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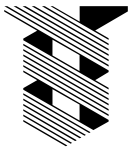

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ADRENERGIC RECEPTORS — EVOLVING CONCEPTS AND CLINICAL IMPLICATIONS

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THE endogenous catecholamines — norepinephrine and epinephrine — are involved in the regulation of virtually every organ system. Norepinephrine acts as a neurotransmitter at certain sites in the central nervous system and in the sympathetic nervous system at postganglionic neuroeffector junctions. Epinephrine is primarily a circulating hormone produced by the adrenal medulla and other chromaffin tissue. Because norepinephrine comes from chromaffin tissue and overflows from sympathetic-nerve synapses, plasma concentrations of norepinephrine exceed those of epinephrine. Hence, norepinephrine can also act as a circulating hormone.

Norepinephrine and epinephrine act through adrenergic receptors (also termed adrenoceptors). In this review, I will summarize and highlight recent advances in our understanding of these receptors (which have been reviewed extensively[1-6]) by considering four questions: How many kinds of adrenergic receptors exist? How do adrenergic receptors regulate target-cell function? How do target cells regulate adrenergic receptors? And finally, how do alterations in adrenergic receptors contribute to pathophysiology?

TYPES AND SUBTYPES OF ADRENERGIC RECEPTORS

Those of us who attended medical school in the 1960s recall the paradigmatic importance of the division of adrenergic responses and adrenergic receptors into two principal types, α and β (Table 1). This division was largely an extension of the seminal work of Ahlquist, who noted two patterns in the relative ability of adrenergic agonists to initiate physiologic responses.[7] The division was further substantiated with the identification and, in some cases, clinical use of type-selective antagonists (e.g., phenoxybenzamine and phentolamine for α receptors; dichloroisoproterenol and propranolol for β receptors). The discovery that certain agonists and antagonists could be used to distinguish β-adrenergic responses among tissues such as cardiac muscle and bronchial smooth muscle implied the existence of subtypes of β-adrenergic receptors (β_1 and β_2).[8] Later, the existence and differential tissue localization of α_1 and α_2 subtypes of α-adrenergic receptors were discovered and defined.[1,9] Because norepinephrine appeared to be somewhat more potent at α_1- than at α_2-adrenergic receptors and substantially more potent at β_1- than at β_2-adrenergic receptors, it was inferred that α_1 and β_1 receptors were located at postsynaptic sympathetic neuroeffector junctions, where they mediated physiologic responses on sympathetic-nerve activation. In contrast, α_2- and β_2-adrenergic receptors were thought to be more responsive to circulating catecholamines. Thus, they were thought to be found at sites outside neuroeffector junctions or to be "autoreceptors" — receptors located on sympathetic nerves that participate in an autofeedback loop regulating the synaptic release of norepinephrine.[9,10]

The development of radioligand-binding methods represented a major advance in the classification and study of adrenergic receptors.[11,12] These methods allowed receptors in tissue to be identified and quantitated, and the results suggested the existence of subtypes of α_1- and α_2-adrenergic receptors.[1,3] Data from radioligand binding, combined with studies of the second messengers formed when different types and subtypes of receptors were activated, suggested that there were at least six types and subtypes of adrenergic receptors (α_{1A}, α_{1B}, α_{2A}, α_{2B}, β_1, and β_2).

The most recent methods, involving molecular biology, have uncovered several additional adrenergic-receptor subtypes. The complementary DNA and gene for the β_2-adrenergic receptor were first isolated in 1986[13]; the isolation of genes for several other types and subtypes followed rapidly.[1]

Adrenergic receptors are members of a large superfamily of receptors linked to guanine-nucleotide–binding proteins (G proteins). All G-protein–coupled receptors (Fig. 1) share the following structural features: extracellular amino terminals with sites for *N*-linked glycosylation, seven α-helical domains that are each thought to span the plasma membrane, and intracellular carboxy terminals containing amino acid sequences that indicate probable sites of phosphorylation by one or more protein kinases. The superfamily of G-protein–coupled receptors, which has several hundred members, includes receptors not only for catecholamines and other small molecules (such as acetylcholine, dopamine, histamine, and prostaglandins) but also for peptides (such as vasopressin, oxytocin, and angiotensin), proteins (such as glucagon, follicle-stimulating hormone, luteinizing hormone, and thyrotropin), odorants, light,

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Table 1. Types and Subtypes of Adrenergic Receptors.

Receptor Type	Year Defined	Method of Identification
Adrenoceptor	Early 1900s	Tissue response
α, β	1948	Tissue response
β_1, β_2	Late 1960s	Tissue response Second-messenger analysis
α_1, α_2	Mid-to-late 1970s	Tissue response Second-messenger analysis Radioligand binding
α_{1A}, α_{1B}, α_{2A}, α_{2B}	Mid-to-late 1980s	Radioligand binding Second-messenger analysis Tissue response
α_{1A}, α_{1B}, α_{1D}, α_{2A}, α_{2B}, α_{2C}, β_1, β_2, β_3	Late 1980s to early 1990s	Molecular cloning

and taste molecules. Thus, adrenergic receptors probably evolved from a common ancestor along with the receptors that recognize other hormones and neurotransmitters or environmental stimuli.

The cloning of adrenergic receptors has revealed important structural information about types and subtypes, as well as clues about function. Three subtypes each of α_1-adrenergic (α_{1A}, α_{1B}, and α_{1D}), α_2-adrenergic (α_{2A}, α_{2B}, and α_{2C}), and β-adrenergic (β_1, β_2, and β_3) receptors have been definitively identified, and the existence of additional subtypes is being investigated.[1,14] The expanding list of subtypes of adrenergic receptors parallels findings in many other receptor systems and reflects the limitations of early systems of classification based on synthetic or naturally occurring agents that could stimulate (agonists) or block (antagonists) receptors.

The identification of new subtypes of receptors offers the promise of new therapeutic agents. The tissue distribution and functions mediated by the new subtypes may make it possible to develop subtype-specific drugs that are more effective and have fewer side effects than those currently available. For example, the α_1-adrenergic receptors on the prostate gland that promote smooth-muscle contraction are predominantly α_{1A}-adrenergic receptors.[15] Therapy directed at α_{1A}-adrenergic receptors may prove beneficial to men with benign prostatic hypertrophy and could avert the side effects (such as postural hypotension) associated with the α-adrenergic blocking drugs currently used to treat this condition, which do not distinguish between subtypes of α receptors.

β_3-Adrenergic receptors, which are found at unique sites such as in brown adipose tissue and the gallbladder, are also potential targets of innovative type-specific therapy.[16] Although the function of these receptors in humans has not been defined, they appear to have a role in promoting lipolysis and heat generation in fat.[16,17] Thus, β_3-adrenergic agonists may prove useful as antiobesity drugs.

In summary, at least nine subtypes of adrenergic receptors have now been identified. The precise function of all these receptors is not yet defined, in part because of a dearth of highly specific agonists and antagonists. An alternative way to examine receptor function is to use molecular genetic techniques to overexpress or to "knock out" the expression of particular subtypes in laboratory animals.[18-20]

Adrenergic Receptors and Regulation of Target-Cell Function

The G proteins to which adrenergic receptors link are heterotrimeric proteins with α, β, and γ subunits. The discovery and role of G proteins, for which the Nobel Prize in Physiology or Medicine was awarded in 1994 to Drs. Martin Rodbell and Alfred Gilman, involved, in part, the observation by investigators in Dr. Rodbell's laboratory that the activation of the enzyme adenylyl cyclase (previously termed adenyl or adenylate cyclase) by hormones required guanosine triphosphate as a cofactor. Dr. Gilman's laboratory used protein purification and the reconstitution of adenylyl cyclase activity in cells deficient in cyclase activity to prove the existence of a protein, G_s, that stimulated adenylyl cyclase activity and that also regulated the binding of agonists to β-adrenergic receptors.

The α, β, and γ subunits of G proteins have subsequently been isolated and cloned. Each subunit is part of a family consisting of multiple members[21]: approximately 20 α subunits (which have been divided into four subfamilies — α_s, α_i, α_q, and α_{12}), at least 5 β subunits (β_{1-5}), and at least 6 γ subunits (γ_{1-6}). Although several hundred different subunit combinations (heterotrimers) are theoretically possible, the repertoire of G proteins used by a particular receptor system is limited.[22] Each type of G protein can be used for signaling by more than one type of receptor. For example, many different types of receptors that stimulate adenylyl cyclase activity can activate G_s.

Each type of adrenergic receptor (Table 2) preferentially couples to a different major subfamily of G_α proteins: β-adrenergic receptors to $G_{\alpha s}$, α_1-adrenergic receptors to $G_{\alpha q}$, and α_2-adrenergic receptors to $G_{\alpha i}$. In turn, each of these G_α proteins can link to numerous effector

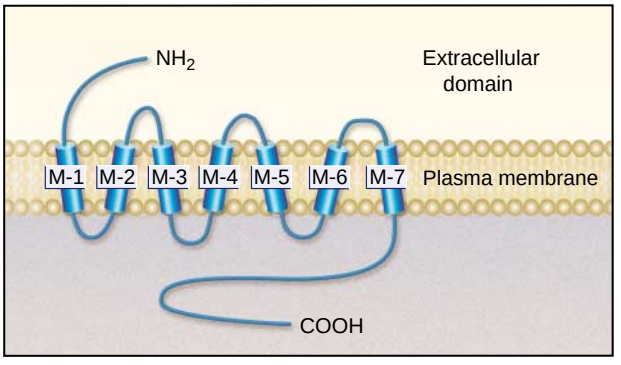

Figure 1. Proposed Arrangement of an Adrenergic Receptor Spanning the Plasma Membrane.

This arrangement is proposed for adrenergic receptors and other types of G-protein–linked receptors that span plasma membranes. M-1 through M-7 denote the seven α-helical membrane-spanning regions that create three intracellular and three extracellular loop domains. See text for details.

molecules, although most target cells have preferred linkages. Thus, β-adrenergic receptors are preferentially coupled by G_s to the activation of adenylyl cyclase (and calcium-ion channels in some tissues), α_1-adrenergic receptors by G_q to the activation of phospholipases, especially phospholipase C_β, and α_2-adrenergic receptors by G_i to the inhibition of adenylyl cyclase and in some tissues to the regulation of potassium and calcium channels. Each of these linkages leads to changes in intracellular concentrations of second messengers such as cyclic AMP, calcium ion, diacylglycerol, and inositol 1,4,5-triphosphate. These second messengers modulate cellular events, regulating the phosphorylated states of cell proteins by changing the activity of a variety of protein kinases. For example, cyclic AMP activates protein kinase A, diacylglycerol and calcium ions activate protein kinase C, and calcium ions and calmodulin activate calmodulin-dependent kinases.

Information provided by the cloning of adrenergic receptors and G proteins has provided new insights into the way agonists promote the formation of second messengers (Fig. 2). Catecholamines, which are hydrophilic, do not bind to the highly charged extracellular domains of the receptors as might be expected but bind instead in the more hydrophobic membrane-spanning domains.[5,6,23] Occupancy by an agonist appears to produce conformational changes within the receptor, causing certain regions, in particular the third intracellular loop, to interact with G protein. Under basal conditions, the G proteins are inactive, and the guanine-nucleotide–binding site on the G_α subunit is occupied by the inactive nucleotide guanosine diphosphate. When agonist binds to the receptor, cellular guanosine triphosphate replaces guanosine diphosphate on the G_α subunit. This, in turn, promotes a conformational change in the G_α subunit, facilitating its dissociation from the β and γ subunits, which are tightly bound and appear to function as a dimer. Both the G_α subunit and the $G_{\beta\gamma}$ subunit dimer can regulate the activity of effector molecules and the formation of second messengers.[24] The G protein is activated until guanosine triphosphate is hydrolyzed to form guanosine diphosphate, which facilitates the reassociation of the subunits. Thus, G proteins are in a sense molecular light switches that cycle between "on" (bound to guanosine triphosphate) and "off" (bound to guanosine diphosphate) when agonist binds to receptor.

Key questions remain: Are there sites of amplification in the signal-transduction cascade? And which steps are rate-limiting in this multicomponent scheme? To address these questions, my colleagues and I have used radioligand-binding assays for β-adrenergic receptors and for adenylyl cyclase (for the latter we used [^{3}H]forskolin, a diterpene that directly activates adenylyl cyclase) in studies with cultured cells and freshly isolated cardiac myocytes.[25,26] We found that activation (subunit dissociation) of G_s by β-adrenergic receptors is a principal mechanism of amplification of β-adrenergic–receptor signaling and that the number of adenylyl cyclase molecules limits the response to activated G_s.[25-27] Studies of purified and reconstituted receptors and G_s show that each β-adrenergic receptor can activate many G_s molecules, a finding consistent with data on the retina, where activation of the receptor rhodopsin by a photon of light can activate many molecules of the retinal G protein transducin.[28,29] In the β-adrenergic–receptor system, the number of G-protein molecules greatly exceeds the number of receptors and effector molecules.[25,26]

Thus, adrenergic receptors exert their effect by activating G proteins, and this activation is a mechanism for amplification of receptor signaling, whereas the G-protein–mediated activation of effector molecules is apparently not subject to amplification. The number of receptors and perhaps the number of effector molecules would appear to limit the response.

Table 2. Preferred Linkages of Adrenergic Receptors to G-Protein Families and Effectors.

Receptor Type	G Protein	Effectors
α_1	G_q	Phospholipase C_β ? Other phospholipases
α_2	G_i	Adenylyl cyclase Calcium channels Potassium channels
β	G_s	Adenylyl cyclase Calcium channels

Target-Cell Regulation of Adrenergic Receptors

Many factors regulate adrenergic receptors. Receptor biosynthesis, processing, and insertion in the plasma membrane are not well understood, but these processes are imagined to be similar to those elucidated for other plasma-membrane receptors.[30] Glucocorticoids, thyroid hormone, and other classes of "gene active" hormones regulate the expression of several types of adrenergic receptors through transcriptional and in some cases post-transcriptional events.[31]

The regulation of adrenergic receptors by receptor-specific agonists and antagonists has been actively studied for many years and is important clinically. Examples include β-agonist–promoted desensitization in asthma, α-agonist tachyphylaxis in patients receiving sympathomimetic nasal decongestants, and the β-blocker withdrawal syndrome, in which the abrupt discontinuation of therapy with certain β-adrenergic antagonists apparently causes cardiac and systemic adrenergic hyperactivity. Since treatment of normal subjects with β-adrenergic antagonists can increase the number of β-adrenergic receptors on peripheral-blood leukocytes, the number of receptors expressed on the cell surface is probably regulated by the ambient catecholamine concentration.[32]

The regulation of adrenergic receptors by agonists (desensitization) appears to be a multistep process that involves several discrete events, including the rapid phosphorylation of receptors; the sequestration of the receptor in a cellular compartment not readily accessible from outside the cell; the uncoupling of the receptor, so

that ligand binding still occurs but second-messenger formation is decreased; and the internalization of the receptor to intracellular sites. Persistent exposure to agonist can also result in an actual loss of receptors, presumably through degradation, but this type of receptor down-regulation occurs more slowly. Susceptibility to these agonist-promoted events differs among the various types and subtypes of adrenergic receptors.

Studies of the mechanisms of receptor regulation by β-adrenergic–receptor agonists and antagonists have focused on enzymes involved in phosphorylating receptors, such as the well-known multifunctional kinases protein kinase A and protein kinase C.[33] In addition, the members of a novel family of kinases — originally termed β-adrenergic–receptor kinases and recently renamed G-protein–receptor kinases — have been implicated because of their propensity to phosphorylate numerous types of agonist-occupied receptors that link to G proteins.[34] G-protein–receptor kinases have a unique structure and several interesting features. In resting cells they are cytosolic enzymes, but some can bind to the plasma membrane on activation of the receptor, in particular to $\beta\gamma$ subunits derived from activated (dissociated) G proteins. At least six types of G-protein–receptor kinases with unique tissue distribution and localization have been identified. Finally, such kinases work in concert with other proteins called arrestins (β-arrestins), which together with receptors phosphorylated by G-protein–receptor kinases blunt the interaction of the receptors with G proteins, thereby promoting uncoupling from these proteins.

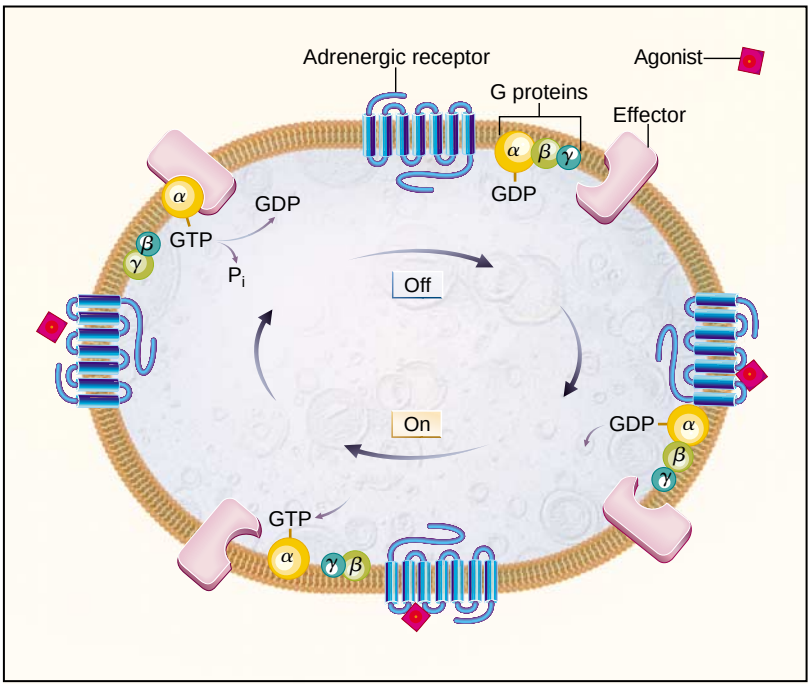

Figure 2. G-Protein–Mediated Signal Transduction Promoted by Adrenergic Receptors.

An adrenergic receptor is shown as it binds an agonist and then associates with a G protein consisting of three heterogeneous subunits (α, β, and γ). The agonist promotes the exchange of guanine triphosphate (GTP) for guanine diphosphate (GDP) (the "on" reaction) in the presence of magnesium, thereby promoting the dissociation of the receptor from the G protein as well as the dissociation of the G_α subunit from the $G_{\beta\gamma}$ subunits and the agonist from the receptor. The dissociated G_α subunit and, in some cases, $G_{\beta\gamma}$ subunits activate effector molecules. Intrinsic GTPase activity of G_α hydrolyzes GTP to GDP (the "off" reaction), thereby releasing inorganic phosphate (P_i) and facilitating the reassociation of G_α with $G_{\beta\gamma}$ to form $G_{\alpha\beta\gamma}$.

Recently, multiple forms of G-protein–receptor kinases have been identified in human peripheral-blood mononuclear cells; treatment with lectin prominently stimulates the activity of G-protein–receptor kinase 2 and increases production of the messenger RNA encoding it.[35] In addition, the activity of G-protein–receptor kinase 2 is increased severalfold in myocardium from patients with cardiac failure and dilated cardiomyopathy who have cardiac β-adrenergic desensitization,[36-39] in part as a consequence of down-regulation of β_1-adrenergic receptors (resulting from a decrease in β_1-adrenergic–receptor messenger RNA[36,37]) and in part as a consequence of the uncoupling of β_2-adrenergic receptors.[38] My colleagues and I have reproduced such findings in a porcine model of heart failure (unpublished data). In contrast, the treatment of normal pigs with a β-adrenergic antagonist can decrease the level of G-protein–receptor kinases and their activity in the heart.[40] Thus, changes in the activity of these kinases may accompany both congestive heart failure and treatment with a β-adrenergic antagonist.

Clinical Settings in Which Alterations in Adrenergic Receptors Contribute to Pathophysiology

Given the widespread expression of adrenergic receptors and their role in regulating a wide variety of events, it is not surprising that alterations in these receptors have been suspected in many clinical settings (Table 3). I will discuss briefly two recently identified genetic alterations in adrenergic receptors that may have clinical importance.

There is a high degree of polymorphism at certain loci in β_2-adrenergic receptors.[41] Of particular interest is a polymorphism that converts arginine to glycine at codon 16 and is substantially more prevalent in patients who have a history of nocturnal asthma.[42] In experimental systems, receptors with this polymorphism are more sensitive to down-regulation in response to adrenergic agonists.[43] It is intriguing to speculate that this phenotype in vivo predisposes patients to the loss of β-adrenergic function and to nocturnal asthma. Other

Table 3. Clinical Conditions Associated with Possible Alterations in Adrenergic Receptors.

Clinical Condition	Type of Adrenergic Receptor	Alteration
Adrenergic-agonist treatment, pheochromocytoma	α, β	Desensitization and down-regulation of receptors
Antagonist withdrawal syndrome	β, ?α	Supersensitization and up-regulation of receptors
Myocardial ischemia	β	Up-regulation and uncoupling of receptors
	α_1	Enhanced receptor coupling
Hypertension	α	Up-regulation and altered coupling of receptors
	β	Down-regulation of receptors
Congestive heart failure	β_1	Down-regulation of receptors
	β_2	Receptor uncoupling, possibly due to increase in G-protein–receptor kinases
Asthma	β_2	Polymorphism predisposing to desensitization
Morbid obesity	β_3	Polymorphism (? with decreased activity)

recent data suggest that the substitution of glutamic acid for glutamine at codon 27, which yields a receptor that has decreased down-regulation, is associated with a decrease in bronchoconstriction.[43,44]

A second example involves the β_3-adrenergic receptor. Several groups of investigators have found a polymorphism at codon 64 of the gene for this receptor that converts tryptophan to arginine.[45-47] This variant appears to be more prominent in certain groups, including Pima Indians and morbidly obese French patients, and is associated, especially when homozygously expressed, with striking obesity. Pima Indians with the mutation have a significantly earlier onset of non-insulin-dependent diabetes mellitus. Thus, this polymorphism may lead to decreased function of β_3-adrenergic receptors, perhaps decreasing lipolysis and resulting in obesity and altered energy metabolism.

Conclusions

Almost 50 years after Ahlquist first uncovered evidence of the heterogeneity of adrenergic receptors, the number of receptor subtypes is still unclear, although nine subtypes are well documented (three subtypes each of α_1-, α_2-, and β-adrenergic receptors). Each type preferentially links to members of a subfamily of G protein: α_1 to G_q, α_2 to G_i, and β to G_s, and in turn to effector molecules to which those G proteins link (G_q to phospholipase C_β, G_i to adenylyl cyclase [inhibition], and G_s to adenylyl cyclase [stimulation]). The number of activated G proteins exceeds the number of corresponding receptors and effectors; thus, the activation of G proteins amplifies signaling by adrenergic receptors. Receptor desensitization, mediated in part by G-protein–receptor kinases and β-arrestins, is involved in decreasing the ability of agonists to activate adrenergic receptors. Alterations in adrenergic receptors have a role in many clinical settings. Recent data suggest a role for the increased expression of G-protein–receptor kinases in the hearts of patients with congestive heart failure and for genetic polymorphisms in β_2-adrenergic receptors in patients with nocturnal asthma and in β_3-adrenergic receptors in those with obesity. Studies using molecular and biochemical techniques are likely to provide additional new and unexpected insights into the role of adrenergic-receptor subtypes in both normal physiologic function and disease.

Discussion

Dr. Jeffrey Flier: Several years ago there were reports of β-adrenergic–receptor autoantibodies in patients with asthma and cardiomyopathies. Have these reports been confirmed?

Dr. Insel: The β-adrenergic–receptor autoantibodies that were described several years ago in patients with asthma turned out to be almost equally prevalent in normal subjects. These antibodies were not characterized by methods, such as immunoblotting, that are now available. Perhaps the results will be different when other techniques are used. The data on cardiomyopathy are a little more mysterious: there continue to be some reports of patients with autoantibodies and patients whose serum is more reactive than serum from normal subjects. Determining to what extent this feature has pathogenetic importance in patients with cardiomyopathies of different causes will require larger studies or confirmation by more than one group of investigators.

Dr. Jeffrey Flier: How variable is the desensitization of adrenergic receptors from tissue to tissue? Are there any clinical implications of this variability?

Dr. Insel: The extent of desensitization varies substantially among classes of adrenergic receptors. For example, β_3-adrenergic receptors appear to be much less susceptible than β_1- and β_2-adrenergic receptors, probably because of structural differences in the carboxy-terminal tail of the receptor, whereby the β_3 receptors lack sites for phosphorylation. In addition, studies in vivo and especially in vitro suggest that the susceptibility of receptors to desensitization varies among different tissues. For example, there are prominent in vivo subtype-selective and tissue-selective differences in the down-regulation of both α- and β-adrenergic receptors in rats with norepinephrine-producing pheochromocytomas. The clinical implications of these differences are not yet understood, but they could, for example, relate to different extents of desensitization in tissues in patients receiving β-agonist bronchodilator drugs.

Dr. Flier: Do adrenergic antagonists in clinical use vary in their ability to up-regulate receptors, and does this affect susceptibility to the β-blocker withdrawal syndrome?

Dr. Insel: Patients treated with β-adrenergic antagonists that have intrinsic sympathomimetic activity — that is, partial agonist activity — have less receptor up-regulation than do those treated with antagonists that lack this activity. As one would predict, the β-blocker withdrawal syndrome is less likely to develop in patients given an antagonist with intrinsic sympathomimetic activity. Parenthetically, it is thought that this

syndrome results from the more rapid clearance of the β-blocker after discontinuation of the drug relative to the reversal of the blocker-induced up-regulation of the receptor. Thus, tapering more rapidly cleared drugs or using more slowly cleared β-blockers could reduce the likelihood of this syndrome.

A PHYSICIAN: Is it likely that genetic therapy will be developed that will allow adrenergic receptors or receptor-modifying proteins to be administered, and would such treatments be clinically useful?

DR. INSEL: This is an intriguing, but I would say futuristic, question. Several laboratories are currently developing transgenic animals with altered levels of receptors or G-protein–receptor kinases. One could imagine the development of appropriate targeting vectors to allow the tissue-specific expression of adrenergic receptors or receptor-modifying proteins in humans. The therapeutic value of such approaches is speculative because it is not clear whether providing more receptors or modifying receptor regulation would be beneficial.

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