Foye's Principles of Medicinal Chemistry

FIFTH EDITION

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2. Drug Design and Relationship of Functional Groups to Pharmacologic Activity

JAMES KNITTEL AND ROBIN ZAVOD

Medicinal chemistry is the discipline concerned with determining the influence of chemical structure on biological activity. As such, it is therefore necessary for the medicinal chemist to understand not only the mechanism by which a drug exerts its effect, but also the physicochemical properties of the molecule. The term "physicochemical properties" refers to the influence of the organic functional groups present within a molecule on its acid/base properties, water solubility, partition coefficient, crystal structure, stereochemistry etc. All of these properties influence the absorption, distribution, metabolism and excretion (ADME) of the molecule. In order to design better medicinal agents the medicinal chemist needs to understand the relative contributions that each functional group makes to the overall physical chemical properties of the molecule. Studies of this type involve modification of the molecule in a systematic fashion and determination of how these changes affect biological activity. Such studies are referred to as studies of structure-activity relationships i.e., what structural features of the molecule contribute to, or take away from, the desired biological activity of the molecule of interest.

Because of the fundamental nature of its subject matter, this chapter includes numerous case studies throughout (as boxes) and at the end. In addition, a list of study questions at the end of—and unique to—this chapter provides further self-study material on the subject of drug design.

INTRODUCTION

Chemical compounds, usually derived from plants, have been used by humans for thousands of years to alleviate pain, diarrhea, infection and various other maladies. Until the 19th century these "remedies" were primarily crude preparations of plant material whose constituents were unknown and the nature of the active principal (if any) was also unknown. The revolution in synthetic organic chemistry during the 19th century produced a concerted effort toward identification of the structures of the active constituents of these naturally derived medicinals and synthesis of what were hoped to be more efficacious agents. By determining the molecular structures of the active components of these complex mixtures it was thought that a better understanding of how these components worked could be elucidated.

Relationship Between Molecular Structure and Biologic Activity

Early studies of the relationship between chemical structure and biologic activity were conducted by Crum-Brown and Fraser (1) in 1869. They showed that many compounds containing tertiary amine groups became muscle relaxants when converted to quaternary ammonium compounds. Compounds with widely differing pharmacological properties such as, strychnine (a convulsant), morphine (an analgesic), nicotine (deterrent, insecticide), and atropine (anticholinergic), all could be converted to muscle relaxants with properties similar to tubocurarine when methylated (Fig. 2.1). Crum-Brown and Fraser therefore concluded that muscle relaxant activity required a quaternary ammonium group within the chemical structure. This initial hypothesis was later disproven by the discovery of the natural neurotransmitter and activator of muscle contraction, acetylcholine (Fig. 2.2). Even though Crum-Brown and Fraser's initial hypothesis concerning chemical structure and muscle relaxation was proven to be incorrect, it demonstrated the concept that molecular structure does influence the biological activity of chemical compounds.

With the discovery by Crum-Brown and Fraser that quaternary ammonium groups could produce compounds with muscle relaxant properties scientists began looking

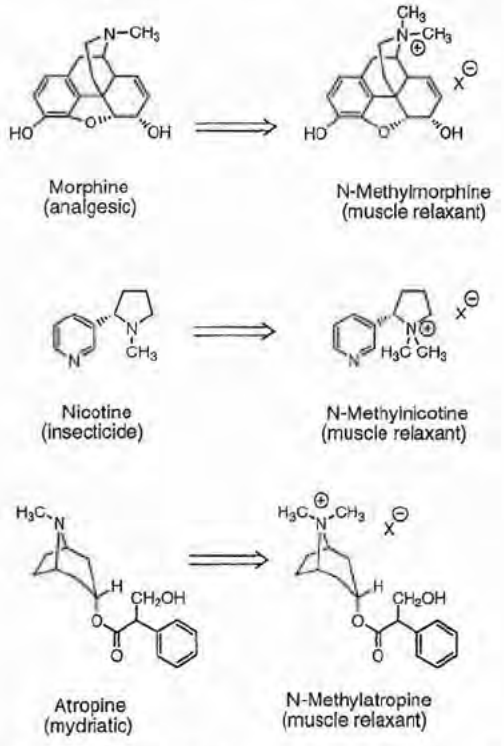

Fig. 2.1 Effects of methylation on biologic activity

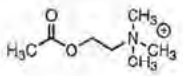

Fig. 2.2. Acetylcholine, a neurotransmitter and muscle relaxant.

for other organic functional groups that would produce specific biologic responses. The thinking at this period of time was that specific chemical groups, or nuclei (rings), were responsible for specific biologic effects. This lead to the postulate, which took some time to disprove, that "one chemical group gives one biological action." (2) Even after the discovery of acetylcholine by Loewi and Navrati (3) which effectively dispensed with Crum-Brown and Fraser's concept of all quaternary ammonium compounds being muscle relaxants, this was still considered dogma and took a long time to replace.

Selectivity of Drug Action and Drug Receptors

Though the structures of many drugs or xenobiotics were known at the turn of the century, or at least the composition of functional groups, it was still a mystery as to how these compounds exerted their effects. Utilizing his observations regarding the staining behavior of microorganisms, Ehrlich developed the concept of drug receptors (4). He postulated that certain "side chains" on the surfaces of cells were "complementary" to the dyes (or drug), thereby allowing the two substances to combine. In the case of antimicrobial compounds, this combining of the chemical to the "side chains" produced a toxic effect. This concept effectively was the first description of what later became know as the receptor hypothesis for explaining the biological action of chemical compounds. Ehrlich also discussed selectivity of drug action via the concept of a "magic bullet" for compounds that would eradicate disease states without producing undue harm to the organism being treated (i.e., the patient). This concept was later modified by Albert (5) and is generally referred to as "selective toxicity." Utilizing this concept Ehrlich developed organic arsenicals that were toxic to trypanosomes as a result of their irreversible reaction with mercapto groups present on vital proteins within the organism. The formation of As-S bonds resulted in death to the target organism. However, it was soon learned that these compounds were not only toxic to the target organism, but also to the host once certain blood levels of arsenic were achieved.

The "paradox" that resulted after the discovery of acetylcholine of how one chemical group can produce two different biologic effects, i.e., muscle relaxation and muscle contraction, was explained by Ing (6) using the actions of acetylcholine and tubocurarine as his examples. Ing hypothesized that both acetylcholine and tubocurarine act at the same receptor but that one molecule fits to the receptor in a more complementary manner and "activates" it, was not elaborated upon. The larger molecule, tubocurarine, simple occupies part of the receptor and prevents acetylcholine, the smaller molecule, from occupying the receptor. With both molecules the quaternary ammonium functional group is a common structural feature and interacts with the same region of the receptor. If one closely examines the structures of other compounds that have opposing effects on the same pharmacologic system, this appears to be a common theme: Molecules that block the effects of natural neurotransmitters (antagonists) are generally larger in size than the native compound. Both compounds share common structural features, however, thus providing support to the concept that the structure of a molecule, its composition and arrangement of chemical functional groups, determines the type of pharmacologic effect that it possesses (i.e., structure-activity relationship). Thus, compounds that are muscle relaxants acting via the cholinergic nervous system will possess a quaternary ammonium or protonated tertiary ammonium group and will be larger than acetylcholine. Structure-activity relationships (SARs) are the underlying principle of medicinal chemistry. Similar molecules exert similar biological actions in a qualitative sense. A corollary to this is that structural elements (functional groups) within a molecule most often contribute in an additive manner to the physicochemical properties of a molecule and therefore its biological action. One need only peruse the structures of drug molecules in a particular pharmacologic class to become convinced of this (e.g., histamine H_1 antagonists; histamine H_2 antagonists; β-adrenergic antagonists; etc.). The objective of the medicinal chemist in his/her quest for better medicinal agents (drugs) is to discover what functional groups within a specific structure are important for its pharmacologic activity, and how can these groups be modified to produce more potent, selective and safer compounds.

An example of how different functional groups can yield compounds with similar physicochemical properties is shown with sulfanilamide antibiotics. In Figure 2.3 the structures of sulfanilamide and p-aminobenzoic acid (PABA) are shown. In 1940, Woods (7) demonstrated that PABA was capable of reversing the antibacterial action of sulfanilamide (and other sulfonamides antibacterials) and that both PABA and sulfanilamide had similar steric and electronic properties. Both compounds contain acidic func-

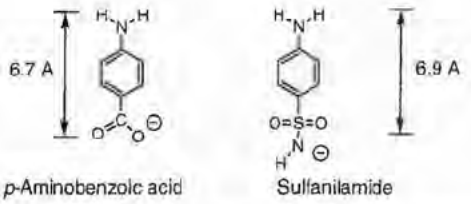

Fig. 2.3. Ionized forms of PABA and sulfanilamide. Comparison of distance between amine and ionized acids of each compound. Note

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