TEXTBOOK OF PHARMACOLOGY

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TEXTBOOK OF PHARMACOLOGY

Foreword to the Fifth Edition

We thank our colleagues and students for their critical comments. We are particularly grateful to Professor Dr. F. K. Ohnesorge, Dr. D. Proppe, Dozent Dr. O. Wassermann, and Professor Dr. P. A. van Zwieten for their advice. We thank Miss Magda Hassemer for her help in the preparation of the manuscript. Suggestions and comments from our readers will be greatly appreciated.

Mainz and Kiel
Autumn 1971

G. Kuschinsky
H. Lüllmann

From the Foreword to the First Edition

This book is an attempt to present concisely pharmacological and toxicological data pertinent to applied medicine. Pathophysiological considerations and the relationship between chemical constitution and activity are stressed in this work. The chemical formulas, schematic diagrams, and figures depicting the experimental results help illustrate the concepts presented.

Spring 1964

G. Kuschinsky
H. Lüllmann

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Translator's Preface

This translation of "A Short Textbook of Pharmacology" was originally of the fourth German edition. However, as a revised German edition appeared prior to publication of this translation, new material was incorporated in this work.

While the original German edition contains as footnotes the trade names for the various drug preparations which are designated in the text by their generic names, the English translation utilizes only generic names in the body of the text. Trade names are cross-referred to the proper generic names in the Index. In addition, a partial list of some drugs which are not available in the United States but which are nevertheless utilized in Germany can be found on page xiii. I have not attempted to verify the availability of every compound mentioned in the text in all English-speaking countries since governmental regulations vary widely. The student should be aware of the fact that some of the newer preparations may in the future become available in the United States.

Philip C. Hoffmann

COMPOUNDS NOT CURRENTLY AVAILABLE IN THE UNITED STATES

Compound	Page on which compound is mentioned
Acetyl digoxin	69
Alprenolol	35
Arvin	87
Bis-*p*-hydroxyphenylcyclohexylidene methane	242
n-Butyl scopolamine	15
Buformin	225
Carbenoxolone	111
Chlorethiazole	167
3-Chlorimipramine	198
Cyclopenthiazide	102
Diethylstilbestrol dimethylether	241
Dihydralazine	42
Ethacridine	260
Glibenclamide	225
Guanaclin	33
Guanoxan	33
INPEA	35
Lidoflazine	78
Mefruside	103
Mesterolone	236
Mesulphen	267
Methenolone	239
Metoclopramide	167
Nifenazone	140
Novamine sulfone	139
Orciprenaline	55
Phenoxypropyl penicillin	227
Pholedrine	26
Practolol	35
Proscillaridin	70
Diethylstilbestrol dimethylether	241
Spiramycin	288
k-Strophanthin	66
Thebacon	152
Toxogonin	263

CONTENTS

CHAPTER 1

ORGANS INNERVATED BY THE AUTONOMIC NERVOUS SYSTEM

Autonomic Nervous System

The vegetative or autonomic nervous system, consisting of a central and a peripheral part, has the task of regulating all visceral functions of the organism. The central components are contained in the spinal cord and the brain stem. A specific pharmacological influence on the central autonomic nervous system is currently possible only to a limited extent, whereas the efferent part of the peripheral autonomic system has gained considerable importance in experimental and therapeutic pharmacology. Anatomical, physiological, and pharmacological considerations allow a differentiation of the autonomic system into a sympathetic and a parasympathetic division (Fig. 1). A schematic diagram of the efferent sympathetic and the parasympathetic systems is shown in Fig. 2 in order to demonstrate the location of synapses, together with the corresponding transmitter substances, and those pharmacological agents that act at these sites.

The pharmacology of the peripheral autonomic nervous system includes not only the pharmacological influence of the nervous system as such, but also that of the organs innervated by this system. In the target organs (smooth muscle, glands) drugs can imitate the excitation or the impairment of the autonomic system.

Cholinergic and adrenergic nerves are differentiated on the basis of the neurotransmitter, acetylcholine or norepinephrine (noradrenaline), which is released at the nerve ending. The expression, cholinergic nerve, cannot be restricted to the autonomic nervous system since the voluntary nerves leading to the skeletal muscles are also of the cholinergic type, i.e., acetylcholine is the transmitter sub-

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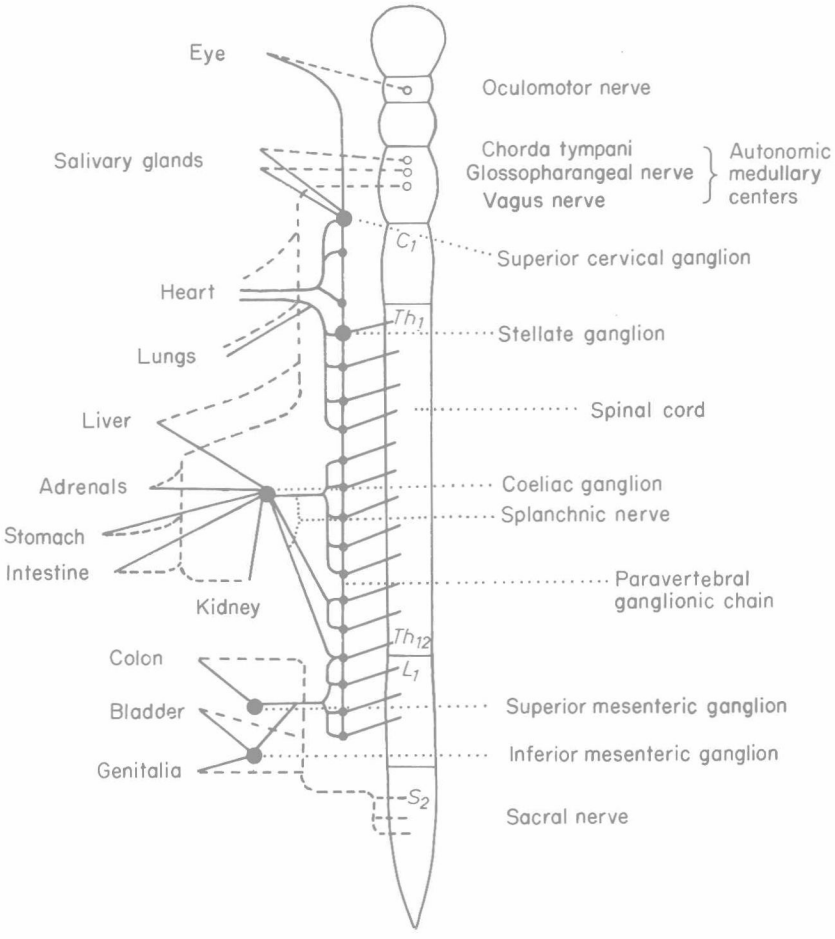

Fig. 1. A schematic representation of the peripheral autonomic nervous system. (—) Sympathetic; (- - -) parasympathetic.

stance at the motor end plate as well (cf. p. 119). The terms cholinergic and adrenergic may also be applied to the characterization of drugs. A cholinergic (cholinomimetic) compound mimics the action of acetylcholine released from the nerve ending, and an adrenergic compound similarly mimics the effect of norepinephrine. While the terms adrenergic drug and sympathomimetic drug are synonymous since the presence of adrenergic nerves is limited to the sympathetic system (at least in the peripheral part), the terms cholinergic drug and parasympathomimetic agent do not necessarily coincide. Thus, pilocarpine is a cholinergic compound as well as a parasympathomimetic agent, whereas succinylcholine is a cholinergic compound without being a parasympathomimetic drug since it acts only at the motor end plate.

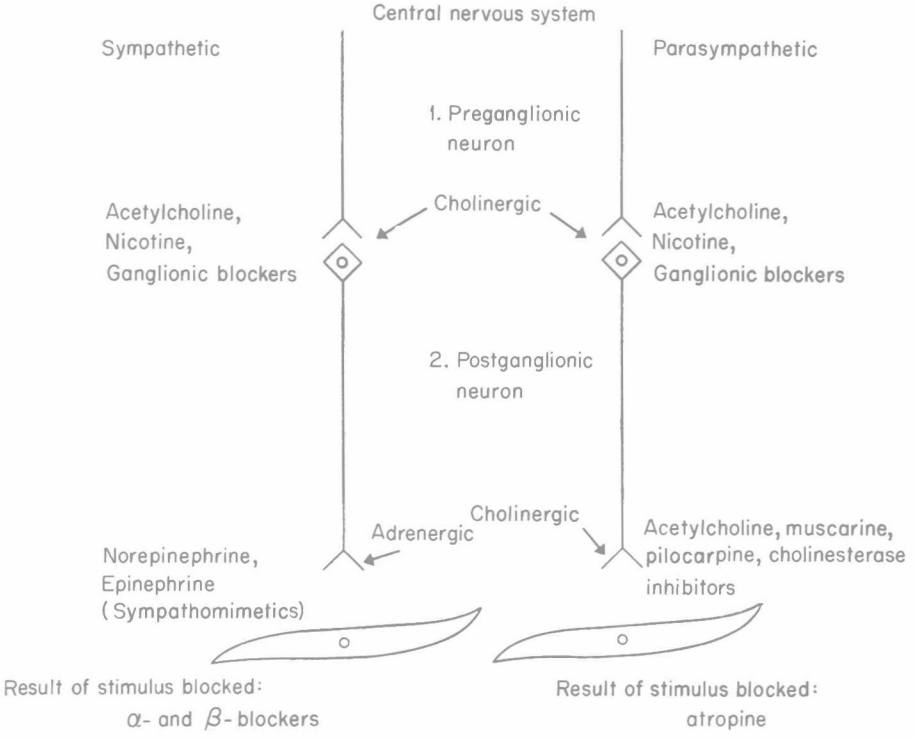

Fig. 2. A schematic representation of the peripheral efferent autonomic system showing synapses, transmitter substances, and excitatory or inhibitory drugs.

Autonomic drugs may be divided into two groups based on their principal mechanism of action.

1. Compounds that react directly with receptors for acetylcholine or norepinephrine (for the definition of "receptors" see page 313). Examples for such drugs in the parasympathetic system are nicotine, with a ganglionic site of action, in contrast to muscarine, pilocarpine, and atropine with a postganglionic site of action. Examples from the sympathetic system are nicotine, with a ganglionic site of action, and isoproterenol, dihydroergotamine, and dichloroisoproterenol showing a postganglionic site of action. Common to all these drugs is their reaction with the receptors themselves. Then either the adrenergic or cholinergic response occurs (direct-acting sympathomimetics or parasympathomimetics), or the receptors are occupied without subsequent reaction. In the latter case the action of the endogeneous transmitter substance is blocked (sympatholytic and parasympatholytic agents).

2. Compounds that interfere in some way with the metabolism of the neurotransmitters, acetylcholine and norepinephrine (synthesis, storage in the tissues, release from nerve endings, and metabolic degradation). Examples of these indirectly acting drugs are ephedrine, which causes the release of norepinephrine;

reserpine, which prevents the storage of norepinephrine; and physostigmine, which prevents the degradation of acetylcholine by acetylcholinesterase. Again, stimulation or blockade of the corresponding part of the autonomic system may be mimicked by these indirectly acting compounds. Therefore, the site at which the transmitters exert their cholinergic or adrenergic functions is of pharmacological importance. Acetylcholine exerts its transmitter function: (1) at the endings of the postganglionic fibers of the parasympathetic system (and of the sympathetic nerves leading to the sweat glands); (2) at all ganglionic synapses in the autonomic system; (3) at certain synapses in the central nervous system; and (4) at the motor end plate of skeletal muscle (cf. motor end plate, p. 119). The transmitter function of norepinephrine is limited to the postganglionic nerve endings of the sympathetic system (except those innervating the sweat glands) and to the central nervous system. In addition, dopamine probably has a transmitter function in the central nervous system (cf. Parkinsonism, p. 129).

Neither the neurotransmitters themselves, nor the various autonomic drugs always exert the same quantitative effect at all cholinergic or adrenergic sites. The pharmacological action of such compounds depends mainly on whether transmission at a peripheral or ganglionic (or motor end plate) site is involved; cholinergic transmission, for example, is blocked by atropine at postganglionic sites, by ganglionic blocking agents in the ganglia, and by curare at the motor end plate. Even if only the responses of the reacting organ are considered, differences in the reactivity to the same agent are frequently very large. There are, for instance, adrenergic substances which are primarily bronchodilators (isoproterenol) and others which are mainly vasoconstrictors (e.g., Paredrinol) or central nervous system stimulants (e.g., amphetamine). In several, but not all cases, the reasons for these differences in activity are known. The differences may be based on a differential distribution of the corresponding drug within the organism or in varying affinities of the compounds involved to the receptors in question. Recently it has become possible to obtain antibodies against the sympathetic nervous system. If such antibodies are administered to newborn animals, such animals do not develop any sympathetic nervous system. Their behavior is quite normal, but their reaction to adrenergic drugs is abnormal.

Postganglionic Site of Action

Parasympathomimetics

Like all cholinergic nerves (see also "motor end plate," p. 119), the postganglionic parasympathetic neuron and the neuroeffector junction in the reacting organ possess a complete "acetylcholine system": (1) the synthesizing enzyme, choline-acetylase; (2) a storage mechanism into which the continuously synthesized acetylcholine is taken up to be released again, either spontaneously or in larger amounts as a result of nerve stimulation; (3) receptors in the effector organ that react with acetylcholine, leading to local alterations in the properties of the cell surface; and (4) the degradative enzyme, cholinesterase (cf. Fig. 10). Two types of esterases are

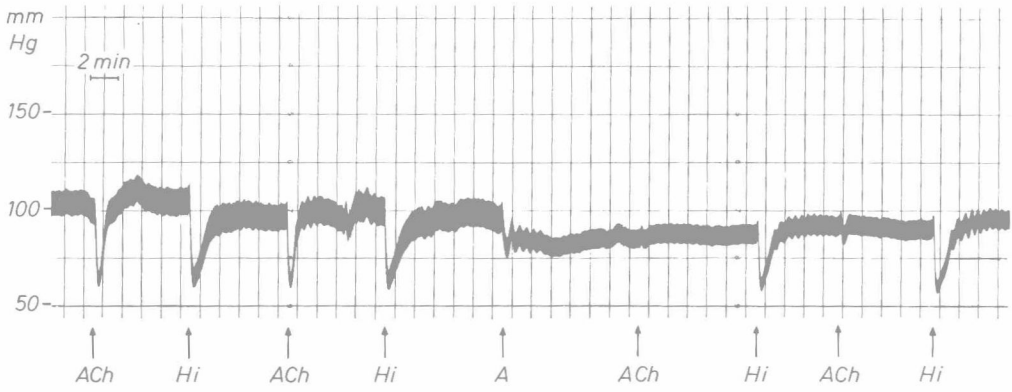

Fig. 3. The effect of atropine on the blood pressure responses to acetylcholine and histamine. The blood pressure of a cat was recorded by means of a pressure transducer on a recorder. The compounds were injected intravenously. ACh, 0.001 mg acetylcholine per kilogram, Hi, 0.004 mg histamine per kilogram; A, 2.0 mg atropine per kilogram. Atropine abolishes the effect of acetylcholine, while the action of histamine remains unchanged.

present in warm-blooded animals: (1) "true" cholinesterase (acetylcholinesterase), which is highly substrate-specific and always structurally bound, and (2) pseudocholinesterase, which belongs to the class of nonspecific esterases, and exhibits optimal activity at high substrate concentrations. This enzyme exists in solution in the body fluids. Along with the cholinergic receptors themselves, acetylcholinesterase is of particular pharmacological and toxicological interest within the "acetylcholine system" because specific inhibitors of this enzyme have become known.

When acetylcholine is injected or infused intravenously into experimental animals or man, the most marked symptoms arise from stimulation of postganglionic parasympathetic structures. These symptoms including lowering of blood pressure by vasodilatation (Fig. 3), negative chronotropic effect, negative inotropic effect on the atrium (Fig. 4), bronchial constriction, increase of intestinal tonus (Fig. 5), and increase of glandular secretion. The same symptoms may be observed in

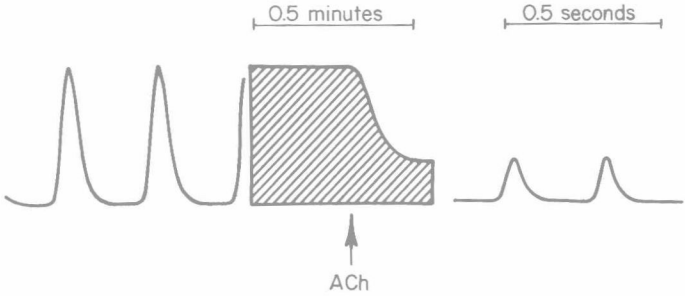

Fig. 4. The effect of acetylcholine on the contractile amplitude of the isolated guinea pig atrium. Isometric recording by means of a strain gauge connected to the recorder. Stimulation frequency, 4 Hz. The contractile amplitude decreases after the addition of 3×10^{-8} gm/ml acetylcholine. Note the two different recorder speeds.

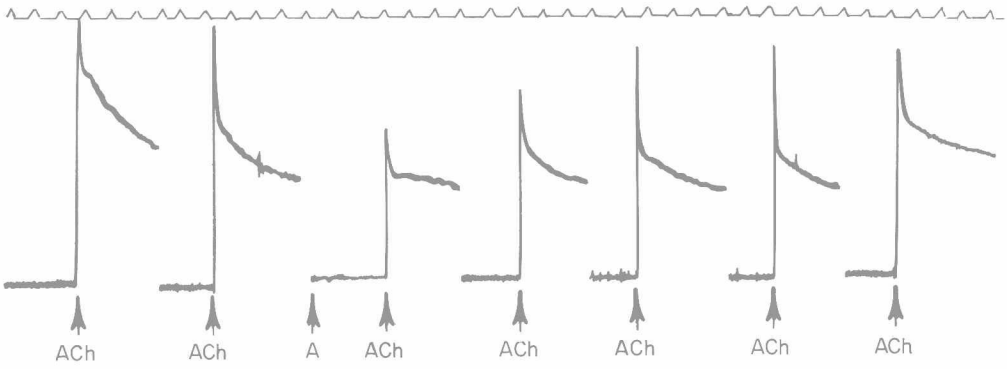

Fig. 5. The effect of atropine on the response to acetylcholine of the isolated guinea pig ileum. ACh, acetylcholine 5×10^{-7} gm/ml; A, atropine 10^{-7} gm/ml; time in minutes. The response to acetylcholine is reduced by atropine at this concentration; the effect of atropine can be slowly washed out.

poisoning with cholinesterase inhibitors (cf. pp. 13 and 263). Ganglionic structures and the motor end plate are less sensitive, so that their stimulation is masked by the above-mentioned parasympathetic effects. The duration of action of acetylcholine is very short since the compound is degraded with extraordinary rapidity (Fig. 3).

The mechanism of action of acetylcholine has excited the interest of physiologists and pharmacologists for a long time. A large number of investigations which in part have been conducted with the most modern and complicated methods have led to the following formulation of this mechanism: When acetylcholine is bound

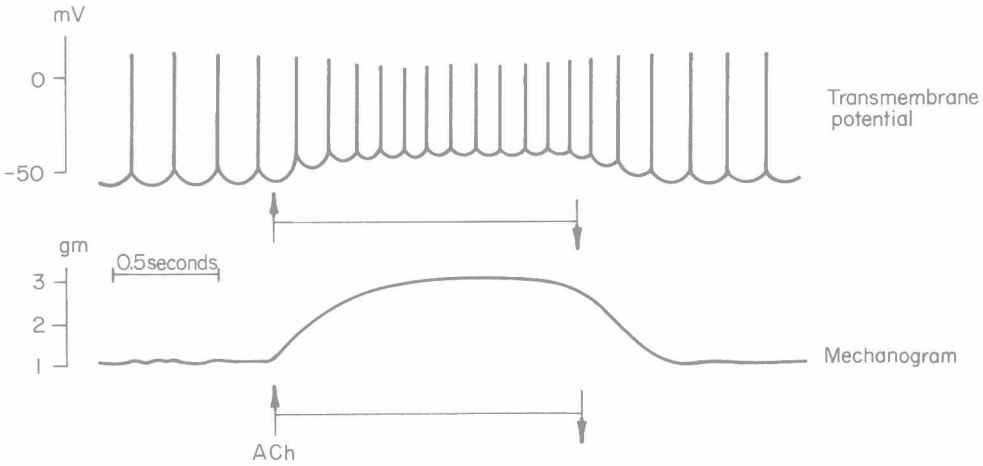

Fig. 6. The effect of acetylcholine on the transmembrane potential and the development of mechanical tension in smooth muscle (schematic). Acetylcholine diminishes the membrane potential and increases the frequency of the action potential; simultaneously muscle tension increases.

to the corresponding receptor in the cell membrane, the membrane permeability at this site is altered. The membrane instantaneously becomes more permeable towards potassium, sodium, and calcium ions, i.e., the preexistent flux equilibrium is disturbed and the membrane potential is altered. The direction of the change depends on the magnitude of the membrane potential and on the ratio between the increases in sodium and potassium conductance. In general, the actual membrane potential (E_m) may be expressed satisfactorily by the equation

$$E_m \sim \frac{[K]_i \times P_K + [Na]_i \times P_{Na} + [Cl]_e \times P_{Cl}}{[K]_e \times P_K + [Na]_e \times P_{Na} + [Cl]_i \times P_{Cl}}$$

where [K], [Na], and [Cl] represent the intracellular (subscript i) and extracellular (subscript e) concentrations of the respective ions. P is a measure of the specific membrane permeability for the designated ion. In the resting state the ratio $P_K:P_{Na}$ is approximately 1:0.01 which means that the potassium gradient (K_i/K_e) is by and large the determining factor. At the peak of excitation the relationship $P_K:P_{Na}$ reverses and E_m then becomes positive because the Na gradient is reversed. Under the influence of acetylcholine the membrane permeabilities for K and Na increase unequally such that the ratio of $P_K:P_{Na}$ may either

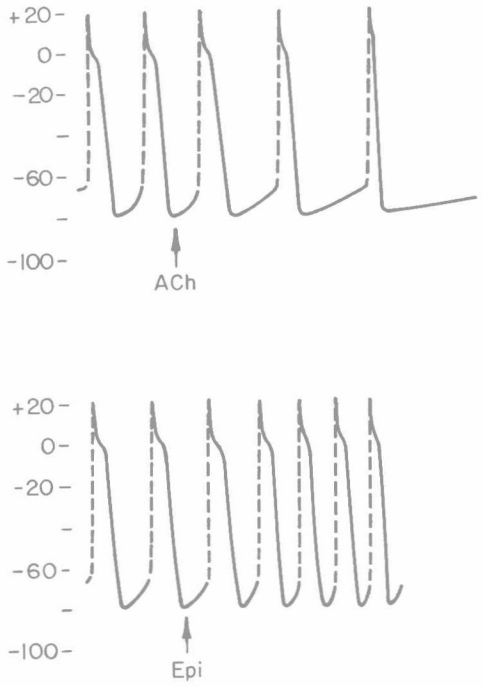

Fig. 7. Schematic representation of the effect of acetylcholine and epinephrine on the pacemaker potentials of the heart. Acetylcholine (ACh) prolongs diastolic depolarization and thereby diminishes the frequency of beating (negative chronotropic effect); epinephrine accelerates diastolic depolarization and thereby increases the frequency of beating (positive chronotropic effect).

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