The Serotonin-7 Receptor as a Novel Therapeutic Target

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Issue: *Blockade of 5-HT$_7$ receptors may be a novel therapeutic approach for achieving antidepressant and memory-enhancing actions.*

There are more than a dozen receptor subtypes for serotonin (5-hydroxytryptamine, 5-HT), but only 2 of them are generally well known to clinical psychopharmacologists[1]: the 5-HT$_{1A}$ receptor, stimulation of which is linked to antidepressant and anxiolytic actions, and the 5-HT$_{2A}$ receptor, blockade of which is linked to the reduction of extrapyramidal side effects and other side effects of the second-generation atypical antipsychotics.[1,2] Now comes the 5-HT$_7$ receptor onto the scene,[2–17] not just because of the development of specific compounds allowing characterization of this receptor,[3,5,7–9] but also because of the discovery that several of the known antidepressants and antipsychotics block 5-HT$_7$ receptors, and that this 5-HT$_7$ antagonism may account in part for the therapeutic properties of these drugs, especially antidepressant actions.[10–17]

Localization and Function of 5-HT$_7$ Receptors

Serotonin-7 receptors are postsynaptic G protein–linked receptors that may regulate serotonin-glutamate interactions.[3,4,7] They are distributed in areas that explain their functions, namely, the suprachiasmatic nucleus of the hypothalamus; the hippocampus, cortex, and thalamus; and also in the midbrain raphe nuclei, probably on GABA interneurons or on glutamate terminals.[3,4,7] Numerous animal studies have demonstrated the role of 5-HT$_7$ receptors in preclinical antidepressant actions, learning, memory, sleep, and circadian rhythms.[3–9]

5-HT$_7$ Receptors as Novel Therapeutic Targets

Although no selective 5-HT$_7$ compounds are available for clinical use, numerous compounds are sufficiently potent blockers of 5-HT$_7$ receptors such that 5-HT$_7$ antagonism could theoretically contribute to their pharmacologic actions (Table 1).[10–17] In particular, several of the compounds listed in Table 1 are effective antidepressants, and in animal models, the antidepressant efficacy of aripiprazole is reversed in animals lacking 5-HT$_7$ receptors,[8] and the serotonin release and antidepressant actions of selective serotonin reuptake inhibitors (SSRIs) are enhanced by selective 5-HT$_7$ antagonists.[3,5,8]

Three novel agents characterized as antipsychotics have 5-HT$_7$ antagonist properties among their most potent pharmacologic actions (Figure 1),[2,10,13,14] and 1 of these, lurasidone, in late-stage clinical development as an antipsychotic, is actually "5-HT$_7$ preferring," with 5-HT$_7$ antagonism its most potent property.[13] Of these, amisulpride (not available in the United States) is a proven antidepressant.[1,2,14] Theoretically, because of their even greater potency for 5-HT$_7$ antagonism, lurasidone and asenapine are good candidates for clinical testing as antidepressants as well.

Combining agents such as lurasidone or asenapine with SSRIs would be predicted to enhance 5-HT release as well as to have antidepressant properties.[3–5,8] Given the recent positive results as an antidepressant for the melatonergic/serotonergic agent agomelatine, which resets circadian rhythms,[18] combining novel 5-HT$_7$ antagonists with melatonin agonism may also enhance the antidepressant actions of 5-HT$_7$ antagonists. In addition, preclinical studies[3,5,8,9] suggest the possibility that agents with potent 5-HT$_7$ antagonism may improve cognition, so cognition in depression, schizophrenia, and other illnesses is a theoretically attractive clinical target, for 5-HT$_7$ antagonists as well.

Table 1. Agents With Potentially Clinically Relevant 5-HT$_7$ Antagonism[a]

Second-Generation Atypical Antipsychotics
Amisulpride
Asenapine
Clozapine
Iloperidone
Lurasidone
Paliperidone
Quetiapine
Risperidone
Sertindole
Ziprasidone
Zotepine
First-Generation Conventional Antipsychotics
Chlorpromazine
Cyamemazine
Fluphenazine
Loxapine
Pimozide
Antidepressants
Amoxapine
Desipramine
Fluoxetine
Imipramine
Mianserin

[a]Based on data from references 10–17.

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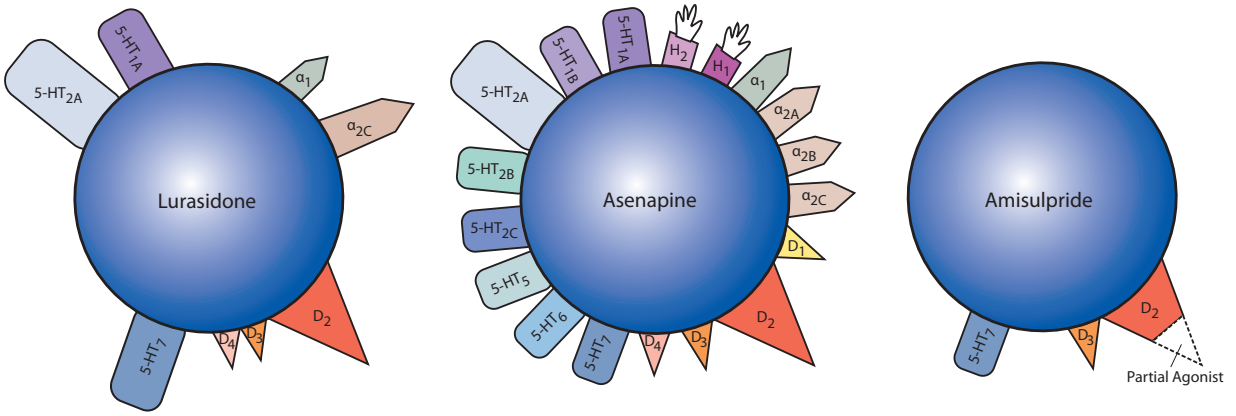
Take-Home Points

- The 5-HT$_7$ receptor is a novel serotonin receptor whose properties have recently been characterized.
- Serotonin-7 receptors are localized in cortex, hippocampus, hypothalamus, thalamus, and brainstem raphe nuclei, where they regulate mood, circadian rhythms, sleep, learning, and memory.
- Several known antipsychotics and antidepressants with multifunctional pharmacologic actions have been recently discovered also to block 5-HT$_7$ receptors, and this mechanism could hypothetically be linked in part to their antidepressant actions.

Figure 1. Novel Multifunctional Drugs With the Most Potent 5-HT$_7$ Antagonist Actions



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