New promises for schizophrenia therapy

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Researchers in the USA have developed the first in a novel class of antipsychotic drugs for schizophrenia [1]. AC90222, developed by ACADIA Pharmaceuticals (San Diego, CA, USA), specifically addresses the neurocognitive deficits related to attention, memory, executive and information processing tasks preceding psychosis.

Although strongly genetic in origin, the risk factors for schizophrenia include maternal malnutrition and viral infection during fetal development, fetal hypoxia, other birth and obstetric complications, winter birth and psychoactive drugs [2]. Aberrations in cortisol secretion, hippocampal abnormalities, and memory deficits are also thought to have a role in the disorder [3]. The main symptoms of schizophrenia can be divided up into positive and negative psychotic symptoms. Positive symptoms include hallucinations, delusions, deranged thought and behavior, whereas negative symptoms manifest as loss of motivation, restricted emotional experience and expression, poverty of speech and reduced hedonic capacity.

Why so intractable?

Although the discovery of the involvement of dopamine in schizophrenia and the use of dopamine-receptor antagonists as antipsychotic drugs won Arvid Carlsson the Nobel Prize for Medicine in 2000, most drugs leave the cognitive impairments and negative symptoms of schizophrenia untouched. Indeed, neurocognitive deficits involving multiple functional domains can be anatomically traced to alterations in the dorsolateral pre-frontal basal ganglia-thalamocortical circuit. These deficits have become defining features in patients with problems related to social skills acquisition, social problem-solving and health and productivity [4]. The second-generation anti-psychotics such as olanzapine and clozapine, which inhibit serotoninergic receptors more than dopamine D2 receptors, often merely reduce secondary negative symptoms (such as depressive anhedonia and neuroleptic akinesia) [5]. 'Drugs active at the D2 receptor control the positive symptoms of delusion and hallucinations. However, they may actually worsen the negative symptoms such as flattening of affect and cognitive dulling, aside from the impaired motor function,' says Herbert Meltzer, Bixler Professor of Psychiatry and pharmacology at Vanderbilt University School of Medicine (Nashville, TN, USA).

Serendipitous breakthrough

ACADIA researchers discovered AC9022 to independently target the pathophysiological mechanisms of each clinical dimension: positive, negative, cognitive and affective. The dual muscarinic M_1-receptor subtype-selective agonist and D2-receptor antagonist neither disrupts the cognitive performance when administered alone, nor induces catalepsy. In fact, it reduces spontaneous and drug-induced locomotor activity, enhances spatial memory and cognitive functions and reduces cognitive dulling while ameliorating other negative symptoms [1]. 'This combination of CNS activities in one class of molecules is unprecedented,' says Herbert Meltzer, also a member of ACADIA's Clinical Advisory Board. 'Based on predominant distribution of M_1 receptors in the cerebral cortex and hippocampus, drugs with M_1-receptor agonist properties are expected to enhance cognitive functions, without any extrapyramidal effects,' he explains [6].

Mark R. Brann, President and CSO of ACADIA says, 'By serendipity, we discovered a novel chemistry that combines muscarinic agonism with dopamine antagonism. The lead compound AC90222 is an optimized bicyclic analog of AC42, a compound that was discovered by screening 140,000 diverse compounds against genetically engineered muscarinic receptors using R-SAT™, a gene-based functional assay [7]. Indeed, the team characterized a novel chemical series of M_1-receptor selective agonists [8]. The initial analogues of AC42 show unprecedented selectivity by binding to a non-conserved region comprising transmembranes 1 and 7 of the M_1 receptor. This contrasts with conventional M_1-receptor ligands, such as acetylcholine, which bind to a conserved part of the receptor. The most highly active compounds have a bulky hydrophobic group at the R4 position of the heterocyclic ring. AC42 has an EC_{50} value of 260 nM for M_1 receptors with a maximum response of 63% without any effect on other muscarinic receptor subtypes.

A cell-based functional assay employing transiently transfected NIH 3T3 cells demonstrated the potency and efficacy of AC90222 across muscarinic receptor subtypes. These data were supported by several other assays. In addition, the affinity of AC90222 for D2 receptors was also determined using [^{3}H] Raclopride. The results reveal an 83% efficacy (relative to carbachol) and a pEC_{50} value

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of 7.1 for M_1-receptors and a pK_i of 7.6 for D2 receptors. AC90222 also improved the spatial memory performance in hippocampus-deficient mice [1] (Fig. 1).

'We have shown that AC90222 is active in a wide range of animal models of schizophrenia, including the pre-pulse inhibition (PPI) model of sensory processing. AC90222 also improves cognitive function as measured in mice in the Morris water maze. By contrast, none of the traditional antipsychotics tested improved cognitive function,' said Brann. He continues: 'AC90222 is orally available, readily passes into the brain, and has more than 1 h duration of action, which might translate to a once or twice a day medication in humans, although this could depend on many unknown factors. We may now also be able to treat similar other disorders such as the senile psychosis accompanying Alzheimer's disease.'

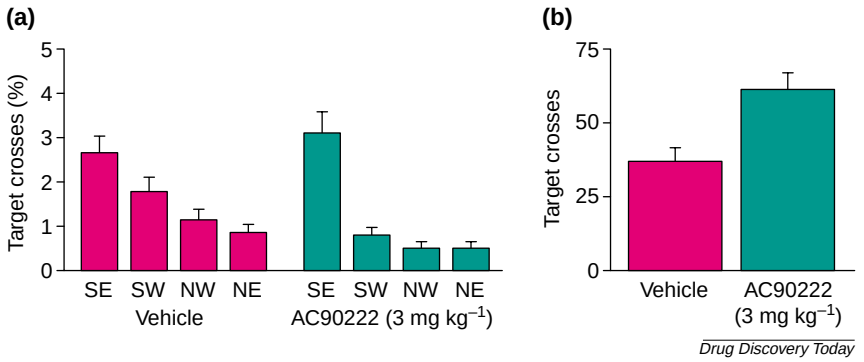

Figure 1. (a) Effect of AC90222 on spatial memory in the Morris water maze. **(b)** AC90222 improved the performance of hippocampus-deficient mice compared with vehicle control, as measured by the percentage of crosses over the target region during the probe trial. Mice did not display any visual or motor impairment (data not shown).

Conclusions

'A specific D2-receptor antagonist [to reduce psychotic symptoms] with M_1-receptor agonism might be of interest clinically because several adverse effects might be avoided [compared with current drugs active at multiple receptors]' comments William T. Carpenter Jr, Professor of Psychiatry and Pharmacology, University of Maryland School of Medicine (Baltimore, MD, USA). 'It is plausible that combining M_1-receptor agonism with D2 antagonism will convey a clinical advantage. It is worth noting, however, that the only drug with documentation of superior antipsychotic efficacy in refractory schizophrenia [i.e. clozapine] has an antagonistic effect at M_1 receptors,' adds Carpenter, who is also Director, Maryland Psychiatry Research Center (Baltimore, MD, USA).

However, Carpenter comments that, 'There seems little reason to expect the D2 effects to contribute beyond having sufficient dopamine antagonism while avoiding adverse cognitive and negative symptom effects. It is an asset that AC90222 enhanced rather than impaired spatial memory. However, whether any clinical effect – compared with established drugs – can be anticipated with AC90222 is entirely speculative, especially with cognitive and negative psychopathologies, but there is currently little scientific basis for predicting these effects.'

Mark Brann responds, 'Our enthusiasm comes from extremely promising results in animal models of schizophrenia. We are currently fine-tuning these molecules to optimize both their M_1-receptor agonist and D2-receptor antagonist properties, and we are working on compounds with improved potency and DMPK properties. The team hope to select a clinical development candidate for this program in 2002. On the clinical side, support of our muscarinic approach comes from observations that clozapine can activate M_1 receptors under certain conditions, and that a potent muscarinic agonist recently showed therapeutic activity in schizophrenia [9].'

References

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