Zoo 400 – Final Project
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A Mini Review of 5HT2A Receptor Agonists: From Microtubules to Altered States of Consciousness

Psychedelic substances (5H2Ar Agonists) have been used for thousands of years in indigenous communities and were discovered by the western world in the early 1940s with the accidental discovery of LSD-25 by Albert Hofmann (Carhart-Harris & Goodwin, 2017). During the mid-century, research exploring these compounds skyrocketed where tens of thousands of patients were treated for various psychiatric disorders, though eventually falling into a few decades of complete arrest due to societal and political pressures. Nevertheless, in the early ’90s, research investigating the therapeutic potential of 5HT2A receptor agonists started emerging again with philanthropy funding, the Multi-Disciplinary Association for Psychedelic Study (MAPS), and pioneering research groups like Johns Hopkins Psychedelic Center publishing unignorable findings (Belouin & Henningfield, 2018).

Nowadays, with the climbing number of studies published every year as well as a growing body of evidence supporting the vast therapeutic potential of these compounds, federal agencies like the NIH and FDA have given “breakthrough therapy” status to accelerate the exploration (Kozlowska et al., 2021). The focus of researchers thus far has been the potential therapeutic abilities of psychedelics for psychiatric disorders like addiction, depression, anxiety, and obsessive-compulsive disorders (Reiff et al., 2020). However, recently emerging evidence started to accumulate regarding the underlying mechanisms of action shedding light on subjects such as neural plasticity, perception, and altered states of consciousness (Hasler et al., 2004). The serotonergic system is extremely convoluted impacting mood, cognition, perception, memory, and other critical humanistic aspects (Berger et al., 2009). Psychedelics, such as psilocybin (magic mushrooms), Lysergic acid diethylamide (LSD), N, N-Dimethyltryptamine (DMT) exert their action mainly on the serotonergic system, being highly potent agonists on the 5HT2A receptor (Ray, 2010).

This review will briefly cover recent findings regarding the molecular and cellular bio correlates of the mechanisms of action of 5HT2Ar agonist. Then, zooming out to the structural and functional changes corresponding to the effects of psychedelics will be reviewed based on recent evidence and the new profiling as “psychoplastogens”. Finally, the clinical applications of these compounds will be discussed, explicitly concerning core psychiatric disorders, brain traumatic injuries, and immunomodulation.

Underlying Cellular and Molecular Actions

Recent studies have started investigating and exploring the underlying neurobiological correlates of psychedelics. Dakic et al. (2017), published a shotgun mass spectrometry study looking at the effects of 5-MeO-DMT on human cerebral organoids. According to their findings, roughly 14% of total identified proteins were found to be attenuated by exposure to 5-MeO-DMT. Their analysis confirmed the modulation of proteins associated with long-term potentiation, increased plasticity, and microtubule dynamics. More studies looking at this range of phenomena on human cell lines are necessary for other commonly used psychedelics like LSD and psilocybin.

Other studies, interested in the differences between hallucinogenic 5HT2Ar agonists (HC) versus non-hallucinogenic 5HT2Ar agonists (NHC), were looking at differences of downstream effects and transcriptome responses (González-Maeso et al., 2007). In their study, González-Maeso et al. (2007) found that while c-fos changes occurred for both HC (LSD) and NHC (Lisuride), changes in egr-2 of layer V of the cortex was specific to HC. Pointing out that not all 5HT2A receptor agonists are psychedelic substances and that downstream effects should be considered for classifying these compounds.

Further studies used 5HT2Ar agonists to deepen our understanding of the development of the cerebral cortex and microtubules dynamics. In their study, Ohtani et al. (2014) found that exposure of rat's cortical neurons in vitro to DOI promoted increased dynamics in dendritic growth cones. They stated that these results were due to an increase in tyrosinated alpha-tubulin (dynamic tubulin) and decreased acetylated alpha-tubulin (stable tubulin). DOI has also been shown to be a potent TrkA and TrkB activator (Marinova et al., 2017). In their study, Marinova et al. found that DOI phosphorylates both TrkA and B receptors in human cell lines in vitro, supporting the existing body of literature regarding its therapeutic potential.

To sum up this section, studies looking at a vast number of different psychedelics compounds started shedding light on their subcellular mechanism of action. Each compound has a different pharmacological profile, though all share a common affinity to the 5HT2A receptor.

Structural and Functional Plasticity

Emerging evidence started accumulated in the past few years supporting the rapid and potent capacity of 5HT2A receptor agonists to induce neurogenesis and support plasticity (Lukasiewicz et al., 2021). In his seminal paper, Olson (2018) introduced the term "psychoplastogens" to classify compounds that have the potential value of treating various disorders in the central nervous systems. His definition of psychoplastogens

is compounds that induce a measurable change in plasticity after a single administration within a short time frame. In their study, Ly et al. (2018) looked at multiple common psychedelic compounds (LSD, DMT, DOI, ketamine) and showed that all increased dendritic arbor complexity promoted spine growth and stimulated synaptogenesis. Furthermore, ketanserin, a selective 5HT2A receptor antagonist, attenuated these results, pointing out the critical role of this receptor subtype. Lastly, they showed that mTOR and TrkB signaling is required for these plastogenic effects.

In a follow-up study, Ly et al. (2021) showed that even with shorter transient stimulation, clinically relevant periods for human patients, these pro-plastogenic effects are still seen. Several active controls were investigated in their study to rule out more straightforward explanations. For example, BDNF, which is commonly increased in the system post-exposure to psychedelics, was insufficient to induce the same results. Then, using KCl to look at the results following simple excitation by increasing glutamate release produced similar results to BDNF, which were not significant from vehicle. These results suggest that it is most likely that psychedelics work via a combination of multiple pathways converging to produce neural growth.

Another group decided to look at the effect of a single dose of 5-MeO-DMT in vivo. In accordance with previous in vitro literature, Lima da Cruz et al. (2019) found that administration of 5-MeO-DMT stimulates proliferation of neural progenitors and survivability of granule cells in the ventral dentate gyrus. Furthermore, granule cells were characterized by structural changes like more branches and intersections and functional changes such as higher AP threshold and higher frequency firing, which indicate faster maturation.

Clinical applications – TBI, Autoimmune, and Psychiatric disorders

Even though there are not enough replication studies regarding the psychplastogenic effects or robust knowledge explaining the underlying molecular mechanisms, it is hard to stay ambivalent to the potential therapeutic effects of psychedelics. So far, the vast majority of research was dedicated to psychiatric disorders, most likely due to the seeds which were planted during the ’60s. However, it is essential to take into consideration other avenues as well.

One of the earlier studies in the second wave of psychedelic research, was looking at the function of N, N-DMT, and 5-MeO-DMT not as neuromodulators but as immunomodulators (Szabo et al., 2014). In their study, both DMT derivative compounds attenuated both innate and adaptive immunity via the sigma-1 receptor. In addition, these actions were seen as an increased production of anti-inflammatory cytokine IL-10, and downregulation of pro-inflammatory cytokines and chemokines such as IL-6 and TNFalpha.

Another clinically relevant area of research in which 5HT2Ar agonists might offer benefits in treating traumatic brain injuries. For example, a recent in vivo study found that N, N-DMT significantly helps rats recover from focal brain ischemia (Nardai et al., 2020). Furthermore, their experiment found that rats treated with DMT showed reduced cerebral lesion volumes, which was likely mediated by reduced mRNA expression of APAF1, an activator of mitochondrion-dependent apoptosis pathway, and an increase in BDNF. These results were in accordance with their previous study looking at the protective effect of DMT against induced hypoxia in vitro (Szabo et al., 2016).

Further primary research into different compounds and transitional studies is necessary to see the realization of these compounds for the treatment of autoimmune and chronic inflammatory illnesses and traumatic brain injuries. However, much more evidence exists when it comes to psychiatry that allowed clinical research to be done in recent years. That said, significant gaps in knowledge are present, and more and more groups are tackling this problem from multiple directions.

Preller et al. (2020) showed that psilocybin, similarly to LSD, has significant effects on global brain connectivity mediated by the 5HT2A and 5HT1A receptor systems. They found the psilocybin induced synchronization of sensory networks and disintegration of association function networks using receptor-gene expression maps and fMRI. This study indicates on the impact of 5HT2A receptor agonist on the circuit level as well and goes in accordance with previous studies looking at a decrease in anxiety (Griffiths et al., 2016), increase in cognitive and neural flexibility (Doss et al., 2021), increased EEG complexity signal (Timmermann et al., 2019), long term positive changes in mood (Barrett et al., 2020), and extinction of conditioning (Catlow et al., 2013).

Discussion

This review went over the effects of psychedelics on multiple systems and scales, from genomic changes to the complexity of brain activity. Our knowledge is expanding rapidly, but further research is necessary. Studies looking at aspects like functional crosstalk between GPCRs and other receptors involved in their therapeutic action might offer further explanations (Baki et al., 2016; Poulie et al., 2020).

Many open questions regarding these compounds' action and clinical implications are still present. More research is needed to investigate the long-term effects, exact molecular underpinning, and what brings all these compounds to possess this potent psychoplastic ability. In this review the effects on the glia system were not mentioned at all, however this is another necessary research area where our knowledge is lacking.

Lastly, systematic reviews and meta-analyses are crucial for compiling all the accumulating evidence and determining the effect sizes. Earlier this year, a systematic review (de Vos et al., 2021) and a mini-review like this one (Khan et al., 2021) helped set the stage for future researchers thinking of studying these compounds. Even though the 5HT2A receptor received the most attention, other receptors are bound to play a critical role, just like the sigma1 and 5HT1A receptors mentioned earlier (Ray, 2010)..

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