Therapeutic Potential of Serotonin Type 7 Receptor Modulation

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Although a number of mood-stabilising atypical antipsychotics and antidepressants modulate serotonin type 7 receptor (5-HT7), the detailed contributions of 5-HT7 function to clinical efficacy and pathophysiology have not been fully understood. The mood-stabilising antipsychotic agent, lurasidone, and the serotonin partial agonist reuptake inhibitor, vortioxetine, exhibit higher binding affinity to 5-HT7 than other conventional antipsychotics and antidepressants. The initially expected rapid onset of antidepressant effects—in comparison with conventional antidepressants or mood-stabilising antipsychotics—due to 5-HT7 inhibition has not been observed with lurasidone and vortioxetine; however, several clinical studies suggest that 5-HT7 inhibition likely contributes to quality of life of patients with schizophrenia and mood disorders via the improvement of cognition. Furthermore, it reported that 5-HT7 inhibition might mitigate antipsychotic-induced weight gain and metabolic complication by blocking other monoamine receptors. Further preclinical studies for the development of 5-HT7 modulation against neurodevelopmental disorders and neurodegenerative diseases have been ongoing. Various findings from various preclinical studies indicate the possibility that 5-HT7 modifications can provide two independent strategies. The first is that 5-HT7 inhibition ameliorates the dysfunction of inter-neuronal transmission in mature networks. The other is that activation of 5-HT7 can improve transmission dysfunction due to microstructure abnormality in the neurotransmission network—which could be unaffected by conventional therapeutic agents—via modulating intracellular signalling during the neurodevelopmental stage or via loss of neural networks with aging.

antipsychotics antidepressants mood stabilising schizophrenia serotonin type 7 receptor

1. Introduction

Serotonin (5-HT) receptor type 7 (5-HT7) is one of the most recently (1993) identified members of the 5-HT receptor family [1][2][3][4][5]. It has been demonstrated that 5-HT7 is highly expressed in functionally relevant regions of the brain [6][7]. Indeed, in the central nervous system, 5-HT7 is most predominantly expressed in the thalamus, hypothalamus, hippocampus, prefrontal cortex, basal ganglia, amygdala and dorsal raphe nucleus [8][9][10][11][12][13][14]. The predominant expression of 5-HT7 in the limbic regions provides a candidate hypothesis that 5-HT7 contributes to the regulation of memory processing, cognition and emotional perception [9][10][11][12][15][16]. The expression of 5-HT7 has been also observed in the kidney, liver, pancreas, spleen, stomach and smooth muscle cells of the arteries and gastrointestinal tract [17]. Based on these findings, 5-HT7 modulation is also considered to be a possible therapeutic target for the treatment of peripheral organs [18][19][20][21].

A number of preclinical studies have reported that 5-HT7 plays important roles in the regulation of mood, memory processing, cognition and emotional perception by following various experiments using selective 5-HT7 modulators and 5-HT7 knockout mice models [15][22][23][24][25][26]. Although modulating 5-HT7 is one of the targets for the treatment of schizophrenia and mood and anxiety disorders in current psychopharmacology, unfortunately, the clinical application of selective 5-HT7 receptor modulators has not yet been achieved [16]. However, several conventional mood-stabilising atypical antipsychotics, such as aripiprazole, brexpiprazole, clozapine, lurasidone, olanzapine, quetiapine, risperidone and zotepine are known to be inhibitors of 5-HT7 [12][27][28][29][30][31][32][33][34][35][36][37][38][39][40] (**Table 1**). Lurasidone is an antipsychotic agent with the highest binding affinity to 5-HT7 among mood-stabilising atypical antipsychotics [16][27] (**Table 1**). Furthermore, a novel antidepressant, vortioxetine, which is categorized as a 5-HT partial agonist reuptake inhibitor (SPARI), exhibits distinct pharmacodynamic profiles compared to other monoamine transporter-inhibiting antidepressants, since vortioxetine acutely and chronically suppresses the function of 5-HT7 [38][39][41][42].

Table 1. Receptor-binding profiles of antipsychotics and antidepressants.

Receptor	LUR	APZ	Brex	CLZ	OLZ	PMZ	QTP	RIS	ZTP	VTX
5-HT1A	6.8	5.6	0.12	124	>1000	650	432	423	471	15.0
5-HT2A	2.0	8.7	0.47	5.4	2.3	48.4	100	0.2	2.7	
5-HT3	>1000	630		241	57	>1000	>1000	>1000	472	3.7
5-HT7	0.5	10.3	3.7	18.0	365	0.5	307	6.6	12.0	19.0
H1	>1000	27.6	19	1.13	1.2	692	11	20.1	3.21	
D1	262	>1000	160	266	100	>1000	712	244	71.0	
D2	1.7	3.3	0.3	157	52.3	0.3	245	3.6	25.0	
Reference	[27]	[28][29]	[30]	[31][32]	[33][43]	[34]	[35]	[29][36]	[37]	[38]

Notes: lurasidone (LUR), aripiprazole (APZ), brexpiprazole (Brex), clozapine (CLZ), olanzapine (OLZ), pimozide (PMZ), quetiapine (QTP), risperidone (RIS), zotepine (ZTP) and antidepressant vortioxetine (VTX) against serotonin (5-HT) type 1A (5-HT1A) type 2A (5-HT2A), type 3 (5-HT3), and type 7 (5-HT7) receptor, histamine H1 (H1) receptor, dopamine receptors type 1 (D1) and 2 (D2). Data are equilibrium constant (Ki) values (nM).

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2. Preclinical Findings about Therapeutic Potential of 5-HT7 Modulation

2.1. Depression

The earliest identified physiological function of 5-HT7 was regulation of circadian rhythms [2]. In this context, 5-HT7 was found to be expressed in the suprachiasmatic nucleus [44], which is a major regulatory region of circadian rhythms [45]. The influence of 5-HT7 on sleep regulation is complicated because the 5-HT7 inverse agonist SB269970 [40][42][46][47] increased latency in the onset but decreased the total amount of time spent in rapid eye movement sleep [48]. A number of antidepressants also increased latency in the onset but decreased the total amount of time spent in rapid eye movement sleep, similar to SB269970 [49].

The 5-HT7 knockout mice displayed a reduction of immobility times in both a forced swim test and a tail suspension test, common pharmacological behaviour tests for the screening of antidepressants (decreasing immobility time is considered to correlate to antidepressant action in humans) [22][50]. Based on this finding, 5-HT7 inhibitors/antagonists were actively explored and developed as antidepressants in the early years of this century. SB269970, an inverse agonist of 5-HT7, has been shown to reduce immobility time in forced swim and tail suspension tests; as a result, it became a candidate for use as an antidepressant [22][23][51]. Additionally, the administration of subeffective concentration of SB269970 enhanced the anti-immobility action of subeffective doses of desipramine, citalopram and imipramine in the forced swim and tail suspension tests [51][52][53]. Most notably, SB269970 generated significantly rapid onset of antidepressant-like effects in olfactory bulbectomised models, when compared to fluoxetine [54]. As a result, 5-HT7 inhibitors were anticipated to join the rapid onset antidepressant class, since it is recognised that one of the major problems of monoamine transporter-inhibiting antidepressants, a currently/commonly prescribed antidepressant class, is that they require 2-4 weeks for the onset of antidepressive effects. The target regions for antidepressant effects of 5-HT7 inhibitors remain controversial. Injection of SB269970 into the hippocampus generated antidepressant-like activity in the forced swim test [55]. Injection of SB269970 into the lateral habenular nucleus lesion model using 6-hydroxydopamine also exhibited antidepressant-like activity, whereas injection into the medial prefrontal cortex lesion of a model, conversely, displayed the enhancement of depressive-like activity [56][57]. AS19, a 5-HT7 agonist, demonstrated the opposite region-dependent effect against SB269970 [56][57].

2.2. Anxiety

The potential function of 5-HT7 on anxiety demonstrated the inconsistent results between pharmacological and molecular biological studies, similar to the case of depression. Expression of 5-HT7 mRNA increased by acute restraint stress but not by chronic variable stress in the rat hippocampus, indicating that 5-HT7 contributes to the regulation of response to stress [58]; however, the anxiety-like behaviour in the light/dark transfer or elevated plus maze tests did not affect both 5-HT7 knockdown or knockout models [50][59][60]. On the other hand, the anxiolytic-like activity of SB269970 (both systemic and intra-hippocampal local administrations) was demonstrated by the Vogel drinking test, the elevated plus maze test and the four plates test [23][55]. Both SB269970 and 5-HT7 knockout mice demonstrated anxiolytic-like activity in the marble-burying test, which is a model of anxiety and obsessive–compulsive disorder [61]. These inconsistent results among molecular biological and pharmacological experiments suggest that the level of 5-HT7 inactivation required for anxiolytic effects is probably dependent on the model utilized. In other words, appropriate 5-HT7 inhibition may be beneficial for anxiolytic effects.

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2.3. Schizophrenia

A number of pharmacological studies reported the therapeutic potential in components of positive and negative symptoms and cognitive dysfunction of schizophrenia using chemical-induced schizophrenia models. Compared with wild-type mice, 5-HT7 knockout mice were less susceptible to prepulse inhibition deficits of phencyclidine [62]. SB-269970 suppressed hyperactivity induced by ketamine, phencyclidine and amphetamine [63][64], whereas the effects of 5-HT7 on prepulse inhibition deficits were inconsistent. SB-269970 improved amphetamine-induced prepulse inhibition deficits [64], but did not affect those induced by an NMDA/glutamate inhibitor, phencyclidine or ketamine [62][65]; however, SB-258741, a 5-HT7 antagonist, did not affect the amphetamine-induced prepulse inhibition deficits, but suppressed phencyclidine-induced prepulse inhibition deficits [66]. Ketamine-induced negative symptoms associated with social withdrawal were attenuated by SB269970, but not affected by SB-258741 [65][66]. The effects of SB269970 on positive symptoms are possibly involved in dopaminergic transmission but not in glutamatergic transmission, whereas, conversely, the effects of SB-258741 on positive symptoms are possibly involved in glutamatergic transmission but not in dopaminergic transmission. Furthermore, social withdrawal induced by NMDA/glutamate receptor inhibition is prevented by SB269970 but not by SB258741. These discrepancies between SB269970 and SB258741 could not be explained by their receptor-binding profiles alone, since these compounds displayed binding affinity to 5-HT7, D2 and D3 receptors [66]. These findings suggest that the effects between SB269970 and SB258741 are probably dependent upon the materials (pharmacological and molecular biological models) and compounds employed.

On the other hand, the effects of 5-HT7 inhibition on neurocognitive dysfunction (procognitive effects) demonstrated its promise. SB269970 attenuates amnesia in short-term memory induced by ketamine and MK801 [67][68], and this effect was suppressed by AS19 [69]. The new valuable tool for exploring the neurobiological bases of cognitive dysfunction in schizophrenia, five-choice serial reaction time task (including attention, response inhibition, cognitive flexibility and processing speed), demonstrated that SB269970 improved the impairment of working memory and impulsivity, without affecting premature responding induced by MK801 [70].

3. Clinical Evaluation of 5-HT7 Modulators

3.1. Vortioxetine

Vortioxetine is an antidepressant belonging to the family of monoamine transporter-inhibiting antidepressants; its antidepressant effect is thought to arise from not only its monoamine transporter inhibition but also 5-HT7 inhibition. The binding affinity of vortioxetine to 5-HT7 is relatively low compared to serotonin transporter, 5-HT1A and 5-HT3 [38], but the relevant therapeutic concentration of vortioxetine functionally suppresses 5-HT7 [39][41].

3.2. Lurasidone

A mood-stabilising antipsychotic agent, lurasidone possesses the highest binding affinity to 5-HT7 among antipsychotics [27] (**Table 1**). Several meta-analyses reported that lurasidone significantly improves positive and

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negative depressive symptoms [71][72][73][74]. Therefore, the general efficacy of lurasidone for the treatment of schizophrenia is considered to be comparable to that of other atypical antipsychotics [16]. Meta-analyses also demonstrated that lurasidone has antidepressant effects comparable to those of other mood-stabilising antipsychotics against major depressive disorder and bipolar depression [75][76]. The efficacy of lurasidone in the acute treatment of bipolar depression, as both monotherapy and adjunctive therapy to lithium/valproate, has been reported in clinical trials [77][78][79]. Like vortioxetine, the rapid onset of the antidepressive effects of lurasidone have not been demonstrated [75][80][81][82][83].

4. Intracellular Signalling Associated with 5-HT7

Four splice variants of 5-HT7 were identified. These were distinct in their carboxyl terminals due to introns in the 5-HT7 gene, including 5-HT7a, 5-HT7b and 5-HT7c in rodents, and 5-HT7a, 5-HT7b and 5-HT7d in humans [6][84][85][86][87][88]. All of these four splicing variants directly affect three intracellular signalling pathways via activations of Gαs, Gα12 and metalloproteinase-9 [4][89][90]. Significant differences among 5-HT7 splicing variants in localisation, ligand-binding affinity and adenylate cyclase activity have not been observed [6], whereas 5-HT7a isoform specifically activates the abovementioned cAMP-dependent signalling through the activation of type 1 and 8 adenylyl cyclase via Ca^{2+}/calmodulin-dependent and Gs-independent signalling [91].

Activation of 5-HT7 enhances synthesis of cyclic adenosine monophosphate (cAMP) via activation of adenylyl cyclase [4]. Increasing cAMP activates signalling of both protein kinase A (PKA) and the exchange protein directly activated by cAMP (EPAC) [10][90][92]. These two signalling pathways affect various signalling transductions via phosphorylation of target proteins, leading to the propagation of the signalling to the next biochemical events. Subsequently, enhanced PKA stimulates cyclin-dependent kinase 5 (Cdk5) [10][90] and Ras [93][94], resulting in serine/threonine extracellular signal-regulated kinases (Erk) signalling activation [93][95]. Activation of EPAC also indirectly enhances Erk signalling [93][95]. The second signalling pathway regulates adenosine monophosphate-dependent protein kinase (AMPK) [42][96][97] via inhibitory PKA and stimulatory EPAC [98].

Two other types of signalling associated with 5-HT7 were also identified: Gα12 [90] and metalloproteinase-9 (MMP9) [89]. It has been shown that 5-HT7/Gα12 activates cell division cycle protein 42 (Cdc42) [90][99] and activates signalling pathways associated with Gα12 [90]. In addition, it is recognized that 5-HT7/Gα12 activates both Ras homolog gene family member A (RhoA) and cell division cycle protein 42 (Cdc42) [90][99].

It has been established that the serotonergic system plays crucial roles in the organisation of the neural system, such as generation of neurogenesis, cell migration, axon guidance, dendritogenesis, synaptogenesis and brain wiring during the development of the mature brain [100]. During the embryonic stage, 5-HT7 leads neurite outgrowth through activations of Cdk5 with mTOR [94][101]. Therefore, 5-HT7 contributes to the establishment and maintenance of neural connectivity and synaptic plasticity in early developmental stages [102]. In other words, the reorganization of dendritic morphology induced by 5-HT7 plays important roles in new synapse growth and initial neuronal network formation, which is the target of event-related structural and functional plasticity in the early developmental stage [103][104].

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5. Effects of 5-HT7 on Neuronal Transmission

Behavioural study demonstrated that 5-HT7 knockout mice displayed impairments of contextual learning, seeking behaviour and allocentric spatial memory [105]. Electrophysiological study also demonstrated that 5-HT7 knockout mice exhibited impaired hippocampal long-term potentiation [59]. In addition, 5-HT7-induced activation of PKA signalling enhanced N-methyl-D-aspartate (NMDA)-evoked currents, resulting in the enhancement of population spike amplitude and bursting frequency in hippocampal CA1 and CA3 regions, respectively [106][107][108]. Furthermore, 5-HT7 activates hippocampal transmission postsynaptically due to enhanced phosphorylation of the AMPA glutamate receptor induced by cAMP/cAMP response element-binding protein (CREB) signalling [109][110]. Additionally, 5-HT7 reversed long-term depression associated with metabotropic glutamate receptor (mGluR) [26].

Activation of 5-HT7 during adolescence induced persistent upregulation of 5-HT7 [13]. Chronic exposure to methylphenidate during postnatal life and adolescence probably provides persistent structural rearrangements of the brain's reward pathways associated with 5-HT7 [111]. During the pre- and postnatal periods, exposure to selective serotonin reuptake inhibitors generates long-term anxiety in adulthood without affecting the morphological alterations of the brain [112][113]. The molecular mechanism underlying 5-HT7-induced remodelling increases neurites and dendritic spine elongation via MMP-9/CD44 with Cdc42 in neural learning and neuronal regeneration [89]. Therefore, the impacts of 5-HT7 on neuronal plasticity during early development are not limited to embryonic and early postnatal development but can also persist in adolescence and adulthood.

Although activation of hippocampal 5-HT7 contributes to the formation of learning and memory, suppression of 5-HT7, conversely, improved other cognitive components, such as executive function, which play important roles in quality of life. Traditionally, enhanced mesocortical dopaminergic transmission via dopamine release in the frontal cortex induced by blockade of D2 in the ventral tegmental area are considered to be key players in the improvement of positive and negative symptoms of schizophrenia [32]. Additionally, thalamocortical glutamatergic transmission are considered to play important roles in neurocognitive function [32][114][115][116].

Tonic hyperactivation of thalamocortical glutamatergic transmission was observed in schizophrenia, ADHD and autism [12][39][115][116][117][118][119][120][121][122][123][124][125][126]. Other 5-HT7 molecules, such as group II and III mGluRs and α2 adrenoceptor, which compensate thalamocortical glutamatergic transmission, have also been identified [116][117][118][120][125]. The behavioural importance of neuronal networks is affirmed by lesion studies demonstrating that lesions to hub regions are associated with task impairments across multiple functional domains [127][128][129]. Notably, the prediction of the thalamocortical pathway on task-specific cortical activity patterns was outperformed compared to the prediction of the cortical and hippocampal pathway [127][128][129]. The mediodorsal thalamic nucleus is reciprocally connected with the medial prefrontal cortex and receives glutamatergic inputs from the hippocampus [40][41][124][130][131]. The glutamatergic neurons in the mediodorsal thalamic nucleus were mainly suppressed but were activated by propagation of ripple burst during the non-rapid eye movement sleep phase [130][131][132]. Therefore, the mediodorsal thalamic nucleus plays important roles in memory processing during sleep and sensory integration during wakefulness [16][133][134][135][136].

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6. Therapeutic Potential in Other Disease and Disorders Based on the Preclinical Findings

6.1. Neurodevelopmental Disorders

Activation of 5-HT7 was a potential candidate target for relieving symptoms in patients with Rett syndrome. Rett syndrome is the second most common cause of mental retardation in females and plays a role in severe neurodevelopmental disorders such as breathing dysfunction, loss of coordination, abnormal eye and hand movements, epilepsy, aberrant sleeping behaviour and cognitive impairment [137]. The prime pathogenesis of Rett syndrome is known to be various genetic mutations in methyl CpG-binding protein 2 gene (MeCP2) on the X chromosome, cyclin-dependent kinase-like 5 (CDKL5), forkhead box G1 (FOXG1), WD repeat domain 45 (WDR45) or syntaxin binding protein 1 (STXBP1) [138][139]. Restoring MeCP2 function can normalise functional abnormalities of MeCP2 knockout mice, whereas overexpression of the MeCP2 gene led to neurological defects [140]. Therefore, recent preclinical studies explored the targets in MeCP2 downstream effectors and other signalling, including 5-HT7. Based on the reduced 5-HT7 expression in Rett syndrome models, the systemic administration of 5-HT7 agonist relieved the related symptoms, anxiety, environment-related exploratory behaviour and motor learning ability of Rett syndrome mice models [141][142].

6.2. Neurodegenerative Diseases

Non-selectively activation of 5-HT receptors using 5-HT transporter inhibitors has shown little clinical benefit in neurodegenerative disorders [143][144]; however, several preclinical studies reported the attractive findings that 5-HT7 is a therapeutic candidate target for neurodegenerative disorders. Administration of 5-HT7 agonist also suppressed impairment of long-term potentiation and apoptosis in hippocampal streptozotocin-mediated neurodegeneration in murine models [145]. Amyloid-β induces neurotoxicity through several mechanisms including apoptosis, excitotoxicity and oxidative stress [146]; these were reverted by selective 5-HT7 agonist [147]. Amyloid-β is a key player in pathomechanisms of various neurogenerative diseases, such as Alzheimer's disease, frontotemporal dementia, cerebral amyloid angiopathy and cerebral amyloidosis, through multiple pathways [146][148]; however, the detailed roles of 5-HT7 in pathomechanisms of neurodegenerative disease associated with amyloid-β remain to be clarified [149][150].

6.3. Epilepsy

Various studies have reported on antiseizure activities—using audiogenic seizures in DBA/2J mice, or the absence of seizures in WAG/Rij rats—following the administration of selective and non-selective antagonists [151][152]. These studies demonstrated that SB269970 and AS-19 decreased and increased the frequency of pilocarpine-induced temporal lobe epilepsy seizures in rat models, respectively [153].

6.4. Carcinoma

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There are some findings indicating that 5-HT7 modulation may be therapeutic targets for the treatment of cancer. Notably, it has already been proposed that 5-HT7 antagonists would be useful for the treatment of hepatocellular cancer and small intestinal neuroendocrine neoplasms, since 5-HT7 contributes to hepatocyte proliferation [18][19][20]. Serotonergic function activates proliferation of hepatocellular cancer and the expression of β-catenin, which plays an important role in the pathomechanisms of hepatocellular cancer via the activation of 5-HT7. The expression of 5-HT7 increased in hepatocellular cancer cell lines, but the 5-HT7 antagonist SB258719 suppressed 5-HT-induced increase in β-catenin levels and cell viability. Furthermore, SB258719 also suppressed proliferation and tumour growth. When small intestinal neuroendocrine neoplasms, which are tumours derived from enterochromaffin cells, metastasize to the liver, the liver produces 5-HT, resulting in hyperactivation of 5-HT7 in the liver [20]. Hyperactivation of 5-HT7 in the liver leads to secretion of the growth factor IGF-1, which accelerates proliferation of metastatic tumour cells. Based on these findings, 5-HT7 inhibition is considered to be a candidate target for the treatment of hepatic metastasis cancers. It has been reported that 5-HT7 expression increased in certain types of breast cancers; this increase was amplified with tumour grade [154]. Indeed, SB269970 suppressed tumour formation in an MDA-MB-231 cancer cell [21].

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