptors and their subtypes, particularly due to their ability to modulate serotonin receptors by agonists and antagonists, provide a promising drug target to mitigate denervation in AD pathology.

Considered one of the oldest neurotransmission systems in the animal kingdom, serotonin plays a pivotal part in cognition and behavioral control and is implicated in AD pathology [9]. Post-mortem studies conducted on AD brains verify the direct involvement of the serotonergic system in denervation. Serotonergic processes are considered dysregulated in AD patients including subsequent alterations in 5-HT system function that leads to depression, one of the many behavioral changes experienced by AD patients [10]. The administration of selective serotonin reuptake inhibitors (SSRI) have been used as a long-term anti-depressant tool to slow the advancement of AD. In the mouse overexpressing APP/PS1 model of AD, SSRIs reduced the level of Aβ found in the brain's interstitial fluid, particularly the ERK pathways, confirming that ERK is necessary for the serotonin-dependent depression of ISF Aβ. SSRIs are considered safe neuroactive compounds with

minor side effects. Clinical studies additionally determined that SSRI antidepressant drug treatment significantly reduced the amyloid load in cognitively normal elderly patients as compared to those who were not cognitively normal. These studies suggest that serotonin signaling is linked to decreased amyloid and plaque reduction in both transgenic mice and humans [11]. Several studies have been carried out to identify the specific 5-HT receptors that are involved in modulating the serotonergic signaling for AD treatment.

5-HT4 receptors mediate serotonergic induced memory and learning functions in the hippocampus, cortex, and striatum [12]. On activation, the agonists BIMU 1 and BIMU 2 facilitate the release of acetylcholine. Thought integral to cognition, experiments conducted on rat frontal cortex, strongly suggest that serotonergic activity is pivotal to improving cholinergic impairments related to memory and learning dysfunction [13]. Besides the cholinergic system, several studies have also concluded that 5-HT4 receptors and their agonists modulate the non-amyloidogenic processing of APP responsible for generating the soluble amyloid beta precursor protein (sAPPα). sAPPα, considered a neuroprotective protein, reportedly increases the amount of these soluble fragments and is another likely approach to treat AD. 5-HT4 receptor agonists have been shown to increase sAPPα levels in the cortex and hippocampus areas of the mouse model, making them a promising pharmacological target for AD treatment [14][15]. In the non-amyloidogenic APP metabolism, 5-HT4 receptors, in the absence of agonist activation, are believed to enhance the production of sAPPα fragments by interacting with ADAM10 with the subsequent release of the soluble APP proteins in HEK-293 cells and cortical neurons. This process is independent of cAMP production, however, in the presence of an agonist, the 5-HT4 receptors are triggered to enhance the formation of sAPPα proteins via cAMP/Epac signaling, conferring the role of 5-HT4 receptors in α-secretase ADAM10 and sAPPα release [16]. Similarly, the potentiality of type 4-hydroxytryptamine receptor as an AD modifying agent has been supported by the chronic administration of 5-HT4 receptor agonist RS67333 during the prodromal phase of the disease. In this case, the agonist compound was reported to reduce the Aβ levels in 5XFAD mouse models with successive improvement in NOR (novel object recognition) test impairments 168. In addition, SL65.0155, an activator of 5-HT4 receptors, has also been reported to ameliorate learning and memory performances in object recognition task by activating cAMP production [17][18].

Serotonin-6 receptors (5-HT6) are similar to the type 4 (5-HT4) receptors and have also garnered considerable attention as a promising candidate pharmacological intervention in AD pathology. Several studies have introduced a myriad of antagonists, to ameliorate serotonergic mediated cognitive dysfunction and memory performance in a number of behavioral tests conducted on memory deficient adult male Wistar rats. For instance, an activator of serotonin-6 receptor, Ro4368554, has been shown to enhance the serotonergic and cholinergic cognitive effects in object recognition tasks [19]. Similarly, dimebolin, an antagonist of 5-HT6 receptors is thought to boost cognitive function [20]. Idalopirdine (Lu AE58054), a selective 5-HT6 receptor antagonist, combined with donepezil, was shown to ameliorate the cognitive functions in mild AD cases [21]. Another compound, SB271036, improves memory performance by reducing Aβ generation. SB271036 inhibits the activity of γ-secretase and inactivates astrocytes and microglia in the mouse model of AD [22].

5-HT4 receptor activators and 5-HT6 receptor inhibitors of receptors have been considered excellent drug targets in several clinical trials, due particularly to their memory and behavioral performance. Both of these receptors have amassed significant attention from the AD research community as promising therapeutic targets compared to the other receptors. Nonetheless, a number of studies have also noted the potential promise of 5-HT1 receptors in terms of memory and behavioral. 5-HT1A receptor antagonists are believed to activate glutamatergic and cholinergic neuro signal and subsequently enhance cognitive impairments as observed in AD pathogenesis [23]. Postmortem AD tissue correlates with known aggressive patient behavior providing the basis for developing 5-HT1A receptors as a target for treating behavioral symptoms in AD pathology [24]. Likewise, administration of S15535, agonist of 5-HT1A receptor, increased the response accuracy and reduced the delayed response in mouse models. In addition, these receptors increased the release of ACh in the frontal cortex and dorsal hippocampus regions of freely moving rat model, thereby facilitating cognitive function in a varied behavioral performance [25]. In a recent study, 5-HT1A receptor inhibitor (NAD-299) and 5-HT2A receptor activator (TCB-2) have been shown to decrease neuronal loss and oxidative stress in a rat model of AD, implying that these receptors may also be explored as a preventative for AD progression [26].

Serotonergic neurotransmissions are an integral system that modulate hippocampal and neo cortical cognitive and learning performance. This system, by its very nature, leads to denervation and age-related cognitive and behavioral disorders, thereby serving as a potential therapeutic target in AD pathology. Consequently, AD progression can be ameliorated by limiting serotonin receptor functioning through the use of agonists for 5-HT4, 5-HT2A/2C and antagonists of 5-HT6, 5-HT1A or 5-HT3 and 5-HT1B [27]. The use of either the activator or inhibitor of a specific serotonin receptor not only prevents memory impairment, but also enables learning processes in situations requiring high cognitive demand. Together, this provides a novel therapeutic opportunity for treating AD.

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