Pharmacological modulation of cardiac function and blood vessel calibre

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Abstract

Sympathomimetics such as noradrenaline, adrenaline and dopamine all have a positive inotropic effect and may be useful in treating different aspects of cardiovascular collapse. Digoxin, which inhibits the cardiac Na^+/K^+ ATPase pump and the phosphodiesterase III inhibitors milrinone and amironone, which both increase in cAMP may also be useful for treatment of angina and heart failure respectively. The cardiac effects of β-blockers, L-type Ca^{2+} channel antagonists, K^+ channel openers, I(f) inhibitors and nitrovasodilators and their role in angina are described in this article. The list of pharmacological control mechanisms that regulate the calibre of blood vessels is ever-expanding and, for ease of understanding, they have been divided into neural, humoral and local mechanisms capable of inducing either vasodilation or vasoconstriction. Moment-to-moment sympathetic nerves and α_1 adrenoceptors maintain vascular tone but, locally, L-type Ca^{2+} channels (LTCC) also have an important function. LTCC antagonists inhibit influx at three sites on the α-subunit of the channel (dihydropyridine, phenylalkylamines and benzothiazepines) to alleviate hypertension. Inhibiting circulating hormones or the receptor targets for hormones, such as angiotensin-II or vasopressin may also be useful for the treatment of hypertension or shock. Nitric oxide (NO) is also one of the most important vasodilator local-control mechanisms, via stimulation of guanylyl cyclase and increased cGMP, and this is counteracted by endothelin-1, one of the most potent vasoconstrictors, which, like NO, also has an important role in diseases such as sepsis.

Keywords angina; hypertension; L-type calcium channels; nitric oxide; sympathomimetics

Learning objectives

After reading this article, you should be able to:

- suggest three sympathomimetics that could be used to treat cardiogenic shock
- describe three different inotropic mechanisms and two other mechanisms that can be utilized for treatment of angina
- list three different types of L-type calcium channel inhibitors
- describe at least two humoral and two local mechanisms of vasodilation that may also be targeted in the treatment of hypertension.

Modulators of cardiac function

Sympathomimetic inotropes

Sympathomimetics: sympathomimetics include a number of structurally similar neurotransmitters, which are released from post-ganglionic sympathetic nerve terminals and induce changes in heart rate (chronotropic effect) and force of contraction (inotropic effect), along with changes in blood vessel diameter via post-synaptic α and β-adrenoreceptors. β_1 predominate in the heart, but only β_2 are found in blood vessels. β-adrenoceptors induce a positive inotropic effect, as they increase the Ca^{2+} sensitivity of the contractile machinery and troponin phosphorylation via an increase in cAMP and protein kinase A (PKA). The rise in Ca^{2+} also increases the action potentials involved pacemaker activity of the heart.

Dopamine is the precursor to noradrenaline that acts by displacing noradrenaline from nerve terminals and storage vesicles. It acts on α_1 and β_1 adrenoceptors, but induces a positive inotropic effect via cardiac β_1. Dopamine receptors are classified into D(1)-like (D(1) and D(5)) and D(2)-like (D(2), D(3) and D(4)). Vascular D(1)-like receptors cause cerebral, coronary, renal and mesenteric dilatation and hence hypotension, whereas vascular D(2)-like receptors cause indirect vasodilatation, due to inhibition of sympathetic vasoconstrictor tone. In some organs, however, vasoconstriction may occur because dopamine activates α_1 adrenoceptors. Therefore, dopamine has a mixture of effects on the cardiovascular system that combine to make it an effective first-line treatment during infarction or shock. Dobutamine is another catecholamine β_1 agonist that can be used during myocardial infarction, cardiogenic or septic shock because it increases force of cardiac contraction, with little vasoconstriction or tachycardia. Dopexamine can also be used for inotropic support for heart failure during surgery, having a direct effect on β_2 and an indirect effect via β_1, secondary to inhibition of catecholamine uptake. Furthermore, it may cause systemic vasodilation via β_2 on vascular smooth muscle (VSM), peripheral D(1) and prejunctional D(2) receptors.

Positive inotropes

Digoxin: digoxin, also known as digitalis, is a cardiac glycoside purified from the foxglove plant *Digitalis lanata*. It has two mechanisms of action: (1) it decreases the conduction of electrical impulses through the AV node and (2) it inhibits the Na^+/K^+ ATPase pump by binding to the extracellular surface of the α-subunit. The former causes a decrease in heart rate; the latter an increase in the force of contraction. It is an effective anti-arrhythmic therapy for controlling atrial fibrillation but is no longer in common use during heart failure, possibly because no beneficial effects on mortality or morbidity have been demonstrated in clinical trials.

Potassium (K^+) channels: K^+ channels are found as pores spanning almost all membranes throughout the body and may be classified as either calcium-activated big conductance (BK), intermediate conductance (IK) or small conductance (SK) potassium channels, inwardly rectifying (ROMK; $K_{ir}1.1$, GPCR

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regulated; $K_{ir}3.x$, ATP-sensitive; $K_{ir}6.x$), tandem pore domain (TWIK, TRAAK, TREK, TASK) or voltage-gated (HERG; $K_v11.1$, KvLQT1; $K_v7.1$) potassium channels. K_{ATP} channels contain eight protein subunits, four of these being members of the $K_{ir}6.0$ subtype ($K_{ir}6.1$ or $K_{ir}6.2$), the other four comprising sulfonylurea receptors (SUR1, SUR2A and SUR2B). The SUR subunits are activated by sulfonylureas, MgATP and specific pharmacological agents. K_{ATP} opening is also thought to be the mechanism involved in ischaemic preconditioning.

Nicorandil is used in the treatment of angina, as it causes dilation of coronary arteries, but does not alter heart rate or blood pressure. It is a combined K_{ATP} channel opener and nitric oxide (NO) donor. Unlike nitrates however, tolerance does not develop. Levosimendan causes both K_{ATP} opening and increased contractility of the heart by increasing Ca^{2+} binding to troponin and is used for inotropic support in acutely-decompensated severe congestive heart failure (CHF).

Phosphodiesterases (PDE): PDE include a family of 14 enzymes that exist physiologically to degrade phosphodiester bonds. PDE IV, VII and VIII hydrolyse cAMP; PDE V, VI and IX hydrolyse cGMP, whilst PDE I, II, III, X and XI can degrade both. Milrinone and amironone specifically inhibit PDE III, which leads to an increase in cAMP within cardiac muscle, in turn inducing a positive inotropic effect. Milrinone also increases Ca^{2+} ATPase activity on the cardiac sarcoplasmic reticulum in conjunction with arteriolar vasodilation. Thus, milrinone may be used in the treatment of heart failure, particularly when treatment with diuretics and vasodilators has proved ineffective. Enoximone is also a PDE III inhibitor that is recommended for use in the treatment of CHF.

Beta blockers

Non-selective β-adrenoceptor antagonists include drugs that non-selectively block β_1 and β_2, such as propranolol; those that selectively inhibit β_1 such as practolol (now withdrawn) and atenolol; non-selective inhibitors with partial agonist activity, such as oxprenolol and alprenolol (has some $5\text{-}HT_{1A}$ receptor antagonism, no longer available); β_1 selective with no agonist activity, such as atenolol; and non-selective β inhibitors with an α_1 blocking action, for example, carvedilol. The newer agent nebivolol is also a highly selective β_1 antagonist, but its beneficial effects are further mediated through concurrent release of NO. β-Blockers are used to treat hypertension, with atenolol and metoprolol (β_1 selective) being two of the most commonly prescribed. They are often used in patients with essential hypertension who do not respond sufficiently to thiazide diuretics, or in combination with thiazides or β-blockers. These anti-hypertensive effects are achieved by slowing heart rate and cardiac output, which reduces peripheral resistance.

Calcium (Ca^{2+}) influx inhibitors

Ca^{2+} channels may be subdivided in to voltage-gated and ligand-gated types. Voltage-operated Ca^{2+} channels (VOCC) include the L-type/$Ca_v\alpha$(1.1, 1.2, 1.3, 1.4), N-type/$Ca_v\alpha$2.2, P-type/$Ca_v\alpha$2.1, Q-type/$Ca_v\alpha$2.1, R-type/$Ca_v\alpha$2.3 and T-type/$Ca_v\alpha$(3.1, 3.2, 3.3), whereas the ligand-gated or receptor-operated channels (ROCC) include the inositol triphosphate receptor (IP_3), ryanodine, two pore channels and cation channels of sperm. The L-type Ca^{2+} channels (LTCCs) are important in cardiac muscle contraction, as intracellular influx of Ca^{2+} through these channels prolongs depolarization of cardiac muscle cells. When the heart contracts, there is calcium-induced calcium release (CICR) from the sarcoplasmic reticulum. Ca^{2+} then binds to troponin, which causes myosin and actin to form the cross-bridges that cause contraction.

LTCC antagonists can be divided into three groups:

- Dihydropyridines, such as amlodipine, felodipine, nicardipine and nifedipine, which cause relaxation of both arteries and veins.
- Phenylalkylamines, such as verapamil, which have a negative inotropic effect.
- Benzothiazepines, such as diltiazem, which have a slightly negative inotropic effect.

LTCCs contain a 190–250-kDa α_1 subunit, comprising the channel itself, plus α_2, β, γ and δ subunits, which modulate the function of the channel. All LTCC antagonists bind to the α_1 subunit, with dihydropyridines binding to an extracellular part of the channel, whereas other benzothiazepines and phenylalkylamines bind to the intracellular part of the channel. Further subdividing the extracellular α_1 subunit, α_{1S} are found in skeletal muscle, whereas α_{1C} are present in the heart, smooth muscle, brain, pituitary, adrenal and α_{1D} are found within the brain, pancreas, kidney, ovary and the cochlea. However, both verapamil and diltiazem can only access their receptor-binding site by passing through an open channel. As LTCCs tend to spend more time in the open state in the heart, compared with those in the vasculature, phenylalkylamines and benzothiazepines can alleviate angina directly by reducing the rate and force of cardiac contraction. Amlodipine and nifedipine are indicated for use in the treatment of stable (exercise-induced) angina, but not during unstable angina. The T-type Ca^{2+} channel (TTCC) can also appear in the ventricles of the heart when in failure and is a possible new target for the treatment of heart failure. Efonidipine can inhibit both LTCC and TTCC, but is still undergoing clinical trials.

Other inotropic drugs

Other inotropic drugs include ranolazine, which is thought to increase the late Na^+ current in cardiac cells, leading to increased myocardial relaxation and decreased left ventricular stiffness. Ranolazine is used in the treatment of angina, often in combination with β-blockers, nitrates, Ca^{2+} channel blockers, ACE inhibitors or angiotensin receptor antagonists. I(f) inhibitors cause specific inhibition of the sinoatrial node mixed K^+/Na^+ current (I(f)), which results in a decrease in heart rate only. The first member of this class available for clinical use is ivabradine, which is effective during stable angina pectoris, compared with placebo, β-blockers and Ca^{2+} antagonists.

Nitrovasodilators

NO: NO is a gas produced endogenously in endothelial cells from L-arginine via endothelial nitric oxide synthase (eNOS). However, it may also be produced by iNOS during inflammation and by nNOS in neuronal cells. NO then diffuses into adjoining VSM cells to induce vasorelaxation via production of cGMP. Drugs that exploit this pathway may be classified as NO donors or pro-drugs, whereby the NO released activates guanylyl cyclase (GC) and produces the second messenger cGMP; or those that activate some component of the endogenous NO pathway. NO

