

Antidepressant, Antipsychotic, and Hallucinogen Drugs for the Treatment of Psychiatric Disorders

A Convergence at the Serotonin-2A Receptor

ABSTRACT

Antidepressant, atypical antipsychotic, and hallucinogen drugs mediate their actions in part by interactions with the serotonin-2A (5HT_{2A}) receptor. Serotonergic hallucinogen drugs, such as psilocybin, bind most potently as agonists at the 5HT_{2A} receptor, producing profound changes in perception, mood, and cognition. Some of these drugs have been or are currently being investigated in small Phase 2 studies for depression, alcoholism, smoking cessation, anxiety, and posttraumatic stress disorder. However, unlike the synergistic effects of combining antidepressant and atypical antipsychotic drugs, the potential therapeutic effects of hallucinogen drugs may be attenuated by the concurrent use of these medications because antidepressant and atypical antipsychotic drugs desensitize and/or down-regulate 5HT_{2A} receptors. This finding has important implications for optimizing the potential therapeutic use of hallucinogen drugs in psychiatry. [*Journal of Psychosocial Nursing and Mental Health Services*, 54(7), 21-24.]



Evidence from autopsy and brain imaging studies suggests that serotonin-2A (5HT_{2A}) receptor binding is decreased in the frontal cortex of patients with schizophrenia (Rasmussen et al., 2010), but that 5HT_{2A} receptor density is increased in the frontal cortex of patients with major depression (Bhagwagar et al., 2006; Meyer et al., 2003; Shelton, Sanders-Bush, Manier, & Lewis, 2009). Many psychotropic drugs, including

antidepressant, atypical antipsychotic, and hallucinogen drugs, mediate their actions in part by interactions with the 5HT_{2A} receptor (Gray & Roth, 2001).

PIMAVANSERIN AND THE 5HT_{2A} RECEPTOR

In last month's column, I described the atypical antipsychotic drug pimavanserin (Nuplazid®), which is an inverse agonist at the 5HT_{2A} receptor (Howland, 2016). An inverse

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agonist drug reduces the signaling activity of an intrinsically active receptor below its basal level of activity, and also blocks the activating effects of a ligand (e.g., serotonin or agonist drug) at the receptor. Pimavanserin is approved by the U.S. Food and Drug Administration (FDA) for the treatment of hallucinations and delusions associated with Parkinson's disease.

Serotonergic hallucinogen drugs, such as psilocybin, produce profound changes in perception, mood, and cognition (Halberstadt & Geyer, 2011), and these drugs are now being investigated for putative therapeutic effects in various psychiatric disorders (Mithoefer, Grob, & Brewerton, 2016; Vollenweider & Kometer, 2010). Psilocybin is a prodrug that is physiologically converted to psilocin (Passie, Seifert, Schneider, & Emrich, 2002).

because the regulation of 5HT_{2A} receptors is peculiar and paradoxical (Eison & Mullins, 1996), pimavanserin may have potentially beneficial mood effects that should be investigated.

REGULATION OF 5HT_{2A} RECEPTORS

Desensitization is a short-term adaptive mechanism by which cells regulate receptor responsiveness to repetitive stimuli (Gray & Roth, 2001). Hence, repeated exposure of a cell to a receptor agonist drug may result in desensitization of the cell's responsiveness to an agonist. Following prolonged or repetitive activation of receptors by agonists, however, there is an actual reduction in the number of receptors within the cell, a phenomenon known as *down-*

receptor down-regulation is roughly correlated with their affinity for the 5HT_{2A} receptor (Gray & Roth, 2001). Serotonin selective reuptake inhibitor (SSRI) drugs are associated with desensitization of 5HT_{2A} receptor function (Yamauchi, Miyara, Matsushima, & Imanishi, 2006), and some SSRI drugs also down-regulate 5HT_{2A} receptors (Gray & Roth, 2001). Pharmacological synergism between 5HT_{2A} antagonist drugs and SSRI drugs may account for enhanced therapeutic effects when these drugs are used in combination (Marek, Carpenter, McDougle, & Price, 2003).

ANTIDEPRESSANT EFFECTS OF ATYPICAL ANTIPSYCHOTIC DRUGS

Inverse agonism at the 5HT_{2A} receptor is a pharmacological characteristic common among atypical antipsychotic drugs (Meltzer & Massey, 2011; Weiner et al., 2001). Many atypical antipsychotic drugs have antidepressant effects (Wright, Eiland, & Lorenz, 2013). Aripiprazole (Abilify[®]), brexpiprazole (Rexulti[®]), and quetiapine (Seroquel[®]) are FDA-approved as adjuncts (together with antidepressant drugs) for the treatment of major depression. The olanzapine (Zyprexa[®]) and fluoxetine (Prozac[®]) combination product (Symbyax[®]) is approved for treating major depression and bipolar depression. Quetiapine and lurasidone (Latuda[®]) are each approved by the FDA for the treatment of bipolar depression. Therefore, therapeutic potential of pimavanserin alone or together with an antidepressant drug for the treatment of major depression or bipolar depression warrants clinical study.

HALLUCINOGEN DRUGS AND THE 5HT_{2A} RECEPTOR

Converging evidence from pharmacological, electrophysiological, and behavioral studies in animals

Converging evidence from pharmacological, electrophysiological, and behavioral studies... suggest that hallucinogen drugs produce their effects...through agonist actions at cortical 5HT_{2A} receptors.

Psilocin and other serotonergic hallucinogen drugs interact with different serotonin receptors, but they bind most potently as agonists at the 5HT_{2A} receptor. In my article on pimavanserin (Howland, 2016), I suggested that, as an inverse agonist at the 5HT_{2A} receptor, it might have adverse mood effects because psilocybin appears to have antidepressant effects (Carhart-Harris, Bolstridge, et al., 2016).

It is important to emphasize, however, that the mood effects of pimavanserin have not been systematically evaluated in clinical studies. Indeed,

regulation. Desensitization is rapidly reversible following the removal of an agonist, but recovery following down-regulation is slower and depends on the synthesis of new receptors.

Unlike other types of receptors, a seemingly paradoxical finding demonstrated with 5HT_{2A} receptors is that they are also susceptible to down-regulation by many antagonists (Eison & Mullins, 1996; Gray & Roth, 2001). This has been observed with antidepressant drugs that are high affinity antagonists at the 5HT_{2A} receptor, and the ability of antipsychotic drugs to induce 5HT_{2A}

suggest that hallucinogen drugs produce their effects in animals and possibly in humans primarily through agonist actions at cortical 5HT_{2A} receptors (Vollenweider & Kometer, 2010), although interactions with other receptor systems contribute to their psychopharmacological and behavioral effects (Halberstadt & Geyer, 2011). Lysergic acid diethylamide (LSD) has been demonstrated to down-regulate 5HT_{2A} receptors (Buchborn, Schroder, Holtt, & Grecksch, 2014). The effect of hallucinogen drugs on the 5HT_{2A} receptor provides a plausible mechanism to explain and justify their potential therapeutic use in the treatment of depression, anxiety, and other psychiatric disorders (Carhart-Harris, Bolstridge, et al., 2016; Mithoefer et al., 2016; Vollenweider & Kometer, 2010).

THERAPEUTIC USES OF HALLUCINOGEN DRUGS

Early clinical research during the 1950s and 1960s suggested a number of therapeutic applications for hallucinogen drugs (Johnson, Richards, & Griffiths, 2008). A review of 42 older studies reported improvement in patients with anxiety disorders, depression, personality disorders, sexual dysfunction, and obsessive-compulsive disorders, although the methodological quality of these studies was poor (Vollenweider & Kometer, 2010). Psilocybin and methylenedioxymethamphetamine (MDMA) have been or are currently being investigated in small Phase 2 studies for alcoholism, smoking cessation, anxiety, and posttraumatic stress disorder (Mithoefer et al., 2016). Psilocybin was found to have antidepressant effects in an open-label feasibility study of 12 patients with treatment-resistant depression (Carhart-Harris, Bolstridge, et al., 2016).

Hallucinogen drugs generally lack physiological toxicity (Johnson

et al., 2008). Although these drugs can be misused or abused (such as other psychotropic and psychoactive drugs), they are not considered drugs of dependence because they are not associated with compulsive drug seeking or with a known withdrawal syndrome. Acute psychological distress (i.e., anxiety, fear, panic, dysphoria, and/or paranoia) can occur, but prolonged psychosis or lasting perceptual abnormalities are rare when these drugs have been administered using fixed doses in controlled research settings (Carhart-Harris, Kaelen, et al., 2016; Johnson et al., 2008). Controlled studies and observational follow-up studies describe acute psychological distress in a minority of participants, with enduring benefits over time and no evidence for increased rates of mental health problems (Carhart-Harris, Kaelen, et al., 2016).

IMPLICATIONS OF INTERACTIONS AT THE 5HT_{2A} RECEPTOR

Because 5HT_{2A} receptor antagonist drugs block the subjective effects of hallucinogen drugs (Halberstadt & Geyer, 2011; Vollenweider & Kometer, 2010), atypical antipsychotic drugs are not likely to be useful adjuncts as they are with SSRI antidepressant drugs. Moreover, because antidepressant and atypical antipsychotic drugs desensitize and/or down-regulate 5HT_{2A} receptors, the therapeutic effects of hallucinogen drugs may be attenuated by the concurrent use of these medications. This finding is a potentially important concern for developing strategies to optimize the therapeutic use of hallucinogen drugs. For example, in an open-label feasibility study of 12 patients with treatment-resistant depression (Carhart-Harris, Bolstridge, et al., 2016), psilocybin was found to have a substantial antidepressant effect in 11 patients after 1 week, but the substantial benefit

did not persist and seven patients had mild-moderate or severe levels of depressive symptoms after 3 months. Because even low levels of depression symptoms are associated with significant impairment (Howland, 1993; Howland et al., 2008), enhancing the antidepressant effect of psilocybin may require other pharmacological or nonpharmacological approaches. The Phase 2 studies of psilocybin and MDMA (Mithoefer et al., 2016) use these drugs as adjuncts to psychotherapy, rather than as stand-alone drug treatments or as adjuncts to other psychotropic drugs.

CONCLUSION

Negative publicity shut down clinical research on hallucinogen drugs more than 40 years ago, but there has been a renewed interest in studying their potential therapeutic use(s) in psychiatry. Previous clinical studies and the effect of hallucinogen drugs on the 5HT_{2A} receptor provide a justifiable reason to pursue additional clinical studies. Antidepressant, atypical antipsychotic, and hallucinogen drugs mediate their actions in part by interactions with the 5HT_{2A} receptor. How these drugs interact with the 5HT_{2A} receptor is important for understanding some of their clinical effects, as well as for understanding possible synergism or antagonism when they are combined.

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