Calcium Antagonists

During electrical excitation of the cell membrane of heart or smooth muscle, different ionic currents are activated, including an inward Ca^{2+} current. The term Ca^{2+} antagonist is applied to drugs that inhibit the influx of Ca^{2+} ions without affecting inward Na^+ or outward K^+ currents to a significant degree. Other labels are *Ca-entry blocker* or *Ca-channel blocker*. Therapeutically used Ca^{2+} antagonists can be divided into three groups according to their effects on heart and vasculature.

I. Dihydropyridine derivatives. The dihydropyridines, e.g., nifedipine, are uncharged hydrophobic substances. They induce a *relaxation* of vascular smooth muscle in *arterial beds*. An effect on cardiac function is practically absent at therapeutic dosage. (However, in pharmacological experiments on isolated cardiac muscle preparations a clear negative inotropic effect is demonstrable.) They are thus regarded as *vasoselective Ca^{2+} antagonists*. Because of the dilatation of resistance vessels, blood pressure falls. Cardiac afterload is diminished (p. 306) and, therefore, also oxygen demand. Spasms of coronary arteries are prevented.

Indications for nifedipine include *angina pectoris* (p. 308) and, — when applied as a sustained release preparation, — hypertension (p. 312). In angina pectoris, it is effective when given either prophylactically or during acute attacks. **Adverse effects** are palpitation (reflex tachycardia due to hypotension), headache, and pretibial edema.

Nitrendipine and *felodipine* are used in the treatment of hypertension. *Nimodipine* is given prophylactically after subarachnoidal hemorrhage to prevent vasospasms due to depolarization by excess K^+ liberated from disintegrating erythrocytes or blockade of NO by free hemoglobin.

II. Verapamil and other catamphiphilic Ca^{2+} antagonists. Verapamil contains a nitrogen atom bearing a positive charge at physiological pH and thus represents a *cationic amphiphilic molecule*. It exerts inhibitory effects not only on *arterial smooth muscle*, but also on *heart muscle*. In the heart, Ca^{2+} inward currents are important in generating depolarization of sinoatrial node cells (impulse generation), in impulse propagation through the AV- junction (atrioventricular conduction), and in electromechanical coupling in the ventricular cardiomyocytes. Verapamil thus produces negative chrono-, dromo-, and inotropic effects.

Indications. Verapamil is used as an antiarrhythmic drug in supraventricular tachyarrhythmias. In atrial flutter or fibrillation, it is effective in reducing ventricular rate by virtue of inhibiting AV-conduction. Verapamil is also employed in the prophylaxis of *angina pectoris attacks* (p. 308) and the treatment of hypertension (p. 312). **Adverse effects:** Because of verapamil's effects on the sinus node, a drop in blood pressure fails to evoke a reflex tachycardia. Heart rate hardly changes; bradycardia may even develop. AV-block and myocardial insufficiency can occur. Patients frequently complain of constipation.

Gallopamil (= methoxyverapamil) is closely related to verapamil in both structure and biological activity.

Diltiazem is a catamphiphilic benzothiazepine derivative with an activity profile resembling that of verapamil.

III. T-channel selective blockers. Ca^{2+}-channel blockers, such as verapamil and mibefradil, may block both L- and T-type Ca^{2+} channels. Mibefradil shows relative selectivity for the latter and is devoid of a negative inotropic effect; its therapeutic usefulness is compromised by numerous interactions with other drugs due to inhibition of cytochrome P_{450}-dependent enzymes (CYP 1A2, 2D6 and, especially, 3A4).

Inhibitors of the RAA System

Angiotensin-converting enzyme (ACE) is a component of the antihypotensive renin-angiotensin-aldosterone (RAA) system. Renin is produced by specialized cells in the wall of the afferent arteriole of the renal glomerulus. These cells belong to the juxtaglomerular apparatus of the nephron, the site of contact between afferent arteriole and distal tubule, and play an important part in controlling nephron function. Stimuli eliciting *release of renin* are: a drop in renal perfusion pressure, decreased rate of delivery of Na^+ or Cl^- to the distal tubules, as well as β-adrenoceptor-mediated sympathoactivation. The glycoprotein renin enzymatically cleaves the decapeptide angiotensin I from its circulating precursor substrate angiotensinogen. ACE, in turn, produces biologically active angiotensin II (ANG II) from angiotensin I (ANG I).

ACE is a rather nonspecific peptidase that can cleave C-terminal dipeptides from various peptides (dipeptidyl carboxypeptidase). As "kininase II," it contributes to the inactivation of kinins, such as bradykinin. ACE is also present in blood plasma; however, enzyme localized in the luminal side of vascular endothelium is primarily responsible for the formation of angiotensin II. The lung is rich in ACE, but kidneys, heart, and other organs also contain the enzyme.

Angiotensin II can raise blood pressure in different ways, including (1) vasoconstriction in both the arterial and venous limbs of the circulation; (2) stimulation of aldosterone secretion, leading to increased renal reabsorption of NaCl and water, hence an increased blood volume; (3) a central increase in sympathotonus and, peripherally, enhancement of the release and effects of norepinephrine.

ACE inhibitors, such as *captopril* and *enalaprilat,* the active metabolite of enalapril, occupy the enzyme as false substrates. Affinity significantly influences efficacy and rate of elimination. Enalaprilat has a stronger and longer-lasting effect than does captopril. **Indications** are *hypertension* and *cardiac failure.*

Lowering of an elevated blood pressure is predominantly brought about by diminished production of angiotensin II. Impaired degradation of kinins that exert vasodilating actions may contribute to the effect.

In heart failure, cardiac output rises again because ventricular afterload diminishes due to a fall in peripheral resistance. Venous congestion abates as a result of (1) increased cardiac output and (2) reduction in venous return (decreased aldosterone secretion, decreased tonus of venous capacitance vessels).

Undesired effects. The magnitude of the antihypertensive effect of ACE inhibitors depends on the functional state of the RAA system. When the latter has been activated by loss of electrolytes and water (resulting from treatment with diuretic drugs), cardiac failure, or renal arterial stenosis, administration of ACE inhibitors may initially cause an excessive fall in blood pressure. In renal arterial stenosis, the RAA system may be needed for maintaining renal function and ACE inhibitors may precipitate renal failure. Dry cough is a fairly frequent side effect, possibly caused by reduced inactivation of kinins in the bronchial mucosa. Rarely, disturbances of taste sensation, exanthema, neutropenia, proteinuria, and angioneurotic edema may occur. In most cases, ACE inhibitors are well tolerated and effective. Newer analogues include lisinopril, perindopril, ramipril, quinapril, fosinopril, benazepril, cilazapril, and trandolapril.

Antagonists at angiotensin II receptors. Two receptor subtypes can be distinguished: AT1, which mediates the above actions of AT II; and AT2, whose physiological role is still unclear. The sartans (candesartan, eprosartan, irbesartan, losartan, and valsartan) are AT1 antagonists that reliably lower high blood pressure. They do not inhibit degradation of kinins and cough is not a frequent side-effect.

Drugs Used to Influence Smooth Muscle Organs

Bronchodilators. Narrowing of bronchioles raises airway resistance, e.g., in bronchial or bronchitic asthma. Several substances that are employed as *bronchodilators* are described elsewhere in more detail: β_2-sympathomimetics (p. 84, given by pulmonary, parenteral, or oral route), the methylxanthine *theophylline* (p. 326, given parenterally or orally), as well as the parasympatholytic *ipratropium* (pp. 104, 107, given by inhalation).

Spasmolytics. N-Butylscopolamine (p. 104) is used for the relief of painful spasms of the biliary or ureteral ducts. Its poor absorption (N.B. quaternary N; absorption rate <10%) necessitates parenteral administration. Because the therapeutic effect is usually weak, a potent analgesic is given concurrently, e.g., the opioid meperidine. Note that some spasms of intestinal musculature can be effectively relieved by organic nitrates (in biliary colic) or by nifedipine (esophageal hypertension and achalasia).

Myometrial relaxants (Tocolytics). β_2-Sympathomimetics such as fenoterol or ritodrine, given orally or parenterally, can prevent premature labor or interrupt labor in progress when dangerous complications necessitate cesarean section. Tachycardia is a side effect produced reflexly because of β_2-mediated vasodilation or direct stimulation of cardiac β_1-receptors. Magnesium sulfate, given i.v., is a useful alternative when β-mimetics are contraindicated, but must be carefully titrated because its nonspecific calcium antagonism leads to blockade of cardiac impulse conduction and of neuromuscular transmission.

Myometrial stimulants. The neurohypophyseal hormone *oxytocin* (p. 242) is given parenterally (or by the nasal or buccal route) before, during, or after labor in order to prompt uterine contractions or to enhance them. Certain *prostaglandins* or analogues of them (p. 196; $F_{2\alpha}$: dinoprost; E_2: dinoprostone, misoprostol, sulprostone) are capable of inducing rhythmic uterine contractions and cervical relaxation at any time. They are mostly employed as abortifacients (oral or vaginal application of misoprostol in combination with mifepristone [p. 256]).

Ergot alkaloids are obtained from *Secale cornutum* (ergot), the sclerotium of a fungus *(Claviceps purpurea)* parasitizing rye. Consumption of flour from contaminated grain was once the cause of epidemic poisonings *(ergotism)* characterized by gangrene of the extremities (St. Anthony's fire) and CNS disturbances (hallucinations).

Ergot alkaloids contain lysergic acid (formula in **A** shows an amide). They act on uterine and vascular muscle. *Ergometrine* particularly stimulates the uterus. It readily induces a tonic contraction of the myometrium (tetanus uteri). This jeopardizes placental blood flow and fetal O_2 supply. The semisynthetic derivative methylergometrine is therefore used only *after* delivery for uterine contractions that are too weak.

Ergotamine, as well as the ergotoxine alkaloids (ergocristine, ergocryptine, ergocornine), have a predominantly vascular action. Depending on the initial caliber, constriction or dilation may be elicited. The mechanism of action is unclear; a mixed antagonism at α-adrenoceptors and agonism at 5-HT-receptors may be important. Ergotamine is used in the treatment of migraine (p. 322). Its congener, dihydroergotamine, is furthermore employed in orthostatic complaints (p. 314).

Other lysergic acid derivatives are the 5-HT antagonist methysergide, the dopamine agonists bromocriptine, pergolide, and cabergolide (pp. 114, 188), and the hallucinogen lysergic acid diethylamide (LSD, p. 240).

Overview of Modes of Action (A)

1. The pumping capacity of the heart is regulated by sympathetic and parasympathetic nerves (pp. 84, 105). Drugs capable of interfering with autonomic nervous function therefore provide a means of influencing cardiac performance. Thus, **anxiolytics** of the benzodiazepine type (p. 226), such as diazepam, can be employed in myocardial infarction to suppress sympathoactivation due to life-threatening distress. Under the influence of **antiadrenergic agents** (p. 96), used to lower an elevated blood pressure, cardiac work is decreased. **Ganglionic blockers** (p. 108) are used in managing hypertensive emergencies. Parasympatholytics (p. 104) and β-blockers (p. 92) prevent the transmission of autonomic nerve impulses to heart muscle cells by blocking the respective receptors.

2. An isolated mammalian heart whose extrinsic nervous connections have been severed will beat spontaneously for hours if it is supplied with a nutrient medium via the aortic trunk and coronary arteries (Langendorff preparation). In such a preparation, only those drugs that act directly on cardiomyocytes will alter contractile force and beating rate.

Parasympathomimetics and **sympathomimetics** act at membrane receptors for visceromotor neurotransmitters. The plasmalemma also harbors the sites of action of **cardiac glycosides** (the Na/K-ATPases, p. 130), of Ca^{2+} antagonists (Ca^{2+} channels, p. 122), and of **agents that block Na^+ channels** (local anesthetics; p. 134, p. 204). An intracellular site is the target for phosphodiesterase inhibitors (e.g., amrinone, p. 132).

3. Mention should also be made of the possibility of affecting cardiac function in angina pectoris (p. 306) or congestive heart failure (p. 132) by reducing venous return, peripheral resistance, or both, with the aid of vasodilators; and by reducing sympathetic drive applying β-blockers.

Events Underlying Contraction and Relaxation (B)

The signal triggering **contraction** is a propagated action potential (AP) generated in the sinoatrial node. Depolarization of the plasmalemma leads to a rapid *rise in cytosolic Ca^{2+} levels*, which causes the contractile filaments to shorten **(electromechanical coupling).** The level of Ca^{2+} concentration attained determines the degree of shortening, i.e., the force of contraction. Sources of Ca^{2+} are: a) extracellular Ca^{2+} entering the cell through voltage-gated *Ca^{2+} channels;* b) Ca^{2+} stored in membranous sacs of the *sarcoplasmic reticulum* (SR); c) Ca^{2+} bound to the inside of the plasmalemma. The plasmalemma of cardiomyocytes extends into the cell interior in the form of tubular invaginations (transverse tubuli).

The trigger signal for **relaxation** is the return of the membrane potential to its resting level. During repolarization, Ca^{2+} levels fall below the threshold for activation of the myofilaments (3×10^{-7} M), as the *plasmalemmal binding* sites regain their binding capacity; the SR pumps Ca^{2+} into its interior; and Ca^{2+} that entered the cytosol during systole is again extruded by plasmalemmal *Ca^{2+}-ATPases* with expenditure of energy. In addition, a carrier (antiporter), utilizing the transmembrane Na^+ gradient as energy source, transports Ca^{2+} out of the cell in exchange for Na^+ moving down its transmembrane gradient *(Na^+/Ca^{2+} exchange).*

Cardiac Glycosides

Diverse plants **(A)** are sources of sugar-containing compounds (glycosides) that also contain a steroid ring (structural formulas, p. 133) and augment the contractile force of heart muscle **(B):** *cardiotonic glycosides. cardiosteroids,* or *"digitalis."*

If the inotropic, "therapeutic" dose is exceeded by a small increment, signs of poisoning appear: arrhythmia and contracture **(B).** The *narrow therapeutic margin* can be explained by the **mechanism of action.**

Cardiac glycosides (CG) bind to the extracellular side of Na^+/K^+-ATPases of cardiomyocytes and inhibit enzyme activity. The Na^+/K^+-ATPases operate to pump out Na^+ leaked into the cell and to retrieve K^+ leaked from the cell. In this manner, they maintain the transmembrane gradients for K^+ and Na^+, the negative resting membrane potential, and the normal electrical excitability of the cell membrane. When part of the enzyme is occupied and inhibited by CG, the unoccupied remainder can increase its level of activity and maintain Na^+ and K^+ transport. The effective stimulus is a small elevation of intracellular Na^+ concentration (normally approx. 7 mM). Concomitantly, the amount of Ca^{2+} mobilized during systole and, thus, *contractile force,* increases. It is generally thought that the underlying cause is the decrease in the Na^+ transmembrane gradient, i.e., the driving force for the Na^+/Ca^{2+} exchange (p. 128), allowing the intracellular Ca^{2+} level to rise. When too many ATPases are blocked, K^+ and Na^+ homeostasis is deranged; the membrane potential falls, *arrhythmias* occur. Flooding with Ca^{2+} prevents relaxation during diastole, resulting in *contracture.*

The **CNS effects** of CG **(C)** are also due to binding to Na^+/K^+-ATPases. Enhanced vagal nerve activity causes a decrease in sinoatrial beating rate and velocity of atrioventricular conduction. In patients with heart failure, improved circulation also contributes to the reduction in heart rate. Stimulation of the area postrema leads to nausea and vomiting. Disturbances in color vision are evident.

Indications for CG are: (1) *chronic congestive heart failure;* and (2) *atrial fibrillation or flutter,* where inhibition of AV conduction protects the ventricles from excessive atrial impulse activity and thereby improves cardiac performance **(D).** Occasionally, sinus rhythm is restored.

Signs of intoxication are: (1) *cardiac arrhythmias,* which under certain circumstances are life-threatening, e.g., sinus bradycardia, AV-block, ventricular extrasystoles, ventricular fibrillation (ECG); (2) *CNS disturbances* — altered color vision (xanthopsia), agitation, confusion, nightmares, hallucinations; (3) *gastrointestinal* — anorexia, nausea, vomiting, diarrhea; (4) *renal* — loss of electrolytes and water, which must be differentiated from mobilization of accumulated edema fluid that occurs with therapeutic dosage.

Therapy of intoxication: administration of K^+, which *inter alia* reduces binding of CG, but may impair AV-conduction; administration of antiarrhythmics, such as *phenytoin or lidocaine* (p. 136); oral administration of *colestyramine* (p. 154, 156) for binding and preventing absorption of digitoxin present in the intestines (enterohepatic cycle); injection of *antibody (Fab) fragments* that bind and inactivate digitoxin and digoxin. Compared with full antibodies, fragments have superior tissue penetrability, more rapid renal elimination, and lower antigenicity.

Substance	Fraction absorbed %	Plasma concentr. free (ng/mL)	Plasma concentr. total (ng/mL)	Digitalizing dose (mg)	Elimination %/d	Maintenance dose (mg)
Digitoxin	100	~1	~20	~1	10	~0.1
Digoxin	50–90	~1	~1.5	~1	30	~0.3
Ouabain	<1	~1	~1	0.5	no long-term use	

The **pharmacokinetics of cardiac glycosides (A)** are dictated by their polarity, i.e., the number of hydroxyl groups. Membrane penetrability is virtually nil in ouabain, high in digoxin, and very high in digitoxin. **Ouabain** (**g**strophanthin) does not penetrate into cells, be they intestinal epithelium, renal tubular, or hepatic cells. At best, it is suitable for acute intravenous induction of glycoside therapy.

The absorption of **digoxin** depends on the kind of galenical preparation used and on absorptive conditions in the intestine. Preparations are now of such quality that the derivatives *methyldigoxin* and *acetyldigoxin* no longer offer any advantage. Renal reabsorption is incomplete; approx. 30% of the total amount present in the body (s.c. full "digitalizing" dose) is eliminated per day. When renal function is impaired, there is a risk of accumulation. **Digitoxin** undergoes virtually complete reabsorption in gut and kidneys. There is active hepatic biotransformation: cleavage of sugar moieties, hydroxylation at C12 (yielding digoxin), and conjugation to glucuronic acid. Conjugates secreted with bile are subject to enterohepatic cycling (p. 38); conjugates reaching the blood are renally eliminated. In renal insufficiency, there is no appreciable accumulation. When digitoxin is withdrawn following overdosage, its effect decays more slowly than does that of digoxin.

Other positive inotropic drugs. The **phosphodiesterase inhibitor amrinone** (cAMP elevation, p. 66) can be administered only parenterally for a maximum of 14 d because it is poorly tolerated. A closely related compound is *milrinone*. In terms of their positive inotropic effect, β-sympathomimetics, unlike dopamine (p. 114), are of little therapeutic use; they are also arrhythmogenic and the sensitivity of the β-receptor system declines during continuous stimulation.

Treatment Principles in Chronic Heart Failure

Myocardial insufficiency leads to a decrease in stroke volume and venous congestion with formation of edema. Administration of (thiazide) diuretics (p. 62) offers a therapeutic approach of proven efficacy that is brought about by a decrease in circulating blood volume (decreased venous return) and peripheral resistance, i.e., afterload. A similar approach is intended with ACE-inhibitors, which act by preventing the synthesis of angiotensin II (↓ vasoconstriction) and reducing the secretion of aldosterone (↓ fluid retention). In severe cases of myocardial insufficiency, cardiac glycosides may be added to augment cardiac force and to relieve the symptoms of insufficiency.

In more recent times β-blocker on a long term were found to improve cardiac performance — particularly in idiopathic dilating cardiomyopathy — probably by preventing sympathetic overdrive.