

The Serotonin-7 Receptor as a Novel Therapeutic Target

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Issue: Blockade of 5-HT₇ 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 psychopharmacologists¹: 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-HT₇ 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-HT₇ receptors, and that this 5-HT₇ antagonism may account in part for the therapeutic properties of these drugs, especially antidepressant actions.¹⁰⁻¹⁷

Localization and Function of 5-HT₇ 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-HT₇ receptors in preclinical antidepressant actions, learning, memory, sleep, and circadian rhythms.³⁻⁹

5-HT₇ Receptors as Novel Therapeutic Targets

Although no selective 5-HT₇ compounds are available for clinical use, numerous compounds are sufficiently potent blockers of 5-HT₇ receptors such that 5-HT₇ 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-HT₇ receptors,⁸ and the serotonin release and antidepressant actions of selective serotonin reuptake inhibitors (SSRIs) are enhanced by selective 5-HT₇ antagonists.^{3,5,8}

Three novel agents characterized as antipsychotics have 5-HT₇ 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-HT₇ preferring,” with 5-HT₇ 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-HT₇ 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-HT₇ antagonists with melatonin agonism may also enhance the antidepressant actions of 5-HT₇ antagonists. In addition, preclinical studies^{3,5,8,9} suggest the possibility that agents with potent 5-HT₇ antagonism may improve cognition, so cognition in depression, schizophrenia, and other illnesses is a theoretically attractive clinical target, for 5-HT₇ antagonists as well.

Table 1. Agents With Potentially Clinically Relevant 5-HT₇ 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	

^aBased on data from references 10-17.

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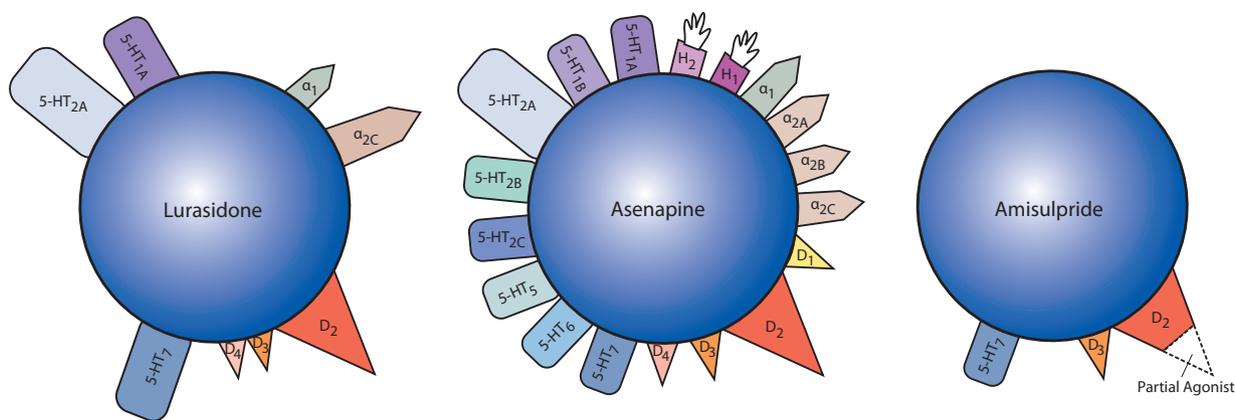
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TAKE-HOME POINTS

- ◆ The 5-HT₇ 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-HT₇ receptors, and this mechanism could hypothetically be linked in part to their antidepressant actions.

Figure 1. Novel Multifunctional Drugs With the Most Potent 5-HT₇ Antagonist Actions



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