1. Introduction

Catecholamines, acting through a variety of membrane-bound receptors, produce a wide range of physiological effects. Most mammalian organ systems are affected by either circulating or locally released epinephrine or norepinephrine. These agents produce their effects by interacting with two major classes of receptors, termed alpha-adrenergic and beta-adrenergic receptors. In this chapter, I shall deal exclusively with the beta-adrenergic receptor system. In 1967, Lands provided physiologic evidence for the existence of two subtypes of beta-adrenergic receptors, which he termed beta-1 and beta-2 (Lands et al., 1967). Subsequently, radioligand binding and biochemical analysis has confirmed the existence of these two subtypes (Stiles et
al., 1984). This topic is covered in more detail in other chapters. It has become clear that both beta-1 and beta-2 adrenergic receptors stimulate the membrane-bound enzyme adenylate cyclase, thus increasing the intracellular concentration of cyclic AMP. Cyclic AMP appears to be the second messenger of beta-adrenergic agonists in all tissues examined (Sutherland and Rall, 1960).

With the advent of radioligand binding techniques in 1974, it was quickly realized that beta-adrenergic receptors were present in most tissues and were not static entities, but rather were under dynamic regulation (Stiles et al., 1984). Receptor number was found to increase (upregulation) or decrease (downregulation) in response to a wide variety of pathophysiologic interventions or hormonal manipulations (Stiles et al., 1984). Over the subsequent 15 y, our knowledge of the components of the beta-adrenergic receptor—adenylate cyclase system has increased dramatically, and this newly acquired information has indicated that there are multiple steps in the transmembrane signaling process that may be altered by pathophysiologic conditions. Thus, it is now abundantly clear that alterations in receptor number represent but a single mechanism utilized by the organism to alter sensitivity to catecholamines. In this chapter, I shall discuss a multiplicity of mechanisms whereby the sensitivity of the beta-adrenergic receptor—adenylate cyclase system is altered by drugs and hormones.

The beta-adrenergic receptor—adenylate cyclase system consists of at least three major protein components. These are the hormone receptor, the catalytic moiety of the enzyme adenylate cyclase, which converts ATP to cyclic AMP, and a coupling protein known as the stimulatory guanine nucleotide regulatory protein, variously abbreviated as $G_s$ or $N_s$. This latter protein is regulated by guanine nucleotides such as GTP and is involved in the "coupling" of the receptor to its effector, the enzyme adenylate cyclase. The $G_s$ protein has been purified from a variety of tissues and is known to consist of a heterotrimer of molecular mass 45, 35, and 8 kDa (Sternweis et al., 1981; Codina et al., 1984). This G protein, by directly interacting with GTP, produces two effects: The first is to perturb the interaction of agonists with the beta-adrenergic receptor; the second is to activate the catalytic moiety of the enzyme adenylate cyclase. Using radioligand binding