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New advances in receptor pharmacology

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Objective: *The goal of this review is to give the clinician a broad perspective on recent updates in cardiovascular pharmacology. Specifically, this review discusses new drugs, old drugs used in new ways, and a glimpse into the future of cardiovascular pharmacogenetics.*

1. INTRODUCTION AND REVIEW OF CURRENT CARDIOVASCULAR MEDICATIONS

1.A. Cardiovascular system

The cardiovascular system consists of a complex array of pipes (vessels), flexible tubing (smooth muscle capable of constriction and relaxation), flow restrictors (venous and cardiac valves), and mechanical pump (myocardium). Due to its many functions, chemical modulation of the cardiovascular system by neurotransmitters, hormones, and drugs is distributed over vast physical locations and spans numerous receptor systems. Ultimately, distinct receptors bind drugs (both agonists and antagonists) to mediate clinical responses. In order to rationally administer cardiovascular drugs, it is imperative to understand interactions between the sympathetic nervous system, endogenous neurotransmitters, receptors, and drugs, as well as the resultant impact on modulation(s) of cardiovascular physiology.

1.B. Receptors

Distinct individual receptor sites bind drugs, both activating agonists and inhibiting antagonists. Receptor sites can take the form of cell membrane receptors (as is the case for most water soluble drugs and hormones), ion channels, ligand-gated receptor complexes, enzyme systems, and other cytoplasmic and nuclear proteins. Since most cardiovascular drugs used in anesthesia still rely on adrenergic receptor (AR)-mediated pathways, these receptors will be used as a model system for this review. ARs are membrane bound receptors which bind catecholamines (endogenous hormones epinephrine and norepinephrine, and other synthetic drugs). Binding of agonist drugs on the extracellular surface of ARs

stabilizes specific receptor conformations ranging from inactive to active states; the active conformation can then interact with second messenger (effector) systems directly or via intermediary guanine nucleotide (G) proteins. Nine AR subtypes have been described using molecular cloning techniques (α_{1a} , α_{1b} , α_{1d} , α_{2a} , α_{2b} , α_{2c} , β_1 , β_2 , β_3), although thus far cardiovascular pharmacology tends to be based on only four "classic" AR subtypes (α_1 , α_2 , β_1 , β_2). Continuous activation of adrenergic receptors by stress, long term catecholamine therapy, or selected disease states results in a dampening of AR response; this process is called desensitization. Desensitization is important in congestive heart failure (CHF), where β_1 AR number and function decreases by 75%, with relative sparing of β_2 AR number and function.

1.C. Standard adrenergic inotropic drugs

Most inotropic agents (drugs which mediate increases in myocardial contractility) available for clinical use today are catecholamines, either endogenous (epinephrine, norepinephrine, dopamine) or synthetic catecholamine derivatives (isoproterenol, dobutamine, dopexamine, arbutamine). Catecholamine structure is distinctive and includes a catechol ring moiety, catechol hydroxyl groups, and side chains of varying length and composition. Naturally occurring catecholamines such as epinephrine, norepinephrine, and dopamine, tend to bind all adrenergic receptor subtypes, but have relative selectivity depending on the dose used. At low doses, dopamine binds to dopamine receptors, while epinephrine and norepinephrine bind to predominantly β ARs. At moderate doses, both dopamine and epinephrine bind predominantly to β ARs, while norepinephrine already binds α ARs; this dose range mediates increases in inotropy via stimulation of myocardial β ARs. At high doses, all three endogenous catecholamines bind to α ARs and vasoconstrictive effects predominate. Epinephrine is commonly used for cardiac resuscitation, but new data suggests that epinephrine may significantly increase the severity of post-resuscitation myocardial dysfunction. Hence an α_1 AR agonist, or epineph-

rine combined with a β_1 AR antagonist, may reduce post-resuscitation myocardial impairment and prolong survival.

Subtle changes in catecholamine side-chain groups can alter AR subtype selectivity, hence synthetic catecholamines tend to be more subtype selective. AR subtype selectivity for synthetic catecholamines includes the following: isoproterenol (β_1 AR, β_2 AR), dobutamine (β_1 AR, β_2 AR), dopexamine (β_2 AR), and arbutamine (β_1 AR, β_2 AR, α_1 AR). The physiologic effects of synthetic catecholamines can be predicted based on their adrenergic receptor selectivity. For example, drugs binding predominantly to β_2 ARs will produce positive inotropy, chronotropy, vasodilation, and bronchodilation. Agents which bind to only β_1 ARs produce inotropy and chronotropy. Sometimes synthetic catecholamines are developed for a specific clinical purpose. Arbutamine (a β_1 AR selective agonist) was developed primarily for use in stress echocardiography because of its tachycardia properties without vasodilation (especially since it results in fewer arrhythmias than isoproterenol).

1.D. Sympathomimetics

Sympathomimetics have many of the same properties as catecholamines, but do not contain the catechol ring moiety in their structure. Phenylisopropylamines such as ephedrine and denopamine are the only sympathomimetics which have significant β AR properties. Ephedrine has both direct (receptor binding) and indirect (release of norepinephrine at the nerve terminal) actions; stimulation of both α AR and β ARs results, however β AR stimulation predominates. Hence ephedrine is frequently used in obstetrical settings to raise maternal blood pressure without exaggerated vasoconstrictor effects. Denopamine has selective β_1 AR agonist properties combined with α_1 AR antagonists properties. Thus denopamine provides positive inotropic effects while simultaneously reducing afterload.

1.E. Sympatholytics

Dexmedetomidine is a non-subtype selective α_2 AR agonist. Technically this drug is a sympathomimetic due to its agonist properties at α_2 ARs, while clinically it acts as a sympatholytic agent. A brief review of α_2 AR pharmacology clarifies this paradox. α_2 ARs reside both presynaptically (α_{2A} sympathetic nerve terminals and brain) and post-synaptically (α_{2B} vessels, α_{2C} brain). An intravenous bolus of dexmedetomidine results in acutely increased blood pressure (BP) via agonist activity at postsynaptic α_{2B} ARs resulting in vasoconstriction. However, over time, presynaptic α_{2A} ARs are stimulated and predominate in terms of clinical effects. Stimulation of presynaptic α_2 ARs results in inhibition of the release of further norepinephrine from the nerve terminal.

Therefore, over time, very little endogenous epinephrine is available to act and the clinical picture is sympatholysis; in terms of the cardiovascular system, BP decreases. In addition to effects on BP, dexmedetomidine has potentially beneficial anxiolytic and anesthetic sparing properties. Use of dexmedetomidine during heart surgery, albeit in lower doses than originally proposed, has shown effect in limiting the use of other anesthetic drugs as well as helping in transitioning patients through the intensive care unit.

1.F. Phosphodiesterase inhibitors

In order to understand inotropic properties of phosphodiesterase inhibitors, it is important to review β AR signal transduction. Stimulation of β ARs by catecholamines results in activation of the G protein subtype G_s , which in turn activates the enzyme adenylyl cyclase, ultimately resulting in the production of cAMP in the cell. Phosphodiesterase inhibitors (such as amrinone and milrinone) act indirectly through the β AR system by inhibiting phosphodiesterase enzymes responsible for the breakdown of cAMP generated with β AR stimulation; the net result is enhanced cAMP levels in the cell. Since tonic stimulation of β ARs occurs from nanomolar concentrations of circulating catecholamines, enough cAMP is being generated in the myocyte at baseline for phosphodiesterase inhibitors to have inotropic properties on their own. However, when combined with other β AR agonist drugs, phosphodiesterase inhibitors provide additive (and sometimes synergistic) effects. Several classes of phosphodiesterase inhibitors have been described, with some subtypes demonstrating upregulation in the presence of β AR agonists. It is important to note that phosphodiesterase inhibitors have vasodilating properties, and often this effect is seen 15 minutes prior to the onset of clinically significant inotropic effects; hence these agents are frequently referred to as "inodilators."

1.G. Calcium chloride

Calcium is important in myocardial excitation-contraction coupling, hence intravenous calcium can be of short term benefit as an inotropic agent in the setting of cardiopulmonary bypass. However, caution should be exercised when using calcium since ischemic myocardial cells are "leaky" to calcium and calcium overload can cause myocardial cell death. This is one of the reasons the use of calcium in cardiac resuscitation has been severely curtailed.

2. New inotropic drugs

Traditionally, inotropic drugs have exploited the β AR signal transduction cascade. However, AR pathways are only one

of several potential targets for drug intervention to increase myocardial inotropy. Figures 1 and 2 schematize a wide array of potential inotropic targets. These include several membrane receptors (histamine₂ [H₂], vasoactive intestinal peptide [VIP], 5HT₄, PGE₁, α_1 AR, endothelin-1 [ET₁, especially during acidosis]); ion channel modulators (calcium channel activators BayK8644, BayY; sodium channel activator BDF9148); myofilament calcium sensitizers (levosimendan, pimobendan, sulmazole); nuclear receptors (T₃); phosphatase inhibitors (cantharidin), and agents which enhance calcium release from the sarcoplasmic reticulum (carnosine). Myofilament calcium sensitizers (“calcium sensitizers”) are an exciting class of inotropic agents that have been tested clinically. Calcium sensitizers enhance calcium binding to the calcium-specific regulatory site on cardiac troponin C; these compounds also stabilize this conformation. In addition, calcium sensitizers increase sympathetic tone, and most calcium sensitizers also have phosphodiesterase inhibiting properties. Three calcium sensitizer drugs are currently available for clinical trials—levosimendan (the pharmacologically active [-]-enantiomer of simendan), pimobendan, and sulma-

zole. An additional compound, which has potential for use as an inotropic agent in the future, is carnosine. Carnosine is an endogenous dipeptide present in mM concentrations in myocytes. Carnosine activates opening of the ryanodine receptor calcium release channel in the sarcoplasmic reticulum, resulting in increased intracellular calcium. In rat hearts, carnosine enhances both systolic function and diastolic relaxation; hence this compound may one day become an important inotropic agent.

Another possible inotropic agent recently investigated is triiodothyronine (T₃). While T₃ has been approved for acute intravenous therapy for myxedematous coma (severe life-threatening hypothyroidism), its acute inotropic properties are only now being discovered and examined in humans. Chronically, T₃ activates nuclear proteins which increase β AR number over 12 to 24 hours. In addition, acute inotropic effects occur in animal models (within minutes of administration), thought to be related to increased Na-K-AT-Pase activity in the cell cytoplasm as well as accompanying sensitization of adrenergic receptors to catecholamines. Animal experiments demonstrate acute inotropic effects of intravenous T₃, particularly in the setting of myocardial ischemia. In spite of these potentially interesting results in animals, acute inotropic effects of intravenous T₃ in humans has remained controversial until recently. However, two large, double blind, placebo controlled clinical trials failed to find significant inotropic effects of T₃ in the setting of human heart (coronary artery bypass) surgery. Although these studies examined patients at high risk for requiring postoperative inotropic support, patients with acute debilitating ischemia (i.e. patients receiving preoperative intra-aortic counterpulsation) were specifically excluded. Hence while T₃ demonstrates no dramatic inotropic effects in most cardiac surgery patients, it is possible that specific subpopulations might benefit.

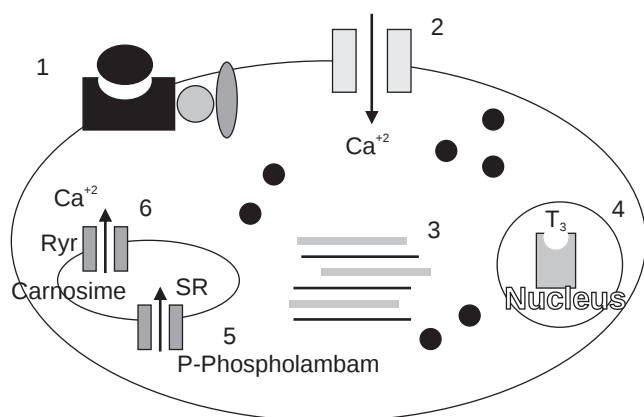


Figure 1. Inotropic drug targets.

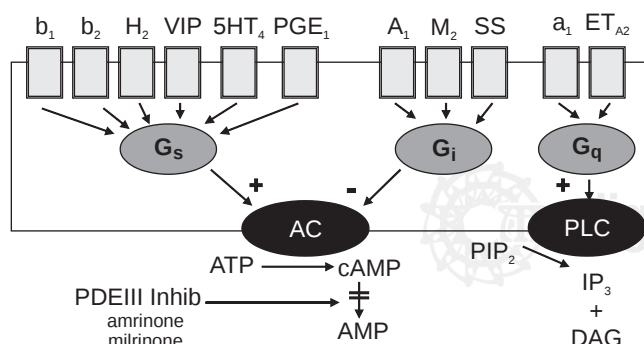


Figure 2. Myocardial membrane receptors.

3. “Old” Cardiovascular drugs used in new ways (the β AR antagonist story)

As described above in section 1.B., CHF is an example of a disease where β ARs, particularly β_1 ARs, become downregulated with disease. As cardiac output progressively decreases with worsening CHF, the body compensates by increasing sympathetic nerve traffic. This results in excessive and continuous agonist exposure, a situation which may be detrimental to the myocardium. Transgenic murine models overexpressing β_1 ARs in the presence of agonist, or overexpressing Gs, result in myocardial fibrosis. In order to protect the myocardium, receptor stimulation initiates phosphorylation events which ultimately dampen receptor responsiveness, a process called desensitization. If agonist stimulation continues for more than several hours, receptors are

internalized and destroyed, a process called downregulation. In human myocardium, CHF results in relative β_1 AR selective desensitization and downregulation (75% β_1 AR downregulated *versus* 25% for β_2 ARs). Interestingly, going back to murine models, fibrosis does not occur when β_2 ARs are overexpressed, suggesting distinct subtype specific regulatory pathways may be present (the coupling of β_2 ARs to both Gs and Gi is thought to be one of its distinctive properties that may be protective). In normal aging sympathetic stimulation also increases, and a similar pattern is discerned in aging myocardium with relatively β_1 AR-selective downregulation. Thus in the future, elderly patients and/or those with CHF may benefit acutely from targeting the β_2 AR with more selective agonists.

While β AR desensitization and downregulation may be protective, it is not helpful in terms of therapies designed to increase cardiac output during CHF since the heart is now less responsive to agonist stimulation. One of the most major advances in the treatment of CHF over the last decade has been the introduction of low dose β AR antagonist therapy. While initially counterintuitive, low concentrations of β AR antagonists are thought to break the cycle of agonist exposure. Indeed, β AR antagonist therapy has been shown to improve New York Heart Association CHF class and increase survival. From a practical perspective, in order to be successful, initiation of β AR antagonist therapy should be done in a carefully controlled medical setting (where worsening heart failure could be treated acutely) under the guidance of a cardiovascular expert (often a cardiologist). Once the patient is shown to tolerate β AR antagonists in very low doses, the dose is gradually increased as tolerated. This new use for an old drug has become standard of care in cardiology.

Can this therapeutic approach be translated into the operating room? Certainly administration of β AR antagonists in the perioperative non-cardiac surgery setting has been shown to improve patient outcome in the immediate and distant future after surgery (decreased myocardial infarctions, survival). Some of this benefit may be due to simple prevention of heart rate and inotropy increases in the setting of acute pain and catecholamine surges during surgery, especially in patients with occult coronary artery disease. However, the effect may be less direct since catecholamines have been shown to initiate many proinflammatory pathways in the myocardium and other tissues. By blocking even some of these effects, there may be benefit. The true mechanism remains to be elucidated in the non-cardiac surgery setting. In the setting of heart surgery, however, further information is available. In this setting, high levels of catecholamines, particularly during cardiopulmonary bypass (CPB), have been shown to result in acute myocardial β AR desensitization (both β_1 and β_2 ARs). In a dog model, intravenous treatment with non-subtype selective β AR antagonist esmolol before and

during CPB completely prevents acute myocardial β AR desensitization. However, in humans the story is somewhat more complicated. Metoprolol, a relatively β_1 AR selective antagonist, appears to improve the incidence of postoperative atrial fibrillation, but does not prevent acute desensitization. Esmolol has been suggested to have possible benefits when given intravenously and/or intracoronary, but the doses required to reach even a trend toward prevention of acute myocardial desensitization are very close to those where toxicity exists (bradycardia and/or depressed inotropy). Hence these drugs cannot be recommended at this time for use in preventing acute myocardial desensitization in humans.

The existence of acute myocardial β AR desensitization is clear, having been reproduced in several human and animal studies from multiple laboratories and research groups over the last 10 years. Furthermore blockade of sympathetic agonist stimulation (achieved via total spinal anesthesia in humans) has been shown to decrease catecholamine spill-over to the circulation, prevent acute myocardial β AR desensitization in heart surgery patients requiring CPB > 60 minutes, and enhances postoperative myocardial function. What then is the reason for the lack of effects of β AR antagonists during heart surgery in humans? One of the main reasons human studies designed to test whether β AR antagonists are beneficial during cardiac surgery may be inconclusive is that wide variation in baseline and stimulated adenylyl cyclase activity occurs in human myocardium; this is not seen as much in a dog model. Genetic variants of β ARs present in human myocardium have been shown to have altered signaling capabilities, leading to predisposition to various cardiovascular diseases (see discussion below). Therefore in the future it may be more relevant to use genetics to determine who should receive β ARs, and/or stratify populations in clinical trials based on β AR genotypes in order to increase the power to detect differences.

4. Genetic variability and cardiovascular disease

Some genetic variability in humans can be considered "background," leading to distinctive personal traits, but having no biologic consequence. Other genetic variants, however, are important clinically since they may be linked to patient outcome. Indeed, β_2 AR genetic polymorphisms have been shown to be clinically relevant in diseases such as hypertension, asthma, and congestive heart failure (Figure 3). In the β_2 AR gene, genetic alterations in the upstream leader sequence (an introductory regulatory gene sequence occurring immediately upstream from where the protein coding region begins) result in enhanced β_2 AR expression. Resultant increased airway β_2 ARs have been shown to be protective against methylcholine-induced bronchoconstriction. Another β_2 AR genetic variant (Arg16) enhances down-

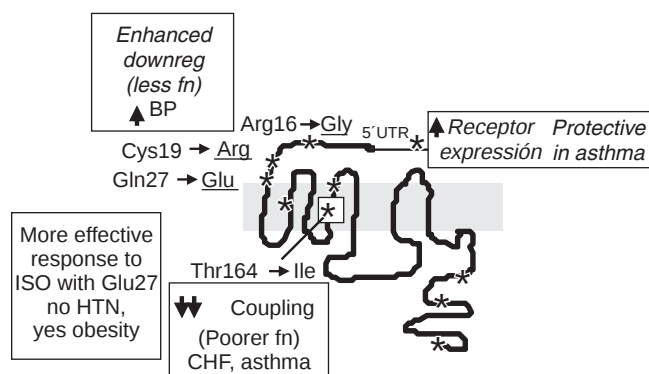


Figure 3. Genetic regulation of receptor function.

regulation, or dampening of receptor function. Since β_2 ARs mediate vasodilation, it is not surprising that this dampened variant results in increased blood pressure. In fact this variant is associated with hypertension. It is important to note at this point that the 16Gly, 19Arg, and 27Glu variants travel together (Figure 3), as do the more common Arg16, Cys19, and Gln27; in other words they define a haplotype. This means that if an individual has the 16Gly

variant, he/she will most likely also have the other 2 variants since this “chunk” of DNA is inherited together in most individuals. Finally, a very rare, but clinically important β_2 AR variant is the Thr164Ile; this variant appears to have no clinical cardiac effects until patients experience congestive heart failure (CHF), often later in life. Once CHF appears, however, patients with 164Ile have a more rapid downhill course clinically. If such an individual is considered for cardiac transplantation, it may be prudent to them toward the top of the list.

Cardiovascular pharmacology continues to evolve in exciting and new ways. Often, as insights are gained in cardiovascular physiology, not only can new drugs be developed, but old drugs can be used in new ways. However, the future of cardiovascular medicine is genetics. Whether utilizing genetic variability to predict response to drugs, predict perioperative outcome, target therapeutic strategies, and/or to better select individuals likely to respond positively to an intervention, the genetic era is here. With anesthesiologist's understanding of perioperative medicine, our profession is in a unique position to translate genetic discoveries into novel uses in the operating room of tomorrow.

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