available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

Fifty years of *Biochemical Pharmacology*: The discipline and the journal

S.J. Enna [a], G.Z. Feuerstein [b], J. Piette [c], M. Williams [d,*]

[a] Department of Molecular and Integrative Physiology and Department of Pharmacology, Toxicology, and Therapeutics, University of Kansas Medical Center, Kansas City, KS, USA
[b] Discovery Translational Medicine, Wyeth Research and Development S2302, Collegeville, PA, USA
[c] Laboratory of Virology and Immunology, Institute of Pathology, University of Liège, Belgium
[d] Discovery Research, Cephalon, Inc., 145 Brandywine Parkway, West Chester, PA, USA

ARTICLE INFO

Article history:
Received 31 March 2008
Accepted 31 March 2008

Keywords:
Receptors
Enzymes
Human disease
Drug discovery
Pharmacology

ABSTRACT

The discipline of biochemical pharmacology emerged in the late 1940s as a result of an increasing emphasis on understanding drug mechanisms at the cellular level. This research approach has contributed significantly to the development of many new drug classes including antihypertensive, antifective, cholesterol lowering, anti-inflammatory, and anticancer agents, as well as antipsychotics, antidepressants and anxiolytics. Biochemical pharmacology remains a major tool in drug discovery, being employed in the search for novel therapeutics for the above and other conditions and clinical challenges, such as neurodegenerative disorders, for the treatment of pain, and for development of agents that do not induce, or can overcome, antibiotic/antiviral resistance. Together with chemical, molecular, genetic, physiological, and clinical sciences, biochemical pharmacology will in the coming decades continue to be a critical component of the drug discovery process.

© 2008 Elsevier Inc. All rights reserved.

1. Introduction

Two milestones in the history of pharmacology are being celebrated this year. One is the 100th anniversary of the founding of the American Society for Pharmacology and Experimental Therapeutics (ASPET) by J.J. Abel [1] and the other is the 50th anniversary of *Biochemical Pharmacology*. The journal was created to document "research into the development of biologically active substances and their mode of action at the biochemical and cellular level" [2]. Founded by the pioneering oncologist Peter Alexander [3] and colleagues in 1958, the launch of *Biochemical Pharmacology* was: (i) *coincident* with the emergence of a number of technologies developed during World War II that facilitated the ability to make more precise and reliable measurements in biological systems that found ready application in biomedical research and; (ii) *congruent* with the biochemically based advances in the understanding of enzyme structure and function and natural product synthesis in the 1940s, the latter of which led to the facile, fermentation-based production of penicillin [4].

* *Corresponding author*. Tel.: +1 610 738 6658; fax: +1 610 738 6630.
E-mail addresses: mazarine1643@comcast.net, mwilliam@cephalon.com (M. Williams).

Abbreviations: ACE, angiotensin-converting enzyme; RAS, renin–angiotensin system; SARs, structure–activity relationships; NSAIDs, nonsteroidal anti-inflammatory drugs; NCEs, novel chemical entities; RA, rheumatoid arthritis; VRSA, vancomycin-resistant *S. aureus*; MRSA, methicillin-resistant *S. aureus*.

0006-2952/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.bcp.2008.03.024

The emerging discipline of biochemical pharmacology provided the means therefore to initiate the search to identify the molecular targets through which drugs and other bioactive compounds produce their effects on normal and diseased tissue. This initiated the efforts to provide a systematic molecular framework for defining more precisely disease causality and the mechanisms whereby drugs provide therapeutic benefit(s). It was another 40 years, however, before this concept became reality with the cloning of a variety of genes, including those responsible for the production of hormone and neurotransmitter receptors [5,6]. Besides representing some of the most important targets for drug action, receptors have been a major topic of interest for biochemical pharmacologists.

1.1. *Receptor concepts*

From the mid 19th century until the early 20th, the empirical and physiological techniques perfected by Claude Bernard to study the effects of xenobiotics on tissue function [6] provided the intellectual context necessary for the development of the 'lock and key' theory of drug action. While the concept of 'receptive substances' is ascribed jointly to J.N. Langley and Paul Ehrlich at the turn of the 20th century [7,8], the former may have first suggested the idea as early as 1858 [9]. Receptors are macromolecules present both on the surface of, and within, the cell. Over time this term was used to describe every conceivable drug target including enzymes, DNA binding motifs, RNA and protein/protein interactions. This formalized further the concept of molecular targets at which the 'magic bullets' obtained from both synthetic and natural product sources produced their effects, both beneficial and detrimental.

The receptor concept was initially proposed on the basis of the actions of compounds in bioassays or in animal models in the total absence of any direct physical evidence for their existence [10]. This early deficiency notwithstanding, the concept has been the basis for understanding disease causality and drug actions for over a century [8], and continues to guide the search for new therapeutics.

When first proposed, the receptor concept was more qualitative than quantitative in nature and therefore met with considerable resistance from prominent pharmacologists, including Rudolf Magnus and Henry Dale [10,11]. Indeed, Dale considered the receptor concept a ''cloak for ignorance'' [9]. It was not until the 1930s that A.J. Clark and John Gaddum provided crucial support for the receptor theory by undertaking a quantitative analysis of drug action [8,12]. While the subsequent work of H.O. Schild, Everhardus Ariens and R.P. Stephenson elaborated on the work of Clark and Gaddum, it was the seminal work of Raymond Ahlquist in 1948 [13] attributing the different pharmacodynamic effects of epinephrine to different types of adrenoceptors, α- and β, that became a seminal point in the acceptance of the receptor theory as a basis for drug action [10,14]. The subsequent work of Bjorn Folkow, Georg Kahlson and James Black on adrenergic and histamine receptor subtypes [15] led to the successful development of propranolol, a β-adrenoceptor antagonist, and cimetidine, the first of the histamine H_2 receptor blockers. Both of these agents were developed utilizing a cyclical iteration to assess compound activity at the biochemical target that entailed a close working relationship between medicinal chemists and pharmacologists in defining structure–activity relationships (SARs) [16].

Historically, few of the quantal iterations in the conceptualization of receptor function have been readily embraced by pharmacologists. For example, the concepts of transmitter co-release [17], allosteric modulation and ligand efficacy, including inverse agonism and constitutive activity [8,9], were all met with varying levels of skepticism by those in the discipline. As a group, pharmacologists may be viewed as highly conservative, although sufficiently objective to ultimately succumb to the persuasive power of data.

1.2. *Biochemical pharmacology*

By studying the effects of novel chemical entities (NCEs) on tissue and cellular function, it became possible to define more precisely the causes of human disease at the molecular level and to, in turn, develop safer and more efficacious drugs for the treatment of these conditions. This biochemical approach to drug discovery predominated from the early 1950s until the late 1980s. These techniques proved highly successful in the development of new therapeutics. Among the novel drug classes identified with this approach were antidepressants, antipsychotics, β-adrenoceptor antagonists, loop diuretics and angiotensin converting enzyme inhibitors [15]. While the emphasis on biochemical pharmacology as a tool in drug discovery declined over the past two decades with the ascendancy of molecular biology [18,19], the interest in examining drugs and drug candidates at the biochemical level has been rekindled in recent years under the rubric of chemical genomics/genetics. Thus, once again, NCEs are being used to characterize or modify drug targets and targets are utilized to characterize the efficacy and selectivity of NCEs *in vitro* before advancement into more costly and complex *in vivo* animal models [20,21].

Two fundamentally important concepts arose from the era of biochemical pharmacology. The first was that knowledge of the mechanism of action of an NCE is critical in defining the agent. Using biochemical techniques, NCEs were iteratively evaluated and optimized for potency, efficacy and target selectivity *in vitro* at defined molecular targets before being tested in more complex tissues, organ systems or intact animals. This approach made possible the rapid identification of the most promising candidates independent of the variables associated with their pharmacokinetic differences. Historically, drug mechanisms were defined in organ systems or in whole animals by determining structure–activity relationships of a series of agonists and antagonists to assess effects on phenotypes. The results of these studies were often ambiguous as many of the test agents were nonselective in their effects and because differences in response were often more the result of pharmacokinetic rather than pharmacodynamic properties. Testing an NCE *in vitro* at a known molecular target made it possible to more precisely characterize its ability to interact selectively at this site independent of its other properties, thereby enhancing the characterization of the compound and the receptor system under investigation. This led to a somewhat naïve variation on

Download English Version:

https://daneshyari.com/en/article/2514928

Download Persian Version:

https://daneshyari.com/article/2514928

Daneshyari.com