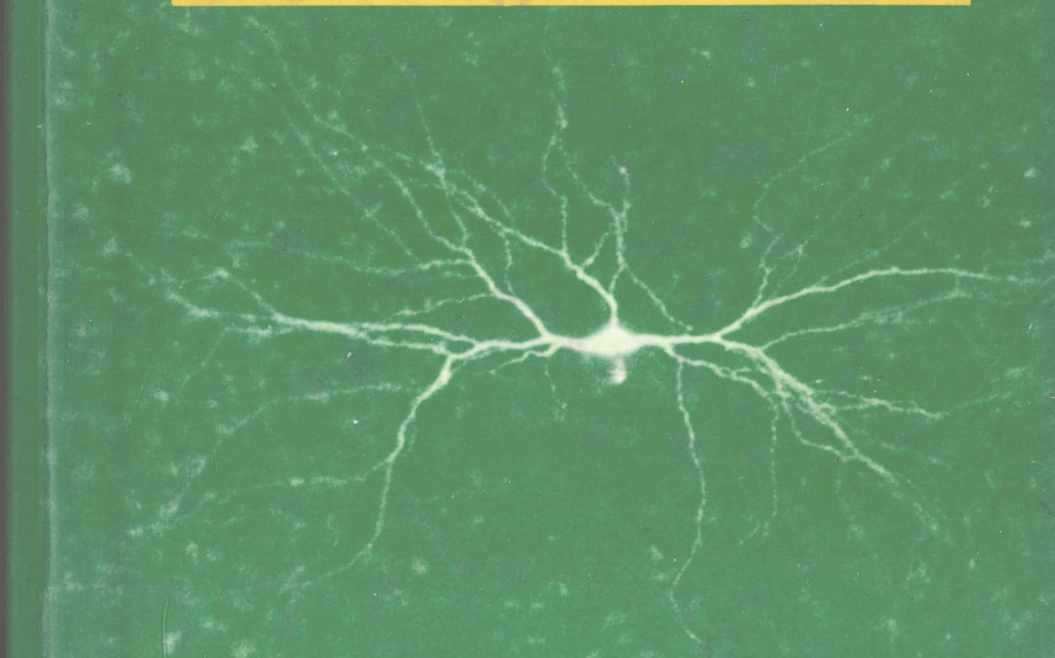
Mechanisms of drug action on the nervous system

Second edition



R. W. Ryall

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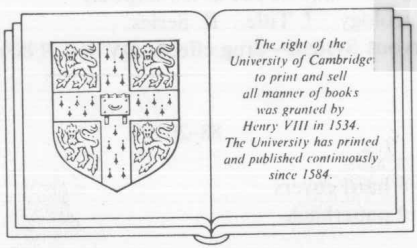

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To Audrey

PREFACE TO THE SECOND EDITION

Since the first edition of this book was published in 1979 there have been some major advances in all areas of knowledge concerning the physiology and pharmacology of the nervous system, although some advances are much greater than others. Each of these advances can on the whole be attributed to advances in technology. New technology for the measurement of receptor binding and immunological techniques, combined with the production of monoclonal antibodies, have been responsible for the greatly increased understanding and apparent complexity of receptors and their ligands. Only recently have some notes of caution been raised concerning the interpretation of ligand binding data as necessarily reflecting the properties of receptors. Advances in electrophysiological techniques now permit not only noise analysis of single channel events but also direct recording of the electrical currents flowing through those channels: I refer of course to single channel current recording with 'patch-clamp' techniques and the use of modern, high frequency, voltage-clamp amplifiers. Considerations of space in a book of this size and scope does not allow more than a brief mention of the technology. Finally, the age of the computer has brought with it considerable benefits, together with some consequential difficulties. Among the benefits is the ability to analyse complex events or to build up complex pictures of three dimensional objects which was not possible in an earlier generation. Complex experiments are now easier to perform than ever before. Among the potential hazards is the proliferation of trivial data which are impediments rather than aids to understanding.

There has been an explosion of information concerning the presence of polypeptides in the peripheral and central nervous

systems, but there is still a deficit in our understanding of their functions at specific locations. Despite immense efforts, a therapeutic advance from such studies has yet to appear. All too often excessive enthusiasm can lead to false conclusions: the mere presence of a particular substance in a nerve or that beautiful coloured picture of its distribution in nerve networks that stirs one's artistic imagination or the fact that binding sites exist, even when they are high affinity sites, does not preclude the possibility that the substance may normally function neither as a neurotransmitter nor as a neuromodulator. The next few decades will hopefully tell us whether the present has been guilty of the scientific crime of stretching conclusions beyond those justified by the data available.

Two areas in particular have 'blossomed' since the first edition: these are the discovery of the wealth of endogenous opioid and other peptides and their receptors and the benzodiazepines and their receptors. In the case of the opioids both receptors and endogenous peptide ligands for them have been identified. As I write, I am conscious that fresh interest is currently being evoked in the possibility that morphine itself might be an endogenous ligand for the receptor!

In contrast, the benzodiazepine receptors are probably still 'looking' for their endogenous ligands, although plenty of the synthetic variety are available and enthusiastic suggestions for candidates abound. In both of these areas there are drugs available which have a therapeutic use.

I am intrigued that, despite the enormous amount of basic science that has been carried out, the increasing sophistication of technology and the tremendous increase in understanding of the actions of known drugs, there have been few major new conceptual advances in new drugs for the treatment of diseases of the peripheral or central nervous system over the last decade. One begins to wonder whether the 'sight of the wood is getting lost by the obscurity of the trees'. Put in another way, is there now too much emphasis on molecular mechanisms and too little on function and its disturbance in disease states? If the answer is yes then we shall continue to see an expansion in knowledge of the action of currently popular drugs but will see few new drugs developed.

However, there are some grounds for optimism. In the field of transmitters the excitatory amino acids are currently in vogue and are beginning to eclipse the 'conventional' neurotransmitters and even the peptides. This renewed interest (attention was first drawn to them in the 1950s) is largely attributable to the production of interesting new compounds, rather than the study of old ones. There is a good involvement in the function of endogenous excitatory amino acids and their receptors and the current speculation on the possible role of NMDA receptors in memory and even Alzheimer's disease and stroke gives grounds for enthusiasm and hope for the possible emergence of radically new therapies.

It is disappointing that no radically new therapies have been developed for the treatment of psychotic mental illness although in this case it is perhaps attributable to the poor understanding of the underlying neuropathology. There is hope, but little evidence on which to base it, for the development of new anti-schizophrenic compounds which interact with $5HT_3$ receptors. It is surprising that we can say little more than was possible ten years ago about the action of general anaesthetics. The difficulty may still be our lack of knowledge about the nature of the synaptic transmitters at specific synaptic locations, despite the extensive knowledge about how they work on isolated bits of membrane.

The approach to this book and its objectives have changed little, if at all. Essentially, the objective has been to present a 'story' about each class of drugs which will give undergraduate students in science and medicine some broad insight into basic disorders of the nervous system and the way in which the drugs work to alleviate symptoms. If others find the book of value then this will be an added bonus since this was not the objective. A narrative style has been adopted and there is a deliberate avoidance of references in the text to help attain this objective. No attempt has been made to mention all drugs which are used: only those which have attributes making them worth special mention are presented. Nevertheless, the average student will not find that there are too many drug names to remember. He should take hope in the thought that before too long, especially if he is a medical student, each of these drugs, or perhaps a 'better' version, will soon become a 'household word'. The student is not spared con-

troversy, where this is appropriate, although I would hope that I have not included too much.

Most of the book has been rewritten and reorganised, although a few chapters are little changed. The section on the autonomic nervous system has been expanded considerably since this was not given adequate treatment in the first edition. The book now gives a fairly balanced perspective of the action of most classes of drugs which act on the nervous system. Stimulant drugs, such as amphetamine, ritalin, lysergic acid diethylamide, cannabis (is it a stimulant?) and cocaine are not particularly useful therapeutically, even though many of them are of importance as drugs of abuse. Too little is known about their mechanisms to give a coherent picture and too little space was available to do justice to the problem of abuse. However, references to some of them will be found sporadically through the book. Perhaps I can be excused for this deliberate omission.

PREFACE TO THE FIRST EDITION

In recent years there have been many important advances in knowledge concerning the mechanisms of chemical synaptic transmission, the identification of the neurotransmitters and the mechanisms by which drugs act on the nervous system. These advances have necessitated a change in approach to the teaching of the pharmacology of the nervous system to undergraduate science and preclinical medical students from a basically therapeutic orientation to one which is more mechanistically minded. In giving such courses to students in Cambridge, the author has become painfully aware of the need for an undergraduate text which could fulfil the needs of students in this respect. There are of course many excellent textbooks of therapeutics available but few of them attempt to cope in detail with mechanisms of drug action, especially on the central nervous system, except from rather specialised viewpoints. It was therefore considered to be unnecessary to discuss therapeutic applications in detail in this book, although an attempt has been made to give a fairly balanced account of the physiological basis, applications and mechanisms of action of each class of drugs, within the limitations imposed by the objective of producing a concise account of drug actions.

Advances are occurring at such a rate that some of the concepts which are current today may be superseded tomorrow: this is probably true for any subject that is 'alive' and progressing. However, this does create problems in deciding what to omit and what to include. As far as possible, the basic approach adopted in this volume is to present a coherent 'story' which will enable the student to develop concepts and, perhaps, ideas of his own. Only in this way is it likely that a continuation of progress can be

assured and that future medical graduates will not see drugs simply as liquids in bottles to be administered in an empirical manner without understanding to patients with diseases of the nervous system: a reasonable concept, compatible with contemporary information, even if subsequently found to be incorrect in detail, is surely better than no concept at all. Nevertheless, where concepts are relatively insecure, or mechanisms completely unknown, no attempt has been made to disguise this fact in order to present a 'story': such an approach could lead to unjustified complacency.

ABBREVIATIONS

ACh	Acetylcholine
ACTH	Adrenocorticotropic hormone
Adr	Adrenaline
AMP	Adenosine monophosphate
ANS	Autonomic nervous system
ATP	Adenosine triphosphate
B_{max}	Concentration at which all receptors are saturated
CAT (scan)	Computer aided axial tomography
C10	Decamethonium
β-CCE	β-carboline-3-carboxylic acid ethyl ester
CCK	Cholecystokinin
CNS	Central nervous system
COMT	Catechol-O-methyl transferase
CSF	Cerebrospinal fluid
DA	Dopamine
DOPA	Dihydroxyphenylalanine
d-Tc	d-Tubocurarine
EC_{50}/ED_{50}	Concentration/dose to cause 50% effect
ECF	Extracellular fluid
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
EMG	Electromyogram
epp	End plate potential
EPSP	Excitatory postsynaptic potential
GABA	γ-Amino-butyric acid
GAD	Glutamic acid decarboxylase
GDP	Guanosine diphosphate
GMP	Guanosine monophosphate
GTP	Guanosine triphosphate

HC-3	Hemicholinium
5-HT	5-Hydroxytryptamine
5-HTP	5-Hydroxytryptophan
IC_{50}/ID_{50}	Concentration/dose to cause 50% inhibition
K_A	Affinity constant = $1/K_D$
K_D	Dissociation constant
K_i	Dissociation constant for inhibition
LHRH	Luteinising hormone releasing hormone
LSD	Lysergic acid diethylamide
MAO (-A or -B)	Mono amine oxidase (A & B forms)
mepp	Miniature end plate potential
MPTP	N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NA	Noradrenaline
N_i	Inhibitory regulatory protein
N_s	Stimulatory regulatory protein
NMDA	N-methyl-D-aspartic acid
NMR	Nuclear magnetic resonance
6-OHDA	6-Hydroxydopamine
PET	Positron emission tomography
PG	Prostaglandin
PTMA	Phenyltrimethyl ammonium
PTP	Post-tetanic potentiation
SIF	Small intensely fluorescent neurone
SPECT	Single photon emission tomography
TEA	Tetraethyl ammonium
TOH	Tyrosine hydroxylase
TRF	Thyrotrophin releasing factor
VIP	Vasoactive intestinal polypeptide

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