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conference report

Progress towards better understanding and treatment of major psychiatric illnesses

Psychiatric Drug Discovery and Development
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The *3rd Annual Psychiatric Drug Discovery and Development* conference, held on 11–12 April in Princeton, NJ, USA, focused on the treatment of schizophrenia, anxiety and mood disorders and depression. This conference, attended by individuals from industry and academia, emphasized several important issues. A major discussion topic was the desire to address major areas of need, particularly with regard to relieving the disabilities associated with many of the major psychiatric illnesses. Other speakers focused on the identification of novel pharmacologic targets and new or improved approaches to screening for therapeutic agents. Developments in a wide variety of disparate topics concerning drug development were also presented in an informative manner.

Understanding and treating schizophrenia

Schizophrenia was a major focus, in part because of the enormous societal cost of this illness (estimated in the high tens of billions of USD$ per year). Herbert Meltzer (Vanderbilt University, Nashville, TS, USA) argued that schizophrenia is better understood as a widely variable, multidimensional syndrome rather than a discrete disease entity. Meltzer further posited that clinical observations suggest that deconstructing schizophrenia into its elements, such as positive and negative symptoms, cognitive impairment and suicidality, and treating these independently might prove to be the most useful way to treat this illness. It was shown that present treatments have either minimal or no effect on the cognitive impairment associated with schizophrenia, which is generally thought to be the most disabling component of the disease. Finally, Meltzer discussed possible neurochemical targets for the treatment of cognitive impairment and suggested the possibility that pro-cognitive agents might be prophylactic in genetically susceptible individuals.

Examining the changes in mRNA and protein expression, in conjunction with understanding the effects of allelic variation of putative susceptibility genes, may provide insight into developing novel treatment strategies for schizophrenia. The Clinical Brain Disorders Branch of the Intramural Research Program at the National Institute of Mental Health (NIMH) has amassed a large number of human brains of schizophrenic and control individuals for use in postmortem studies. *COMT*, *GRM3*, and *DTNBP1*, all susceptibility genes for schizophrenia, were discussed in detail. As an example, data were presented concerning the *COMT-val* allele, which is associated with impaired cognitive performance. It was shown that the met to val mutation makes the COMT enzyme ~50% more active, thereby decreasing cortical dopamine (DA) levels. It was shown that the overactive COMT results in increased tyrosine hydroxylase mRNA levels in dopaminergic neurons, concomitant with an in increase in midbrain DA levels (Joel Kleinman, NIMH).

Novel approaches, targets and compounds in the treatment of psychiatric illness

Recent advances in understanding the role of metabotropic glutamate receptor (mGluR) modulation in anxiety, psychosis, depression, and other psychiatric diseases and syndromes were presented by Darryle D. Schoepp (Eli Lilly). LY354740, an orthosteric mGluR2/3 agonist, has been shown to reduce anxiety in human preclinical tests without benzodiazepine-like side effects. Also, the efficacy of mGluR2/3 agonists in antagonizing at least some PCP- and amphetamine-induced behaviors in rats was shown. Later, P. Jeffrey Conn of Vanderbilt University argued that MPEP is an mGluR5 antagonist which potentiates the psychotomimetic effects of PCP, suggesting the potential utility of mGluR5 agonists in the treatment of schizophrenia. Agonists such as CDDPB have been identified and are being characterized *in vivo* and *in vitro*.

A rational bioaminergic modulatory approach to the treatment of depression was also discussed. WAY163426, a combination 5-HT transporter inhibitor and 5-HT_{1A} antagonist, raises serotonin levels more rapidly than just an SSRI, and the drug exhibits activity in chronic models of depression that is consistent

1359-6446/05/$ – see front matter PII: S1359-6446(05)03523-3

conference report

with a more rapid onset. Also, the 5-HT_6 agonist WAY466 was shown to promote neuronal survival and neurite outgrowth in cortical neurons. Given recent findings showing decreased cortical and hippocampal (the two major sites of 5-HT_6 expression) volume in depressed and PTSD patients, 5-HT_6 agonists show therapeutic promise. 5-HT_6 agonists might address deficits common to today's anti-depressants, such as delayed onset, sexual dysfunction, nausea and treatment resistance. (Lee Schechter, Wyeth Research).

Several other novel potential targets were highlighted by speakers. Sharon Rosenzweig-Lipson (Wyeth Research) discussed WAY163909, a 5-HT_{2C} selective agonist, which might have utility in treating obesity, schizophrenia and depression. PDE10A inhibitors, which show antipsychotic-like activity in PPI tests, are also being explored (Judith A. Siuciak, Pfizer). CRF1-R antagonists such as DMP696 are being characterized and show efficacy in reducing anxiety in some *in vivo* paradigms (Nicholas Lodge, Bristol Myers Squibb). Finally, the trace amine receptor TA-1 was discussed as a potential target for the treatment of psychosis and perhaps ADHD and drug abuse (Toni D. Wolinsky, Lundbeck Research, USA).

Novel approaches in screening and characterizing drugs and their effects

SmartCube™ addresses many of the limitations common to established screening strategies by being mouse-based, continuous, unbiased and predictable. The system uses a powerful computer capable of machine learning to track >2000 aspects of behavior and shows a high correspondence to human scoring. Once the system was developed, reference compounds were used to generate a behavioral signature database (SmartBase™), which has been validated for antipsychotics, antidepressants and anxiolytics. The SmartCube™ is now being used to screen compounds to predict those that might have therapeutic efficacy. There have been several hits, including potential novel antipyschotics. All the hits were confirmed with an examination of prepulse inhibition, and all hits showed antipsychotic-like activity in the PCP open field test. Interestingly, one of the hits shows no DA activity. Another compound identified as a potential anxiolytic reduced the stress-induced hyperthermic response and has a novel mechanism of action (Paul McGonigle, Psychogenics).

Novel high-throughput strategies are providing opportunities to develop new theranostic applications, such as the identification of responsive patient populations and side-effect liable subpopulations. The potential utility of rhinoneuroepithelial cell biopsies in diagnosing and treating psychiatric illnesses was of particular interest. These are progenitor cells that can easily be taken from the nasal cavity and differentiated into neuronal cells. Measurable rhinoneuroepithelial changes have been shown after treatment with drugs such as valproate and buspirone. Also, measurable differences between schizophrenic, bipolar and control populations have been shown in cell-death and cell proliferation assays (Michael G. Palfreyman, Novace).

The utility of receptorome (all receptors in the genome) screening as a useful tool for unbiased drug discovery was discussed in detail. The NIMH Pyschoactive Drug Screening Program K_i database (http://kidb.case.edu) contains over 32,000 K_i values and provides an *in silico* solution to identifying drug targets that could be of interest in examining their therapeutic potential and side-effect liability. For example, receptorome screening identified 5-HT_{2B} agonism as the cause of fenfluramine induced valvulopathy. The interesting case of the hallucinogenic plant *Salvia divinorum* was also presented. Receptorome screening identified the only major site of action of salvinorin A (the active component of the plant) as the kappa opioid receptor (KOR), where it acts as an agonist. Interestingly, KORs are elevated in Alzheimer's disease, suggesting the possible utility of KOR antagonists in treating pyschosis associated with the dementia of Alzheimer's (Bryan Roth, CWRU).

C. Anthony Altar (Psychiatric Genomics, MD, USA) discussed his company's genetic-based approach to treating schizophrenia, which has led them to develop a dual inhibitor of COMT and D_2 receptors, PGX200112. In addition, Psychiatric Genomics has characterized a bipolar drug therapeutic signature by using multi-parameter high throughput screening (MPHTS℠) on human neuroblastoma flat cells to identify important genes whose levels are modulated by valproate. PGX5188 was then identified as having a similar signature and thus therapeutic potential. A similar MPHTS strategy for schizophrenia was also presented.

Clinical research

Recent advances in the clinical research field were highlighted. In pursuing an indication for fibromyalgia treatment, Cypress Bioscience participated in the development of a more accurate, less biased methodology for measuring pain which also addressed the problem of poor compliance in previous studies (R. Michael Gendreau, Cypress Bioscience). Alan Feiger (Research Training Associates of Colorado) stressed the centrality of rater skill level at clinical testing sites used by pharmaceutical companies in the ability of a study to detect the effect of drug versus placebo. A Rater Applied Performance Scale (RAPS) was developed to assess rater skill, and it was shown that poor rater skill level in several areas masked the detection of clinical efficacy. He finally showed the utility of an enriched training program for raters which could raise the success rate of large clinical studies undertaken by pharmaceutical companies. Gary Sachs (Massachusetts General Hospital, USA) also addressed the problem of the high failure rate of clinical studies. The solution that was developed was intensive site monitoring using interactive computer interviews (ICI) intended to repeat rater interviews to monitor rater compliance with proper interviewing protocols. Data were shown that validated ICI as a reliable tool, and the benefits of this method of monitoring were discussed.

Concluding remarks

The conference served to highlight several relevant topics concerning the development and characterization of novel drugs and therapies. Also, a new pre-conference workshop was organized to facilitate cooperation and alliances between biotech and large pharmaceutical companies, and several new drugs at various stages of development were discussed here. During the

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conference proper, areas of major concern were highlighted, and research directions and conceptions with the greatest potential were proposed and rationally justified. Novel approaches to therapy were discussed, along with new screening strategies that may yield efficacious drugs that would be difficult to discover using more established strategies.

There were several informative presentations concerning important issues in drug development such as the optimal use of biomarkers, gene expression based *in vivo* assays, neuroimaging in psychiatric drug development, challenges in obtaining novel indications for drugs, and commonly overlooked issues related to successfully selling a drug (David Michelson, Eli Lilly; Michael Mallamaci, Astrazeneca; Terry Brown, MIICRO, Inc.; Steve Romano, Pfizer; and Martin Brecher, Astrazeneca). Innovations in clinical research that should aid the characterization of drugs in humans were highlighted. Also, data were presented concerning several novel targets and compounds that could be therapeutically more effective than presently favored drugs in the treatment of various psychiatric disorders such as schizophrenia, mood and anxiety disorders and depression.

Overall, the conference served to give an overview of the broad array of challenges facing the psychiatric drug development community and addressed those challenges by highlighting newly developed strategies. Only time will tell which of these strategies will prove fruitful in addressing those challenges.

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Memorable mnemonics

A thought-provoking tonic on the lighter side

Column by Raymond C. Rowe, AstraZeneca, UK

Please note that these are the personal opinions of the author and do not necessarily represent those of AstraZeneca.

One of my most popular articles of recent years as judged by both the number of full-text downloads and the number of e-mails I received was on mnemonics [1]. My interest in the subject was rekindled on receiving from a reader (my sincere thanks to him) a copy of a long out of print book, which I had been itching to get hold of ever since I had read an article on it in the Lancet [2]. Entitled Irving's Anatomy Mnemonics by Alastair Smith [3], it provides lists of fascinating word mnemonics and extended acronyms dedicated, as stated in the preface ' to the simple-minded, to the crammers for exams and to those whose stumbling feet find the anatomical pathway difficult'. At about the same time I decided to seek out other mnemonics on chemistry, biochemistry and biology and the more research I have done, the more fascinated I have become in this form of memory device. Some mnemonics are memorable indeed!

Chemical mnemonics

It is not surprising that the majority of chemical mnemonics relate to the periodic table. The first ten elements (H, He, Li, Be, B, C, N, O, Fe, Ne) can easily be memorised by the mnemonic 'Hi Helen, Little Betty Boron Can Not Often Find Neddy' Of course this is not the only one around. Others are ' Hell, Here're Little Beatniks Brandishing Countless Numbers Of Flick kNives' and 'Happy, Healthy Little Beggar Boys Catching Newts Or Fish' My favourite for the following seven elements (Na, Mg, Al, Si, P, S, Cl) is 'Naughty Maggie Always Sips Pure Sweet Claret'. There are several mnemonics for remembering the Lanthanides (La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Tb, Lu); among the most memorable are 'Let's Collect Pleasingly Novel Pansies Since Every Good Type Does Have Extra Thin Young Leaves' and the more risqué 'Little Cute People Need Plenty Sex Every Given Time Despite Having Enough Through Young Love'. Mnemonics also exist for remembering the elements vertically in the periodic table. For example for the alkali metals (Li, Na, K, Rb, Cs, Fr) there is a mnemonic 'Limping Native King Robbed Caesar's Friend'. An interesting feature of this mnemonic is that each word contains the second letter, if appropriate, of the element it alludes to.

Of course, mnemonics exist for many other series in chemistry and biochemistry. I have trouble remembering the electromagnetic spectrum detailing the distribution of

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