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5-HT2AR and its implication on anti-depression therapy development

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Abstract. Major depression disorder (MDD) affects a big population and causes disability and productivity loss worldwide. Yet, fast-onset, powerful cure with minor side effects is scant. Therefore, there is an urging need to examine the biological bases for MDD treatment to design novel antidepressants. The serotonin system in the brain has long been a hot spot for research in this field, leading to accumulating biochemical discoveries of specific serotonin receptors. In this review, we briefly summarized the serotonin hypothesis of MDD, then focused on the implication of serotonin 2A receptor (5-HT2AR) in MDD therapy. Latest genomic evidence of 5-HT2AR gene variations related to MDD was presented. 5-HT2AR antagonists and agonists with antidepressive effects and their possible mechanisms of action was discussed. Based on current understanding of the 5-HT2AR's involvement in MDD therapy, we enumerated several future directions for developing applicable 5-HT2AR-targeting MDD treatment.

Keywords: Serotonin 2A receptor, 5-HT2AR, major depression disorder, agonist, antagonist, serotonin.

1. Introduction

Major depression disorder (MDD) has long been a severe concern for the modern society. It is characterized by a consistent depressed mood or an anhedonic state (diminished pleasure in almost all activities). Its symptoms include deviations in appetite, sleep pattern or psycho-motor function, fatigue, inappropriate guilt, concentration deficit or suicidal tendency [1]. At the same time, comorbidity such as anxiety disorders, pain and diabetes are common [2]. As reported by WHO, the estimated global number of people living with MDD in 2015 is 322 million, which translates to 4.4% of the population, with women more heavily affected than men (5.1% compared to 3.6%) [3]. MDD or depressive episode is also a well-established risk factor for suicide [4, 5]. Longitudinal studies suggest that the increase of prevalence of MDD trended younger in the US, with an increment of 5.4 million in 2010 to 8.3 million in 2018 among adults aged 18-34. In the meanwhile, despite a drop in the direct cost of MDD treatment, the total economic burden of adults with MDD in the US rose by 37.9% over the 8-year period [6]. Therefore, the amelioration of MDD management is of imperative and consistent need.

The development of antidepressants started off after the serendipitous discoveries of the anti-depressive properties of iproniazid (designed to treat tuberculosis) and imipramine (antihistamine) in 1950s. further studies revealed that these molecules increase the extracellular level of serotonin and noradrenaline by inhibiting their degradation or reuptake [7]. This leads monoaminergic systems, particularly serotonergic system to become the hot spot for drug design. Since then, medicine targeting

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monoamine functions, including SSRIs (Selective Serotonin Re-uptake Inhibitors), SNRIs (Serotonin and Nor-epinephrine Re-uptake Inhibitors), MAOIs (Monoamine Oxidase Inhibitors) and TCAs (Tricyclic antidepressants) have dominated the pharmacotherapeutic management of MDD [8]. SSRIs are the most often prescribed first-line medication (in America [2]; in China [9]) for they are safer compared to MAOIs and TCAs. However, the clinical performance of prevailing drugs is far from ideal. Although acute administration of mainstream antidepressants is efficacious [10], it is estimated that approximately one third of the treated individual with MDD in the US in 2017 is "treatment resistant" (fail to respond or achieve remission after 2 or more sessions of medication) [11]. At the heart of the issue, the pharmacological mechanisms underlying the clinical profile of antidepressants, especially the delayed onset of therapeutic effects, have remained debatable (for review, see [12]).

Currently, no comprehensive psycho-physiological model accounting for the mechanisms of MDD has been robustly established [13], which unarguably brings difficulties to the design of solid treatment regimes. Nevertheless, more researches into the serotonergic system have brought promising therapeutic possibilities. Accumulating evidence suggest that serotonin receptor 2A (5-HT2AR) may serve as a potential candidate for MDD pharmacotherapy development [14]. 5-HT2AR antagonists such as atypical anti-psychotics could augment the efficacy of antidepressants [15, 16, 17]. On the other hand, psychedelics as 5-HT2AR agonists had demonstrated fast-acting and sustained mood-lifting performance, indicating their clinical competence as qualified antidepressants [18]. Genetic studies had also identified *HTR2A* polymorphisms as suggestive modulators in MDD severity and antidepressant response of patients [19, 20]. In this review, we update the latest understanding of 5-HT2AR in relation to MDD physiology and pharmacology. We will present the biological and functional properties of 5-HT2AR following a brief summary of the debate over the etiology of MDD. The emphasis will be put on emerging 5-HT2AR ligands that manifest anti-depressive properties and the progress in the study of their action mechanisms.

2. Serotonin and the serotonin theory of depression

Serotonin is synthesized from dietary tryptophan by tryptophan hydroxylase and aromatic L-amino acid decarboxylase successively, in peripheral and in CNS separately [21]. In the CNS, 5-HT is released into a variety of forebrain regions by 5-HT neurons residing along the dorsal and median raphe nuclei [21], and is recycled by serotonin transporters (SERTs) [22] and other high-capacity monoamine transporters [23]. 5-HT is quickly metabolized by the mitochondrial membrane enzyme monoamine oxidase (MAO) to the more stable 5-hydroxyindoleacetic acid (5-HIAA) [24]. 14 sub-types of 5-HT receptors are found across species and display kaleidoscopic neurochemical properties [25], serving concerted or opposing roles considering certain brain functions [26]. The serotonergic system is intensely intertwined with several neuronal systems [21], thus is involved in a spectrum of pathological conditions, especially affective disorders.

First-generation antidepressants iproniazid and imipramine were shown to inhibit monoamine oxidase or monoamine reuptake in the brain. This revelation encouraged subsequent hypotheses that increase monoamine levels in CNS could benefit depressive patients [27]. Imipramine and iproniazid were further classified as TCA and MAOI, respectively [28]. The hypotheses culminated when SSRIs proved their efficacy by targeting SERT to inhibit serotonin reuptake and intensify 5-HT concentration within synaptic clefts [29]. However, further evidence of MDD pathophysiology had indicated that a monoamine view of the disorder might be overly simplistic.

The first evidence came from acute tryptophan depletion (ATD) studies conducted on MDD patients in remission. 10 of 15 remitted female without antidepressants for over 6 months experienced a partial or full recurrence of depressive symptoms after 7 hours of ATD, while no relapse occurred on the control session [30]. In patients in remission who continued on SSRIs treatment, ATD led to a 29% increase of relapse rate after 6 hours [31]. A similar result was reproduced in 17 patients who recently remitted (within 12 weeks), with 8 cases of relapse happened during the ATD session. [32] According to a meta-analysis including 90 studies, ATD, but not acute depletion of the essential amino-acids (APTD, depletion of norepinephrine and dopamine), has a mood lowering effect in remitted MDD patients with

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or without current medication [33]. The above lines of evidence suggest that a decrease of 5-HT levels might lead to recurrence of depressive symptoms in recovered MDD patients.

Disturbed plasma tryptophan (TRP) levels in MDD were also reported. A meta-analysis in 2014 addresses a significant decrease of plasma TRP concentration in MDD patients, regardless of antidepressant treatment. This study found a weak negative association between plasma TRP level and depression severity [34]. Later meta-analyses involving more subjects (Pu et al. [35], N > 2000; Almulla et al. [36], N > 5000) also found significant lower peripheral [plasma and serum] TRP concentrations in MDD patients. The negative correlation between peripheral TRP level and MDD severity is also found in Pu et al. [35]. Almulla et al. (2022) analyzed the level of TRP's competing ammino acids (CAAs) and revealed that MDD patients harbor a significant lower peripheral TRP/CAAs ratio than healthy controls, which is associated with a diminished transportation of TRP into CNS [36]. Decreased peripheral TRP levels measured in MDD patients could indirectly refer to lowered 5-HT in these patients.

However, direct measurements of 5-HT and its metabolite 5-HIAA in MDD resulted in inconsistent outcomes. A case-control study of 173 MDD patients experiencing depressive episodes reports a 97% decrease of plasma 5-HT level in MDD patients compared to healthy controls, which was in support of the serotonin hypothesis [37]. On the other hand, a meta-analysis including 3 databases of postmenopausal women (N > 600) reveals that decreased plasma 5-HT level only exist in subjects who were receiving antidepressants [38]. Lower 5-HIAA level in cerebrospinal fluid (CSF) was detected in a group of 75 MDD patients, but further analysis suggested that antidepressant use is related to the decrease [39]. These results point to a possibility that it is the antidepressant use that lowers the 5-HT level in MDD patients. Another study including 40 drug-free patients didn't identify significant low CSF 5-HT or 5-HIAA concentrations in severe MDD [40]. Meanwhile, meta-analyses considering drug-free patients fail to obtain significant differences of CSF 5-HIAA concentration between MDD patients and healthy controls [41, 42]. In the contrast, homovanillic acid (HVA), the major metabolite of dopamine, was decreased in the CSF of drug-free patients compared with drugged patients [41, 42]. These findings could impair the credulity of the serotonin hypothesis.

In genomics, there is also a lack of strong evidence of serotonergic transmission dysfunction causing depression. Among the 269 genes and 102 variants involved in depression identified in a genome-wide meta-analysis (GWAS) over 100,000 patients, genes connected with the serotonergic systems (e.g. the serotonin transporter *SLC6A4*; the serotonin receptor *HTR2A* and tryptophan hydroxylase) have been largely absent [43]. More recent GWAS incorporating African, Asian and Hispanic individuals along with Caucasian data also found no serotonin-related genes on the top list that associated with MDD [44]. This implies a separation or indirect relation of serotonergic system with the etiology of MDD. Yet it is not to say that serotonergic system should not be considered as a candidate for functional pharmacotherapy. It is suggested that a focus down to specific molecular elements, e.g., individual receptor sub-types, might be the key to decipher the conundrum [45].

3. 5-HT2ARs in depression: evidence from genomics

The 5-HT receptors have been grouped into 7 sub-families, including 13 G-protein coupled receptors (GPCRs) and 1 ligand-gated ion channel receptor (5-HT3 receptor) [25]. Although several other serotonin receptors, e.g. 5-HT1Rs, 5-HT2CR, have received much attention for their implication in MDD [46], both the antagonists and agonists of 5-HT2A receptor appear to have antidepressant-like effects [14]. 5-HT2AR is also relevant in MDD-relating cognitive functions such as fear extinction acquirement (reviewed elsewhere in [47]). In particular, 5-HT2AR-activating psychedelics as therapies for MDD patients has been an active field of research in recent years for their fast onset and persistent antidepressant-like effects [48]. Thus, we chose to focus on the involvement of 5-HT2AR in MDD development and therapy.

Serotonin 2A receptor is a class A GPCR consists of an extracellular N-terminus, 7 transmembrane α-helices connected by 3 intracellular and 3 extracellular loops, an amphipathic helix 8 and an intracellular C-terminus [49]. Of importance, the rodent and human 5-HT2A receptors possess several point variations in their amino acid sequences, which could account for marked species difference in

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selective ligand binding affinity or binding kinetics [50]. 5-HT2A receptors canonically couple via $G_{q/11}$ protein to phospholipase C and phospholipase A2. Upon activation, it leads to increases in inositol trisphosphate, diacylglycerol and intracellular Ca^{2+} as well as the release of arachidonic acid [51]. 5-HT2ARs could also recruit *β*-Arrestin2 in neurons. *β*-Arrestin2 is found to be colocalize with 5-HT2AR in rat prefrontal cortical neurons, and is engaged in desensitization and internalization of the receptor [52]. *β*-Arrestin2 also promotes extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation in mouse frontal cortex [53], possibly acting as scaffolds to facilitate the three-kinase cascade of ERK1/2 phosphorylation [54]. The preference towards G-protein or Arrestin2 signaling pathway *in vivo* depends on the ligand, the cell type and micro-environment surrounding the receptor [52].

Peripherally, 5-HT2ARs function to mediate cardiovascular activities, e.g., platelet aggregation and smooth muscle contractile responses [25]. In the CNS, an *in vivo* PET- and MRI-based study using radioligand [^{11}C]Cimbi-36 (has a strong selectivity for 5-HT2ARs in the cerebral cortex [55]) reveals that 5-HT2ARs are densely expressed across human cerebral cortex, and of medium density in subcortical areas including hippocampus, amygdala and nucleus accumbens [56]. Neocortical regions (e.g. prefrontal cortex), amygdala and hippocampus function in emotion regulation or cognitive control and are implicated in MDD pathology. For example, hippocampal volume is reduced in MDD patients. Prefrontal cortex function, which is involved in cognitive tasks, is usually disturbed or impaired in MDD [13]. 95% of glutamatergic pyramidal neurons and 16-20% GABAergic interneurons in layer II−V of monkey and human prefrontal cortex [PFC] express 5-HT2AR mRNA [57]. Immunolabel studies suggest that the majority of 5-HT2ARs reside post-synaptically at apical dendrites of pyramidal neurons in the primate cortex [58].

Results from studies focusing on *HTR2A* single nucleotide polymorphisms (SNPs) indicate that variations in 5-HT2AR gene may not cause MDD to occur more easily, but may affect the treatment of MDD. Rs6311 (-1438 A>G) is the most studied SNP in the upstream or promoter region of *HTR2A*. The G allele of rs6311 is related to more expression of the extended 5' untranslated region of *HTR2A* mRNAs [59]. Existing data suggest that rs6311 is associated with mood disorders such as schizophrenia [60, 61] and alexithymia [62]. Regarding to MDD, recent large-scale meta-analyses show that, a significant relationship between rs6311 and MDD vulnerability is absent [43, 63]. However, rs6311 is reported to be correlated to treatment response to antidepressants in another meta-analysis including a total of 1962 subjects [64]. Although the 5HT2AR SNP is not found to be associated with the cause of depression across various GWAS studies, it is suggested to be related to antidepressant response. In a Chinese population, Sun et al. reported an association between *HTR2A* SNP rs3803189 and early response to SSRIs [65]. Qesseveur et al. found another *HTR2A* SNP rs7333412 (GG > AG/AA) to be suggestive of a poorer therapeutic outcome under antidepressant monotherapy in a French population [66]. 12 other *HTR2A* SNPs related to antidepressant response of MDD patients were identified in a GWAS study conducted on a Chinese cohort, among which appeared rs7333412 and rs3803189 [20]. Hence, regulating 5-HT2AR may influence the response to serotonergic antidepressants.

4. Target 5-HT2AR for antidepressant-like effects: antagonism

5-HT2AR activation appear not to be causational in the development of depression, further confirmed by results from genetically modulated rodent models. In mice, there were no difference between 5-HT2AR knock out and wild type individuals in baseline forced swim test (FST) or tail suspension test (TST) performance, tests that are wildly used to measure behavioral despair [67, 68]. 5-HT2AR knock-out mice, with approximately 68% decrease of 5-HT2AR in the brain, exhibited no increase in immobility in TST compared to their wild type counterparts [69]. Additionally, 5-HT2AR deficiency didn't prevent mice from developing anhedonic behavior after chronic corticosterone treatment, a classic method to simulate stress exposure [70]. 5-HT2AR knock-out also didn't prevent mice from displaying despair following chronic unpredictable stress [71]. Considering these facts, 5-HT2AR might not be the main player in mediating stress' ability to trigger depressive symptoms.

On the other hand, pre-clinical evidence indicates that targeting 5-HT2AR might alleviate depression or facilitate existing antidepressants. SSRI fluoxetine was known to increase the number of

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reinforcements received by rats in differential reinforcement of low rate 72s test (DRL-72s). This test schedule requires rats to properly withhold a lever-pressing behavior for 72 seconds after the previous response to receive the reinforcement; increased reinforce rate and inter-response time are indicative of antidepressant-like effects. When selective 5-HT2AR antagonist MDL100907 was administrated alone, it increased rats' reinforcement number to the same extent as fluoxetine [72] MDL100907 alone (1 or 2mg/kg) also reversed the increased immobility in FST of Wistar rats in nicotine withdrawal [73].

More evidence indicates that 5-HT2AR antagonists could enhance the performance of traditional serotonergic antidepressants. Fluoxetine and MDL100907 had synergistic antidepressive effects measured by rat DRL-72s when administered simultaneously [72]. MDL100907 (2mg/kg) also potentiated sub-effective dose of SSRI escitalopram in mice FST [74]. Similar phenomenon was seen in another selective 5-HT2AR antagonist, BIP-1. BIP-1 was capable of augment the effect of amitriptyline (TCA) and harmane (MAOI) at the minor doses in mice FST and TST [75]. Since activation of 5-HT2AR in rodents attenuated the firing rate of dorsal raphe nuclei serotonin neurons [66], it was proposed that antagonizing 5-HT2AR may decrease the inhibition of 5-HT outflow following SSRI, TCA or MAOI, thus increase the 5-HT level in the brain and alleviate depressive symptoms. Nevertheless, electrodialysis experiments shows that, compared to sub-effective dose of escitalopram, the 5-HT outflow in mouse frontal cortex after co-administration of escitalopram and MDL100907 (2mg/kg) did not change. However, the noradrenaline outflow in the same region increased by 40-50% [74]. This study didn't rule out the possibility of noradrenergic system being involved the mechanism of 5-HT2AR antagonists.

Clinical evidence comes from atypical antipsychotics (including aripiprazole, brexpiprazole, quetiapine and risperidone) that are known for their higher affinity as antagonists of 5-HT2ARs over dopamine receptor 2 [76]. Two recent meta-analyses show that these drugs behave as effective augmentation of typical serotonergic antidepressants in MDD [77] or treatment resistant depression (TRD) [78]. Thus, it was proposed that antagonizing 5-HT2ARs may potentiate serotonergic antidepressants' therapeutic effect in human as well [79].

5. Target 5-HT2AR for antidepressant-like effects: agonism

On the other hand, molecules demonstrate agonism at 5-HT2AR had also revealed their potential as treatments for depression. 5-HT2AR targeting psychedelics, including a) ergolines such as lysergic acid diethylamide [LSD], b) tryptamines such as *N,N*-dimethyltryptamine (DMT) and psilocybin/psilocin (active metabolite of psilocybin), and c) phenethylamines such as 2,5-dimethoxy-4-iodoamphetamine (DOI) have received growing attention for their strong capability to mitigate several mental illnesses in a fast-acting and long-lasting manner [18, 48].

A pilot study on MDD in 2016 reported that two consecutive doses of oral psilocybin intake (10 mg followed by 25mg) along with psychotherapy support following drug administration achieved significant therapeutic outcome in TRD patients (who showed limited response to typical antidepressants). The effect appeared less than one week after the last dose, and persisted up to 3 months [80]. In comparison, SSRIs typically start to reduce depressive symptoms after several weeks of daily intake [8]. Following double-blinded trials also detected fast-onset improvement of mood after two sessions of psilocybin treatment (20 and 30mg/70kg, separately) in antidepressant free MDD patients [81]. Depression severity remained low for 12 months post-treatment, according the follow-up study of the same cohort [82]. The largest randomized trial involving 233 TRD patients shows that a single injection of psilocybin could generate anti-depressive and anxiety-relieving effect which lasts for at least 3 weeks [83]. All trials suggest that under these doses (below 30mg/70kg), the adverse events are mild and normally subsides within 6 hours [80, 81, 83]. Psilocybin therapy appeared to be fast-onset, persistent, and effective to treatment-resistant MDD patients.

Enduring antidepressive-like effects of 5-HT2AR targeting psychedelics were also observed in rodents. A Single injection of psilocybin or LSD caused decreased FST immobility time of rats [84]. DOI reduced FST immobility and facilitated fear extinction learning in wild type mice [85]. Importantly, although psilocybin, LSD or DOI could activate several other receptors in the brain (for example, 5-

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HT1 receptors and dopamine receptors), preclinical studies imply that the therapeutic effects of these psychedelics appear to be 5-HT2AR dependent, as discussed below.

The postulated mechanism underlying the mood-modulating property of psychedelics might be their capability of fueling dendrito- and spino-genesis in crucial regions including hippocampus (HPC) and prefrontal cortex (PFC). It has been proposed that neural atrophy in regions such as hippocampus and frontal cortex is responsible for depression development, thus inducing neuroplasticity might rescue depressive symptoms (reviewed elsewhere in Vargas et.al. [48]). The hypothesis is consistent with that, elevated neuroplasticity in frontal cortex or hippocampus was observed after SSRIs or ketamine (NMDA receptor antagonist, fast-acting antidepressant) treatment in rodent models [86, 87]. Meanwhile, psychedelics have also been demonstrated to be profoundly promote neuroplasticity, possibly via 5-HT2ARs. Higher synaptic density in pig PFC and HPC following administration of 0.08mg/kg psilocybin persisted 7 days [88]. Ly et al. showed that LSD, DMT and DOI could potentiate dendritic harboring and functional synapse formation in rat cortical neurons *in vitro* or *Dorsophila* larvae *in vivo*, while 5-HT2AR selective antagonist ketanserin completely blocked compound-induced effects [89]. Subsequent study suggested that serotonergic psychedelics recruited brain-derived neurotrophic factor (BDNF) -TrkB signaling to promote neuroplasticity [89, 90]. It is reasonable to suggest that the antidepressant-like effects of 5-HT2AR-targeting psychedelics are also related to their ability to enhance neuroplasticity.

Unfortunately, the notorious hallucination-generating property of psychedelics is attributed mainly to 5-HT2AR activation in the neocortex as well (for reference, see Vollenweider et al. [91]), which makes these compounds unfavorable for extensive application. In human, plasma psilocin concentrations and CNS 5-HT2AR binding was highly correlated with the intensity of hallucination [92]. In rodents, the hallucination-generating potency of psychedelics is measured by counting head twitch response (HTR), for the EC50 of psychedelics for HTR in mice is highly correlated with their EC50 for human-reported intensity of hallucination [93]. Furthermore, psychedelics that activate 5-HT2AR (including DOI, LSD and psilocybin) failed to induce HTR in 5-HT2AR knock out mice. HTR was rescued in mice re-introduced with cortical 5-HT2ARs [94]. This indicates that hallucination is specifically mediated by cortical 5-HT2ARs.

6. Future 5-HT2AR targeting treatments in development

To better design 5-HT2AR-related treatment for MDD, we must understand whether the deleterious hallucinogenic property of cortical 5-HT2AR agonism can separate from its beneficial antidepressant-like effects. Some results suggest no. 2023 study by Cameron et al. found that 5-MeO-DMT (10mg/kg) produced head twitch behavior and decreased immobility in FST in mice. These effects were blocked simultaneously by pretreatment with ketanserin (4mg/kg) [70]. Another study revealed that 5-HT produced apparent HTR, reduced immobility in FST and generate spinogenesis in mice PFC at the same time [95]. Above evidences imply that activating 5-HT2ARs would elicit HTR and promote neuroplasticity simultaneously; vice versa, deactivating the same receptor would cancel out both effects.

In a different manner, the discoveries of several non-hallucinogenic 5-HT2AR agonists raised the possibility that the two properties discussed might be orthogonal. 5-HT2AR partial agonist lisuride, structurally related to LSD yet induce no HTR, acutely reduced TST immobility time in an intrinsic mouse model of depression (vesicular monoamine transporter 2 mice, VMAT-HET). Nevertheless, lisuride targets monoamine receptors other than 5-HT2AR, for example, 5-HT1AR and dopamine receptor 2. The contributions of these receptors were not ruled out from the study design [96]. Another compound 2-Br-LSD, also an LSD derivative, decreased immobility in FST in naive mice 1 day post injection. The effects were blocked by pretreatment with MDL100907 [97]. Modified from psychedelic ibogaine, the third compound tabernanthalog were reported to produce antidepressant-like effects via 5-HT2ARs [98]. Using developed biosensor psychLight that predicts hallucinogenic potency of 5-HT2AR ligands, another non-hallucinogenic molecule AAZ-A-154 was sifted out and were shown to relieve anhedonia in VMAT-HET mice for at least 12 days [99]. On VMAT-HET mice, selective 5-HT2AR agonist R-69 and R-70 enhanced active coping behaviors in mice TST, which is a sign of alleviated

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despair [100]. Other two compounds, IHCH-7079 and IHCH-7086 caused immobility time to decrease in TST and FST in chronic corticosterone treated mice, which was blocked by MDL100907 [101]. The above listed 5-HT2AR agonists all didn't trigger HTR. The discovery of these compounds accentuates the possibility of designing 5-HT2AR agonists to solely exert anti-depressive effect.

The team which designed IHCH-7079 and IHCH-7086 calculated the transduction efficacies of several 5-HT2AR agonists, and found that compared to DOI, LSD and psilocin, non-hallucinogenic lisuride, IHCH-7079 and IHCH-7086 had overall lower Gq or β-Arrestin2 transduction efficacies at 5-HT2AR [101]. Meanwhile, Wallach et al. found that only phenethylamines having a Gq pathway efficacy over 70% at 5-HT2AR possess potential to produce hallucination [102]. It is probable that psychedelics might not alter consciousness if doses are small enough. In the meanwhile, micro doses of psychedelics might still achieve antidepressant-like effects. For instance, no HTR in mice was observed ensuing a dose of 0.015mg/kg LSD, while swimming did increase in FST and TST, suggesting that controlling the dosage of psychedelics might be useful to avoid hallucination [101]. Thus, chronic, intermittent intake of psychedelics might, in theory, act like antidepressants without undesirable side effects.

Application of 1 mg/kg DMT (that does not induce HTR) on every third day was tested on rats. The result showed increased swimming in FST and enhanced fear extinction learning after 10 and 13 doses, respectively. However, adverse events such as severely disturbed metabolism occurred in male rats, as well as loss of PFC layer V pyramidal dendritic spine density [103]. Desensitization of 5-HT2ARs in mice occurred following 14 days of consecutive administration of hallucinogenic 5-HT2AR agonists DOI, TCB-2 and 25CN-NBOH, accompanied by an increment of proBDNF protein levels in frontal cortex, which could weaken synaptic strength [104]. With clinical evidence of psychedelic microdosing scarcely presented, the overall feasibility of microdosing remains inconclusive.

On the other hand, there are evidence implying that a partial 5-HT2AR blockade applied jointly with psychedelics could eliminate hallucination while retaining the antidepressant-like effects. Tracking spine morphology *in vivo* using two-photon imaging, Shao et al. reported robust increase in dendrite functional spine formation in mouse medial PFC after a single injection of psilocybin (1mg/kg). Surprisingly, pretreatment with ketanserin [1mg/kg] 10 minutes ahead was sufficient to block psilocybin-induced HTR, yet failed to prohibit the generations of new spines. The author postulated that since only 30% of cortical 5-HT2AR was preoccupied by ketanserin under this dose, it would be possible to erase hallucination following psilocybin by an incomplete 5-HT2AR blockade [105]. In the meanwhile, Hesselgrave et al. reported that lessened anhedonia in chronically stressed mice produced by psilocybin (1mg/kg) was not abolished by ketanserin (2mg/kg) pretreatment 60 minutes ahead. Notably, mice showed high or low HTR level following psilocybin regained reward behaviors to the same extent, suggesting a dissociation between hallucination and anti-depressive efficacy [106].

7. Conclusion

In this review, we provided a basic overview of the serotonin hypothesis of MDD, then focused on the 5-HT2AR and its implication in MDD etiology and therapy. Evidence at hand suggest that while 5-HT2AR may not contribute to the development of MDD, it could be important in the treatment of MDD. Both antagonists and agonists of 5-HT2AR could be useful drugs for depression, especially agonists that alleviate depressive symptoms of treatment-resistant patients in a fast-acting, long-lasting manner.

Based on evidence presented in our review, four approached could be proposed regarding utilizing 5-HT2AR ligands to achieve antidepressive effects. First, selective 5-HT2AR antagonists could be given along with traditional serotonergic antidepressants as an augmentative strategy. Second, microdosing of existing 5-HT2AR-targeting psychedelics could be designed to prevent hallucination following 5-HT2AR activation while retaining mood-elevating efficacy. Thirdly, incomplete 5-HT2AR blockade could be introduced with effective doses of 5-HT2AR-targeting psychedelics to eliminate hallucination. Lastly, fueled by more accurate understanding of 5-HT2AR binding structures with different ligands and their corresponding down-stream transduction events, novel non-hallucinogenic compounds could be tailored to perform as antidepressants. However, the mechanisms underlying the therapeutic effects

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of 5-HT2AR antagonists and agonists remain to be elucidated. It should be clearly demonstrated whether synaptogenesis and rescuing neuroplasticity mediates antidepressant-like effects of 5-HT2AR agonists. The precise set of cellular events distinguishing hallucinogenic compounds from non-hallucinogenic ones is also crucial for drug modification.

In summary, eligible data confirmed the important and complicated involvement of 5-HT2AR in MDD treatment. The possibility of optimizing 5HT2AR-targeting MDD therapies warrants further investigation.

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