Worldview of Psychiatry

CINP 2004 Congress Preview

The Collegium Internationale Neuropsychopharmacologicum (CINP) is the oldest international group dedicated to the advancement of psychopharmacology. The CINP was founded in the late 1950s, following the discovery of the antipsychotic properties of chlorpromazine by Delay, Deniker, and colleagues in Paris. In those days, an international meeting was the best way to communicate with colleagues about current developments. Through the CINP, the psychopharmacology revolution took hold; psychiatrists around the world heard firsthand about the then miraculous results in treating schizophrenia and mania.

Fast-forward 50 years. The CINP is still at the forefront of communication of information about psychopharmacology. Its biennial meetings move from major city to major city on 4 continents, bringing together the world's best clinicians and basic scientists from academia, government, and industry for 4 days of fascinating symposia, panels, workshops, posters, and entertainment. Recent meetings of note were Montreal 2002, Brussels 2000, Glasgow 1998, Melbourne 1996, and Washington, D.C., 1994. In Montreal, the 3 Nobel laureates in Physiology or Medicine for 2000, Arvid Carlsson, Paul Greengard, and Eric R. Kandel, each gave plenary lectures. At each meeting, the CINP also honors 3 pioneers, men and women who have contributed to the birth of one of the great advances in healing in the 20th century.

This year's XXIV CINP Congress in Paris, June 20–24, 2004, will bring together foremost scientists in the field of clinical and basic neuropsychopharmacology. Floyd E. Bloom and Colin Masters will give plenary lectures. As President, I will give one as well. In addition, a magnificent lineup of symposia will cover the full range of clinical neuropsychopharmacology and selected basic science areas. The program is geared for the clinical psychiatrist. It will include a course in psychopharmacology developed by Stephen M. Stahl and me, as part of the basic registration fee, for those who want a state-of-the-art review of the field in a more didactic manner. The CINP will provide CME credit as well.

We have contracted with *The Journal of Clinical Psychiatry* to provide meeting previews each month, beginning with the symposium on the new generation of antipsychotic drugs.

We urge you to consider attending. Information is readily available at http://cinp2004.com/.

Herbert Y. Meltzer, M.D.

Dr. Meltzer is President of CINP and Professor of Psychiatry, Vanderbilt University Medical Center, Nashville, Tenn. (e-mail: herbert.meltzer@vanderbilt.edu).

Second Generation of Antipsychotic Drugs: From Bench to Bedside

Frank I. Tarazi, Ph.D., Chair, and W. Wolfgang Fleischhacker, M.D., Co-Chair

Treatment of idiopathic psychotic disorders including schizophrenia and mania was revolutionized by the serendipitous discovery of the phenothiazines (initially, chlorpromazine) and subsequent development of the thioxanthenes (e.g., thiothixene), butyrophenones (e.g., haloperidol), and their congeners in the 1950s. Virtually all of these drugs block dopamine D_2 receptors in direct correlation with their clinical potency as antipsychotic agents. However, these classic or "typical" neuroleptic agents regularly induce characteristic neurologic and endocrinologic side effects including dystonia, akathisia, bradykinesia, acute or late dyskinesias, and hyperprolactinemia. In addition, their effectiveness is limited, largely palliative, and diagnostically nonspecific. These limitations prompted the development of newer or "atypical" antipsychotic agents that have less risk of extrapyramidal side effects (EPS) and at least similar, or possibly superior, beneficial effects particularly against negative symptoms and cognitive deficits of schizophrenia.

The reintroduction of the early prototype atypical antipsychotic clozapine in the late 1980s was a major step in this direction. Clozapine has a very low risk of producing EPS or hyperprolactinemia and substantial evidence of superior antipsychotic effectiveness. Clozapine also improves cognitive impairments in patients with schizophrenia, particularly verbal memory and fluency and visual attention. Clozapine can also lead to enhanced social and occupational functioning, less substance abuse, reduced hostility and violence, and a reduced risk of suicide attempts. The pharmacologic basis of its unusual clinical properties remains unclear. Clozapine interacts with high or moderate potency at dopamine D_4, serotonergic ($5\text{-}HT_{2A}$, $5\text{-}HT_{2C}$, and others), acetylcholinergic (muscarinic), adrenergic (α_1, α_2, β_2), and histaminic (H_1) receptors, but has only moderate affinity for both D_1 and D_2 receptors. Despite its favorable characteristics, clinical use is complicated by its high risk of potentially fatal bone marrow toxicity, as well as dose-dependent risk of epileptic seizures, excessive sedation, weight gain, and increased risk of hyperglycemia and hyperlipidemia.

Interest is keen in developing novel drugs with less adverse risk than clozapine, but comparable antipsychotic effects. In recent years, several newer agents representing the second generation of antipsychotic drugs have been introduced. Among them are the benzazepine analogs of clozapine (olanzapine and quetiapine), the benzisoxazole derivative risperidone, the indole derivative ziprasidone, and the quinolinone derivative

aripiprazole. Although their mechanisms of action are not yet well-defined, these newer antipsychotics offer effective palliative treatment of schizophrenia and other psychotic and bipolar disorders with a neurologic safety profile superior to typical neuroleptics. Accordingly, a symposium aimed at reviewing salient aspects of this rapidly evolving research field and its relevance to basic and clinical neuropsychopharmacology is timely.

Behavioral Pharmacology and New Preclinical Models

Prof. John Waddington (*Royal College of Surgeons, Ireland*) will review the evolution of behavioral paradigms used in the evaluation of antipsychotic drugs. Traditional, empirical models of antipsychotic efficacy (e.g., antagonism of amphetamine-induced hyperactivity, disruption of conditioned avoidance) and EPS liability (e.g., inhibition of apomorphine-induced stereotypy, induction of catalepsy) from the era of first-generation agents are utilitarian but have resulted in only limited advances together with false positives. Newer models used for the evaluation of second-generation agents have sought psychological-pharmacologic homology (e.g., PCP- or early isolation–induced disruption of prepulse inhibition, latent inhibition, and social interaction) or pathologic isomorphism (e.g., neonatal hippocampal lesions) with features of schizophrenia. As the only property known to be shared, to varying extent, by *all* current antipsychotics remains antagonism (or partial agonism) at D_2 receptors, identification of truly novel antipsychotics would be facilitated by the application of behavioral paradigms in circumstances independent of D_2 receptor involvement. Mutant mice with D_2 receptor "knockout" provide such a platform and may be of particular potential in this regard. Recently, the emergence of replicable findings regarding several genes of small effect that contribute to vulnerability to schizophrenia (e.g., the developmental gene *neuregulin*, COMT) has been accompanied by the construction of mutant mice that now allow the functional roles of these genes to be explored and the behavioral effects of antipsychotics on mutant phenotype to be evaluated.

Molecular Pharmacology

Dr. Frank I. Tarazi (*Harvard Medical School, USA*) will analyze the unique pharmacologic properties and complex receptor profiles of second-generation antipsychotics. Like clozapine, these compounds have multiple sites of molecular interaction and affect various neurotransmitter systems. They share with clozapine its greater affinity for 5-HT_{2A} than D_2 receptors. This receptor-interaction pattern may contribute to low EPS risk. Dr. Tarazi will also review evidence that long-term administration of representative newer antipsychotic drugs (olanzapine and risperidone) increases expression of D_2 receptors in rat prefrontal cortex, nucleus accumbens, and caudate putamen. In addition, repeated treatment with olanzapine and risperidone increases levels of D_4 receptors in nucleus accumbens and caudate putamen. In contrast, prolonged administration of clozapine, olanzapine, risperidone, and quetiapine does not alter D_1 and D_3 receptor binding in rat forebrain regions. He hypothesizes that cortical D_2 and forebrain D_4 receptors represent pivotal and common sites mediating beneficial antipsychotic effects of most older and newer antipsychotic drugs. In contrast, elevation of D_2 receptors in caudate putamen by both olanzapine and risperidone, and not clozapine or quetiapine, resembles that by typical neuroleptics and is consistent with the dose-dependent ability of both agents to induce some EPS. Lack of significant changes in D_1 and D_3 receptors by several dissimilar antipsychotics supports the hypothesis that these sites are not crucial for antipsychotic drug actions.

Neuroimaging Studies

Dr. Robert M. Kessler (*Vanderbilt University, USA*) will present clinical findings with positron emission tomography (PET) brain imaging of the occupancy of D_2 and 5-HT_{2A} receptors in patients treated with different antipsychotics and will discuss the potential clinical and theoretical requirements of novel agents to achieve "atypicality." These studies assist in predicting clinical efficacy, EPS, and clinical dosing of antipsychotic drugs that interact with D_2 or 5-HT_{2A} receptors. Occupation of D_2 receptors in the basal ganglia between 60% to 80% appears to represent an optimal level for beneficial clinical effects of antipsychotics, whereas higher levels of D_2 receptor occupation are associated with risk of acute EPS and are commonly encountered with clinical doses of typical neuroleptics. In contrast, therapeutic doses of clozapine are usually associated with relatively low D_2 receptor occupancy (40%–50%), but higher (70%–90%) cortical 5-HT_{2A} receptor occupancy. Quetiapine, similar to clozapine, occupies D_2 receptors by 40% to 50% and 5-HT_{2A} receptors by 50% to 70%. Olanzapine and risperidone block cortical 5-HT_{2A} receptors at high levels (80%–100%) and yield relatively higher levels of D_2 site occupation (50%–90%) than clozapine or quetiapine. In addition to its relatively high levels of D_2 occupation, olanzapine is more antimuscarinic than risperidone, perhaps contributing to its lower risk of acute EPS.

Clinical Studies

Prof. W. Wolfgang Fleischhacker (*University of Innsbruck, Austria*) will discuss the superior clinical effects of second-generation antipsychotics against psychotic symptoms and cognitive deficits in psychotic patients and will highlight their advantages as improved and safer alternatives to traditional neuroleptic agents. Dr. Fleischhacker will also present evidence that some newer agents, including olanzapine and risperidone, are highly effective in long-term maintenance therapy, although their efficacy in treatment-refractory schizophrenia and effectiveness relative to clozapine is not well established. Finally, he will discuss characteristic adverse effects. In risk of dystonia and bradykinesia, newer antipsychotic drugs rank clozapine < quetiapine < ziprasidone = olanzapine < risperidone, paralleling their D_2 antidopaminergic potency. Risks for akathisia and malignant syndrome are not well established. High 5-HT_{2A} antiserotonergic potency of risperidone, clozapine, ziprasidone, and olanzapine, but not quetiapine, as well as anticholinergic activity of olanzapine and clozapine, also may limit risk of EPS. In general, except for clozapine and quetiapine, the newer generation has brought only *relative* avoidance of EPS, strongly encouraging continued search for novel antipsychotic agents.

Discussant

Dr. Ross J. Baldessarini (*Harvard Medical School, USA*) will provide a translational review of basic and clinical material and present his vision on the prospects for novel treatments. He will point out that the rate of development of novel antipsychotic agents has again slowed following a burst of innovative activity. Novel principles are needed, particularly involving targets other than dopamine receptors, which have dominated antipsychotic drug development for a half-century.

Aims of the Symposium

Overall, the objectives are to cover the most recent behavioral, pharmacologic, imaging, and clinical developments of second-generation antipsychotic drugs and to integrate their preclinical and clinical findings in a comprehensive manner. This effort should contribute to improved understanding of mechanisms of action in the brain and involvement of these agents in new principles aimed at improved treatments.