Handbook of Experimental Pharmacology 260

James E. Barrett
Clive P. Page
Martin C. Michel *Editors*

Concepts and Principles of Pharmacology

100 Years of the Handbook of Experimental Pharmacology

Springer

Handbook of Experimental Pharmacology

Volume 260

The *Handbook of Experimental Pharmacology* is one of the most authoritative and influential book series in pharmacology. It provides critical and comprehensive discussions of the most significant areas of pharmacological research, written by leading international authorities. Each volume in the series represents the most informative and contemporary account of its subject available, making it an unrivalled reference source.

HEP is indexed in PubMed and Scopus.

More information about this series at http://www.springer.com/series/164

James E. Barrett • Clive P. Page •
Martin C. Michel
Editors

Concepts and Principles of Pharmacology

100 Years of the Handbook of Experimental Pharmacology

Springer

Editors
James E. Barrett
Center for Substance Abuse Research
Lewis Katz School of Medicine at Temple University
Philadelphia, PA, USA

Clive P. Page
Sackler Institute of Pulmonary Pharmacology,
Institute of Pharmaceutical Science
King's College London
London, UK

Martin C. Michel
Department of Pharmacology
Johannes Gutenberg University
Mainz, Rheinland-Pfalz, Germany

ISSN 0171-2004 ISSN 1865-0325 (electronic)
Handbook of Experimental Pharmacology
ISBN 978-3-030-35361-2 ISBN 978-3-030-35362-9 (eBook)
https://doi.org/10.1007/978-3-030-35362-9

This Springer imprint is published by the registered company Springer Nature Switzerland AG.
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

This volume celebrating the 100th anniversary of the *Handbook of Experimental Pharmacology* acknowledges several significant milestones in the discipline of Pharmacology. Moreover, it is a testimony to the evolution of the scientific scope and breadth and of the important role the *Handbook* has had in capturing the many advances over this 100-year period. The *Handbook* was founded in 1919 by Arthur Heffter as the "Handbuch der Experimentellen Pharmakologie." As of Volume 50 in 1978, the series was renamed to its current title. The first volume published in English was in 1937, titled "General Pharmacology" and the entire volume was written by Alfred Joseph Clark from the University of Edinburgh. The series has published more than 250 volumes, representing a continuing tradition and commitment to the evolution of pharmacology as a vibrant discipline in generating innovative basic and clinical research that have facilitated the development of safe and effective therapeutics. While originally designed as a handbook, each chapter and the entire volumes are now available electronically and primarily used in this way.

The collection of volumes of the *Handbook of Experimental Pharmacology* over the past 100 years reflects the tremendous growth of the discipline of pharmacology and provides tangible stepping-stones to the many significant advances in the discovery and development of new drugs for a wide range of diseases. The *Handbook* has consistently provided critical and comprehensive reviews of the most significant areas of pharmacological research, written by leading international authorities, and contributing significantly to the tremendous progress evidenced over the past 100 years.

The *Handbook* has captured and disseminated the dynamic nature of the discipline of pharmacology, celebrating and publishing new discoveries from basic understanding of mechanisms of drug action to the delivery of new, safe, and effective therapeutics. Writing in the *Handbook* over 50 years ago, the Nobel Laureate Sir Henry Dale, commented that "Heffter's great Handbuch der Experimentellen Pharmakologie may be regarded, perhaps, as giving some measure of the prodigious growth, during the past half-century, of those areas of scientific knowledge which can properly be regarded now as belonging to the domain of Pharmacology. And to make its full contribution to experimental progress on these lines, pharmacology would now have to work in an increasing intimacy of cooperation, with the accelerating growth of relevant knowledge in physiology,

biochemistry, pathology, and immunology, and, indeed, in any of the more fundamental scientific disciplines." That growth and the "intimacy" predicted by Dale have continued as pharmacology has evolved and embraced those interactions. The imprint of the evolution of pharmacology is strongly reflected in the series, which includes contributions from over 20 Nobel Laureates. These fundamental advances have generated newer and deeper insights into signaling pathways, elucidated our understanding of molecular mechanisms of drug action, while also witnessing remarkable advances in Quantitative Systems and Computational Pharmacology, as well as in enabling technologies such as Pharmacogenomics, Metabolomics, Natural Products, and Drug Delivery Systems, to name just a few.

While it is difficult to cover all the developments in pharmacology over the 100-year period, we hope that this volume will capture much of the progress in pharmacology, hoping to provide a window to some of the past achievements as well as an anticipation of future progress. Perhaps even more importantly, several chapters provide visions for the future of pharmacology. We thank the authors for their contributions to this important volume in the history of this prestigious series, while also expressing our deep appreciation to the many scientists whose passion and commitment to pharmacology have made it a vibrant discipline, translating advances in basic science to safe and effective therapeutics.

We would also like to express our sincere appreciation to Susanne Dathe, Springer Editor for Neurosciences/Pharmaceutical Sciences/Protocols, whose commitment and competence have helped to continue the tradition of this remarkable series, and to the past and current editorial board members who have dedicated time and effort into establishing this series as one of the most recognized publications in pharmacology.

Philadelphia, PA, USA — James E. Barrett
London, UK — Clive P. Page
Mainz, Rheinland-Pfalz, Germany — Martin C. Michel

Contents

Perspectives of Pharmacology over the Past 100 Years

James E. Barrett, Clive Page, and Martin C. Michel

Contents

Abstract

It is fitting that the 100th anniversary of the *Handbook of Experimental Pharmacology* celebrates not only its founding but also the founding of experimental pharmacology as both had their beginnings in Germany. Founded in 1919 by Arthur Heffter (1859–1925) as the "Handbuch der Experimentellen Pharmakologie" and renamed to its current title in 1937, the Handbook has continued to capture the emergence and developments of experimental pharmacology since the initial systematic work of Rudolf Buchheim and his student Oswald Schmiedeberg. Heffter, the first Chairman of the German Society of Pharmacology, was also responsible for isolating mescaline as the active

J. E. Barrett (✉)
Center for Substance Abuse Research, Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA
e-mail: jeb92@drexel.edu

C. Page
Sackler Institute of Pulmonary Pharmacology, Institute of Pharmaceutical Science, King's College London, London, UK

M. C. Michel
Department of Pharmacology, Johannes Gutenberg University, Mainz, Germany

J. E. Barrett et al. (eds.), *Concepts and Principles of Pharmacology*,
Handbook of Experimental Pharmacology 260, https://doi.org/10.1007/164_2019_334

psychedelic component from the peyote cactus, thereby initiating a series of studies along with an Institute that, much like the Handbook and the discipline of pharmacology, continues to discover and disseminate new findings to this day. These early endeavors to establish pharmacology as a viable and valuable contributor to the medical sciences met with considerable resistance and challenges. However, the persistence and dedication of these early pharmacologists placed pharmacology on a firm foundation from which to spread this discipline globally, leading ultimately to our current understanding of the principles of drug action and with an impact likely unanticipated by these founding scientists. Summarizing the beginnings of these efforts and their early spread to other countries provides an appropriate context in which to document the many contributions pharmacological research has made over the past 100 years and provide an opportunity to anticipate expectations around its future developments.

Keywords
Buchheim · Heffter · History of German pharmacology · Krayer · Schmiedeberg

1 Introduction

Pharmacology is a discipline with a rich history that, since its emergence during some rather challenging times, has exerted a tremendous impact as a vibrant science with an exciting and promising future. Some have argued that pharmacology is the oldest discipline in the health sciences (Norton 2005), with medicines derived from plants used since prehistoric times. In China, the use of various plant sources such as herbs and herbal remedies dates back some 3,000 years, imbuing traditional Chinese medicine with an interesting and extensive history that continues with great momentum with the current interest in natural products. Despite the very early realization that compounds derived from natural sources could have therapeutic value, the term "pharmacology" was not used in print until the seventeenth century (Norton 2005). Early practitioners such as Theophrastus Bombastus zu Hohenheim (a.k.a. Paracelsus) attempted to determine the active ingredients of these early preparations and formulated the earliest concept of dose-response functions by suggesting that the dose determines potential therapeutic value or toxicity. Writing the "Third Defense Pertaining to the Description of the New Prescriptions" in 1564, Paracelsus asked: "What is there that is not poison, all things are poison and nothing is without poison. Solely the dose determines that a thing is not a poison" (Deichmann et al. 1986). Although Paracelsus is acknowledged for this remarkable insight on the importance of dose, it is not often recognized that he also described the first recognition of "species specificity" in the context of his general principle of toxicology, also described by Deichmann et al.:

> For instance, the food placed on the table: if eaten by a man, it becomes the flesh of man; if ingested by a dog, it is converted into dog flesh and in the cat, to cat flesh. With medicine, it is the same, its fate depends on the species or what you do with it. It is possible that something good will cause harm, just as it is possible that something harmful may become beneficial.

2 The Emergence of Pharmacology in Germany: Rudolf Buchheim

The research on curare and carbon monoxide poisoning in the early part of the nineteenth century helped to establish Francois Magendie and his student, Claude Bernard, as important precedents to what was to become pharmacology. Although both were physiologists, their techniques and some of the principles stemming from their studies were useful in the development of pharmacology (Parascandola 1980). These early precedents of pharmacology reached fruition in the mid-nineteenth century, with several significant developments in Germany that included the founding of the world's first Institute of Pharmacology ("Pharmakologisches Institut") established at the University of Dorpat (now Tartu) by Rudolf Buchheim in 1847. Buchheim was a professor of Materia Medica, Dietetics, and History of Medicine. As Trendelenburg (1998) has stated in his review of "Pharmacology in

Germany," "the cradle for our hobby was located in the very improbable site of a university in Tsarist Russia, situated in a then largely German-speaking town of today's Estonia." For several years, the laboratories of this "institute" were housed in the basement of Buchheim's home (Koch-Weser and Schechter 1978; Rang 2006). In 1860 the Institute, with its focus on experimental pharmacology, was moved into a large building specifically constructed to include the Institute of Pharmacology. It was this stimulus, initiated by Buchheim and developed by his students, that fostered the emergence of pharmacology as a well-defined discipline.

At the time of the founding of the first Institute of Pharmacology, the contribution that pharmacology had to make to medicine was increasingly questioned. Pharmacology had been dropped from the final medical examinations in most German states, and physicians were being counseled to forget as soon as possible what they might remember about drugs from their lectures or books (Meyer 1922). The development of pharmacology as a scientific discipline comparable to physiology or pathology received little or no support from the medical establishment and only gradually gained acceptance and a firm foundation in medical school education and research. The attitude of most clinicians was expressed by the famous Viennese surgeon T. Billroth:

> Considering how little he has to teach and that half of what he teaches is superfluous, it is difficult to keep a professor of pharmacology busy in a full-time teaching position. What is needed is merely a short review of the most important drug groups and an experimental demonstration of the most intensive poisons. This can be done in 3–4 h. The students should not be burdened with more lectures. How to use drugs one can only learn in the clinics anyway (cited in Koch-Weser and Schechter 1978).

Even when Buchheim convincingly and compellingly defended pharmacology, he concluded with this statement: "What can a man who gives his whole strength to pharmacologic research achieve today under the best of circumstances? A professorship with a minimum salary and an empty auditorium."

Rudolf Buchheim was born into a time when an appreciation of scientific methods and thinking were growing and some of the fundamentals of modern medicine were being established. These included the work of Pasteur, who opened the path to microbiology, and Darwin who developed the theory of evolution, while Virchow published on cellular pathology, and Helmholtz and Mayer formulated the law of conservation of energy along with other principles of vision and perception. Chemistry, physics, and physiology had advanced relatively rapidly, and there was a growing need for a scientific foundation of therapeutics (Habermann 1974). Buchheim was convinced that pharmacology should progress beyond the descriptive approach of materia medica and, by experimentation, explore how drugs cause their effects, regardless of whether those effects are beneficial or undesirable. Buchheim introduced a principle that would have a considerable bearing on the discipline of pharmacology – the "Natural System of Drugs" – which was the formulation of a system for the classification of drugs based on elucidating their mode of action. Buchheim essentially envisioned and postulated a new, independent science, formulating objectives and establishing a methodological approach while also

expressing a reaction to apparent objections from other disciplines surrounding the existing skepticism of pharmacology as a science when he wrote:

> If we translate our often obscure ideas about drug actions into an exact physiological language: this should, without doubt, be a considerable achievement. However, scientific cognition of the action of a given drug would imply our ability to deduce each of its actions from its chemical formula. The new era of pharmacology will bear its date not from the discovery of chloral hydrate, but from that time when pharmacology will cease to ornate itself by the waste of other disciplines; when pharmacology with its own area and aided by related sciences, will become equivalent to its sisters, chemistry and physiology (cited in Habermann 1974).

2.1 Schmiedeberg's Contribution to the Development of Pharmacology

An early student of Buchheim was Oswald Schmiedeberg (1838–1921) who was strongly influenced by Buchheim's teaching and with whom Schmiedeberg obtained his Dr. of Medicine degree in 1866 for his work determining chloroform in the blood. Schmiedeberg was largely responsible for pursuing and disseminating Buchheim's concepts and methods into pharmacological research and continuing the movement initiated by Buchheim. In the words of Koch-Weser and Schechter, writing in 1978:

> One century ago pharmacology was an antiquated, denigrated and waning discipline content with transmitting impressionistic and largely erroneous dictums. In one generation one man in one city redefined its tasks, demonstrated its experimental methods and trained its work force … Schmiedeberg brought scientific pharmacology into being.

Schmiedeberg's profound influence on pharmacology was accomplished through his excellence as a researcher, as a passionate and dedicated teacher, and as a prolific writer. His experimental scope was extensive and included work on muscarine, isolating the alkaloid from the mushroom *Amanita muscaria*. Its analysis through the experimental study of its actions remains a model of the pharmacological investigation of natural substances. Schmiedeberg's interest in muscarine led to investigations into the action of nicotine on the heart and to later studies on cardiac innervation and on the whole pharmacology of the autonomic nervous system. Schmiedeberg also studied the actions of caffeine and related xanthines on striated muscles as well as their diuretic effects. Schmiedeberg and his Strassburg group of researchers and students performed the first experimental studies on the pharmacology of most of the important drugs and poisons known at that time. Much of their work was published in the *Archiv für Experimentelle Pathologie und Pharmakologie*, founded in 1873 by Schmiedeberg, B. Naunyn, and E. Klebs (this journal is now the *Naunyn-Schmiedeberg's Archives of Pharmacology*). In this way these individuals succeeded in giving pharmacology a solid scientific foundation and assured its position alongside the other biomedical sciences (Starke 1998).

Schmiedeberg's work in this institute during the next five decades was largely responsible for the initial rise of pharmacology to a respected scientific discipline and as an indispensable foundation for medical practice. Schmiedeberg unquestionably has had a profound impact in forming and cultivating the discipline of pharmacology, not only due to his expansive and pioneering experimental work but also for his training of over approximately 200 pharmacologists from over 20 countries during his 46 years at the University of Strassburg. At the time of his death in 1921, an astonishing number of over 40 chairs of pharmacology were held by his students around the world (Koch-Weser and Schechter 1978).

3 The Spread of Pharmacology

The seeds of experimental pharmacology as a distinct discipline with a different focus from that of physiology were founded and developed in Germany, but the growth and continuing shaping of pharmacology rapidly became global. Many of the discoveries over the past hundred-year period have been documented in articles which, themselves, provide testimony to the seminal discoveries made by the growing number of academic pharmacologists. For example, Rubin (2007) has written a comprehensive review on the history of great discoveries in pharmacology to celebrate the centennial anniversary of the founding of the American Society of Pharmacology and Experimental Therapeutics (ASPET), while Cuthbert (2006) traced the history of the British Pharmacological Society to celebrate its 75th anniversary. One of Schmiedeberg's students was J.J. Abel who brought pharmacology to the United States. Abel occupied the first professorship of experimental pharmacology in the United States at the University of Michigan in 1891 and subsequently moved to Johns Hopkins University 1893 to hold the first Chair of Pharmacology in the United States. Johns Hopkins was established in 1876, modeled after the German research universities, and one of the missions for medicine was to focus on the physiological action of drugs. The physiologist Henry Newell Martin, a member of the Johns Hopkins faculty, in a lecture to the Medical and Chirurgical Faculty of Maryland in 1885, selected pharmacology as his topic "because I believe that it is destined in the near future to acquire an importance in regard to therapeutics which is not properly appreciated" (Parascandola 1992). Abel had spent the 1883 academic year working in Martin's laboratory prior to going to Strassburg to work under Schmiedeberg. The contributions of Abel to the development of pharmacology in the United States were substantial as his efforts greatly expanded pharmacology research and education in several universities; pharmacology also spread and established a firm footing with the movement of pharmacologists into the growing pharmaceutical industry and into the federal government with the founding of the Food and Drug Administration (FDA) in 1930. Abel contributed significantly to the development of pharmacology in the United States, principally by his founding of the American Society of Pharmacology and Experimental Therapeutics (ASPET) and the *Journal of Pharmacology and Experimental Therapeutics*. These many initiatives are thoroughly researched and

documented in the volume *The Development of American pharmacology: John J. Abel and the Shaping of a Discipline* by Parascandola (1992). Among his many other contributions, Abel introduced significant participation in laboratory work as part of the medical school curriculum but, quite ironically, was opposed to the creation of a Ph.D. in pharmacology which, at Johns Hopkins, was not established until 1969, more than 30 years following his retirement (Parascandola 1992).

The launching of the *Journal of Pharmacology and Experimental Therapeutics* by Abel provided a much-needed outlet for pharmacological papers in the English language, with the earlier volumes of that journal offering effective hospitality to papers by British scientists pursuing pharmacology (*British Medical Journal*, "A Milestone in Pharmacology" 1946). In a remarkable parallel to the early difficulties of establishing pharmacology in Germany, there was hesitation in England for according pharmacology full academic recognition and the opportunities for publication had been limited to weekly medical journals and *The Journal of Physiology*. The editor of that journal, J. N. Langley, was showing a steadily increasing reluctance to accept papers which could be regarded as pharmacology based on the view that pharmacology was encroaching unduly on his space (Cuthbert 2006; Forward, Dale 1946). The result of this apparent impasse for Abel was to provide joint editorial control of the *Journal of Pharmacology and Experimental Therapeutics* in 1912 to both himself and to A.R. Cushny with an editorial board comprised of a number of British Pharmacologists.

In Britain, pharmacology also had some difficulties getting established, not just with regard to publishing. Those difficulties were attributed to a number of factors including the fact that trainee doctors were taught little about drugs in their medical school curriculum and, what was taught, was more aligned with pharmacy and prescription writing than pharmacology (Cuthbert 2006). A few chairs of Materia Medica and Therapeutics existed in universities in Scotland, but it was not until 1905 that such a position was established in England when a chair in pharmacology was established for Arthur Cushny at University College London. Cushny, originally from Scotland and one of the pioneer pharmacologists of England, also a pupil of Schmiedeberg, had been Abel's successor at Ann Arbor, Michigan. After approximately 12 years at the University of Michigan, Cushny returned to England in 1905 to be the first holder of a new Chair of Materia Medica and Pharmacology at University College, London (Abel 1926; Parascandola 1992). Abel's (1926) tribute to Cushny on the occasion of his premature death by a cerebral hemorrhage is a remarkable testimony to his life and provides a detailed account of Cushny's prolific contributions to the science of pharmacology and medicine, including a contribution to Heffter's *Handbuch der Experimentellen Pharmakologie* on the nitrites, the members of the atropine group, and ergot. Pharmacology rapidly established a foothold in England, led in large part by both Cushny and W.E. Dixon who held a part-time chair of Materia Medica and Pharmacology at King's College London, and moved subsequently to the position of Reader in Pharmacology at Cambridge in 1919 (Cuthbert 2006).

One of the more dominant figures in this early period of pharmacology in Britain was H.H. Dale. Dale, the recipient of a Nobel Prize in 1936, accepted a position at

the Wellcome Physiological Research Laboratories in 1904 where his research involved substances found in ergot and also included the study of the role of histamine in allergic reactions (Cuthbert 2006). A third individual working around this time was J.A. Gunn who became a professor of pharmacology at Oxford in 1912. These three individuals – Dixon, Dale, and Gunn – were responsible for undertaking the formation of the British Pharmacological Society (BPS) that held its first formal meeting in 1931 (Cuthbert 2006). Writing in the Forward of the inaugural issue of the *British Journal of Pharmacology and Chemotherapy*, Sir Henry Dale (1946) commented on the "growing volume and importance of pharmacological publication … seen throughout the scientific world … [adding that] pharmacology has rapidly risen to a major rank among the group of scientific disciplines which come from within the scope of experimental medicine" (p.1).

3.1 Otto Krayer and the Origins of Behavioral Pharmacology

One other German pharmacologist warrants recognition among those that fostered and further developed pharmacology and added branches to the foundation established in Germany that were expanded to the United States and Great Britain. Otto Krayer (1899–1982) had embarked on a promising career in pharmacology that was initiated when he was a medical student working with Paul Trendelenburg at the University of Freiburg. When Trendelenburg became Chair of Pharmacology at the highly prestigious University of Berlin in 1927, Krayer moved with him and continued to work in his laboratory. Unfortunately, Trendelenburg became ill with tuberculosis in 1930 and passed away the following year. The Chair at Berlin could only be filled by someone who held an existing chair, and when the new Chair, Professor Heubner, from the University of Göttingen arrived, he appointed Krayer Professor Extraordinarius of Pharmacology and Toxicology (Anderson 2005). In 1933, Krayer was offered, but turned down the offer to become the Chair of Pharmacology and Toxicology at the Medical Academy of Düsseldorf with the reason that the Jewish incumbent Chair, Philipp Ellinger, had been removed according to Nazi law (Anderson 2005). The decision by Krayer, based on his personal convictions that this was an injustice, resulted in Krayer subsequently being banned from teaching, using university or state libraries, while also being forbidden to enter any government academic institution or scientific facility (Trendelenburg 1978). This compassionate decision effectively ended Krayer's career in Germany (Anderson 2005; Goldstein 1987), but he was to continue to have a significant long-term impact on pharmacology. At the time of these events, Krayer was completing Volume 2 of Trendelenburg's *Die Hormone* that was unfinished when Trendelenburg passed away. Friends clandestinely brought him books and journals from the library for him to finish his work which, when completed, resulted in Krayer's providing the proofs to Springer-Verlag and his almost immediate departure from Germany (Dews 1983).

Initially, Krayer took temporary positions at University College London and the American University in Beirut. In 1936 Krayer was offered and accepted an

appointment in the Pharmacology Department at Harvard Medical School. He spent considerable time developing the curriculum and teaching until he was offered a position of Chair of Pharmacology at the Peiping Union Medical College for Columbia University in China. His temptation to accept this position, however, was countered when there was a petition by the medical students to the administration that Krayer remain at Harvard. Krayer was then offered and accepted the Chair of the Pharmacology Department with tenure (Dews 1983; Anderson 2005).

Krayer was interested primarily in molecular mechanisms of drug action and sought to evaluate further those findings in integrated physiological systems. In the 1950s Krayer was able to recruit a large number of faculty, one of whom was U. Trendelenburg, the son of Krayer's first mentor. Another member of the Department who was recruited during this time was Peter B. Dews. As Dews has written (Dews 1978), Krayer, in his effort to embrace diverse approaches to pharmacological research, sent him to meet with B.F. Skinner, the well-known behaviorist in the Psychology Department at Harvard who was conducting experiments with pigeons. Skinner and his students and colleagues were using automated experimental equipment and recording behavior on "cumulative recorders" in real time. Skinner had conducted a few prior experiments in the late 1930s with caffeine and benzedrine but had not further pursued those studies. At the time of Dews' visit to the Harvard Pigeon Lab, Skinner and his colleague, C.B. Ferster, were recording responding of pigeons pecking an illuminated plexiglass key. The key pecking behavior was controlled by a "schedule of reinforcement" that provided access to grain depending on prearranged contingencies such as the passage of time or the number of key pecks. The ability to record behavior objectively and quantitatively over lengthy time periods captured Dews interest and set the stage for the founding of the discipline of behavioral pharmacology.

Pharmacology has traditionally focused on and found order in the study of drug effects on relatively isolated pieces of tissue or organ systems. Progress in behavioral pharmacology, as in other areas of pharmacology, had to await the development and useful integration of suitable techniques that not only permitted but promoted the intensive study of the behavioral effects of drugs. The operant conditioning techniques that employed various schedules of reinforcement to control behavior that were so thoroughly and extensively explored by Ferster and Skinner (1957) provided the impetus for Dews to embrace those techniques and incorporate them into research to characterize the effects of drugs on behavior. Research in behavioral pharmacology has demonstrated that comparable order also exists when drugs are examined at the level of integrated behavior (Barrett 1980). Behavioral pharmacology began as a formal scientific discipline with the finding by P. B. Dews (1955) that the behavioral effects of drugs depended on the specific ways in which behavior was controlled by the schedule of reinforcement. The foresight by Krayer and the implementation by Dews and his colleagues launched an entirely new discipline within the field of pharmacology that coincided with the discovery and introduction of several new psychotherapeutic drugs to treat anxiety, depression, and schizophrenia – developments that necessitated an expansion of pharmacologists into the

pharmaceutical industry and fostered a multitude of new behavioral assays for drug discovery.

4 Pharmacology Through 100 Years and a Future Perspective

The discipline of pharmacology has made many significant advances over the past 100 years and will undoubtedly continue to do so in the future. It is now the "parent" of many subdisciplines that include behavioral pharmacology but also biochemical pharmacology, neuropharmacology, molecular pharmacology, pulmonary pharmacology, immunopharmacology, cardiovascular pharmacology, and other areas of importance such as pharmacoepidemiology, pharmacogenetics, and quantitative and systems pharmacology to name just a few. These areas of pharmacology and pharmacological research are an enduring testimony to the visionary and pioneering efforts of the early pharmacologists Buchheim and Schmiedeberg and their students who persevered in their efforts to establish pharmacology as a scientific endeavor within the field of medicine despite some formidable challenges.

Tremendous advances have been made in the quantitative analysis of drug-receptor interactions, in identifying mechanisms of signaling, and in our ability to predict how drug molecules bind to their protein target (Rachman et al. 2018; Wootten et al. 2018), areas of research whose history is rich in detail beginning with the work of A.V. Hill with subsequent contributions by other legendary figures in pharmacology including A.J. Clark, J.H. Gaddum, and H.O. Schild working at the University College London and the University of Edinburg (Colquhoun 2008; Rang 2006; Vallance and Smart 2006). A brief summary of the first 50 years of pharmacological research starting at the turn of the twentieth century yields evidence of remarkable advances in quantitative pharmacology with the clarification of agonist-antagonist relationships and the existence of partial agonists, along with distinctions between affinity and efficacy. The continued elaboration of these concepts, together with advances that were to follow, such as those of radioligand binding, allosteric and orthosteric modulation, inverse agonists, biased agonism at G protein-coupled receptors (GPCRs), and second messengers – all within the context of receptor theory – has provided the foundation for the study of receptor function at the biochemical and molecular level and the ability to further pursue what Kenakin (2019) has termed "analytical pharmacology," based on initial formulations of the Nobel Laureate pharmacologist Sir James Black. These developments only partially populate the expansive domain of pharmacological research and are complemented by the emergence of other areas that include groundbreaking work in crystallography that enables the stabilization of GPCRs in active conformations, thereby enabling the understanding of binding and aiding in drug development. The complexity of the signaling mechanisms activated by GPCRs and the interaction with cellular proteins represent new challenges to better understand the pharmacology of this important class of proteins that have yielded the rich pharmacology of drugs to treat a wide variety of disorders ranging from hypertension, schizophrenia, and depression. A

detailed review of significant developments within GPCRs including oligomerization and accessory proteins and the processes of desensitization, internalization, and trafficking has been provided by Hill (2006), with suggestions on the further challenges and opportunities existing for this receptor family.

Pharmacology has long been a discipline working closely with, contributing to, and benefiting from other areas in the biomedical sciences, such as physiology, biochemistry, and cell biology. As Lohse (1998) has commented, "while other biomedical sciences are trying to explain the world (of the human body), pharmacologists try to alter it," a statement somewhat similar to that of Kenakin (this volume) that "pharmacology is the chemical control of physiology." Many therapeutic drugs that have a pronounced physiological impact, such as the psychotherapeutic agents, were discovered before their true mechanism of action – the "target" – was identified. Over the past few decades, the pharmaceutical industry has placed considerable emphasis on "target identification" and validation based, in part, on the belief that focusing on a single selective target, presumably associated with the disease, would minimize "off-target" side effects. This approach has been balanced, more recently by the return to phenotypic screening of cells or whole animals (Moffat et al. 2017) and by the focus on multitarget approaches, recognizing that most diseases are complex and involve multiple targets, necessitating "polypharmacological" or multidrug combinations (Weiss and Nowak-Sliwinska 2017). This is certainly true of the heterogeneously complex disorders such as autism and schizophrenia, as well as diseases of the immune system and the targeting of tumors in oncology. Presumed pharmacological selectivity often vanishes under the scrutiny of new techniques and deeper knowledge of other potential targets. Even when a drug has been on the market for some time, it is not uncommon to identify a new mechanism and/or a new therapeutic utility for that compound. Such is the case, for example, with the anthelminthic drug mebendazole, discovered in the 1970s. Recently, using a combination of novel, rapid computational proteochemometric methods coupled to cell-based assays, it was shown that mebendazole should be considered for use in combination with trametinib as a therapeutic option for patients with specific types of melanomas (Simbulan-Rosenthal et al. 2017). This "repurposing" or "repositioning" of existing drugs has captured a great deal of attention to reposition drugs either as combination therapeutics or as stand-alone drugs for other disorders (Frail et al. 2015; Kumar et al. 2019; Polamreddy and Gattu 2019). These efforts clearly require the integration of other disciplines from computational pharmacology and other specialties, further emphasizing the alignment and integration of other techniques and methodologies into pharmacological research.

Significant advances in pharmacology have been made in other areas such as drug metabolism with the focus on metabolomics, as well as pharmacogenomics and pharmacoepidemiology (see chapters in this volume by Chavira et al. 2019; Everett 2019; Moore et al. 2019). The development of in silico models in drug development, coupled to the use of microfluidic devices such as "organs-on-chips," and the incorporation of induced pluripotent stem cells have been enthusiastically integrated into drug discovery and development (Borenstein 2016; Esch et al. 2015; Piñero et al. 2018; Suh 2016) providing relatively rapid assessments of the actions of

various drugs to predict efficacy as well as toxicological actions. The area of quantitative and systems pharmacology incorporates these areas with the perspective of developing more personalized or precision medicine and the integration of artificial intelligence (AI) to deal with complex data sets (see Taylor et al. this volume and Wishart 2016).

5 Conclusions

Progress in pharmacology over the past 100 years has been monumental. However, significant challenges remain in a number of therapeutic areas with significant unmet medical need, not the least of which is in the need for new antibiotics, as resistance to existing drug classes increases. Other areas of unmet need include those of identifying medications to treat substance abuse disorders and pain where these conditions may, under some conditions, be related. The great promise offered by many of the more recent developments suggests that pharmacology will become even more important over the next 100 years. Many of these developments have been spawned in academic research laboratories which will likely to continue to play an important role for pharmacologists and the pharmaceutical industry. As the pharmaceutical industry has consolidated and discontinued a focus on certain therapeutic areas, particularly in the area of neuroscience, much of the effort has shifted to academic research aligned with government funding to fill the gap for new targets and potential therapeutics. Finally, as the discipline of pharmacology has become more diverse and technologically rich, there is a continuing need to emphasize the importance of training, education, and research in the fundamental principles of pharmacology, an area that was emphasized in the early days of academic laboratories in Germany and which continues to be an important contemporary priority.

References

A Milestone in Pharmacology (1946) Br Med J 1:727–728

Abel JJ (1926) Arthur Robertson Cushny and pharmacology. J Pharmacol Exp Ther 27:265–286

Anderson R (2005) The singular moral compass of Otto Krayer. Mol Interv 5:324–329

Barrett JE (1980) Behavioral pharmacology: recent developments and new trends. Trends Pharmacol Sci 1:215–218

Borenstein JT (2016) Organs-on-chips: how microsystems technology can transform the drug development process. IEEE Pulse 7:22–26

Chavira A, Belda-Ferre P, Kosciolek T, Farhana A, Dorrestein C, Knight R (2019) The microbiome and its potential for pharmacology. Handb Exp Pharmacol. https://doi.org/10.1007/164_2019_317

Colquhoun D (2008) The quantitative analysis of drug-receptor interactions: a short history. Trends Pharmacol Sci 27:149–157

Cuthbert AW (2006) A brief history of the British Pharmacology Society. Br J Pharmacol 147: S2–S8

Deichmann WB, Henschler D, Holmstedt B, Keil G (1986) What is there that is not poison? A study of the Third Defense by Paracelsus. Arch Toxicol 58:207–213
Dews PB (1978) Origins of behavioral pharmacology. Life Sci 22:1115–1122
Dews PB (1955) Studies on behavior. I. Differential sensitivity to pentobarbital of pecking performance in pigeons depending on the schedule of reward. J Pharmacol Exp Ther 113:393–401
Dews PB (1983) Otto Krayer 1899-1982. Trends Pharmacol Sci 4:143–146
Esch EW, Bahinski A, Huh D (2015) Organs-on-chips at the frontiers of drug discovery. Nat Rev Drug Discov 14:248–260
Everett JR (2019) Pharmacometabonomics: the prediction of drug effects using metabolic profiling. Handb Exp Pharmacol. https://doi.org/10.1007/164_2019_316
Ferster CB, Skinner BF (1957) Schedules of reinforcement. Appleton-Century-Crofts, New York
Foreword (1946) Br J Pharmacol Chemother 1:1–3
Frail DE, Brady M, Escott KJ, Holt A, Sanganee HJ, Pangalos MN, Watkins C, Wegner CD (2015) Pioneering government-sponsored drug repositioning collaborations: progress and learning. Nat Rev Drug Discov 14:833–841
Goldstein A (1987) Otto Krayer: a biographical memoir. Biogr Mem Natl Acad Sci 57:11–225
Habermann ER (1974) Rudolf Buchheim and the beginning of pharmacology as a science. Annu Rev Pharmacol 14:1–9
Hill SJ (2006) G-protein-coupled receptors: past, present and future. Br J Pharmacol 147:S27–S37
Kenakin T (2019) Analytical pharmacology: how numbers can guide drug discovery. ACS Pharmacol Transl Sci 2:9–17
Koch-Weser J, Schechter PJ (1978) Schmiedeberg in Strassburg 1872-1918: the making of modern pharmacology. Life Sci 22:1361–1372
Kumar R, Harilal S, Gupta SV, Jose J, Thomas Parambi DG, Uddin MS, Shah MA, Mathew B (2019) Exploring the new horizons of drug repurposing: a vital tool for turning hard work into smart work. Eur J Med Chem 182:111602
Lohse MJ (1998) The future of pharmacology. Trends Pharmacol Sci 19:198–200
Meyer HH (1922) Oswald Schmiedeberg. Naturwissenschaften 10:105–107
Moffat JG, Vincent F, Lee JA, Eder J, Prunotto M (2017) Opportunities and challenges in phenotypic drug discovery: an industry perspective. Nat Rev Drug Discov 16:531–543
Moore N, Blin P, Droz C (2019) Pharmacoepidemiology. Handb Exp Pharmacol. https://doi.org/10.1007/164_2019_318
Norton S (2005) Origins of pharmacology in the 16th century. Mol Interv 5:144–148
Parascandola J (1980) Reflections on the history of pharmacology: the 1980 Kremers Award Address. Pharm Hist 22:131–140
Parascandola J (1992) The development of American pharmacology: John J. Abel and the shaping of a discipline. Johns Hopkins, Baltimore
Piñero J, Furlong LI, Sanz F (2018) In silico models in drug development: where we are. Curr Opin Pharmacol 42:111–121
Polamreddy P, Gattu N (2019) The drug repurposing landscape from 2012-2017: evolution, challenges and possible solutions. Drug Discov Today 24:789–795
Rachman M, Barril X, Hubbard RE (2018) Predicting how drug molecules bind to their protein targets. Curr Opin Pharmacol 42:34–39
Rang HP (2006) The receptor concept: pharmacology's big idea. Br J Pharmacol 147:S9–S16
Rubin RP (2007) A brief history of great discoveries in pharmacology: in celebration of the Centennial Anniversary of the American Society of Pharmacology and Experimental Therapeutics. Pharmacol Rev 59:289–359
Simbulan-Rosenthal CM, Dakshanamurthy S, Gaur A, Chen Y-S, Fang HB, Abdussamad M, Zhou H, Zapas J, Calvert V, Petricoin EF, Atkins MB, Byers SW, Rosenthal DS (2017) The repurposed anthelmintic mebendazole in combination with trametinib suppresses refractory $NRAS^{Q61K}$ melanoma. Oncotarget 8:12576–12595

Starke K (1998) A history of Naunyn-Schmiedeberg's archives of pharmacology. Naunyn Schmiedebergs Arch Pharmacol 358:1–109
Suh W (2016) A new era of disease modeling and drug discovery using induced pluripotent stem cells. Arch Pharm Res 40:1–12
Trendelenburg U (1978) Remembrances. Life Sci 22:113–114
Trendelenburg U (1998) Pharmacology in Germany. Trends Pharmacol Sci 19:196–198
Vallance P, Smart TG (2006) The future of pharmacology. Br J Pharmacol 147:S304–S307
Weiss A, Nowak-Sliwinska P (2017) Current trends in multidrug optimization: an alley of future treatment of complex disorders. SLAS Technol 22:254–275
Wishart DS (2016) Emerging applications of metabolomics in drug discovery and precision medicine. Nat Rev Drug Discov 15:473–484
Wootten D, Christopoulos A, Marti-Solano M, Babu NM, Sexton PM (2018) Mechanisms of signaling and biased agonism in G protein coupled receptors. Nat Rev Mol Cell Biol 19:638–653

Emergent Concepts of Receptor Pharmacology

Terry Kenakin

Contents

Abstract

Pharmacology, the chemical control of physiology, emerged as an offshoot of physiology when the physiologists using chemicals to probe physiological systems became more interested in the probes than the systems. Pharmacologists were always, and in many ways still are, bound to study drugs in systems they do not fully understand. Under these circumstances, null methods were the main ways in which conclusions about biologically active molecules were made. However, as understanding of the basic mechanisms of cellular function and biochemical systems were elucidated, so too did the understanding of how drugs affected these systems. Over the past 20 years, new ideas have emerged in the field that have completely changed and revitalized it; these are described herein. It will be seen how null methods in isolated tissues gave way to, first

T. Kenakin (✉)
Department of Pharmacology, University of North Carolina School of Medicine, Chapel Hill, NC, USA
e-mail: kenakin@email.unc.edu

J. E. Barrett et al. (eds.), *Concepts and Principles of Pharmacology*,
Handbook of Experimental Pharmacology 260, https://doi.org/10.1007/164_2019_297

biochemical radioligand binding studies, and then to a wide array of functional assay technologies that can measure the effects of molecules on drug targets. In addition, the introduction of molecular dynamics, the appreciation of the allosteric nature of receptors, protein X-ray crystal structures, genetic manipulations in the form of knock-out and knock-in systems and Designer Receptors Exclusively Activated by Designer Drugs have revolutionized pharmacology.

Keywords
Drug discovery · Pharmacodynamics · Pharmacology history

1 Introduction

Pharmacology is a unique scientific discipline in that it incorporates many 'pure' scientific disciplines such as genetics, chemistry, biochemistry and physiology. Actually, to be more specific, not so much incorporates as 'borrows from'. Therefore pharmacology has evolved as a uniquely separate melding of chemistry and physiology. Since this is the case, advances in any of these contributing sciences, either from the point of technology or understanding of the basic science, necessarily impacts pharmacology and thus changes the discipline. Pharmacology originated from a basic practical need, i.e. humans require chemicals to prevent, diagnose and cure disease and improve health. Therefore a system had to evolve to promote this process. This chapter will discuss the various influences that have shaped receptor pharmacology to where it is at this present time.

2 Shots in the Dark: Null Methods in Pharmacology

Pharmacology began, and in some ways still is, a science operating in a sea of uncertainty, i.e. pharmacologists often do not fully understand the systems they study. Thus from the early days of receptor pharmacology, isolated tissue preparations from animals were used to characterize what then was only a concept, i.e. the 'receptor' was not biochemically characterized nor available for physical study but simply was a unifying concept for pharmacologists and medicinal chemists used to order and modify physiology (Rang 2009). The basic idea behind the use of isolated tissues was that drugs interact with receptors to induce a visible response and the tissue simply amplifies this initial signal (defined by Stephenson (1956) as 'stimulus') to allow quantification of drug response through an undefined biochemical cascade referred to as the 'stimulus-response' mechanism of the cell. The tacit assumption in this process is that the amplification process is uniform and thus ratios of activity seen through the amplified signal accurately reflected ratios of pharmacological effect at the receptor. Such concepts led to some extremely useful tools in drug discovery such as the agonist potency ratio (PR), which allows quantification of relative agonist activity in test systems that ostensibly allowed prediction of

similar activity in all systems. The underlying assumption in this scheme is that stimulus-response cascades are monotonic (only one '*y*', tissue response, for every '*x*', drug concentration); only such systems ensure the accurate translation of receptor events to observed tissue response in a predictable manner.

There are two inherent weaknesses in this historical scenario. The first is obvious in that animal receptors and cells are different from human receptors and cells; thus errors in activity translation occur. The second was not made evident until the emergence of recombinant systems in pharmacology, namely that stimulus response mechanisms are not routinely monotonic in nature. In fact, it was the discovery of this fact that directly led to the discovery of biased receptor signaling (vide infra). Thus the introduction of recombinant technology the 1980s ushered in a new era in receptor pharmacology that essentially overturned many cornerstone assumptions of the previous 60 years.

3 Recombinant Systems Redefine Receptor Pharmacology

To a large extent, the necessarily limited application of functional pharmacological systems (common isolated tissues used by most researchers) led to the apparently harmonious concepts unifying receptor pharmacology at the time. However, the definition of the human genome and the introduction of recombinant systems into pharmacology allowed the study of receptors in a wealth of different interacting systems and this, in turn, unveiled the greater complexity inherent in receptor-response element interaction. These systems also obviated one of the underlying weaknesses of isolated tissue systems in that human receptors now could routinely be used in drug discovery in functional systems in vitro. However, the second weakness in isolated tissue pharmacology was then exposed as numerous instances of failure to adhere to standard PR predictions began to be observed and reported in the literature. Before discussing this latter idea, the emergence of another trend in pharmacology should be considered as it was instrumental in the exploration and exploitation of recombinant systems, namely the introduction of more functional pharmacological assay formats and the de-emphasis of binding as the primary tool for definition of receptor activity.

4 Binding Gives Way to Functional Experiments

Radioligand binding experiments can be extremely valuable to detect and measure direct interaction of molecules with receptor proteins. Such technology became important in pharmacology because it is amenable to robotic high throughput procedures required for high volume screening in drug discovery. On the other hand, the drug response that is most relevant to therapy is cellular function and there are numerous instances where binding falls short of predicting the functional effects of molecules. One reason this is the case is the fact that the two experimental formats measure different protein species; binding captures the protein interacting

with the radioligand while function captures the protein sending the signals to the cells (Kenakin 2009). Theoretically, functional experiments also are superior to binding formats because there are more interrogators of receptor conformation in function (namely the signaling proteins that interact with the receptor); binding relies simply on the interference of the radioligand-receptor interaction. While this has always been known to be true, technological advances were required to bring the state of the art of functional measurement of cellular response to the level of binding technology in terms of high throughput screening and the measurement of drug functional response in lead optimization assays. From the 1990s on, functional assay technology increased tremendously to the point where it could be used for high throughput screening and also for molecule characterization. An added bonus to this change in emphasis is the increase in the capability of detection and characterization assays to discover allosteric action of new ligands (Rees et al. 2002).

5 Understanding Agonism: The Black/Leff Operational Model

Concomitant with the introduction of more extensive functional assay technology was the introduction of arguably the most important model to describe drug agonism, specifically the operational model described by Black and Leff (1983) and Black et al. (1985). The chemical production of cellular response (agonism) had long been a mysterious property of drugs. Pioneers of receptor pharmacology such as Ariens (1954, 1964), Ariens and Van Rossum (1957), Furchgott et al. (1966) and Stephenson (1956) produced useful models to accommodate this intriguing property of some ligands. These approaches led to the insertion of a calibration factor to accommodate the receptor occupancy of agonists with the observed responses produced by agonists; this factor is referred to as efficacy (Stephenson 1956) or intrinsic efficacy (Furchgott et al. 1966). The ad hoc nature of this approach was seen as a shortcoming of pharmacology by Sir James Black and Paul Leff and they formulated a physiologically based model to describe agonism. This model was fundamentally unappreciated when published but subsequently has now become the state of the art approach to the handling of agonism in pharmacology.

The Black/Leff operational model defines the response to an agonist [*A*] as (Black and Leff 1983):

$$\text{Response} = \frac{[A]^n \tau_A^n E_m}{[A]^n \tau_A^n + ([A] + K_A)^n} \tag{1}$$

where agonist affinity is given by the equilibrium-dissociation constant of the agonist-receptor complex (K_A) and the agonist efficacy is denoted τ_A. The slope of the concentration response curve is n and E_m is the maximal window of response for the assay. For partial agonists, unique values for both K_A and τ_A can be derived but for full agonists, an infinite combination of K_A and τ_A values can fit the curve. However, the unique identifier for full agonists then becomes $\log(\tau_A/K_A)$ (Kenakin et al. 2012).

One of the most valuable applications of the Black/Leff operational model is that it gives the capability to compare the activity of full to partial agonists. While potency ratios are theoretically sound for the comparison of full agonists to each other, the location parameter of partial agonist concentration-response curves changes differently from the location parameter of full agonists with changing assay sensitivity. Figure 1 shows the ratio of pEC_{50}'s (−log of molar EC_{50} concentrations) as ΔpEC_{50} as a function of the receptor density in the functional assay. It can be seen that as one of the agonists becomes a partial agonist at lower receptor densities, the linear relationship with receptor density becomes non-linear and not comparable to values found at higher tissue sensitivities. In contrast, the index $\Delta Log(\tau/K_A)$ remains linear for full and partial agonists thus providing a useful scale for comparison that is independent of tissue sensitivity (Kenakin 2017).

The operational model provides a physiologically plausible description of agonist efficacy and a structure within which the affinity and efficacy of an agonist can be quantified in a system independent manner. This, in turn, can be used to predict agonism in all therapeutically relevant systems. The acceptance of this model in the pharmacological approaches to receptor pharmacology was critical to the advancement of the functional systems to the development of new drug candidates in the process of drug discovery.

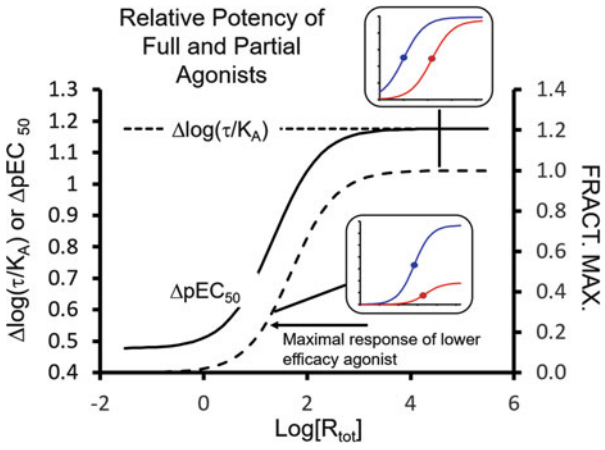

Fig. 1 Changes in relative potency of agonists with changing receptor density (tissue sensitivity). Left ordinate axis is $\Delta Log(\tau/K_A)$ or ΔpEC_{50} of two agonists with a relative efficacy of 0.2 (the more powerful agonist has 5-times the efficacy of the weaker agonist). Right ordinate axis is the maximal response (as a fraction of maximal assay window) of the weaker agonist. Abscissae is the log of the receptor density in the assay system. It can be seen that the relative potency as measured by the ΔpEC_{50} varies with system sensitivity until both agonists produce the full maximal response (both are full agonists). If the weaker agonist is a partial agonist, then pEC_{50} is variable. In contrast, the $\Delta Log(\tau/K_A)$ remains constant throughout the complete range of assay sensitivities being constant whether both agonists are full agonists or if one or both are partial agonists

6 The Shift from Orthosteric to Allosteric Drug Action

Seven transmembrane receptors are nature's prototypical allosteric protein, i.e. these are proteins designed to bind molecules in the extracellular space, change their conformation accordingly, and present different tertiary conformations toward signaling proteins in the cytosol. This is the very definition of allosteric function (etymology 'allo' = other, 'steric'-arrangement of atoms in space) which connotes binding at one site to induce an effect in another. Everything seven transmembrane receptors do is allosteric and can be described by an allosteric vector of 'modulator', conduit (the receptor protein) and guest molecule. Within this context, the natural binding site for the natural agonist (neurotransmitter, hormone) can be considered the 'orthosteric' site and the different site binding the modulator the 'allosteric' site. Thus, an orientation of the vector from the outside to the inside of the cell is agonism with the modulator binding as the agonist, conduit the receptor and guest the signaling protein (Kenakin 2012). A vector along the plane of the membrane describes receptor oligomerization with a modulator being either another receptor or Receptor Activity Modifying Proteins (RAMPs), conduit the receptor and guest the receptor itself. A vector between two drugs binding on the receptor is the conventional 'guest allostery' where one ligand affects the binding and function of another both binding to the receptor protein.

Models of allosteric binding and function involve the interaction of a probe ligand (agonist or radioligand denoted [*A*]) with a protein (receptor *R*) and a guest molecule (modulator denoted [*B*]). Figure 2a shows the allosteric binding model for binding

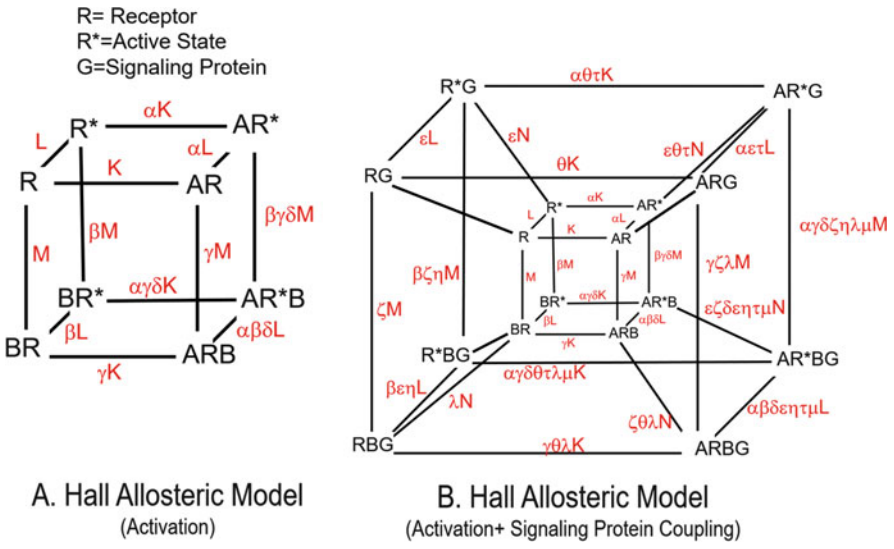

Fig. 2 Allosteric models for an Agonist *A*, allosteric modulator *B*, receptor is *R* and a signaling protein *G*. The model defines the receptor species present in system through formation of an active receptor state (R∗)-Panel **a**, Hall Allosteric model (Hall 2000) or through formation of an active state and allowing the receptor to couple to signaling proteins (Panel **b**) (Hall 2006)

and receptor activation in a relatively simple scheme; Fig. 2b shows how these models rapidly become more complex with the introduction of other receptor behaviors, in this case the interaction of the receptor species with signaling proteins. The problem with these more inclusive models is that they are heuristic and contain a larger number of independently unverifiable parameters. This also belies the notion that an advantage of binding formats is they are 'simple' (Christopoulos and Kenakin 2002).

Allosteric effects can be very complex and can involve changes in the affinity and/or efficacy of the probe molecule. This being the case, not all allosteric effects are detected or can be studied through radioligand binding; functional assays are a much better format for the study of allosteric effects. The lack of functional assays was a hindrance to the effective study of allosteric receptor behavior but as more functional assays became available through technological advances, the more prevalent in the literature allosteric effects became. Thus, a near exponential increase in the prevalence of scientific papers citing the words allosteric or allosterism can be seen from 1990 up to the present day; presumably some of this increased trend is due to increased availability of simple pharmacological functional assays (Rees et al. 2002). Thus in the 2000s, increased emphasis on allosteric mechanisms was evident in pharmacological receptor literature.

There are theoretical reasons why functional response is a more predictive and useful measure of drug activity than binding. A barrier to the creation of a functional allosteric model was that there was no plausible means to process cellular response emanating from the active receptor species. This problem was solved by the melding of the Black/Leff operational model to allosteric binding models – see Fig. 3. Thus,

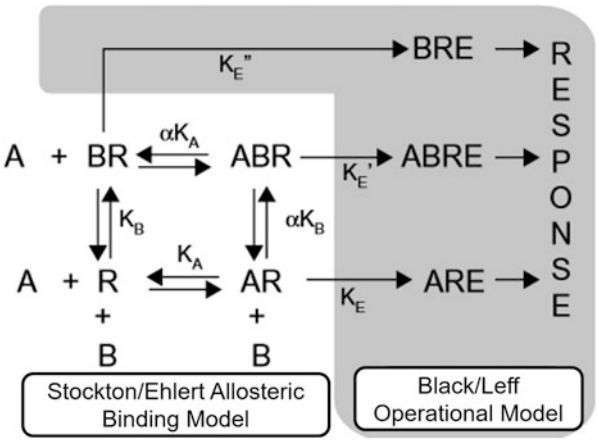

Fig. 3 Model for functional receptor allosterism [46]. A probe ligand [A] (agonist) binds to the receptor and the resulting complex (ARE) can produce response. Similarly, the allosteric modulator B can simultaneously bind to the receptor and produce response through the complex BRE and can modify the agonist response through the species ABRE. Binding to the receptor is described by the allosteric binding model (Stockton et al. 1983; Ehlert 1988) and response is described by the Black/Leff operational model (Black and Leff 1983)