ANNUAL REPORTS IN MEDICINAL CHEMISTRY
Volume 36

Sponsored by the Division of Medicinal Chemistry of the American Chemical Society

Editor-in-Chief: ***ANNETTE M. DOHERTY***

PFIZER GLOBAL RESEARCH & DEVELOPMENT
FRESNES LABORATORIES
FRANCE

ACADEMIC PRESS

ANNUAL REPORTS IN MEDICINAL CHEMISTRY
Volume 36

Sponsored by the Division of Medicinal Chemistry of the American Chemical Society

EDITOR-IN-CHIEF:

ANNETTE M. DOHERTY

PFIZER GLOBAL RESEARCH & DEVELOPMENT
FRESNES LABORATORIES
FRANCE

SECTION EDITORS

JANET M. ALLEN • WILLIAM J. GREENLEE • WILLIAM K. HAGMANN
JACOB J. PLATTNER • DAVID W. ROBERTSON • GEORGE L. TRAINOR

EDITORIAL ASSISTANTS

SYLVIE DUCHESNE • NADÈGE PINGRAY • LISA BAUSCH

ACADEMIC PRESS
A Harcourt Science and Technology Company

San Diego San Francisco New York Boston London Sydney Tokyo

This book is printed on acid-free paper. ♾

Academic Press
A Harcourt Science and Technology Company
525 B Street, Suite 1900, San Diego, California 92101-4495, USA
http://www.academicpress.com

Academic Press
Harcourt Place, 32 Jamestown Road, London NW1 7BY, UK
http://www.academicpress.com

International Standard Book Number: 0-12-040536-9

PRINTED IN THE UNITED STATES OF AMERICA
01 02 03 04 05 06 MB 9 8 7 6 5 4 3 2 1

ANNUAL REPORTS IN MEDICINAL CHEMISTRY

Volume 36

Academic Press Rapid Manuscript Reproduction

CORRECTION-

In Volume 35 of Annual Reports in Medicinal Chemistry, the first author was inadvertently omitted from chapter 6. We apologize for this error. The correct heading for this chapter is as follows:

Chapter 6. Recent Developments In Antitussive Therapy

Robert Aslanian, John A. Hey and Neng -Yang Shih
Schering Plough Research Institute
2015 Galloping Hill Road
Kenilworth, NJ 07033

This chapter has been updated, and appears in this Volume as Chapter 4.

PREFACE

Annual Reports in Medicinal Chemistry continues to focus on providing timely and critical reviews of important topics in medicinal chemistry together with an emphasis on emerging topics in the biological sciences that are expected to provide the basis for entirely new future therapies.

Volume 36 retains the familiar format of previous volumes, this year with 30 chapters. Sections I–IV are disease-oriented and generally report on specific medicinal agents with updates from Volume 35 on antitussive therapy, anticoagulants, antibacterials, and antiretroviral therapies. As in past volumes, annual updates have been limited to the most active areas of research in favor of specifically focused and mechanistically oriented chapters, where the objective is to provide the reader with the most important new results in a particular field.

Sections V and VI continue to emphasize important topics in medicinal chemistry, biology, and drug design as well as the critical interfaces among these disciplines. Included in Section V, Topics in Biology, are chapters on bioinformatics, protein structure prediction, proteonomics, and therapeutic antibodies. Chapters in Section VI, Topics in Drug Design and Discovery, reflect the current focus on mechanism-directed drug discovery and newer technologies. These include chapters on aspartyl protease inhibitors, ADME by computer, PET ligands for assessing receptor occupancy *in vivo,* and strategies for analytical characterization and profiling of compound libraries.

Volume 36 concludes with To Market, To Market — 2000, a chapter on NCE and NBE introductions worldwide in 2000 and chapters on new developments in animal health care and the impact of intellectual property issues on the pharmaceutical industry. In addition to the chapter reviews, a comprehensive set of indices has been included to enable the reader to easily locate topics in Volumes 1–35 of this series.

Volume 36 of *Annual Reports in Medicinal Chemistry* was assembled with the superb editorial assistance of Ms. Sylvie Duchesne, Ms. Nadège Pingray, and Ms. Lisa Bausch and I thank them for their hard work. I have continued to work with innovative and enthusiastic section editors and my sincere thanks goes to them again this year. I hope that you will enjoy and profit from reading this volume.

Annette M. Doherty
Fresnes, France
May, 2001

CONTENTS

III. CANCER AND INFECTIOUS DISEASES

Section Editor: Jacob J. Plattner, Chiron Corporation, Emeryville, California

IV. IMMUNOLOGY, ENDOCRINOLOGY AND METABOLIC DISEASES

Section Editor: William K. Hagmann, Merck Research Laboratories, Rahway, New Jersey

V. TOPICS IN BIOLOGY

Section Editor: Janet M. Allen, Pfizer Global Research & Development, Fresnes Laboratories, Fresnes, France

VI. TOPICS IN DRUG DESIGN AND DISCOVERY

Section Editor: George L. Trainor, DuPont Pharmaceuticals Company, Wilmington, Delaware

VII. TRENDS AND PERSPECTIVES

Section Editor: Annette M. Doherty, Pfizer Global Research & Development, Fresnes Laboratories, Fresnes, France

CONTRIBUTORS

SECTION I. CNS AGENTS

Editor: David W. Robertson, Pharmacia Corporation
Kalamazoo, MI 49007

Chapter 1: Same Brain, New Decade: Challenges in CNS Drug Discovery in the Postgenomic, Proteomic Era

Michael Williams^, Joseph T. Coyle#, Sanober Shaikh* and Michael W. Decker**
^Northwestern University School of Medicine, Chicago, IL 60611, #Harvard Medical School, Belmont, MA 02178, *Genset SA, 91030 Evry Cedex, France and **Abbott Laboratories, Abbott Park, IL 60064

Introduction. The brain is a highly complex organ that mediates conceptual thought, cognition, volition, self-consciousness and emotion (1,2). As "the interpreter and responder to environmental challenges", the brain, working via the peripheral nervous system, processes information and controls behavioral responses via "systems replete with specialized circuits, parallel pathways, and redundant mechanisms to protect the individual, thus ensuring propagation of the genome and survival of the species (3,4). Accordingly, brain dysfunction resulting from genetic, environmental and/or aging factors has a major negative impact on the quality of life and individual survival.

CNS COMPLEXITY AND DRUG DISCOVERY

The human brain contains approximately 100 billion neurons and expresses greater than 60% of known human genes. In comparison, the nervous system of the threadworm, C. elegans, a model system for studying genomic function, has a mere 302 neurons, 3×10^{-6} % the number in the human brain. Neurons in C. elegans are interconnected via 600 electrical and 5000 chemical synapses (5). The C. elegans genome codes for approximately 1000 G-protein coupled receptors (GPCRs), 90 ligand-gated ion channels, 80 potassium-selective ion channels and 228 nuclear receptors providing a virtually infinite number of postgenomic molecular substrates through which neuronal function can be regulated (6,7). Understanding this complexity at the level of the human brain and postgenomic interactions between genes and their products (epigenetics; 8) is a key challenge in understanding human CNS disease pathophysiology and in designing new drugs that are safer and more efficacious to treat these diseases.

The characterization of simpler systems like C. elegans, has prompted a shift away from an increasingly reductionistic approach to the study of the brain and nervous system, focused almost exclusively on molecular function at the synaptic level, to a renewed appreciation of the hierarchical complexity (gene, synapse, pathway, phenotype) of the nervous system (9) and the need to: a) integrate structure with function at the tissue and whole animal level; and b) integrate and iterate animal studies with emerging clinical research at both the systems and compound levels. Given emerging knowledge regarding the intrinsic complexity of the human brain, the success resulting from serendipity in the last 40 years is impressive and has provided a number of highly effective CNS drugs, the majority of which act synaptically, either mimicking (agonists), facilitating (transmitter uptake blockers, allosteric modulators) or antagonizing the effects of endogenous neurotransmitters and neuromodulators (10,11). Not only neurons but also glial cells - astrocytes, microglia, etc. are potential drug targets.

0065-7743/01 $35.00

The function of the brain is extremely dynamic. Neonate, adult and aged brains are morphologically and phenotypically very distinct. Diseased brain can be very different from the 'normal', healthy brain. Transmitters and receptors present during development disappear in adult brain, while receptors change in number and function due to disease and nervous system trauma. Mechanisms to sustain brain homeostasis, including trophic factor maintenance of neuronal viability, are negatively impacted by aging, leading to an accumulation of environmental insults. Brain function is influenced by hormones, via the hypothalamic-pituitary axis (HPA; 3) and by peripheral e.g. cardiovascular/ vascular, system function.

Global sales of CNS drugs in 1999, including pain, exceeded $50 billion, approximately 15% of the total global drug sales. This market will continue to grow as the aging population increases (by 2030, the number of Americans 65 or older will double; 11) and life-style factors, including stress and information overload resulting from a breakdown in societal support systems for the individual (3,12,13).

The Decade of the Brain initiative of the 1990s was intended to "enhance the awareness of the benefits to be derived from brain research" and thus elucidate the cause(s) of CNS disorders, enabling development of effective treatments (14). Despite this and newer drug discovery technologies, both chemical and biological, that include draft sequences of the human genome (15), the discovery and timely development of CNS drugs remains one the most challenging in pharmaceutical research (11). Factors contributing to this include: the inherent complexity of the brain; a paucity of knowledge regarding function at the molecular level - especially in disease states; animal models with limited predictive value; a lack of robust, quantitative diagnostic tools to track disease occurrence and progression; imprecise physician diagnoses of symptomatically related psychiatric disease states that frequently involve ethnic and cultural factors; and challenges in defining efficacy in human trials due to high placebo responses (16,17).

CNS drug discovery to date has thus been highly iterative in nature, building on established mechanism(s) of action of clinically effective compounds with improvements in tolerance and/or safety. The successful antidepressant SSRIs (selective serotonin reuptake inhibitors), e.g., fluoxetine, are mechanistically similar to the traditional tricyclic antidepressants (TCAs), e.g. impramine. In addition, the reason for the superior efficacy of the 'atypical' antipsychotic medication, clozapine – the mechanism(s) of action of which has been repeatedly redefined as new CNS receptors have been identified – as compared with other dopamine (DA) receptor antagonists, has not been elucidated.

An additional complication in developing new CNS drugs is that drugs currently used for one indication can be used to treat different CNS disorders - e.g. valproate for epilepsy, bipolar affective disorder (BPAD), migraine (18) and dementia-associated agitation, and anticonvulsants, e.g. gabapentin, that modulate neuronal firing are used for the treatment of neuropathic pain and, potentially, BPAD.

Diagnosis and classification of CNS disorders relies on two key reference works: the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and the International Classification of Diseases - Revision 10 (ICD-10), the European equivalent of DSM-IV. While invaluable tools, their use is confounded by ethnic -, societal - and gender- related differences in patient diagnosis. CNS diseases also have a high incidence of co-morbidities - depression is associated with chronic pain and excessive stress and alcoholism with depression, anxiety and cognitive impairment. The neuronal loss associated with stroke leads to cognitive dysfunction, mood disorder(s) and

TABLE 1: TRENDS IN PSYCHIATRIC DRUG TREATMENT

Disease State	Current Approaches	Experimental Approaches
Schizophrenia	DA receptor blockers – haloperidol, clozapine, chlorpromazine, risperidone, olanzepine	DA: Clozapine-like agents, partial agonists, D4 receptor antagonists. NMDA receptor/glycine modulators - D-serine, serine racemase α-7 nicotinic receptor agonists $5HT_{2A}$ inverse agonists – AC 90179 Neurokinin-3 and cholecystokinin$_1$ antagonists
Depression	TCAs - impramine, amitriptyline: Monoamine oxidase inhibitors (MAOIs) - tranylcypromine SSRIs- citalopram, fluoxetine SNRIs (5HT/ NE reuptake inhibitors) - venlafaxine	Improved monoamine uptake inhibitors $5HT_{1A}$ receptor ligands NK-1 receptor antagonists Corticotropin releasing factor (CRF) receptor antagonists
Bipolar Affective Disorder	Lithium, valproic acid, carbamazepine	Antiepileptics: pregabalin, topiramate etc. Valproate analogs - TV-1901 etc.
Anxiety: panic disorder, OCD (obsessive-compulsive disorder) GAD (generalized anxiety disorder), PTSD (postraumatic stress disorder), acute stress disorder	Benzodiazepines (BZs)- diazepam, clonazepam $5HT_{1A}$ partial agonists- buspirone SSRIs	Newer BZs: pagaclone, deramciclane $5HT_{1A}$ agonists: lesopitron, S-15535 Orphanin FQ receptor agonists – Ro 64-6198 CRF receptor antagonists
Attention deficit hyperactivity disorder (ADHD)	Psychostimulants – methylphenidate d-amphetamine	α4β2- nicotinic receptor agonists – ABT-089 Histamine H_3 antagonists - GT 2331 Monoamine uptake blockers - atomoxetine
Compulsive/addictive disorders : cocaine, amphetamine, heroin, alcohol, nicotine (smoking) addiction Recreational drug use Cannabinoid, PCP Compulsive disorders: Gambling, sexual behavior, eating (obesity, anorexia, bulimia)	Methadone, LAAM Naloxone Disulfiram Acamprosate Nicotine patches Buproprion Phenylpropanolamine Sibutramine Orlistat PPARγ antagonists - troglitazone	DA transport blockers - RTI -113 D1 receptor ligands - DAS-431, CEE 03-310 Cocaine vaccine (TA-CD) and catalytic antibodies - mAb 15A10 Obesity: Leptin modulators, CART, GLP1, amylin, galanin, neuropeptide Y, α- MSH, famoxin, fatty acid synthase (FAS) inhibitors, orexin, melanocortin - 4 (MC-4)/SLC-1 and SOCS3 antagonists
Sleep disorders: sleep pattern disruption (jet lag) Insomnia, narcolepsy	Hypnotics- Secobarbital, triazolam, estazolam Modafinal, Melatonin	Agomelatine, Adenosine agonists H_3 agonists – SCH 50971 Orexin agonists, NBI 34060
Sexual disorders Erectile dysfunction/ Female sexual dysfunction	Sildenafil Apomorphine	IC-531, BAY 38-9456 DA agonists

dementia; and the loss in cognitive function occurring in Alzheimer's disease (AD) leads to aggression, anxiety and depression. The overlap in symptoms between diagnostically distinct disease states and the high co-morbidity with other distinct CNS disorders makes clinical experimentation an absolute necessity in defining the utility of CNS drugs. The area is historically replete with compounds advancing to the clinic for one indication and being found to be useful for another (10).

TARGET DYNAMICS

Ongoing research, basic and applied, has continued to identify a number of new approaches to the treatment of CNS disorders that are currently to or through clinical trial validation. These are shown alongside existing approaches in Tables 1 and 2; some are incremental improvements on existing mechanisms (D4 antagonists for schizophrenia; valproate analogs) while others (D-serine for schizophrenia (19); caspase inhibitors for neurodegenerative disorders; vaccines for AD and stroke (20,21)) are highly novel approaches. In many instances however, the challenge in CNS drug R & D is in improving (reducing) the side effect liabilities for compounds active at a known CNS drug target (e.g. D2 receptor) to allow higher levels of drug to be administered. This can be accomplished by understanding the mechanism(s) by which known compounds produce their side effects and by then 'tuning out' this property or adding additional properties to newer compounds to overcome side effects. Side effects, while never a trivial issue, are of increasing importance, especially in CNS disorders requiring chronic therapy in a young population that is, apart from their disease-related disability, relatively healthy. For example, antipsychotics show a class-related phenomenon of QT-syndrome prolongation that can result in ventricular tachycardia, heart block and fatalities. This has been a major factor in the comparative lack of new drug approvals for this class (22).

A less obvious instance of potential side effect liability results from approaching the process of compound identification using a highly reductionistic molecular approach that lacks an integrated, pharmacological framework. The logic, a priori, is that by identifying a compound interacting with high affinity at a defined molecular target, it will lack interactions with other molecular targets. Leptin, the 167mer secreted from adipocytes, acts via leptin receptors to reduce food intake and was thought to represent a promising anorectic agent (23) However, acting via the hypothalamus, leptin also inhibits bone formation, an effect that would limit the chronic use of the peptide in obesity (24).

EXPLOITING THE GENOME OF THE BRAIN

A large number of chromosomal loci containing susceptibility genes potentially involved in disease etiology as well as gene candidates for schizophrenia, BPAD, etc. have been identified (25,26). Validation of these is based on epidemiological data showing a significant genetic contribution to disease etiology. Interactions between more than one susceptibility gene and environmental risk factors (the "envirome"; 27) clearly contribute to disease incidence, the norm of reaction factor - indicating that biology – and human behavior - cannot be classified simply in terms of DNA sequences (28). In schizophrenia, concordance rates between monozygotic and dizygotic twins are 50% and 15% with an overall heritability of 68% (29). Focusing on disease genes within chromosomal regions implicated through genetic linkage analysis (using DNA from affected family pedigrees) requires a case control study design involving large cohorts (200-500 of patients and controls) derived from ethnically homogeneous populations matched for age and sex. The quality of the case histories is crucial in assuring the validity of diagnosis and in identifying ethnically unmatched individuals who contribute to stratification effects. The identification of putative disease-associated genes in an initial population should be replicated in additional populations. However, gene association studies often fail to replicate due to locus or genetic heterogeneity or simply because of the poor quality of the collection. With the sequencing of the human genome and identification of more than 2.5 million single nucleotide polymorphisms (SNPs; 30), phenotypic traits will be increasingly correlated with genetic variability with the