

Subtype-Specific Pharmacology

The Magic and the Myth

Thirty-four years ago, Ahlquist concluded that efferent responses of the sympathetic nervous system could be described in terms of two types of adrenergic receptors, alpha and beta. Activation of alpha-adrenergic receptors resulted in constriction of blood vessels, while stimulation of the beta-adrenergic receptor increased heart rate and myocardial contractility. Consistent with most biologic systems, however, the response to various sympathomimetic drugs and blocking agents does not demonstrate absolute specificity. Epinephrine, an endogenous circulating catecholamine, possesses roughly equivalent alpha- and beta-adrenergic activity. Norepinephrine, the endogenous sympathetic neurotransmitter, causes contraction of vascular smooth muscle (alpha-adrenergic effect) but relaxation of airway smooth muscle (beta-adrenergic effect). The synthesis of isoproterenol ushered in an era of "specific" sympathomimetic drugs, but it was readily apparent that the beneficial beta-adrenergic bronchodilator effects of isoproterenol could not be separated from the undesirable cardioinhibitory effects of the drug. Likewise, the widespread use of beta-adrenergic blocking agents for treatment of cardiac, hypertensive, neuropsychiatric, endocrine, and ophthalmologic diseases has produced severe bronchospasm in some asthma patients and patients with chronic obstructive pulmonary disease.

In recent years, the concept of the beta-adrenergic receptors has been modified by the observation that some analogs of beta-adrenergic agonists and blocking agents caused "selective" activation of inhibition of the receptor at different anatomic sites. Beta-adrenoceptors have now been classified as beta1 (heart) and beta2 (lung). Accordingly, terbutaline, salbutamol (albuterol), and several other congeners have been shown to cause "selective" beta2-adrenergic stimulation, while metoprolol and atenolol have been touted as cardioselective beta1-blocking agents.

The subtype-specific approach to the treatment of a number of cardiac and pulmonary diseases is a clinical frontier. Neither the perfect beta1-adrenergic agonist nor the absolutely selective beta2-adrenergic antagonist exists today. Metoprolol, a selective beta1-antagonist, can cause substantial bronchospasm in asthma patients. This is because of the high relative density of beta-adrenoceptors in the lung and the beta1-selectivity of metoprolol is not absolute.

Terbutaline and albuterol cause selective (beta2-adrenergic mediated) airway relaxation when inhaled by nebulizer. However, tachycardia and cardiac arrhythmias may occur after oral ingestion of these drugs, partly from reflex cardiac stimulation resulting from beta2-adrenergic induced relaxation of vascular smooth muscle and partly from direct beta1-adrenergic activity of these drugs. Furthermore, as additional methyl groups are added to the amine end of the catecholamine molecule (providing greater beta2-adrenergic specific activity), the potency and intrinsic activity of the beta2-adrenergic agonists declines. One cannot be absolutely certain that specific beta2-adrenergic activity is desirable, as this could lead to augmented peripheral vascular dilation (a beta2-adrenergic effect) with augmented reflex-mediated beta1-adrenergic effects. This is precisely what one is trying to avoid by administering agonists which possess minimal direct beta1-adrenergic activity.

The point is that the concept of lock-and-key drug membrane receptor model is an oversimplification. Specificity is relative, and at present, "cardioselective" beta-adrenoceptor blockade cannot be achieved. A new generation of subtype-specific drugs may still lead to encounters with some old and familiar problems—those which we have already seen in this generation of cardiac and pulmonary patients.

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