Schizophrenia develops a complex

By Tim Fulmer, Staff Writer

The general strategy for discovering compounds with antipsychotic activity has focused on identifying agonists or antagonists of a specific receptor class. This results in compounds that alleviate only a subset of schizophrenia symptoms without avoiding neurological side effects.

Researchers at the **Mount Sinai School of Medicine** have identified a serotonin/glutamate receptor complex in rodent brain that unites two pathways previously targeted individually to treat psychosis and other symptoms of schizophrenia.¹ Designing compounds or combination therapies that modulate the function of the complex rather than that of each receptor separately could be a strategy for generating a new class of antipsychotics.

First-generation typical antipsychotics like the generic haloperidol antagonize dopamine D2 receptors. Second-generation atypical antipsychotics like Zyprexa olanzapine from **Eli Lilly and Co.** antagonize the serotonin receptor (5-HT_{2A} receptor) in addition to showing moderate affinity for dopamine D2 receptors.

The third wave of approved drugs includes Abilify aripiprazole from **Bristol-Myers Squibb Co.** and **Otsuka Pharmaceutical Co. Ltd.** This small molecule is a partial agonist of the dopamine D2 and serotonin receptors and an antagonist of the 5-HT_{2A} receptor.

More recently, companies have been working on compounds that target metabotropic glutamate receptors (mGluRs). Last year saw the first Phase II data for mGluR agonists in schizophrenia. LY2140023, an oral prodrug of Lilly's LY404039 mGluR2/3 agonist, significantly improved schizophrenia symptoms compared with placebo in a Phase II trial in 97 patients ($p < 0.001$).^{2,3}

The mGluR space is clearly attracting the interest of pharma companies, as evidenced by a pair of deals in January. **Addex Pharmaceuticals S.A.** and **Merck & Co. Inc.** partnered to develop and market ADX63365 and other positive allosteric modulators of mGluR5 to treat schizophrenia and other undisclosed indications.⁴ ADX63365 is in preclinical development.

Also, **Pfizer Inc.** and **Taisho Pharmaceutical Co. Ltd.** partnered to develop and commercialize Taisho's TS-032, an mGluR agonist in preclinical testing to treat schizophrenia.

In their *Nature* paper, the Mount Sinai researchers used several methods, including coimmunoprecipitation and fluorescence reso-

nance energy transfer, to show that 5-HT_{2A} and mGluR2 colocalize, interact and form functional complexes in mouse cortical neurons and in the human frontal cortex. Multiple hallucinogenic compounds, a glutamate receptor agonist and an atypical antipsychotic all influenced signaling through the complex.

Moreover, postmortem brain slices from untreated schizophrenia patients had higher 5-HT_{2A} receptor levels and lower mGluR2/3 levels than brain slices from controls with no history of psychiatric disorders.

The team of researchers, led by Javier Gonzalez-Maeso and Stuart Sealton, both professors in the Department of Neurology at Mount Sinai, hypothesized in the paper that "the 5-HT_{2A} receptor-mGluR2 complex integrates serotonin and glutamate signaling to regulate the sensory gating functions of the cortex, a process that is disrupted in psychosis."

According to the group, the complex "is therefore a promising new target for the treatment of psychosis."

Indeed, the receptor complex provides a target that could potentially combine the effects of two or more antipsychotics into a single therapeutic agent, Gonzalez-Maeso told *SciBX*.

However, John Krystal, professor of clinical pharmacology at **Yale University School of Medicine**, said the data also "raise the question as to whether mGluR2 agonists provide any benefits in addition to 5-HT_{2A}

receptor blockade that is already provided by most antipsychotic medications."

He added: "If mGluR2 receptor stimulation was simply an indirect way to reduce 5-HT_{2A} receptor function, then it might not produce a more effective new approach to the treatment of schizophrenia."

Sealton said the group's next steps include investigating how sequence alteration of one or both of the receptors affects the function of the complex, as well as identifying mutations that

disrupt or prevent formation of the complex but do not affect individual receptor function.

Generating mGluR2 and 5-HT_{2A} receptor knockout mice or knockin mice that express chimeric receptors also would be useful to gain a better understanding of how the complex functions and affects downstream signaling pathways, Gonzalez-Maeso told *SciBX*.

David Bredt, VP of neuroscience research and clinical development at Eli Lilly, told *SciBX* that "while this is the first evidence of a direct interaction between these two receptors," the paper's findings were also consistent with the previous work of the company's scientists that showed behavioral evidence of interactions between hallucinogenic compounds and mGluR2/3 receptors. In mice, mGluR2/3 agonists such as LY354740 or LY379268 blocked the behavioral effects of 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI), a hallucinogenic compound that acts through the 5-HT_{2A} receptor.⁵

Previous work by the Mount Sinai group showed that a specific activation pattern of serotonin receptor pathways in the mouse cortex is necessary for the psychoactive effects of hallucinogenic compounds such as lysergic acid diethylamide (LSD).⁶

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— Vincent Mutel,
Addex Pharmaceuticals S.A.

Bredt thinks future research could examine whether 5-HT_{2A} or mGluR2 receptors “form complexes with other receptors expressed on the surface of neurons, including other groups of metabotropic glutamate receptors. Future studies would also be useful to determine how the formation of these complexes might vary with progression of schizophrenia.”

Research already suggests that interactions exist between mGluR2 and other glutamate receptors in animal models and humans.^{7,8} Krystal told *SciBX* his research team discovered that LY354740 reduced the disruption of working memory caused by the ionotropic NMDA glutamate receptor antagonist ketamine in healthy volunteers. Deficits in working memory, which is a cognitive function, have been reported in some schizophrenia patients, he said.

Vincent Mutel, CEO of Addex, told *SciBX* that the paper “does point out how the various signaling pathways linked to schizophrenia may in fact be closely integrated—which would suggest that, at least in some situations, combining antipsychotic compounds could produce a synergistic effect that might treat multiple symptoms of schizophrenia.”

Nevertheless, he added that the publication will not alter Addex’s general strategy of targeting specific receptors associated with schizophrenia.

“There is evidence in animal models that targeting mGluR5 could treat both positive symptoms of schizophrenia like hallucination as

well as cognitive impairment,” Mutel said. “This is important because although marketed antipsychotics that act on 5-HT_{2A} reduce hallucination, their ability to treat negative symptoms is much less clear. Thus, it’s of the highest priority to develop compounds that treat cognitive deficits associated with schizophrenia.”

REFERENCES

1. Gonzalez-Maeso, J. *et al. Nature*; published online Feb. 24, 2008; doi:10.1038/nature06612
Contact: Stuart Sealfon, Mount Sinai School of Medicine, New York, N.Y. e-mail: Stuart.Sealfon@mssm.edu
2. Patil, S. *et al. Nat. Med.* **13**, 1102–1107 (2007)
3. Mujtaba, U. *BioCentury* **15**(40), A11; Sept. 10, 2007
4. Hansen, S. *BioCentury* **16**(2), A26; Jan. 7, 2008
5. Gewirtz, J.C. & Marek, G.J. *Neuropsychopharmacology* **23**, 569–576 (2000)
6. Gonzalez-Maeso, J. *et al. Neuron* **53**, 439–452 (2007)
7. Moghaddam, B. & Adams, B. *Science* **281**, 1349–1352 (1998)
8. Krystal, J. *et al. Psychopharmacology* **179**, 303–309 (2005)

COMPANIES AND INSTITUTIONS MENTIONED

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