The Organic Chemistry of Drug Design and Drug Action

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To Mom and the memory of Dad,
for their warmth, their humor, their ethics, their inspiration,
but mostly for their genes.

CHAPTER 3

Receptors

I. Introduction

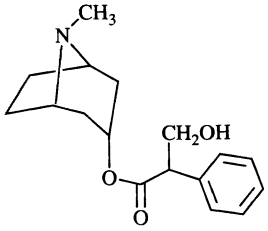
Up to this point in our discussion it appears that a drug is taken, and by some kind of magic it travels through the body and elicits a pharmaceutical effect. *Pharmacokinetics* (absorption, distribution, metabolism, and excretion) was mentioned in Chapter 2, but no discussion was presented regarding what produces the pharmaceutical effect. The site of drug action, which is ultimately responsible for the pharmaceutical effect, is called a *receptor*. The interaction of the drug with the receptor constitutes *pharmacodynamics*. In this chapter the emphasis is placed on pharmacodynamics of general noncatalytic receptors, in Chapter 4 a special class of receptors that have catalytic

properties, called enzymes, will be discussed, and in Chapter 6 another receptor, DNA, will be the topic of discussion. The drug–receptor properties described in this chapter also apply to drug–enzyme and drug–DNA complexes.

II. Receptor Structure

A. Historical

In 1878 John N. Langley,[1] a physiology student at Cambridge University, while studying the mutually antagonistic action of the alkaloids atropine (**3.1**; now used as an antisecretory agent) and pilocarpine (**3.2**; used in the treatment of glaucoma, but causes sweating and salivation) on cat salivary flow, suggested that both of these chemicals interacted with some substance in the nerve endings of the gland cells. Langley, however, did not follow up this notion for over 25 years.



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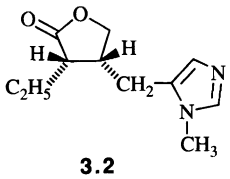

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Paul Ehrlich[2] suggested his *side chain theory* in 1897. According to this hypothesis, cells have side chains attached to them that contain specific groups capable of combining with a particular group of a toxin. Ehrlich termed these side chains receptors. Another facet of this hypothesis was that when toxins combined with the side chains, excess side chains were produced and released into the bloodstream. In today's biochemical vernacular these excess side chains would be called *antibodies*, and they combine with toxins stoichiometrically.

In 1905 and 1906 Langley[3] studied the antagonistic effects of curare (a generic term for a variety of South American quaternary alkaloid poisons that cause muscular paralysis) on nicotine stimulation of skeletal muscle. He concluded that there was a receptive substance that received the stimulus and, by transmitting it, caused muscle contraction. This was really the first time that attention was drawn to the two fundamental characteristics of a receptor, namely, a *recognition capacity* for specific ligands and an *amplification component*, the ability of the ligand–receptor complex to initiate a biological response.

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