

Vasoactive peptides and drugs

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Vasoconstrictors and vasodilators

- | | |
|-----------------------------|---|
| • Vazokonstriktörler | 1. α -agonistler
2. Endotelin
3. Peptitler (örn. AT II, NPY)
4. Serotonin
5. Tromboksan A ₂
6. Vazopressin |
| • Vazodilatörler | 1. Adenozin
2. β_2 -agonistler
3. Anjiotensin antagonistleri
4. α_1 -blokerler
5. Ca ²⁺ kanal blokerleri
6. Dopamin
7. Genel anestetikler
8. Hidralazin
9. Histamin
10. K ⁺ kanal açıcıları
11. Lokal anestetikler
12. Metilksantinler
13. Nitratlar, nitritler
14. Nitrik oksit donörleri
15. Papaverin
16. Peptitler (örn. ANP, VIP, P maddesi, CGRP)
17. Prostatiklin |

Drugs that are used in the treatment of peripheral vascular disease

- **Periferik vasküler hastalıkların tedavisi**
 1. Bensiklan (Angiodel)
 2. Betahistin (Vasoserc)
 3. Flavonoid fraksiyonu (Daflon)
 4. Ginkgo bilabo ekstresi (Tebokan)
 5. İloprost (İlomedin)
 6. Kalsiyum dobesilat (Doxium)
 7. Nimodipin (Nimotop)
 8. Okserutin (Venoruton)
 9. Papaverin (Papaverin)
 10. Pentoksifilin (Azupentat)
 11. Piribedil (Trivastal)
 12. Polidokanol (Aethoxysklerol Kreussler)

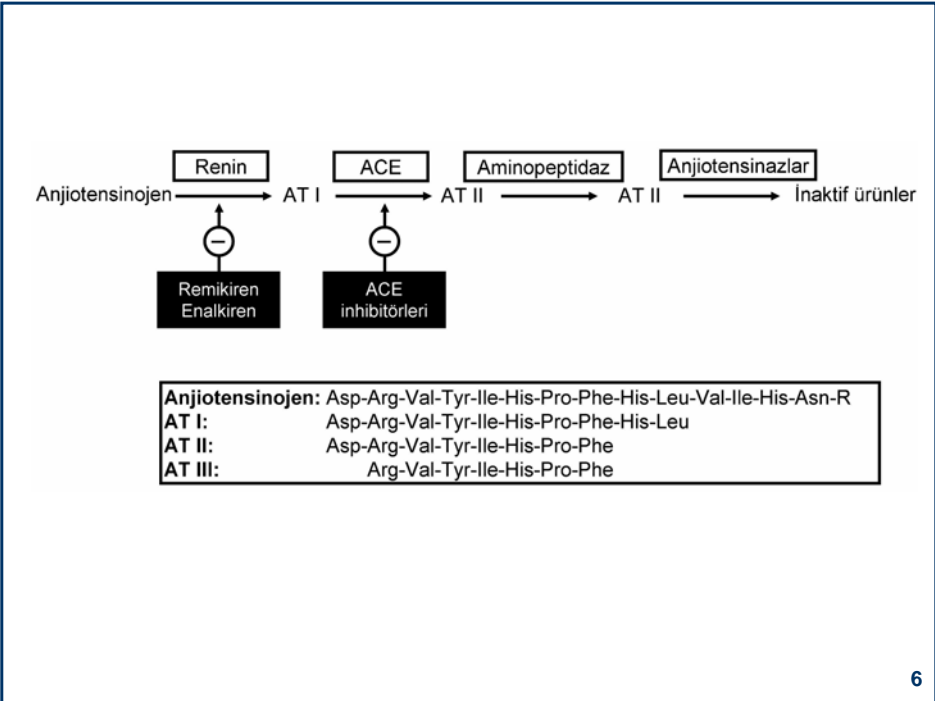
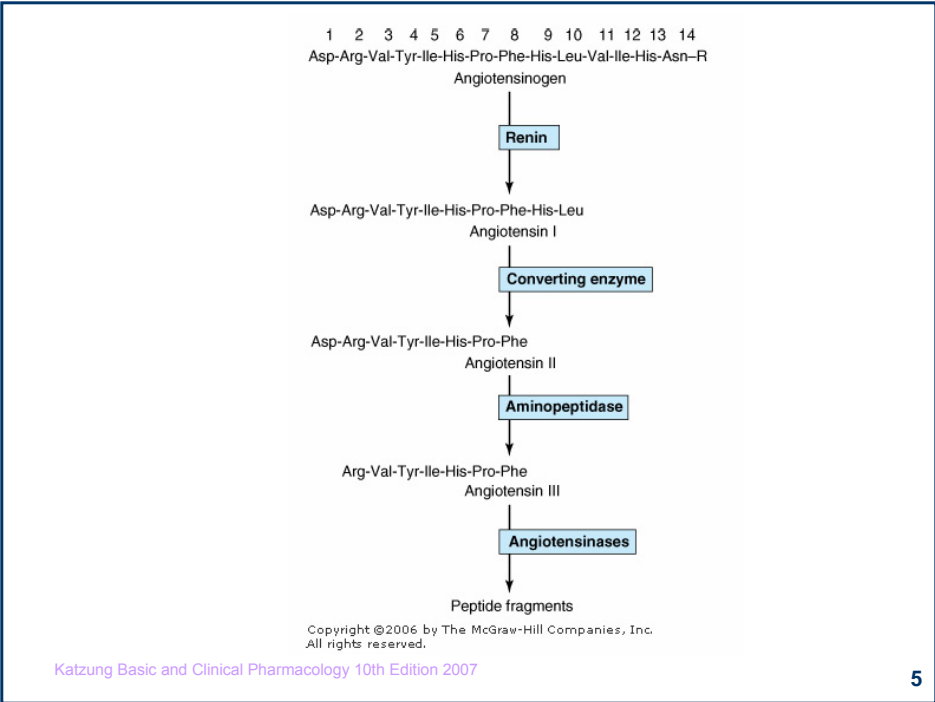
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Vasoactive peptides

- Peptides are used by most tissues for cell-to-cell communication. They play important roles in the autonomic and central nervous systems.
- Several peptides exert important direct effects on vascular and other smooth muscles. These peptides include vasoconstrictors (**angiotensin II, vasopressin, endothelins, neuropeptide Y, and urotensin**) and vasodilators (**bradykinin and related kinins, natriuretic peptides, vasoactive intestinal peptide, substance P, neurotensin, calcitonin gene-related peptide, and adrenomedullin**).

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Kinins

- Kinins are potent vasodilator peptides formed enzymatically by the action of enzymes known as kallikreins or kininogenases acting on protein substrates called kininogens. The kallikrein-kinin system has several features in common with the renin-angiotensin system.

Kallikreins

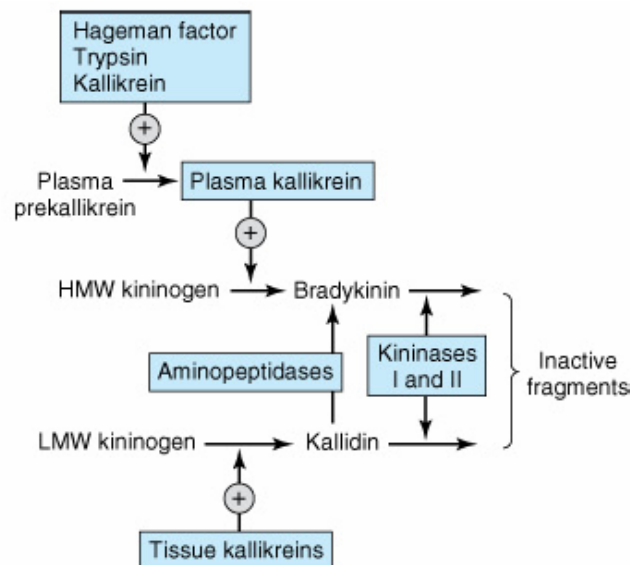
- Kallikreins are present in plasma and in several tissues, including the kidneys, pancreas, intestine, sweat glands, and salivary glands. Plasma prekallikrein can be activated to kallikrein by trypsin, Hageman factor, and possibly kallikrein itself. In general, the biochemical properties of tissue kallikreins are different from those of plasma kallikreins. Kallikreins can convert prorenin to active renin, but the physiologic significance of this action has not been established.

Kininogens

- Kininogens—the precursors of kinins and substrates of kallikreins—are present in plasma, lymph, and interstitial fluid. Two kininogens are known to be present in plasma: a low-molecular-weight form (LMW kininogen) and a high-molecular-weight form (HMW kininogen). About 15–20% of the total plasma kininogen is in the HMW form. It is thought that LMW kininogen crosses capillary walls and serves as the substrate for tissue kallikreins, whereas HMW kininogen is confined to the bloodstream and serves as the substrate for plasma kallikrein

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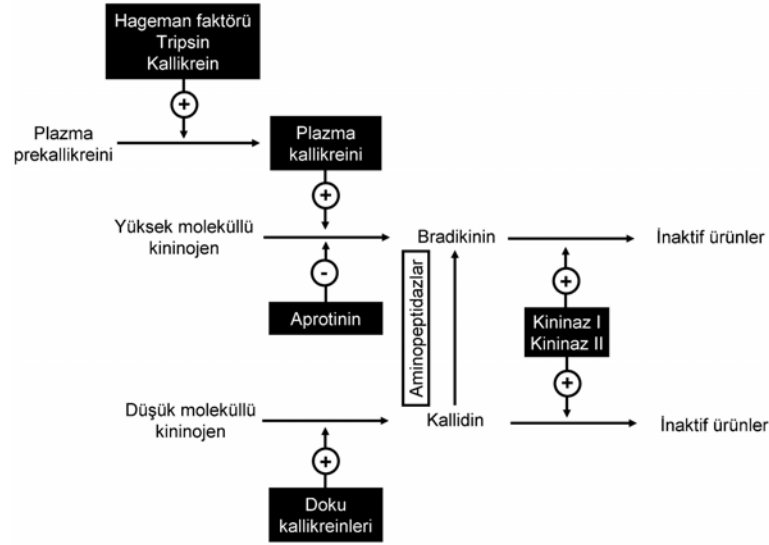
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Bradikininin sentezi ve metabolizması.
Kininaz II, anjiotensin dönüştürücü enzim (ACE) ile aynı enzimdir.

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Kinin receptors

- The biologic actions of kinins are mediated by specific receptors located on the membranes of the target tissues. Two types of kinin receptors, termed B1 and B2, have been defined based on the rank orders of agonist potencies. (Note that *B* here stands for bradykinin, not for β -adrenoceptor.)
- Bradykinin displays the highest affinity in most B2 receptor systems, followed by Lys-bradykinin and then by Met-Lys-bradykinin. One exception is the B2 receptor that mediates contraction of venous smooth muscle; this appears to be most sensitive to Lys-bradykinin. Recent evidence suggests the existence of two B2-receptor subtypes, which have been termed B2A and B2B.
- **Icatibant** is a second-generation B2 receptor antagonist. It is orally active, potent, and selective.

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Effects of Kinins on the Cardiovascular System I

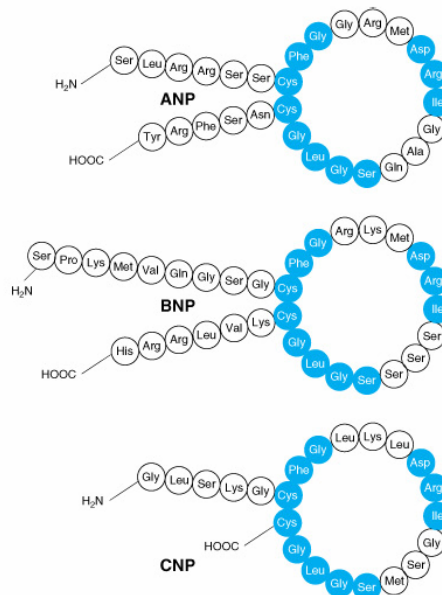
- Kinins produce marked **vasodilation** in several vascular beds, including the heart, kidney, intestine, skeletal muscle, and liver. In this respect, kinins are approximately 10 times more potent on a molar basis than histamine.
- The vasodilation may result from a direct inhibitory effect of kinins on arteriolar smooth muscle or may be mediated by the release of nitric oxide or vasodilator prostaglandins such as PGE₂ and PGI₂.
- In contrast, the predominant effect of kinins on veins is contraction; again, this may result from direct stimulation of venous smooth muscle or from the release of vasoconstrictor prostaglandins such as PGF₂. Kinins also produce contraction of most visceral smooth muscle.

Effects of Kinins on the Cardiovascular System II

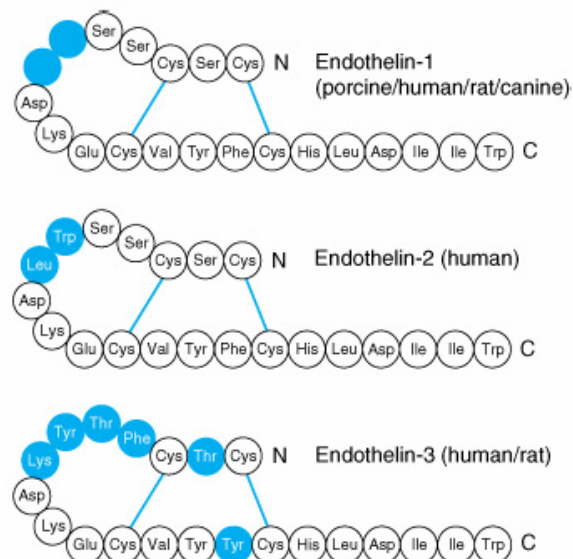
- When injected intravenously, kinins produce a rapid but brief fall in blood pressure that is due to their arteriolar vasodilator action. Intravenous infusions of the peptide fail to produce a sustained decrease in blood pressure.
- Bradykinin increases blood pressure when injected into the central nervous system, but the physiologic significance of this effect is not clear, since it is unlikely that kinins cross the blood-brain barrier.
- Kinins have no consistent effect on sympathetic or parasympathetic nerve endings.

Effects of Kinins on the Cardiovascular System III

- The arteriolar dilation produced by kinins causes an increase in pressure and flow in the capillary bed, thus favoring efflux of fluid from blood to tissues. This effect may be facilitated by increased capillary permeability resulting from contraction of endothelial cells and widening of intercellular junctions, and by increased venous pressure secondary to constriction of veins.
- As a result of these changes, water and solutes pass from the blood to the extracellular fluid, lymph flow increases, and **edema** may result.



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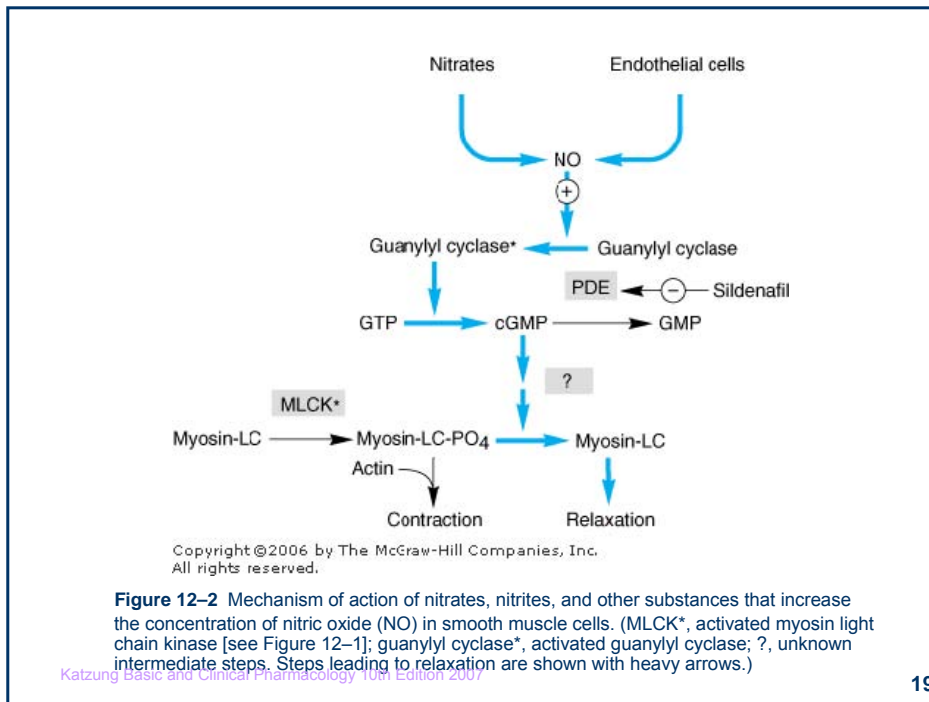
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Mechanisms of vascular smooth muscle relaxation I

- **Increasing cGMP**
 cGMP facilitates the dephosphorylation of myosin light chains, preventing the interaction of myosin with actin.
- Nitric oxide is an effective activator of soluble guanylyl cyclase and acts mainly through this mechanism.
- Important molecular donors of nitric oxide include nitroprusside and the organic nitrates used in angina.

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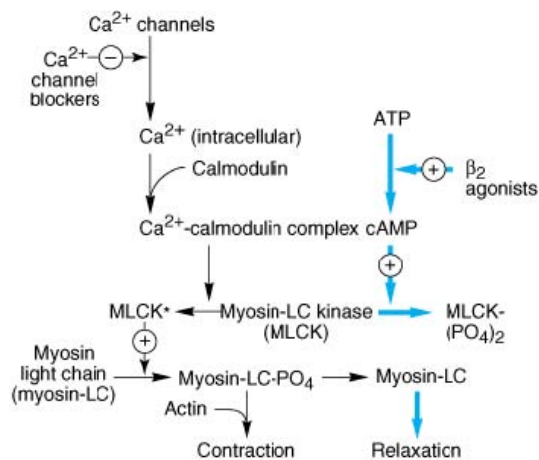


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Mechanisms of vascular smooth muscle relaxation II

- Decreasing intracellular Ca^{2+} :**
 Calcium channel blockers predictably cause vasodilation because they reduce intracellular Ca^{2+} , a major modulator of the activation of myosin light chain kinase.
- Beta blockers and calcium channel blockers reduce Ca^{2+} influx in cardiac muscle, thereby reducing rate, contractility, and oxygen requirement unless reversed by compensatory responses.

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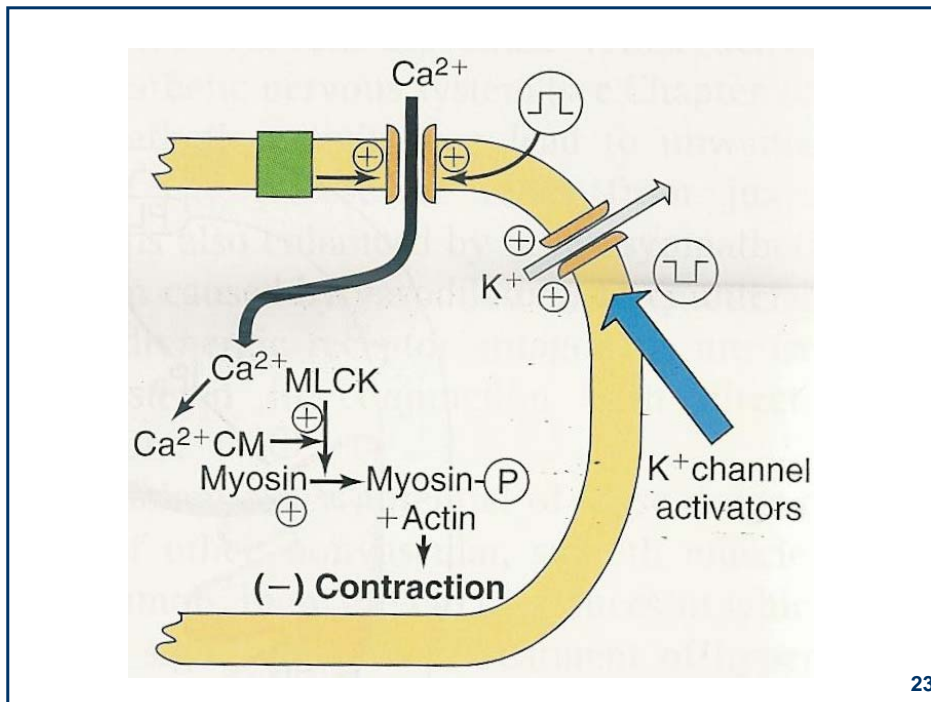


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Figure 12-1 Control of smooth muscle contraction and site of action of calcium channel-blocking drugs. Contraction is triggered by influx of calcium (which can be blocked by calcium channel blockers) through transmembrane calcium channels. The calcium combines with calmodulin to form a complex that converts the enzyme myosin light chain kinase to its active form (MLCK*). The latter phosphorylates the myosin light chains, thereby initiating the interaction of myosin with actin. Beta2 agonists (and other substances that increase cAMP) may cause relaxation in smooth muscle by accelerating the inactivation of MLCK (heavy arrows) and by facilitating the expulsion of calcium from the cell (not shown).

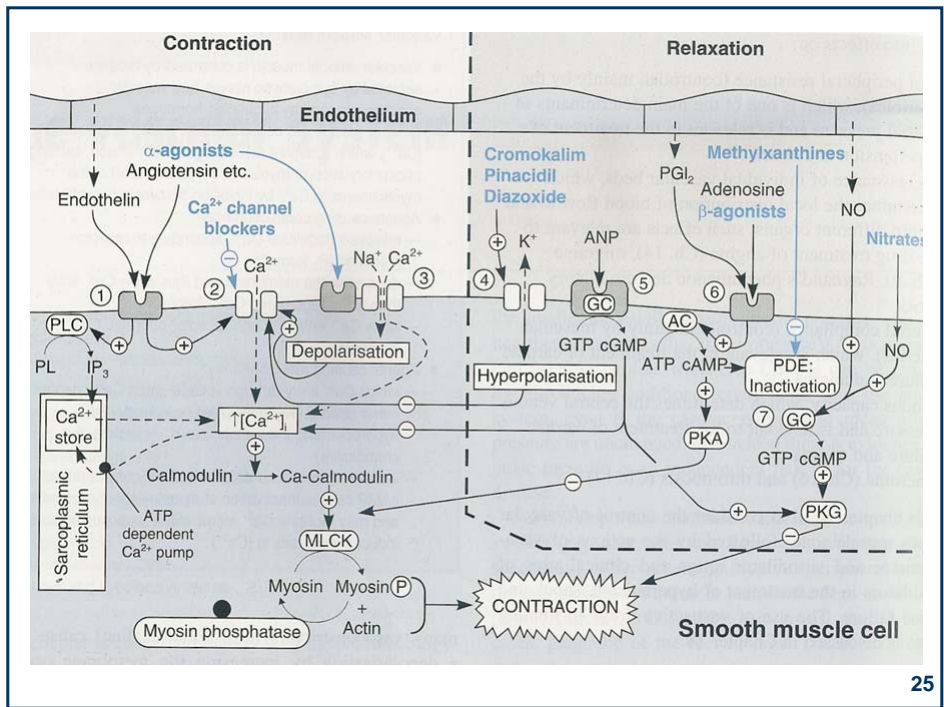
Mechanisms of vascular smooth muscle relaxation III

- Stabilizing or preventing depolarization of the vascular smooth muscle cell membrane:**
 The membrane potential of excitable cells is stabilized near the resting potential by increasing potassium permeability.
- Potassium channel openers, such as minoxidil sulfate, increase the permeability of K^+ channels, probably ATP-dependent K^+ channels.
- Certain newer agents under investigation for use in angina (eg, nicorandil) may act, in part, by this mechanism.



Mechanisms of vascular smooth muscle relaxation IV

- Increasing cAMP in vascular smooth muscle cells:**
 An increase in cAMP increases the rate of inactivation of myosin light chain kinase, the enzyme responsible for triggering the interaction of actin with myosin in these cells.
- This appears to be the mechanism of vasodilation caused by β_2 agonists, drugs that are *not* used in angina.



Thank you