BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY

Fifth Edition

Volume 2: Therapeutic Agents

Edited by

Manfred E. Wolff

Technipharm Consultants
Laguna Beach, California

A WILEY-INTERSCIENCE PUBLICATION

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Burger's Medicinal Chemistry and Drug Discovery

Dr. Alfred Burger

Preface

The final four volumes of this 5th edition of *Burger's* will contain discussions of the important individual drug classes in modern medicine. One of the major decisions considered in undertaking this was whether to confine the chapters to a particular disease category, such as antihypertensive agents, or to a particular therapeutic modality, such as beta blockers. A consistent choice between these two alternatives was sought and the opinions of numerous thought leaders were obtained. But in the end we "decided to be undecided," as Churchill once complained about a British government. It seemed best to structure each chapter in a manner that appeared most appropriate to the topic under consideration, based on the views of the authors. This approach has led to situations where occasionally the same topic is considered from different perspectives in multiple chapters. But we feel it is important to develop chapters that are able to stand alone in delivering their information.

A second question that had to be considered was whether to collect each subject area, such as cardiovascular agents, into a single volume. Although this might have been advantageous with regard to convenience of use, it would have required delaying the production of each volume until the very last chapter in a given area was completed. In the interests of publishing the chapters in a timely manner, a decision was made to divide each subject area into two parts, which could be published in an early and a later volume.

The revolution that has taken place in drug discovery and in medicinal chemistry is in clear evidence in this volume. In every chapter, one can read of the remarkably strengthened biological understanding of each disease category under discussion. Much of this new information has been obtained by the application of the techniques of molecular biology to unsolved questions in biochemistry and pharmacology. These studies have been extraordinarily fruitful for drug discovery since an understanding of biological events at the molecular level, in the end, is essential for the discovery and design of new drug molecules to influence those events.

In addition, the growing army of scientists working in all of the areas of drug discovery and its underlying basic sciences has produced a body of research notable not only for its sophistication, but also for its sheer volume. Thus, both the quantity and the quality of research related to drug discovery has served to enhance our understanding and our capability in this field greatly. Even so, much remains to be done. In the chapter, "Cardiac Drugs," one can read of the remarkable progress made in our knowledge of the action of the cardiac glycosides since the time of William Withering in 1785. At the same time, one can see the great gaps in our perception of this area that still remain. Another valuable lesson to be drawn from this chapter is the difficulty, and importance, of designing a definitive clinical trial in a multifactorial disease.

A notable point that should be made is the economic advantage provided to society by the new drugs whose discovery and development is chronicled in this series. In this volume alone, three enormously significant areas, cardiovascular disease, gastrointesti-

nal disease, and tubercular disease are given consideration. In the past two centuries, tuberculosis is said to have killed one billion people. Today, disease is the most important killer in western-style countries. The costs of healthcare and hospitalization for such diseases is reduced tremendously by the availability of safe and effective medicines. Both for tuberculosis and duodenal ulcer, for example, new drugs virtually eliminated the need for surgical intervention, with its attendant high costs. In addition, the benefits of these pharmaceuticals can easily be brought to any individual on the globe. A crucial medicine discovered through the application of the high technology discussed in these chapters can readily be made available in a remote African village, unlike an MRI installation or other advanced instrument.

Generally we have still not achieved ideal pharmaceuticals, and in numerous areas we are faced with a moving target. Particularly in the field of chemotherapy, drug resistance by pathogenic organisms has seriously eroded the usefulness of existing medicines. Thus, the discovery and development of new agents are required. In doing this, it is important that the lessons of the past not be forgotten, even through they may have been learned in a time of empiricism. The results of the patient molecular manipulations made by medicinal chemists in former years outlined in the chapters on cholinergic and anticholinergic drugs, for example, can still be studied with profit by workers using the modern methods of drug discovery and design reviewed in Volume I.

Once again, it is my pleasant duty to acknowledge the efforts of those individuals who have made this volume of the series possible. Most of all I thank my friends, the dedicated authors, a number of whom had previously contributed to the 4th edition, who generously took time from their already overcrowded schedules to pass their expert knowledge on to others. I am grateful to Michalina Bickford, Managing Editor with John Wiley & Sons, Inc. for all of her work in connection with this series. As always I thank my wife, Gloria, for her steadfast support and encouragement in everything I do.

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1 INTRODUCTION

The transmission of impulses throughout the cholinergic nervous system is mediated by acetylcholine (**1**), and compounds that produce their pharmacologic effects by mimicking or substituting for acetylcholine are called cholinergics or parasympathomimetics.

$$CH_3-CO-O-CH_2-CH_2-\overset{+}{N}(CH_3)_3$$

(1)

Compounds that inhibit or inactivate the body's normal hydrolysis of acetylcholine by acetylcholinesterase in nervous tissue and/or by cholinesterase (pseudocholinesterase, butyrylcholinesterase) in the blood are called anticholinesterases. The gross observable pharmacological effects of both types of compounds are quite similar. More recently, compounds have been found that enhance the release of acetylcholine from cholinergic nerve terminals, thus (like the anticholinesterases) producing cholinergic effects by an indirect mechanism.

Choline is taken into the nerve terminal from the synaptic cleft by a sodium-dependent active transport process, which is the rate-limiting step in biosynthesis of acetylcholine in the nerve terminal (1). In the nerve terminal, choline reacts with acetyl coenzyme A in a process catalyzed by choline acetyltransferase. The acetylcholine thus synthesized is sequestered in the synaptic storage vesicles in the nerve terminal for future use as a neurotransmitter. The active transport of acetylcholine into the storage vesicles has been reviewed (2).

Therapeutic indications for cholinergics, anticholinesterases, and/or acetycholine-releasing agents in contemporary practice include the following:

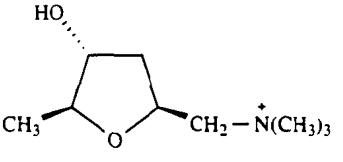
1. Relief of postoperative atony of the gut and the urinary bladder. In such conditions, cholinergic stimulation may relieve the stasis by stimulating peristaltic movements of the intestine and ureters and by constriction of the bladder.
2. Reduction of intraocular pressure in some types of glaucoma by increasing the drainage of intraocular fluid through the canal of Schlemm.
3. Relief of muscular weakness in myasthenia gravis. This condition reflects a failure of an appropriate amount of acetylcholine to reach cholinergic receptors on the postmyoneural junctional membrane following rapidly repetitive nerve impulses. The reduced level of acetylcholine may result from excessive enzyme-catalyzed hydrolysis of it or from diminished production or release; the etiology of the disease remains obscure.
4. Relief of symptoms of Alzheimer's disease and some other types of senile dementia.

A deficiency of functional cholinergic neurons, particularly those extending from the lateral basalis, has been observed in patients with progressive dementia of the Alzheimer type (3). Cholinomimetic therapy has been directed at compensating for the inadequate cholinergic activity in these neurons. However, clinical results with cholinergics and anticholinesterases often have been disappointing or inconsistent (4) due, in some instances, to the inability of quaternary ammonium derivatives to penetrate the blood–brain barrier or to a lack of specificity or selectivity of the drug for the cholinergic receptor(s) involved in the pathological condition. There has been (and continues to be) great emphasis on the search for and study of nonquaternary ammonium molecules (having greater lipophilic character) that will penetrate the blood–brain barrier and interact with appropriate acetylcholine recep-

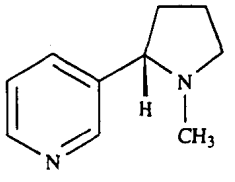
tors in the brain. Thus older tertiary amine drugs such as pilocarpine and arecoline, which demonstrate only modest cholinergic activity and are classed as partial agonists, have been the subjects of intense structure–activity studies. It has been speculated (5) that partial agonists at M_1 receptors probably have less predisposition to cause receptor desensitization than full agonists, which may make partial agonists potentially more valuable from a therapeutic point of view. The utility of cholinergics in correction of other types of deficits in memory and learning has been investigated for many years (6), with largely inconclusive results. However, this remains a fascinating and a potentially significant area of research.

2 CHOLINERGIC (ACETYLCHOLINE) RECEPTORS

Acetylcholine receptors have been subdivided into two pharmacological types (muscarinic and nicotinic), based on their selective response to two alkaloids: muscarine (**2**) and nicotine (**3**).



(2)



(3)

Neither nicotine nor muscarine is a normal physiological component of the mammalian body; hence the muscarinic/nicotinic classification of acetylcholine receptors is artificial. While it seems well established that muscarine is a true cholinergic agonist, it is widely accepted that nicotine has little agonist effect in some parts of the nervous system; its peripheral actions are largely indirect and probably involve presynaptic release of acetylcholine (7–11).

Muscarinic receptors occur peripherally, e.g., at parasympathetic postsynaptic sites on glands and smooth (nonstriated) muscles, and they are involved in gastrointestinal and ureteral peristalsis, pupillary constriction, peripheral vasodilatation, reduction of heart rate, and promotion of glandular secretion. Autonomic ganglia also contain muscarinic receptors. Peripheral nicotinic receptors are found postsynaptically on striated (voluntary) muscle fiber membranes and in all autonomic ganglia (sympathetic as well as parasympathetic). There are also nicotinic and muscarinic pathways in the central nervous system.

On the basis of pharmacological data, muscarinic receptors have been subcategorized as M_1, M_2, and M_3. By definition, M_1 receptors occur in the cerebral cortex; corpus striatum; hippocampus, where they may be involved in cognitive processes relevant to Alzheimer's disease, in particular short-term memory (12); and autonomic ganglia where they are involved in membrane depolarization, which is mediated by stimulation of phospholipase C and subsequent production of inositol-1,4,5-triphosphate and diacyl glycerol (13). M_2 receptors are present in the cerebellum, heart, and ileum; those muscarinic receptors in secretory glands and smooth muscle have been tentatively classed as M_3. The central nervous system contains all known subtypes of muscarinic receptors (13). Molecular cloning studies have revealed that there are at least five subtypes of muscarinic receptors, designated m_1–m_5 (14). Correlation between these receptor subtypes, cloned from different tissues and those identified using classical pharmacological methods (M_1–M_3) is not clear, although m_1–m_3 are generally accepted to have pharmacological charac-

teristics identical to those of M_1–M_3, respectively (14).

Muscarinic receptors are glycoproteins with molecular weights of approximately 80,000. They are located on the outer surface of the cell membrane, and they are of the G-protein–linked type; their stimulation affects intracellular production of second messenger substance(s). It is widely believed that the pathophysiology of Alzheimer's disease involves M_1/m_1 receptors. A recent review (15) describes the molecular basis of muscarinic receptor function.

Nicotinic receptors are of the ion channel type. They are pentameric proteins that are composed of at least two distinct subunits, each of which contains multiple membrane-spanning regions, and the individual subunits surround an internal channel (16). Nicotinic receptors are subcategorized as N_M, found postsynaptically at the (striated) neuromuscular junction. Stimulation produces membrane depolarization and skeletal muscle contraction and N_N, found in autonomic ganglia. Stimulation of these receptors produces depolarization (a result of cation channel opening) and firing of the postganglionic neuron. The nicotinic receptor glycoprotein has been isolated and extensively studied (17–19). Reviews of the structure of nicotinic receptor(s) are available (20,21).

Although acetylcholine has no center of asymmetry and is optically inactive, its *in vivo* receptors exhibit discrimination between enantiomers of synthetic and naturally occurring cholinergic stimulants. Both central and peripheral muscarinic receptors are highly stereospecific; peripheral nicotinic receptors seem to be less so, although these usually show some preference for one or the other member of enantiomeric pairs. Central nicotinic receptors frequently demonstrate a higher degree of stereoselective binding character than is noted with the peripheral receptors. Understanding of nicotinic receptor stereoselectivity and specificity is complicated by the likelihood that many nicotinic agents (in addition to nicotine) are not agonists but rather function indirectly by promoting presynaptic release of acetylcholine (7). However, Casy (7) has presented data suggesting that nicotine may also have a direct (agonist) component of action.

3 ACETYLCHOLINE AND ANALOGS

Although it admirably serves its physiological role in the body, acetylcholine is a poor therapeutic agent. Its rapid rate of hydrolysis in the gastrointestinal tract precludes oral administration, and a similarly rapid hydrolysis by the esterases in the blood and by acetylcholinesterase in the nervous tissue limits its usefulness by injection. Acetylcholine has virtually no clinical uses.

The need for therapeutically satisfactory cholinergic agents and the simple and easily synthesized structures necessary for cholinergic activity have stimulated preparation and biological study of a great number of derivatives, analogs, and congeners of acetylcholine. The following types of structural variations have been addressed:

1. Alteration of the quaternary ammonium head.
2. Replacement of the acetyl group by other acyl moieties.
3. Alteration of the ethylene bridge connecting the quaternary ammonium and the ester groups.
4. Substitution of another group for, or elimination of, the ester moiety.

The "five atom rule," first suggested by work of Alles and Knoefel (22) and stated more formally by Ing (23), proposes that, for maximum muscarinic activity, there should be attached to the quaternary nitrogen atom, in addition to three methyl groups, a fourth group with a chain of five atoms, as illustrated for acetylcholine: C-C-

O-C-C-N. This empirical observation has been found to be valid for a large number of molecules, regardless of the precise nature of the five atoms involved.

Synthesis of compounds and examination of their biological activities have supplied considerable information on structural requirements for cholinergic activity, but especially in the older literature, these data must be examined and interpreted with caution. They have been obtained using a variety of *in vivo* and *in vitro* testing procedures and biological preparations in a variety of animal species. Often, different biological properties associated with stimulation of the cholinergic nervous system were measured. Furthermore, the observed effectiveness of a cholinergic agent in producing a biological response depends, e.g., on its inherent potency and intrinsic activity as well as on the rate at which it is metabolically inactivated (in the case of esters, hydrolysis by acetylcholinesterase and/or by blood esterases). Frequently, especially in the older literature, these individual factors have not been separately and individually assessed. This problem has been cited (24) with respect to lack of consistency among laboratories in the methods used to determine cholinergic receptor subtype selectivity. Therefore, in the following discussion of the relationship of chemical structure to cholinergic activity, only generalized (and tentative) conclusions can be made, and these are frequently based on a composite of the cholinergic activities for which the compound was tested.

3.1 Variations of the Quaternary Ammonium Group

Two types of structural alterations of the quaternary head have been studied: replacement of the nitrogen atom by other atoms and replacement of the *N*-methyl groups by hydrogen, alkyl, nitrogen, or oxygen. Acetylphosphonocholine (**4**) (23), acetylarsenocholine (**5**) (23), and acetylsulfonocholine (**6**) (25) exhibit muscarinic effects, but they are considerably less potent than acetylcholine.

$$CH_3-CO-O-CH_2-CH_2-R$$

(**4**) R = $^+P(CH_3)_3$ (**7**) R = $C(CH_3)_3$

(**5**) R = $^+As(CH_3)_3$ (**8**) R = $^+N(CH_3)_2NH_2$

(**6**) R = $^+S(CH_3)_2$ (**9**) R = $^+N(CD_3)_3$

Ing (23) noted that the potencies of acetylcholine analogs containing other charged atoms than nitrogen (phosphorus, arsenic, sulfur) are in inverse order to the volumes occupied by these atoms. The carbon isostere (**7**) of acetylcholine exhibits no cholinergic activity, but it is an excellent substrate for acetylcholinesterase (26). Studies of the role of nitrogen substituents in the acetylcholine molecule strongly indicate that the *N*,*N*,*N*-trimethyl quaternary ammonium pattern of acetylcholine itself is optimum for potency and activity. The acetate esters of *N*,*N*-dimethylethanolamine, *N*-methylethanolamine, and ethanolamine possess weak muscarinic activity, and they show no nicotinic activity (27). The tertiary amine congener of carbachol exhibits greatly diminished nicotinic and muscarinic effects compared with the *N*,*N*,*N*-trimethyl quaternary compound (28) (Number 19 Table 25.1). These conclusions seem valid for cholinergic agents having, like acetylcholine, a high degree of molecular flexibility. In contrast, in certain acetylcholine congeners in which the nitrogen is a part of a relatively rigid ring system (pyrrolidine, morpholine, piperidine, quinuclidine), tertiary amine salts are more potent muscarinics than their quaternary derivatives (41). The enhanced activity of the tertiary amines has been rationalized on conformational grounds. It must be as-

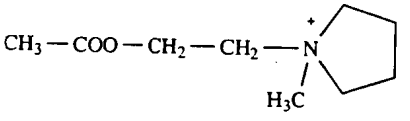
Table 25.1 Representative Esters of Choline

$R\text{-}O\text{-}CH_2\text{-}CH_2\text{-}\overset{+}{N}(CH_3)_3$

Number	R	References
1	HCO	29
2	$BrCH_2CO$	30
3	C_2H_5CO	29, 31
4	H_2NCH_2CO	32
5	*n*-C_3H_7CO	29, 31
6	*i*-C_3H_7CO	31
7	*n*-C_4H_9CO	29, 31
8	C_6H_5CO	31
9	$C_6H_5CH_2CO$	31
10	$C_6H_5CH{=}CHCO$	31
11	$(C_6H_5)_2C(OH)CO$	33
12	$CH_3(CH_2)_{10}CO$	34
13	$CH_3(CH_2)_{14}CO$	34
14	$HOCH_2CO$	29
15	$CH_2{=}CHCO$	35
16	CH_3COCO	29
17	$CH_3CHOHCO$	36
18	O_2N	37
19	H_2NCO	38, 39
20	$(CH_3O)_2PO$	40

sumed that the tertiary amines are protonated at their *in vivo* sites of action.

Replacement of one *N*-methyl group of acetylcholine by ethyl permits retention of most of the cholinergic activity, but as more *N*-methyl groups are replaced by ethyl, there is a progressive loss of cholinergic effect (42). When one *N*-methyl is replaced by *n*-propyl or *n*-butyl, there is almost complete loss of cholinergic activity (25). The hydrazinium congener (**8**), in which one *N*-methyl is replaced by NH_2, was less active than acetylcholine in all assays performed (43). The pyrrolidine congener (**10**) is 20–33% as potent as acetylcholine (44); this compound can be viewed as a cyclic congener of acetyl *N*,*N*-diethylcholine, and

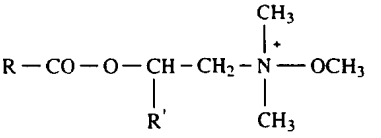


(**10**)

it is decidedly more potent than the diethylcholine ester.

However, in general, incorporation of the choline moiety into a heterocyclic ring markedly lowers potency compared with acetylcholine (45,46). The *tris*-(trideuteromethyl) congener (**9**) showed similar potency to acetylcholine in a dog blood pressure assay (47).

Replacement of one *N*-methyl by methoxyl in acetylcholine and in three congeners (**11–14**) permits retention of some cholinergic effects, and in certain compounds, nicotinic or muscarinic activities are enhanced over the parent *N*,*N*,*N*-trimethyl system (48).



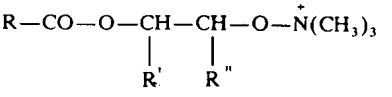
(**11**) $R = CH_3$; $R' = H$

(**12**) $R = R' = CH_3$

(**13**) $R = H_2N$; $R' = H$

(**14**) $R = H_2N$; $R' = CH_3$

The reverse *N*-alkoxy systems (**15**) demonstrated only extremely weak muscarinic activity (49). Amine oxide analogs of cholinergic agonists (**16–19**) exhibit little or no cholinergic effect, and they are not substrates for cholinesterases (50).



(**15**) $R = CH_3$ or NH_2;
R', R'' = combinations of H, CH_3

The observed biological effects of several variations of the quaternary head of acetylcholine and its congeners may be rationalized by invoking results of molecular orbital calculations (51), which indicate that in both muscarine and acetylcholine, the nitrogen atom is nearly neutral and a