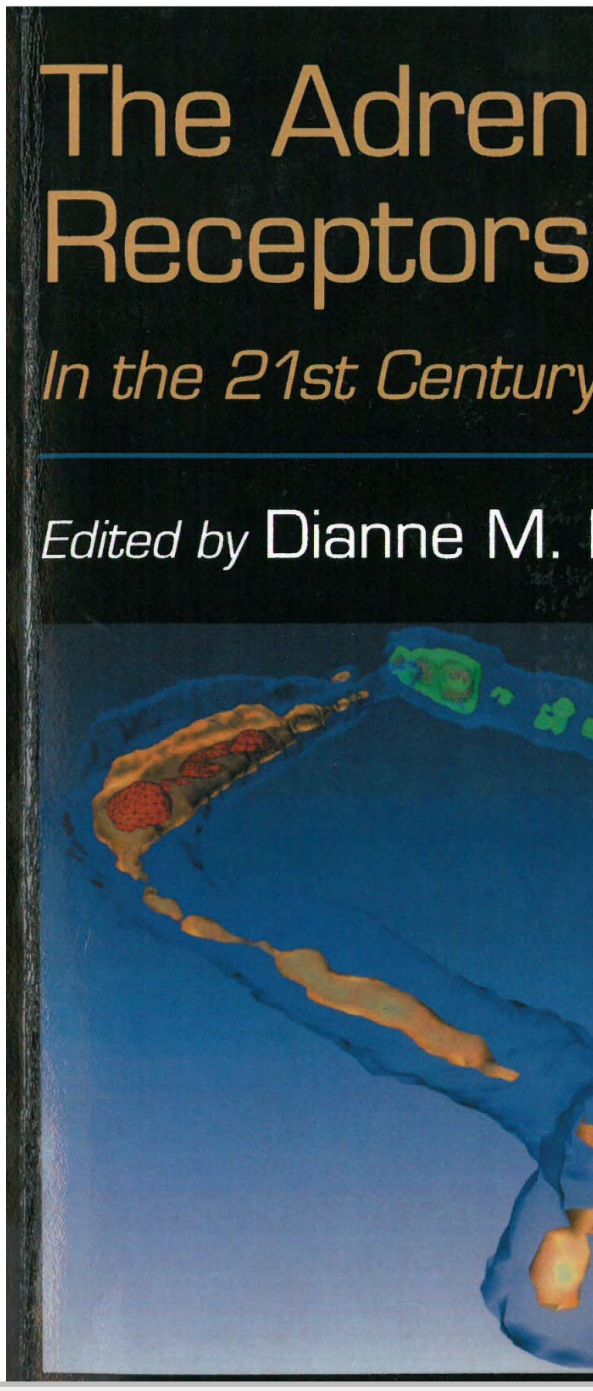

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1

Adrenergic Receptors

Historical Perspectives From the 20th Century

David B. Bylund

Summary

During the 20th century, extraordinary progress was made in our understanding of adrenergic receptors. This progress was the result of the hard work and insightful thinking of a remarkable cadre of investigators throughout the world. A summary of some of the more important developments is presented two ways: as a summary listing by decade and as four major, overlapping eras—biochemical, physiological, pharmacological, and molecular.

Key Words: α_1-Adrenergic receptor; α_2-adrenergic receptor; β-adrenergic receptor; classification; function; history; molecular cloning; pharmacology; radioligand binding; structure.

1. Introduction

Adrenergic receptors mediate the central and peripheral actions of the neurohormones norepinephrine and epinephrine. Both of these catecholamine messengers play important roles in the regulation of diverse physiological systems; thus, adrenergic receptors are widely distributed throughout the body. Stimulation of adrenergic receptors by catecholamines released from the sympathetic branch of the autonomic nervous system results in a variety of effects, such as increased heart rate, regulation of vascular tone, and bronchodilation. In the central nervous system, adrenergic receptors are involved in many functions, including memory, learning, alertness, and the response to stress.

During the 20th century, extraordinary progress was made in our understanding of receptors in general and of adrenergic receptors in particular. The century

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dawned with the crystallization of the receptor concept and closed with the crystallization and determination of the three-dimensional structure of rhodopsin. At the start of the century, epinephrine and norepinephrine had not yet been isolated; by its end, knockout mice were available for all nine adrenergic receptor subtypes, and clinically relevant polymorphisms were being elucidated. This progress was the result of the hard work and insightful thinking of a remarkable cadre of investigators throughout the world. A few of these are mentioned in this chapter, although most (unfortunately) remain unnamed.

A summary listing by decade of some of the more important developments in our understanding of adrenergic receptors is given in Table 1. The accomplishments are indeed impressive. I have chosen to divide the century into four major, overlapping epochs or eras, each named to represent the dominant focus of a given time period. The century started with the biochemical era, which lasted until the mid-1960s and resulted in the isolation of many small compounds, such as norepinephrine, epinephrine, and the second messenger cyclic adenosine 5′-monophosphate (AMP). This was followed by what I term the physiological era, from about 1960 to the early 1980s; it was characterized by elegant use of isolated tissue preparations to elucidate the general characteristics of adrenergic receptors. The pharmacological era, lasting from the mid-1970s to the early 1990s, included not only the use the physiological techniques of the previous era, but also, perhaps more important, radioligand-binding techniques to classify, localize, and characterize the types and subtypes of adrenergic receptors based on their interactions with a rich variety of agonists and antagonists. The molecular era, which is just now ending, started in the mid-1980s and has seen the characterization of receptors by the molecular biological techniques of cloning, site-directed mutagenesis, and genetic engineering.

2. The Biochemical Era (1901–1960)

"Tentatively the first kind of receptor has been called the alpha adrenotropic receptor and the second kind the beta receptor." (Ahlquist, 1948)

John Jacob Abel, a newly appointed professor of pharmacology at Johns Hopkins in Baltimore, Maryland, started work on the isolation of epinephrine about 1896 and by 1901 had a relatively pure preparation. He is generally credited with isolating the first hormone *(1)*. Starting in the 1920s, Cannon attempted to identify the chemical transmitter of the sympathetic nervous system (which he called sympathin) and mistakenly concluded in 1933 that there were two sympathins, sympathin E (excitatory) and sympathin I (inhibitory) *(2)*. This was partly because he was using a natural preparation, adrenaline, which at that time was a variable mixture of epinephrine and norepinephrine. It was not until the late 1940s that von Euler finally established that norepinephrine was the predominant postganglionic neurotransmitter of the sympathetic nervous system *(3)*.

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