PHYSIOLOGICAL PHARMACOLOGY

A Comprehensive Treatise

Edited by

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Central Nervous System Drugs

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Foreword

PHYSIOLOGICAL PHARMACOLOGY is designed to be an authoritative account of the effects of drugs on physiological systems. To achieve this purpose, it is anticipated that this treatise will eventually consist of approximately ten volumes, of which this is the first. The selection of topics for inclusion and the nominations of contributors are made by the Editors in consultation with the distinguished scientists making up the Editorial Advisory Board.

In the past decade there has been an impressive growth in our knowledge of how drugs may alter physiological systems, and many of these newer findings have been ably summarized in reviews. It is not the purpose of this treatise to summarize merely recent data, but, rather, to record and interpret all of the significant findings, regardless of age, and thereby to portray the framework of experimental evidence upon which pharmacodynamics is built.

It is intended that each contribution to this treatise represent an authoritative, systematic presentation of current concepts of the effects of drugs upon physiological systems as well as what is known of their mechanisms of action. Emphasis has been placed upon those experimental findings that have led to our current concepts. Findings have not been excluded because of age nor have they been included solely because of newness. Observations made in human beings have been neither featured nor omitted. The coverage of the literature is international in scope. Moreover, contributors have been encouraged to present not only factual evidence, but also theoretical interpretations presently receiving serious consideration.

It is the hope of the Editors that the scope and the depth of this treatise will make it of value to those who must teach, those who must learn, and those who conduct investigations in the complex area of pharmacodynamics.

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Preface

The central nervous system is undoubtedly one of the greatest challenges to pharmacology. As the site of autonomic and somatic control, the substrate for reflex activity, sensory perception, memory, and emotion, and the center for creative thinking and higher intellectual functions, the brain and spinal cord provide a great variety of specific targets for drug action. Because of the intricacy and complexity of the nervous system and of its metabolism, it is likely that a great variety of biologically active substances will interfere with nervous system activity either directly or indirectly. Atropine, for example, mostly employed as a spasmolytic drug, has a profound effect on the reticular activating system of the brain; digitalis is known to cause visual hallucinations in high doses; carbonic anhydrase inhibitors used as diuretics may exert a distinct anticonvulsant effect. A complete description of drugs acting upon the central nervous system would probably have to include most of the therapeutic agents used today, and this would become impractical. A selection of agents acting predominantly on the central nervous system had to be made, using present therapeutic significance as a guide. As a result a semi-empirical classification emerged which is quite indicative of the present status of research in the central nervous system.

Experimental approaches to brain function are complicated in that biological responses are rather difficult to record and require highly differentiated methodology. It has necessitated the development of new electrophysiological techniques such as intracellular potential analysis with microelectrodes and stereotaxic placement of recording and stimulating electrodes in various brain structures. Changes in electrical activity, however, become only meaningful if the underlying physicochemical mechanism is properly understood. As a consequence biophysicists and biochemists have approached the enigma of central nervous system function from the molecular level, often discarding the well defined anatomical boundaries of functional units within the brain. Yet, histochemistry and electron microscopy have provided many important answers. Finally the study of behavior ranging from observation of naive subjects to application of operant conditioning techniques must be added to the list of promising experimental approaches.

The most important goal, however, is to gain an understanding of central nervous system function as a whole, by integrating the knowledge available from the various disciplines. This includes not only animal experiments, but also observations in the human being. The highly dif-

ferentiated human brain may pose many questions which can be answered only by appropriate human experiments. This is of particular importance to pharmacological investigations on diseases such as schizophrenia. Whether corresponding model psychoses can ever be obtained in animals is questionable at this time. Human pharmacology will therefore become increasingly important and will undoubtedly yield new and specific information on psychotropic drugs.

A wealth of data on the action of drugs on the central nervous system awaits analysis. Many of the more urgent problems are presented and discussed in the chapters of these volumes. A momentary account of a rapidly progressing science and a stepping stone to further progress, these volumes will bring about a better understanding of the physiological principles underlying pharmacological effects.

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I. DEPRESSANT DRUGS

A. General Anesthetics

1. Absorption, Distribution, and Elimination

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I. INTRODUCTION: VOLATILE VERSUS NONVOLATILE DRUGS

Anesthetic drugs produce their effects by modifying the responses of the central nervous system. The sum total of these modifying effects is a reduction in activity which is commonly referred to as *depression*. Central nervous system depressants are usually classed as *volatile* and *nonvolatile* (5). This classification has a number of practical advantages. The individual members of each group have pharmacological characteristics which are common to the group as a whole. Both groups are unlike each other in many of their physiological and pharmacological behaviors. The volatile anesthetics, generally speaking, are "complete" anesthetics (35). By this is meant that they abolish superficial reflexes completely and block pain pathways from the periphery to central neurons. The blockade, in the case of nonvolatile drugs, is incomplete and a partial response to external stimuli persists unless doses beyond the limit of safety are used (4). Volatile substances are administered in the vapor or gaseous state by inhalation. Nonvolatile substances, on the other hand, are injected intravascularly or they are administered orally or rectally and pass into the blood through the gastrointestinal tract or they gain access to the blood stream after intraperitoneal, subcutaneous, or intramuscular injection. Aqueous solutions of some volatile anesthetics are occasionally administered intravenously, but this avenue of administration is impractical.

II. INHALATIONAL ANESTHETICS

A. Types and Characteristics

In order to be effective when administered by the pulmonary route, a substance must be a gas or it must vaporize readily, so that the vapor pressure at room temperature creates an appreciable gradient between

the inspired vapor and the neurons (35). This gradient must be of sufficient magnitude to permit a rapid attainment of adequate molecular concentrations in the brain for pharmacological activity. Not all volatile liquids are suitable for inhalation. The majority of clinically accepted drugs are liquids which boil below or close to room temperature (Table I). Liquids such as alcohol, paraldehyde, and amylene hydrate

TABLE I
BOILING POINTS AND VAPOR TENSIONS OF VOLATILE ANESTHETICS

Anesthetic	B.P.(°C)	Vapor tension (mm Hg at 20°C)	Vapor tension in blood for anesthesia (mm Hg)
Xenon	—107	—	600
Ethylene	—103	—	580
Nitrous oxide	—89	—	610
Cyclopropane	—34	—	152
Ethyl chloride	12.5	988	40
Ethyl ether	35.5	440	25–35
Divinyl ether	28.3	550	30–40
Ethyl vinyl ether	35.8	485	30–40
Trifluoroethyl vinyl ether	42.7	395	25–35
Halothane	50.2	241	5–10
Chloroform	61.0	160	5–10
Trichloroethylene	87.0	60	20–30
Methoxyflurane	104.8	30	5–10

are not suitable for inhalation because the inspired vapor pressure at room temperature is inadequate to produce arterial blood and brain concentrations necessary for narcosis.

B. CHEMICAL NATURE

The clinically useful inhalational anesthetics may be inorganic gases or they may be organic, volatile liquids and gases. The most important and widely used inorganic gas is nitrous oxide (5). Xenon and sulfa-hexafluoride possess anesthetic properties but are impotent and ineffective. Nevertheless, they are of interest from an investigational point of view (5). Carbon dioxide in concentrations exceeding 10% manifests narcotic properties (35). Nitrogen and a number of the rare gases possess varying degrees of narcotic potency when administered under pressures of several atmospheres (3).

The majority of anesthetics are organic substances. The volatile, organic substances are chiefly aliphatic hydrocarbons, aliphatic ethers, and halogenated aliphatic hydrocarbons (4). Specific compounds possessing varying degrees of clinical usefulness are ethylene, cyclopropane,

diethyl ether, methyl propyl ether (Metopryl) ethyl methyl ether, divinyl ether (Vinethene®), ethyl vinyl ether (Vinamar), trifluoroethyl vinyl ether (Fluoromar®), chloroform, ethyl chloride, trichloroethylene (Trilene®), halothane (Fluothane®, bromochlorotrifluoroethane), and methoxylflurane (Penthrane®).

C. Stability in the Body

The inhalational anesthetics, with the exception of trichloroethylene, are inert and are not metabolized in the body (35). They are eliminated unchanged. Any decomposition which occurs is negligible and difficult to detect. After the administration of brominated hydrocarbons, traces of bromine-containing compounds are found in the urine, which suggests that some modification in structure has occurred (5). The total quantity involved is insignificant, however, so that the premise that inhalational anesthetics are not metabolized is generally valid. Hydrocarbons halogenated with chlorine, fluorine, and iodine tend to be less stable chemically in the body than their unhalogenated counterparts. Trichloroethylene undergoes partial changes after being inhaled. Approximately 15% is converted to trichloroethanol which is further oxidized to trichloroacetic acid. This in turn is eliminated in the urine over a period of several days. The remainder is exhaled unchanged (5). The other compounds are inert within the body and, therefore, follow, in an identical manner, the laws of physical behavior of other inert nonanesthetic gases and vapors with respect to uptake, distribution, and elimination (2, 36).

III. BLOOD AND BRAIN CONCENTRATIONS

The level or depth in anesthesia is determined by the molecular concentration in the brain cells (9). The arterial blood level of a volatile drug reflects the concentration in the brain and equals it when equilibrium has been established. This is not necessarily the case with nonvolatile drugs. Haggard (18) many years ago indicated that the essential factor in the induction of anesthesia is that the drug be present primarily in the brain. He demonstrated that this is so by injecting ether into the carotid artery of dogs. Anesthesia quickly ensued. Blood drawn from the jugular vein contained considerable quantities of ether. Venous blood from other areas of the body, on the other hand, contained insignificant amounts. Others (9) have since that time verified these findings. Thus, it was obvious that all that is necessary to establish anesthesia is a state of equilibrium or near equilibrium between the drug in the cerebrovascular space and the neurons. In recent years electroencephalographic studies have confirmed the fact that there is a

close correlation between arterial blood levels of volatile anesthetics and depth of anesthesia (8).

IV. SOLUBILITY AND POTENCY

A. Lipid Solubility

Numerous workers [Bibra, Harless, Meyer, Overton, and others (5)] showed many years ago that substances possessing narcotic activity were highly soluble in lipids. Because of this lipid solubility the term *lipophilic* has been applied to anesthetics (35). All lipophilic substances, however, are not anesthetic. Substances manifesting poor solubility in lipids are often referred to as *lipophobic*. Lipophobic substances are not anesthetic.

B. Water Solubility

It was quickly noted, after the discovery of anesthesia, that the effective agents were not only lipophilic but were in addition poorly soluble in water or *hydrophobic*. Some correlation could be demonstrated between narcotic potency and the decrease in water solubility (6). Potency increased as solubility decreased, up to a point beyond which narcotic effectiveness vanished. The reason for this should be obvious. All anesthetics must be sufficiently soluble in water to be effective. They must be carried in sufficient quantities by the plasma and the interstitial fluids to provide the molecular concentration in the neuron essential for pharmacological activity. In the last analysis, the transfer of a gas or vapor from its medium of transport to the cell, whatever the portal of entry into the body may be, is accomplished by the plasma. Thus, a substance which is extremely hydrophobic and not soluble in water can never pass the various aqueous barriers to reach the cell. Pauling (28) has indicated that anesthetics form hydrates and do so within the cell. These hydrates make possible the formation of stable aggregates of ice crystals within the cells at body temperature. Ordinarily, lower temperatures are required for the formation of ice crystals. The ice, which is not conductive, decreases the electrical activity of the cell and produces narcosis.

V. EFFECTS OF ANESTHETICS ON PROTOPLASM

A. Effects on Cells

All anesthetics, regardless of the type, have a special predilection for nervous tissue (35). Neurons are depressed before other cells, although the depression is not uniform in all neurons. This ability to suppress the activity of neurons has been ascribed to the lipophilic nature of the anesthetic and to the somewhat greater preponderance of lipid materials