Proceedings of the Sixth International Congress of Pharmacology

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Volume 1

RECEPTORS AND CELLULAR PHARMACOLOGY

Editor:

E. KLINGE

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VOLUME 1

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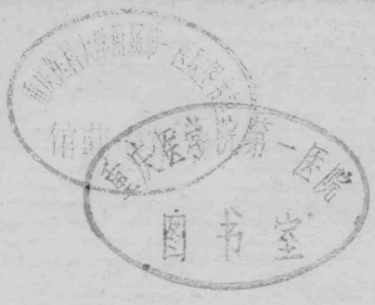
Volume Editor

E. KLINGE
University of Helsinki



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List of Authors

ALBUQUERQUE, E. X	Department of Pharmacology and Experimental Therapeutics, School of Medicine, University of Maryland, Baltimore, Maryland 21201, USA
BARNARD, E. A.	Molecular Pharmacology Division, National Institute for Medical Research, Mill Hill, London NW7 1AA, United Kingdom
BERRIDGE, M. J.	Agricultural Research Council Unit of Invertebrate Chemistry and Physiology, Department of Zoology Downing Street, Cambridge CB2 3EJ, United Kingdom
BLACK J. W.	Department of Pharmacology, University College London, London WC1E 6BT, United Kingdom
BOCKAERT, J.	Laboratoire de Physiologie Cellulaire, College de France, 75231 Paris 05, France
BOURNE, H. R.	Departments of Medicine, Pharmacology, Microbiology, Biochemistry and Biophysis, and the Cardiovascular Research Institute, University of California, San Francisco, California 94143, USA
BUTLEN, D.	Laboratoire de Physiologie Cellulaire, Collège de France, 75231 Paris 05, France
CHANG, C. C.	The Pharmacological Institute, College of Medicine, National Taiwan University, Taipei, Taiwan
CHANGEUX, J.-P.	Neurobiologie Moléculaire, Institut Pasteur, Paris, France
COFFINO, P.	Departments of Medicine, Pharmacology, Microbiology, Biochemistry and Biophysics, and the Cardiovascular Research Institute, University of California, San Francisco, California 94143, USA
DALY, J.	Laboratory of Chemistry, NIAMDD, NIH, Bethesda, Maryland 20014, USA
DANIELS, M. P.	Laboratory of Biochemical Genetics, National Heart and Lung Institute, NIH, Bethesda, Maryland 20014, USA
DESBUQUOIS, B.	Unité 30 INSERM, Hôpital des Enfants-Malades, 149 rue de Sèvres, 75015 Paris, France
DEUTSCH, J.	Church Laboratory of Chemical Biology, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, USA
DOLLY, J. O.	Department of Pharmacology, University of Maryland, School of Medicine, Baltimore, Maryland, USA
ENNA, S. J.	Department of Pharmacology and Experimental Therapeutics, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA
HARDEN, T. K.	University of Colorado Medical Center, Denver, Colorado 80220, USA
HARDMAN, J. G.	Department of Physiology, Vanderbilt University, Nashville, Tennessee, USA
HOCHMAN, J.	Departments of Medicine, Pharmacology, Microbiology, Biochemistry and Biophysis, and the Cardiovascular Research Institute, University of California, San Francisco, California 94143, USA
HURWITZ, L.	Department of Pharmacology, University of New Mexico, Albuquerque, New Mexico, USA
INSEL, P. A.	Departments of Medicine, Pharmacology, Microbiology, Biochemistry and Biophysis, and the Cardiovascular Research Institute, University of California, San Francisco, California 94143, USA
JARD, S.	Laboratoire de Physiologie Cellulaire, Collège de France, 75231 Paris 05, France

JONES, P.	Departments of Medicine, Pharmacology, Microbiology, Biochemistry and Biophysics, and the Cardiovascular Research Institute, University of California, San Francisco, California 94143, USA
KATZ, A. M.	Department of Physiology and Biophysics, Mount Sinai School of Medicine of the City University of New York, New York, New York 10029, USA
KHARKEVICH, D. A.	Institute of Pharmacology of the USSR Academy of Medical Sciences and the Department of Pharmacology, First Medical Institute, Moscow, G-435, USSR
KIRCHBERGER, Madeleine A.	Division of Cardiology, Mount Sinai School of Medicine of the City University of New York, New York. New York 10029, USA
KUKOVETZ, W. R.	Department of Pharmacodynamics and Toxicology, University of Graz, Univ.-Platz 4, 8010 Graz, Austria
LAPA, A. J.	Department of Pharmacology and Experimental Therapeutics, School of Medicine, University of Maryland, Baltimore, Maryland 21201, USA
LECHAT, P.	Institut de Pharmacologie de la Faculté de Médecine, 75006 Paris, France
LEE, C. Y.	The Pharmacological Institute, College of Medicine, National Taiwan University, Taipei, Taiwan,
LEE, T.	Church Laboratory of Chemical Biology, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, USA
MELMON, K. L.	Departments of Medicine, Pharmacology, Microbiology, Biochemistry and Biophysics, and the Cardiovascular Research Institute, University of California, San Francisco, California 94143, USA
MOLINOFF, P. B.	University of Colorado Medical Center, Denver, Colorado 80220, USA
NARAHASHI, T.	Department of Physiology and Pharmacology, Duke University Medical Center, Durham, North Carolina, USA
RAFTERY, M. A.	Church Laboratory of Chemical Biology, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, USA
RAJERISON, R.	Laboratoire de Physiologie Cellulaire, Collège de France, 75231 Paris 05, France
REED, K.	Church Laboratory of Chemical Biology, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, USA
ROBISON, G. A.	Department of Pharmacology, The University of Texas Medical School at Houston, Houston, Texas 77025, USA
ROY, C.	Laboratoire de Physiologie Cellulaire, Collège de France, 75321 Paris 05, France
SCHULTZ, G.	Department of Pharmacology, University of Heidelberg, D-6900 Heidelberg, Federal Republic of Germany
SNYDER, S. H.	Department of Pharmacology and Experimental Therapeutics, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA
TADA, M.	Department of Medicine, Mount Sinai School of Medicine of the City University of New York, New York, New York 10029, USA
TERENIUS, L.	Department of Medical Pharmacology, University of Uppsala, S-751 23 Uppsala, Sweden
TOMKINS, G. M.	Departments of Medicine, Pharmacology, Microbiology, Biochemistry and Biophysis, and the Cardiovascular Research Institute, University of California, San Francisco, California 94143, USA

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Preface

The International Union of Pharmacology (IUPHAR) held the Sixth International Congress of Pharmacology in Helsinki, Finland on 20–25 July 1975. The scientific programme was organised with the help of the International and Scandinavian Advisory Boards and it consisted of 15 invited lectures, 20 symposia, 5 seminars on methods, and volunteer papers, some of them as poster demonstrations. Altogether 1580 communications were delivered by the 2 600 active participants attending the Congress.

The texts of the invited lectures and symposia have been included in the Proceedings of the Congress. It is readily noticeable that all the major areas of pharmacology, including clinical pharmacology and toxicology, are well represented. Special attention has been paid to several interdisciplinary areas which are on the frontiers of pharmacology and have connections with physiology, biochemistry and endocrinology. Many of the topics are of special interest to internists, psychiatrists, neurologists and anaesthesiologists. Chapters on the abuse of alcohol, new teaching methods and the conservation of wild animals reflect the wide scope of the Congress.

One can hardly imagine any other Congress Proceedings where more world-famous authors representing pharmacology and the related sciences have reported the most recent developments in their special fields. The invited lectures give a particularly clear introductions to the areas in question, even for those previously unfamiliar with them.

For the first time the Proceedings of an International Pharmacology Congress have been produced by the photo offset-litho process. This method was chosen in order to publish the volumes in the shortest possible time. It clearly demands the emphasis be placed upon the scientific content of the volumes, possibly at the expense of retaining some infelicities of style or presentation.

We are convinced that these Proceedings present a unique opportunity to keep abreast of the latest developments in pharmacology and related areas of research. Our sincere thanks are due to the authors, the members of the advisory boards and our colleagues of the Programme Committee for making the scientific programme of the Congress so successful and the publication of the Proceedings possible.

The Editors

VANDLEN, R.	Church Laboratory of Chemical Biology, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, USA
VOGEL, Z.	Laboratory of Biochemical Genetics, National Heart and Lung Institute, NIH, Bethesda, Maryland 20014, USA
WARNICK, J. E.	Department of Pharmacology and Experimental Therapeutics, School of Medicine, University of Maryland, Baltimore, Maryland 21201, USA
WESTERMANN, E.	Department of Pharmacology, Medical School of Hannover, 3 Hannover-Kleefeld, Federal Republic of Germany
WITKOP, B.	Laboratory of Chemistry, NIAMDD, NIH, Bethesda, Maryland 20014, USA
WOLFE, B. B.	University of Colorado Medical Center, Denver, Colorado 80220, USA

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. *Invited lectures*

HISTAMINE RECEPTORS

J.W. Black, Department of Pharmacology, University College London, London WC1E 6BT.

Histamine receptors are the molecular sites where histamine acts to initiate characteristic tissue responses. The criteria adopted to distinguish histamine receptors from others, and to test the homogeneity of the class, is an exercise in pharmacological taxonomy.

Pharmacological taxonomy

Physiological regulations are achieved by relatively small, mobile, molecules - hormones, transmitters, substrates - momentarily binding with special, localised, molecular arrangements embedded in cell machinery. Highly selective interactions occur because each site is programmed to decode unique chemical signals. Enzyme identifies substrate; receptor identifies hormone. Each effective interaction provides a quantal stimulus tending to initiate a characteristic change in cell behaviour.

Pharmacology deals with the artificial manipulation of these systems. In particular, pharmacology is concerned with classification; with establishing order and pattern among the multitude of effects which exogenous chemicals can produce in biological systems. Many substances have selective effects on animal tissues because they interact with precisely those active sites and receptors which normally subserve physiological control processes. Enough of the chemical code seems to be present for them to be identified by physiological receptors. This suggests a taxonomic principle; that all drugs and poisons should be classified, along with substrates, hormones and transmitters, in terms of the physiological control points with which they interact.

A biochemically-based classification has been successful for interactions between drugs and enzymes because the control points can often be identified chemically. When concentrations of reactants and products, in enzyme reactions *in vitro*, are known or measured, the effects of foreign substances may be defined with precision. Characteristic dissociation constants can be estimated. The classification of competitive inhibitors has been particularly successful and rigorous criteria for their classification have been developed.

Classification based on hormone receptors is more difficult. These molecular sites have either still to be identified chemically or, at best, have still to be shown to be identical with binding sites extracted from tissues. Receptors, therefore, can only be defined operationally in terms of a hypothetical model. Pharmacological taxonomy starts with the most elementary model. Receptors are assumed to be homogeneous, independent, monovalent and to react with agonist according to the law of mass action. Theoretical receptor occupancy is then a simple, hyperbolic, function of agonist concentration and the notional log concentration-occupancy curve is the familiar symmetrical sigmoid curve. Real concentration-response curves are assumed to be complex distortions of these underlying concentration-occupancy curves. Distortion can be produced by many factors including cellular uptake and metabolism of agonist and spare receptor capacity in relation to the maximum response of the tissue. The resulting ignorance about the concentration of agonist in equilibrium with receptors and about the relation between receptor activation and tissue response makes the chemical interpretation of concentration-response relations an illusion. Fortunately, a chemical interpretation of the effects of competitive antagonists seems to be possible under certain circumstances. Pure competitive antagonists dynamically reduce the concentration of free receptors and the effect on the mass action equation is the same as a reduction in agonist concentration. Therefore, theoretical agonist-occupancy curves are displaced in simple proportion to antagonist concentration and the displacement (or dose ratio) is independent of agonist affinity. Provided that the antagonist does not interfere with any of the factors which convert agonist-occupancy into agonist-response curves, then the real log concentration-response curves will be displaced to the same extent, that is have the same dose ratio, as if they were theoretical concentration-occupancy curves. The concentration of the antagonist giving a dose ratio of 2, that is 50% occupancy, is then an estimate of its dissociation constant. This is the basis for the various tests for competitive antagonism in current use, namely, parallel displacement of log concentration-response curves, a Schild plot (relating antagonist concentration and curve displacement) which does not deviate significantly from linearity and unit slope and, from this, an estimated dissociation constant of the antagonist-receptor complex which is independent of agonist affinity (1). All tests are probably necessary and no single test is sufficient. However, if the quantitative conditions are not met; if the dose-response curves are not displaced in parallel; if the Schild plot is non-linear, or covers too narrow a range of concentration or has a slope widely different from unity; if the measurements are not "constant", but tissue-dependent; if the antagonist is known to interfere with other relevant processes such as uptake or metabolism of agonist or with

the coupling between receptors and cell output; then judgment about interpretation and classification must be reserved.

Measurements of drug-interactions in isolated tissues are technically simple; interpretations can be very difficult. Even in the most favourable circumstances the taxonomist faces logical fallacies involving circular arguments. For example, D is estimated to be a competitive antagonist of A on systems P and Q. The homogeneity, and therefore the set, of A receptors is provisionally defined by D. However, D is now classed as a universal A-receptor antagonist, and this is sometimes treated as a separate statement when, without independent tests, it is logically the same statement. A second fallacy often follows from this; the classification of D in terms of tentative set A leads to repeated use of D as an anti-A and the class of A may soon appear to achieve the status of a piece of evidence rather than an assumption. Finally, the classification of D may also begin to appear objective through use and lead to fallacious arguments of the type that effects X and Y are not due to A because they are not annulled by D.

Still, the classification of drugs by receptors, although more tentative and error-prone than classification by enzymes, can nevertheless be made fruitful by the pursuit of independent tests and by the cultivation of critical assessment of all assumptions.

Has the classification of histamine receptors avoided errors and proved useful?

Classification of histamine receptors

The establishment of a functional role for an endogenous substance predicates the existence of receptors to subserve the selectivity of that function and ideas about a functional role for histamine developed slowly. Dale and Laidlaw (1910) noted the correspondence between the effects of exogenous histamine in different species and the manifestations of anaphylactic shock but they drew back from suggesting that the one might be due to the other. Surprisingly, the demonstration of histamine release from the lungs during anaphylaxis had to wait for over twenty years.

A consequence of the histamine-release theory of anaphylaxis was an attempt to find substances which annul the action of histamine on tissues. One of the earliest substances tried was histamine itself! Schild (26) found that the uterus from hypersensitive animals could be desensitised to histamine without interfering with an anaphylactic response and anticipated subsequent difficulties with antihistamines. The first anti-

histamines came, of course, from Bovet's laboratory in 1937 and it was 1944 before a compound, mepyramine, was produced which had both high potency and high selectivity.

Characteristically, visceral muscles from gut, bronchi, uterus and arteries contract when exposed to histamine. Histamine-induced broncho-constriction in guinea pigs is particularly dramatic and pathognomonic of anaphylaxis in that species. These actions of histamine can all be annulled by suitable doses of antihistamines (20). Early doubts about the mechanism of this antihistaminic action soon gave way to the conviction that histamine and antihistamine competed, on the basis of their relative concentrations and affinities, for a common site - the histamine receptor. However, this classification of mepyramine and related drugs as competitive histamine antagonists raised problems because the various effects of histamine were not equally sensitive to blockade.

Histamine lowers blood pressure in most species, and antihistamines readily antagonise this action. Indeed, blockade of histamine-induced hypotension in cats was the basis of a popular screening test for developing new antihistamines. However, by 1948 there was good evidence that the hypotensive effects of large doses of histamine could not be suppressed and the possibility of different kinds of histamine receptors was suggested.

An anaphylactic reaction in visceral muscle *in vitro* was found to be more difficult to suppress by antihistamines than were the effects of added histamine (20, 26). These drugs were found to be of little benefit in the treatment of human asthma even though histamine-induced contractions in human bronchial muscle could be easily suppressed. By contrast, the dermal vascular reactions in urticaria in man could be easily antagonised while the corresponding wheal and flare reactions to intradermally-injected histamine were only partially suppressed; complete blockade was never possible. To account for these anomalies, Dale (1948) suggested that there might be differences in sensitivity to blockade of intrinsic and extrinsic histamine although this idea was difficult to reconcile with a homogeneous receptor model.

A different kind of problem was presented by histamine-stimulated gastric acid secretion. In all species studied, including man, the antihistamines showed no antagonistic action whatever (20). Perhaps the drugs were unable to reach the active sites? Perhaps there was more than one kind of histamine receptor? This finding was a poser for pharmacologists concerned with classification of drug actions and a source of frustration to physiologists concerned with analysing the relation of histamine to gastric function.

There were other, less notorious, examples of histamine responses apparently refractory to blockade by antihistamines. Uterine muscle of most mammals contracts in response to histamine but, in the rat, spontaneous or induced uterine contractions are inhibited by histamine; this action is refractory to blockade by mepyramine. In the heart, both pacemaker activity and contractile force are stimulated by histamine, without the involvement of catecholamine receptors, and these actions can only be modified, if at all, by very high concentrations of anti-histamines.

On this evidence, the classification of these drugs as anti-histamines, as universal antagonists of histamine receptors, was invalid. Either the classification was inaccurate or the assumption of a homogeneous population of histamine receptors was an error. This question was eventually examined by Schild and his colleagues (1, 2).

The quantitative relations of mepyramine-histamine interaction in isolated guinea pig ileum were shown by them to be characteristic of simple, competitive, antagonism. An empirical pA_2 of 9.36, equivalent to a dissociation constant of 4×10^{-10}M, was estimated (1). Measurement of pA_2 in both trachea and lung from guinea pigs and human bronchi gave similar values, between 9.1 and 9.4, thereby indicating the homogeneity of the histamine receptors in these tissues. An additional test for competitive antagonism was provided by estimating mepyramine pA_2 against a series of histamine derivatives and analogues; virtually identical values were found even though their relative stimulant activities covered the range 0.01 to 100 (2). The diphenhydramine pA_2 was found to average 8.0 and this was not only significantly different from mepyramine but also independent of the tissue used to measure it. Therefore, Ash and Schild (2) proposed the symbol H_1 for this homogeneous group of histamine receptors, subserving visceral muscle contractions, which could be characterised by a single pA_2 value for mepyramine.

Having defined this class of histamine receptors, then the receptors mediating histamine responses in gastric mucosa, sino-arterial node and rat uterus had to be excluded. Using a series of histamine congeners, selective stimulants of H_1-receptors but not of the mepyramine-refractory responses were found. The relative agonist activity of these compounds on rat uterus and acid secretion was found to be correlated and, though suggestive, this was not regarded as strong enough evidence to define a second class of receptors. In the absence of selective antagonists Ash and Schild (2) declined to classify the remainder of the histamine receptors.

Another group of investigators (4) started from the assumption that there were only two classes of histamine receptors, typified by those mediating histamine responses in guinea pig ileum and atrium respectively. They looked for a specific antagonist of mepyramine-refractory receptors by systematic chemical substitution and modification of histamine itself. Selective agonists, partial agonists and selective antagonists were eventually found.

Selective agonist activity was found among simple methyl derivatives of histamine. Using the internationally-agreed trivial system for naming histidine derivatives (6), N^{α}-methylhistamine was found to be nearly as active as histamine on atrium and ileum. The side-chain substituted α- and β-methyl derivates, and the ring-substituted N^{τ}- and N^{π}-methylhistamines were nearly inactive on both tissues. However, 4(5)-methylhistamine was found to be about 0.4 times as active as histamine on atrium but only 0.002 times as active on ileum. Although 2-methylhistamine was only 0.16 times as active as histamine on ileum, it was nevertheless 4 times as active there as on the atrium. When the assays were extended to other tissues, homogeneous H_1-receptor and non-H_1-receptor groups were found. The compound 4(5)-methylhistamine has been particularly useful for exploring histamine receptors. Wherever it has been examined this compound has been found to be a selective stimulant of what are now classified as histamine H_2-receptors, including stimulation of acid secretion in rat, cat, dog and man. However, its activity relative to histamine varies with species because it is not inactivated by the histamine-specific histamine N^{τ}-methyltransferase.

Burimamide was the first selective antagonist produced by modification of histamine. The link between the two compounds was the discovery that replacing the terminal amino group of histamine with a guanidino group gave a compound, N^{α}-guanylhistamine, which was a partial agonist with only very weak antagonist activity at H_2-receptors. The conversion of N^{α}-guanylhistamine to burimamide involved extending the methylene chain from two to four carbon atoms and replacing the guanidino group with a thiourea group. The side chain of histamine withdraws electrons from the ring, whereas the side chain of burimamide releases electrons into the ring, thus significantly altering the ratio of tautomers. Replacement of one methylene group with an isosteric electronegative sulphur atom restores the tautomer ratio towards that found in histamine (5). Subsequent addition of a methyl group at the 4-position in the ring produced metiamide. Most of the studies of H_2-receptor antagonists have been carried out with this compound. However, thiourea derivatives have a reputation for producing bizarre toxicity, and certain features of the animal toxicity of metiamide suggested that the thiourea group