Физиология гладких мышц сосудов.

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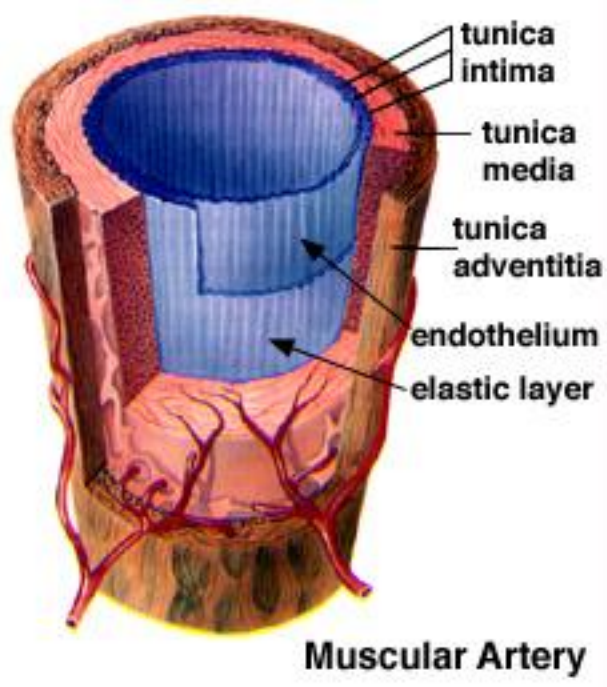
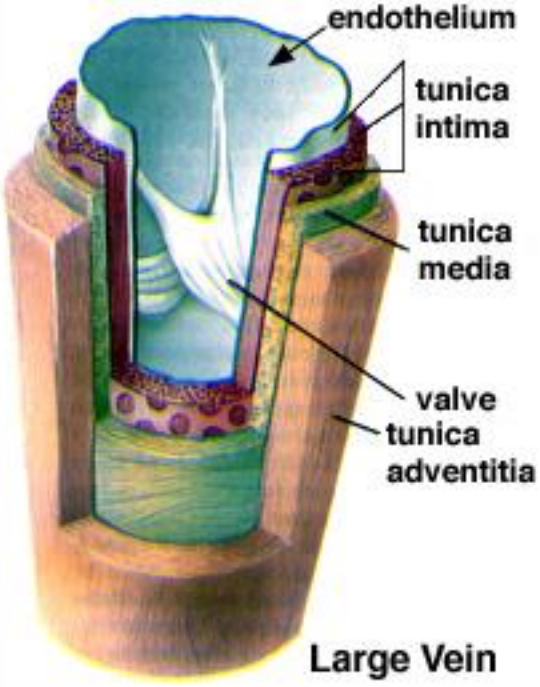
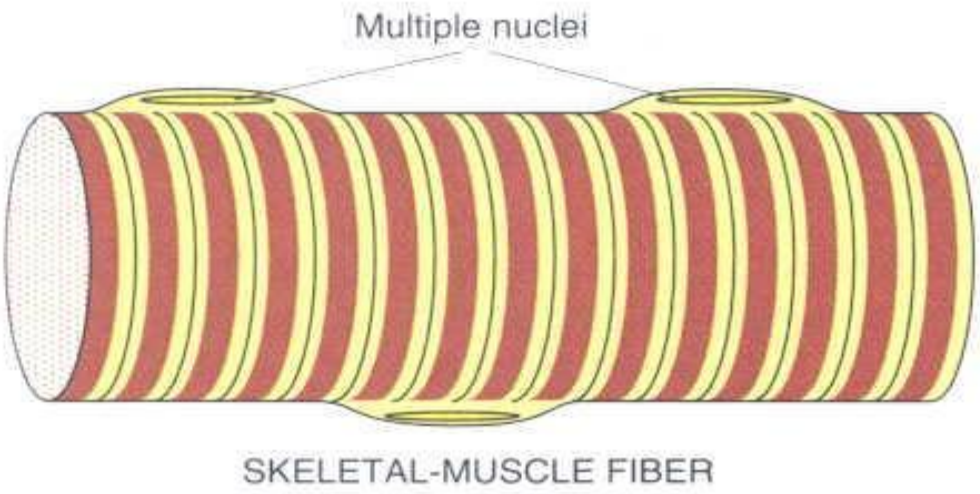
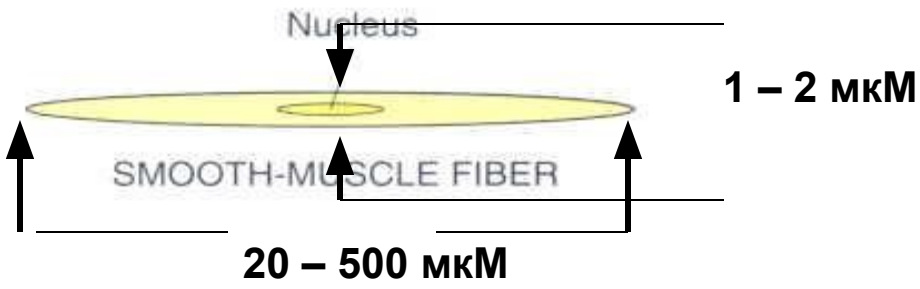
Москва 2013


tunica intima
tunica media
tunica adventitia
endothelium
elastic layer
Muscular Artery

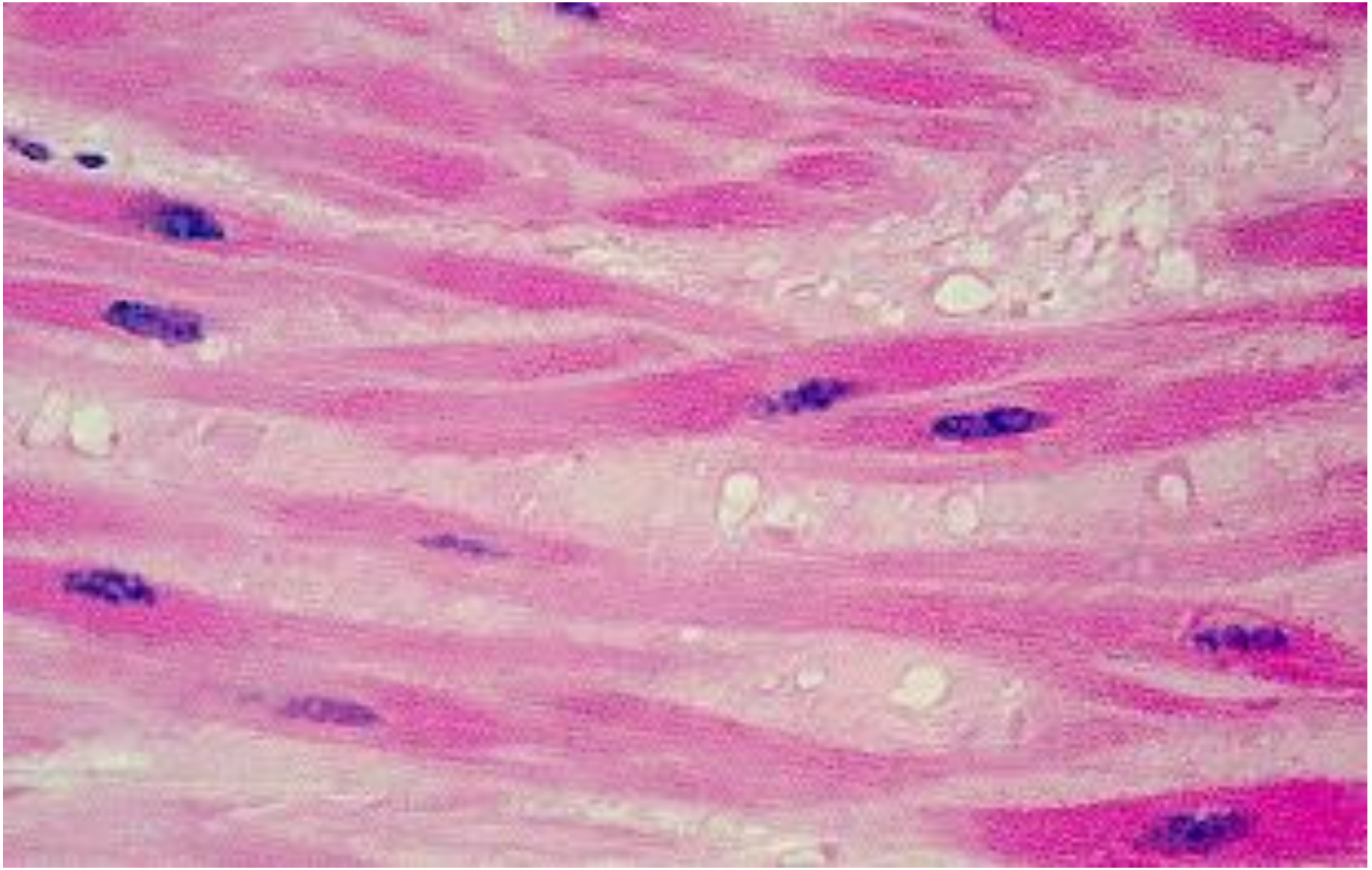

endothelium
tunica intima
tunica media
valve
tunica adventitia
Large Vein

Типы мышечных волокон





Фенотип гладкомышечной клетки



Электронномикроскопическое изображение гладкой мышцы

кавеолы

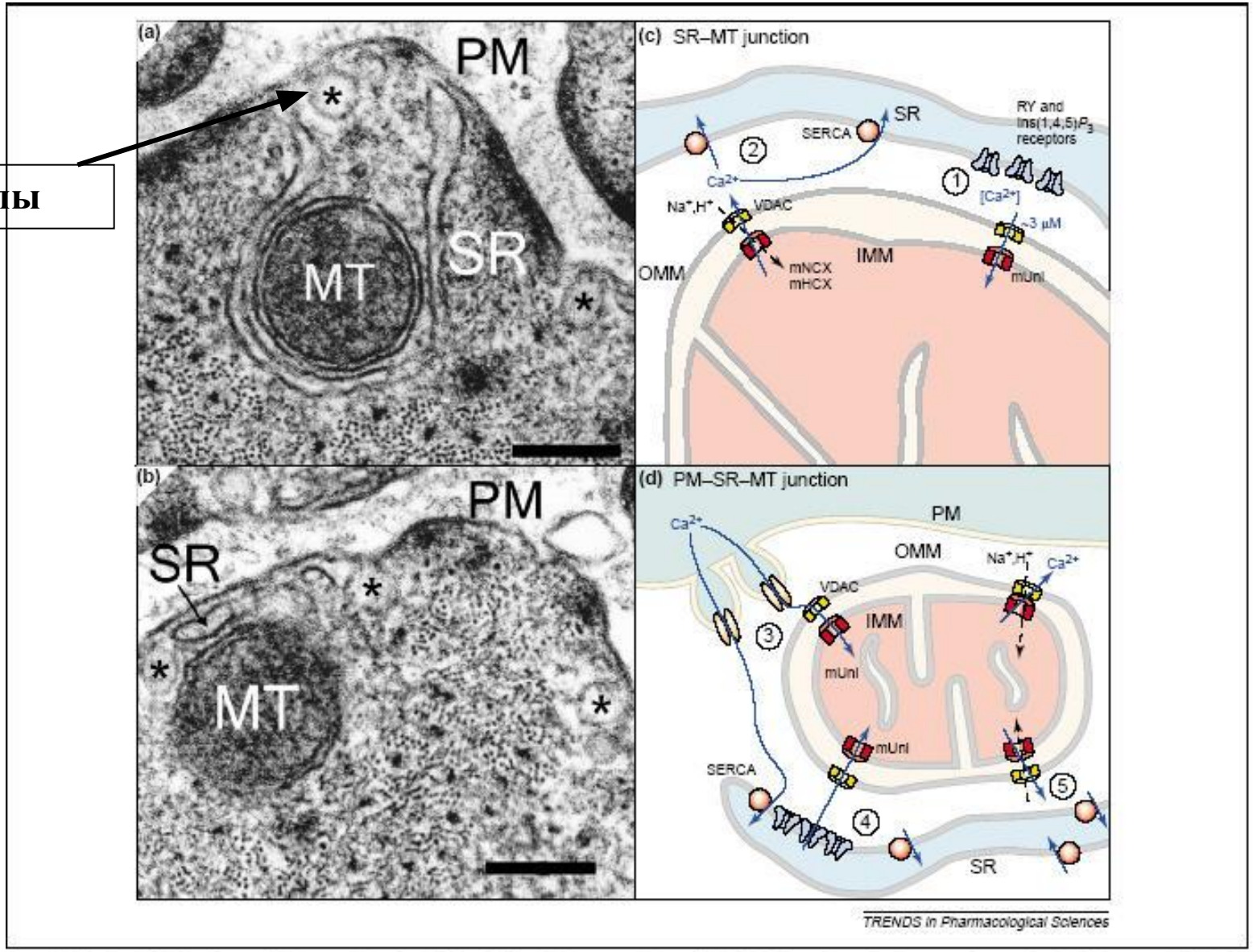


Figure 2. Mitochondrial junctions with the sarcoplasmic reticulum (SR) and plasma membrane (PM). (a,b) Smooth muscle electron micrographs (EMs) that are stained with

Сравнительное изображение трех типов мышц

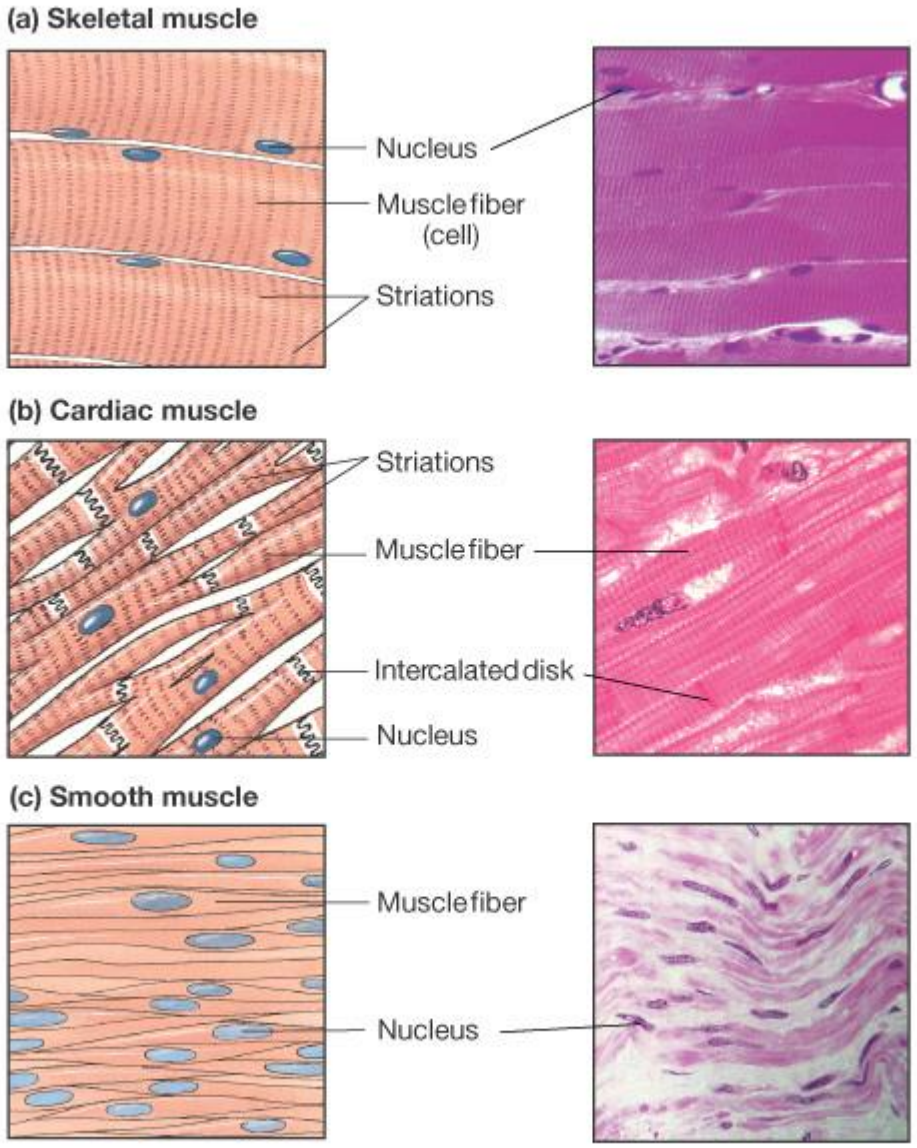
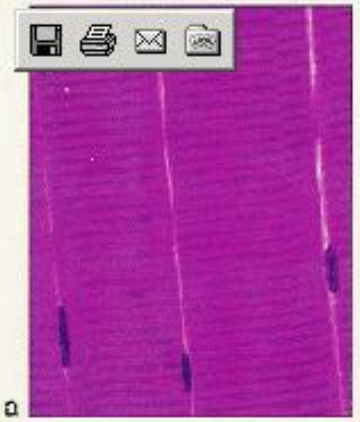


Figure 12-1: Three types of muscles



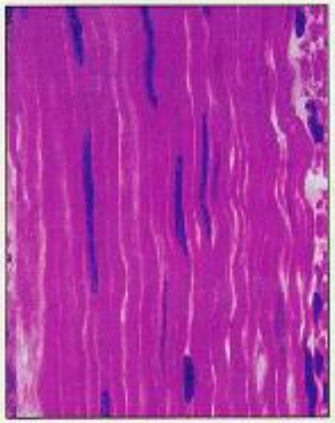
a

TYPE: Skeletal muscle

DESCRIPTION: Long, striated cells with multiple nuclei

COMMON LOCATIONS: In skeletal muscles

FUNCTION: Contraction for voluntary movements



b

TYPE: Smooth muscle

DESCRIPTION: Long, spindle-shaped cells, each with a single nucleus

COMMON LOCATIONS: In hollow organs (e.g., stomach)

FUNCTION: Propulsion of substances along internal passageways

c

TYPE: Cardiac muscle

DESCRIPTION: Branching, striated cells fused at plasma membranes

COMMON LOCATIONS: Wall of heart

FUNCTION: Pumping of blood in the circulatory system

Типы гладкомышечных клеток

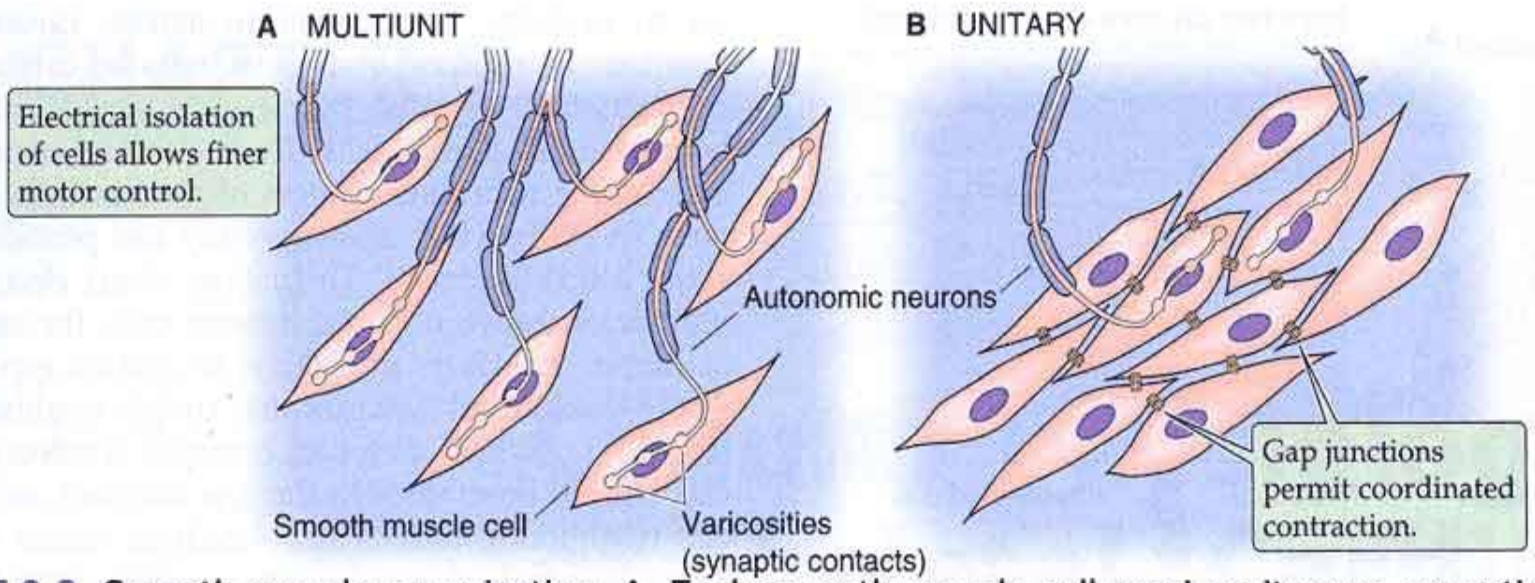


FIGURE 9-2. Smooth-muscle organization. A, Each smooth muscle cell receives its own synaptic input. B, only a few of the smooth muscle cells receive direct synaptic input.

Распространение сократительной активности в гладкой мышце

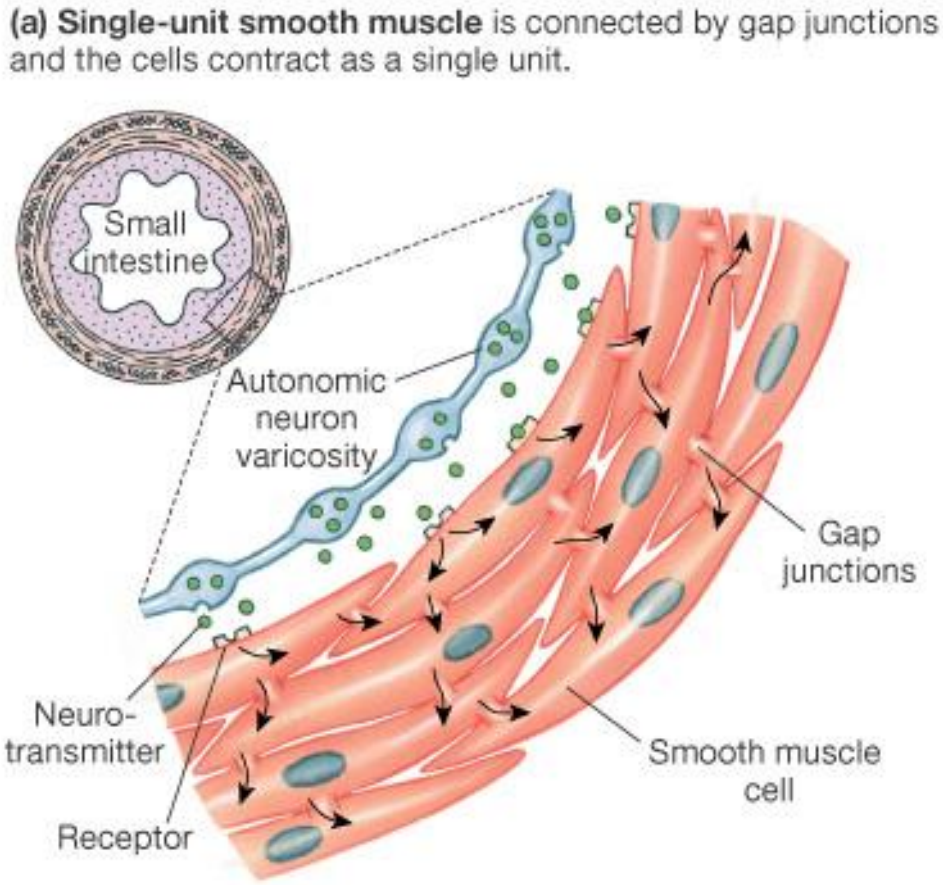
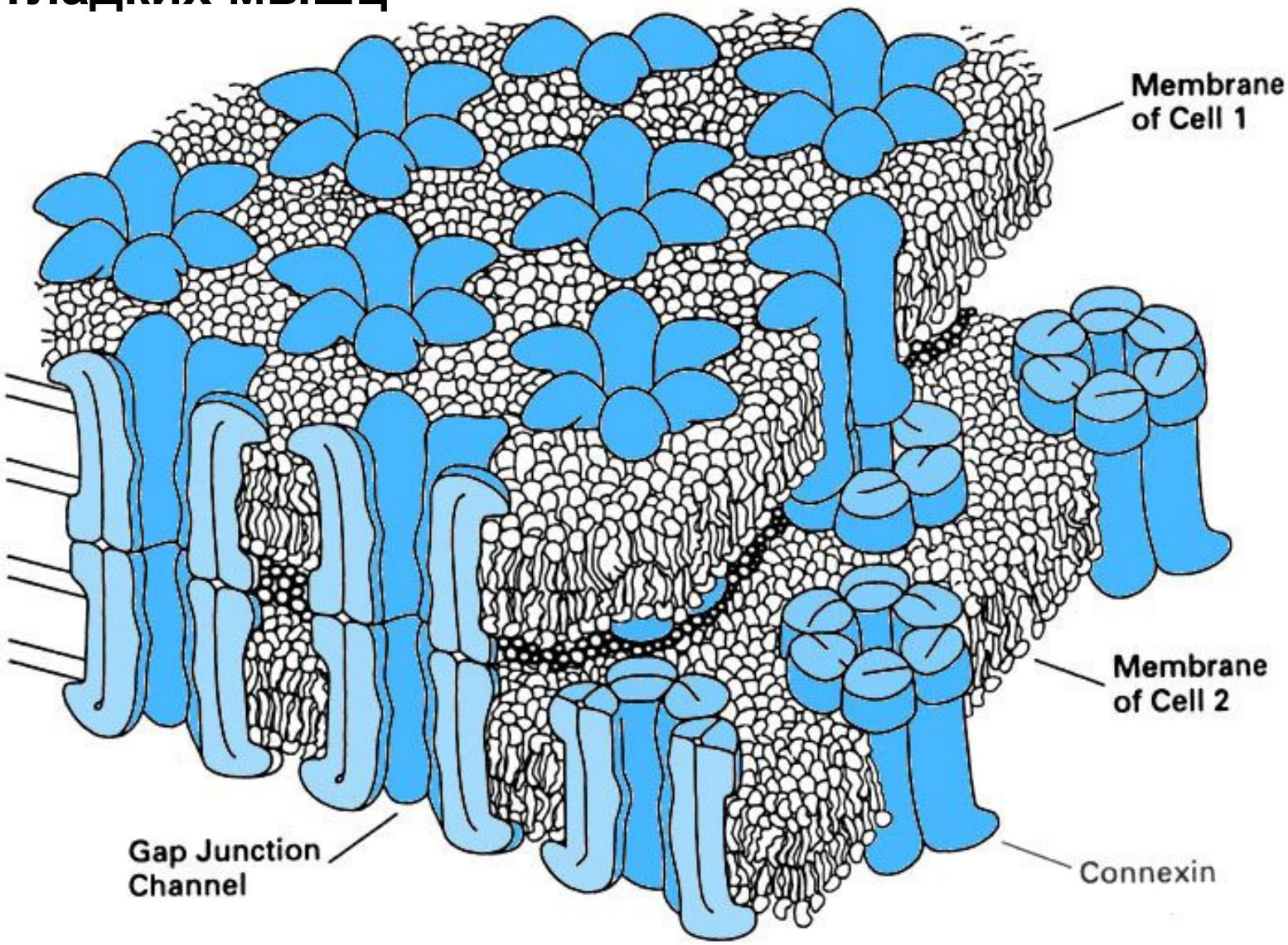
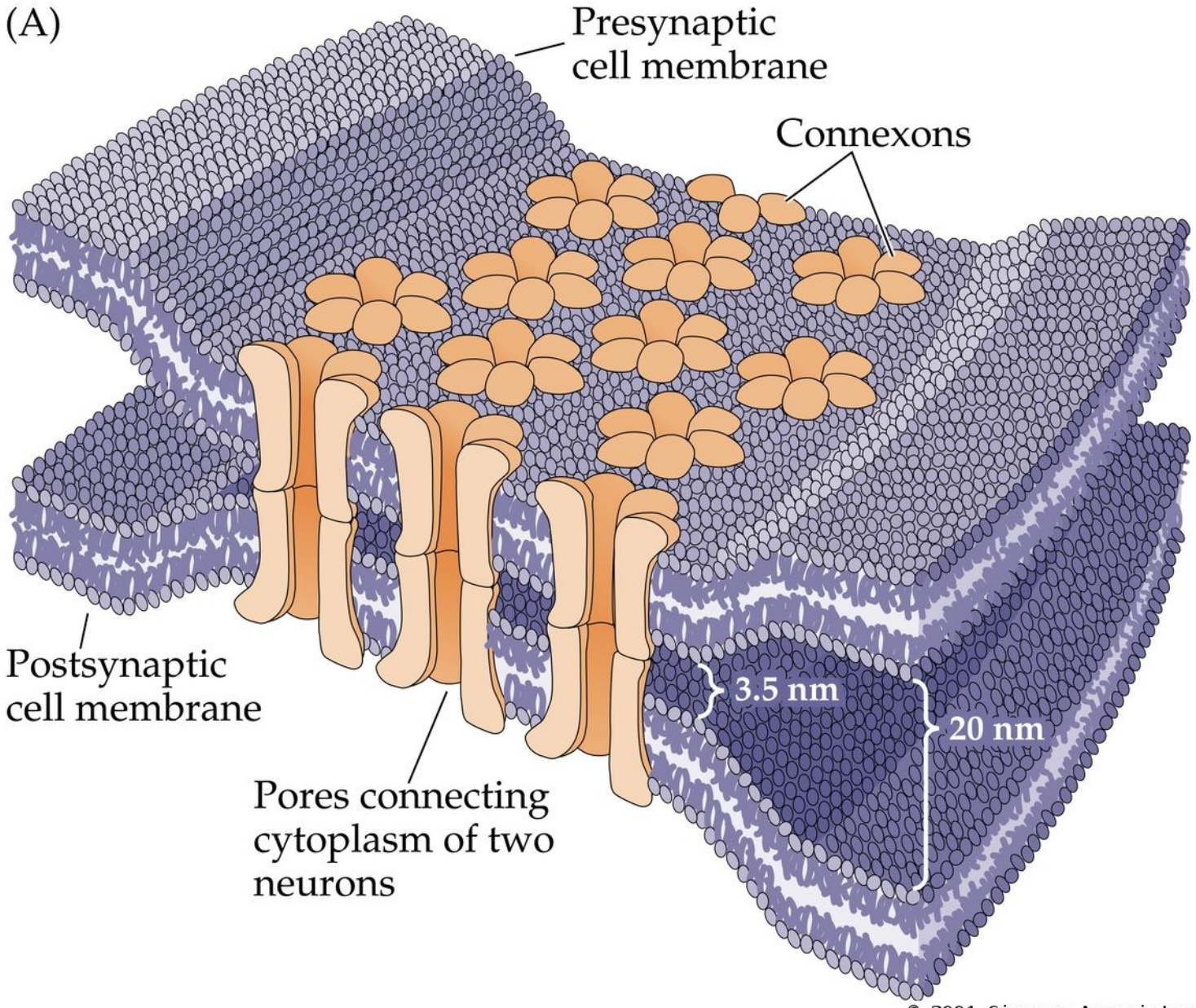


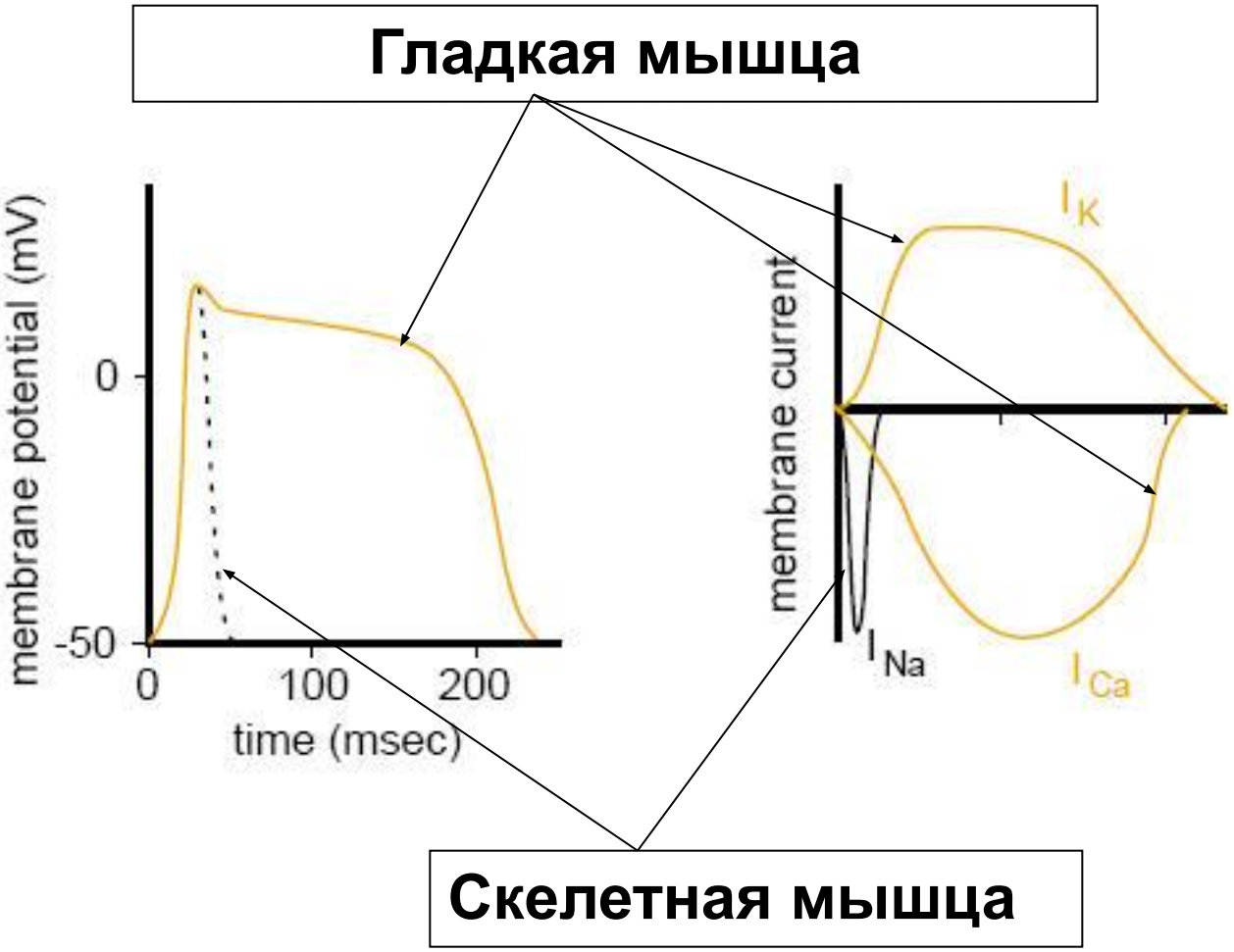
Figure 12-25a: Types of smooth muscle

Щелевые контакты в гладкой мышце осуществляют передачу возбуждения от клетки к клетке в унитарном типе гладких мышц

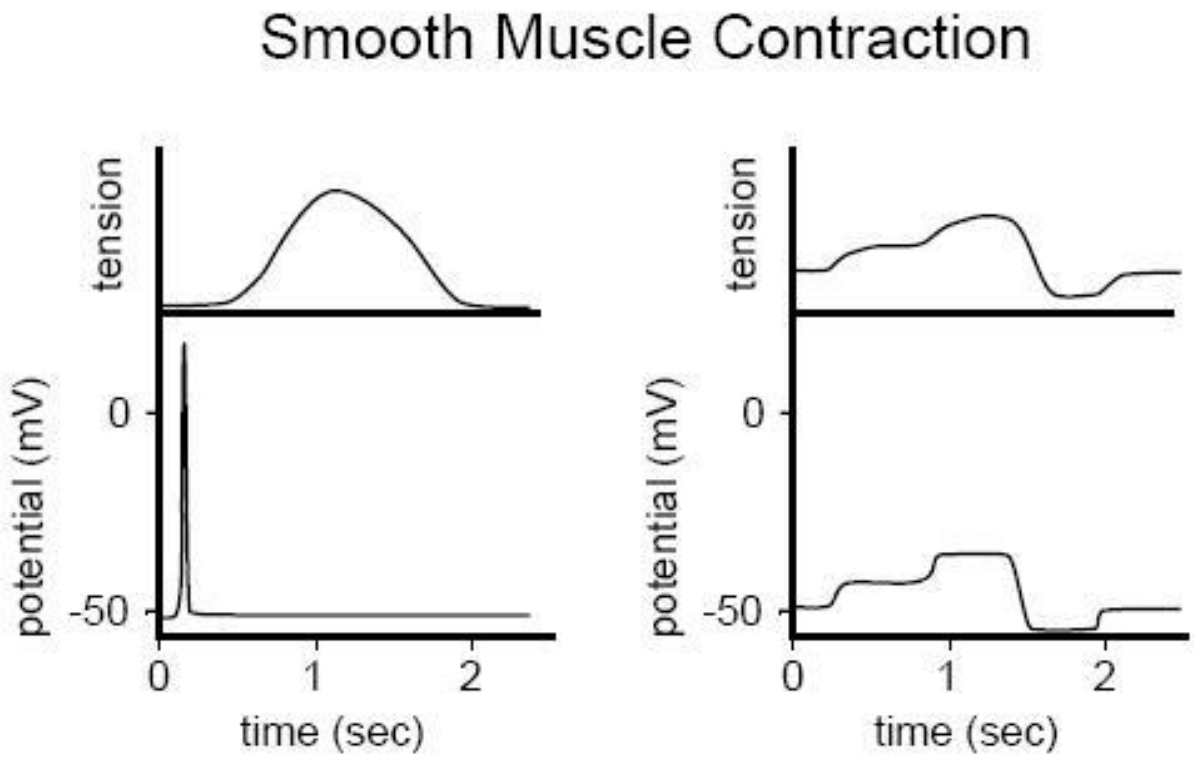




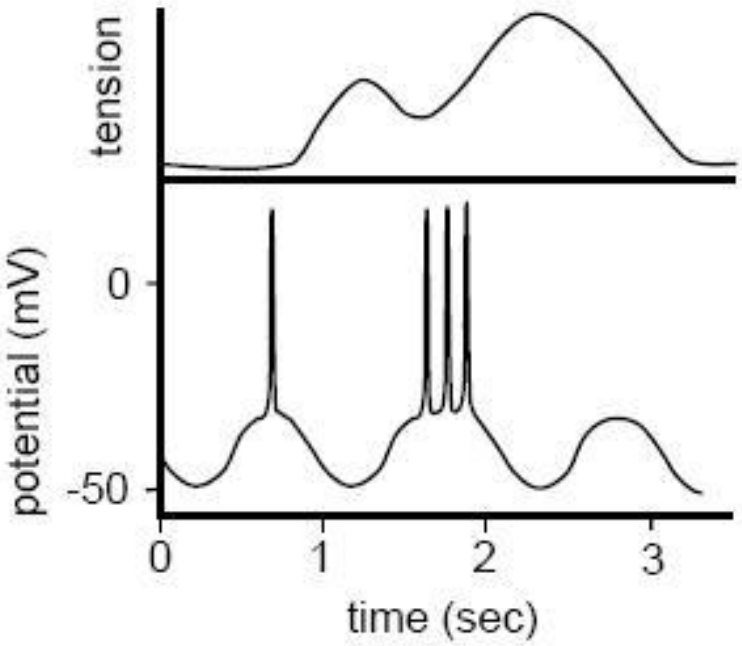
Потенциал действия гладких мышц сосудов



Тонический и фазический тип сокращений гладких мышц



Smooth Muscle Pacemaker Activity



Кривые сокращений скелетной, сердечной и гладкой мышц

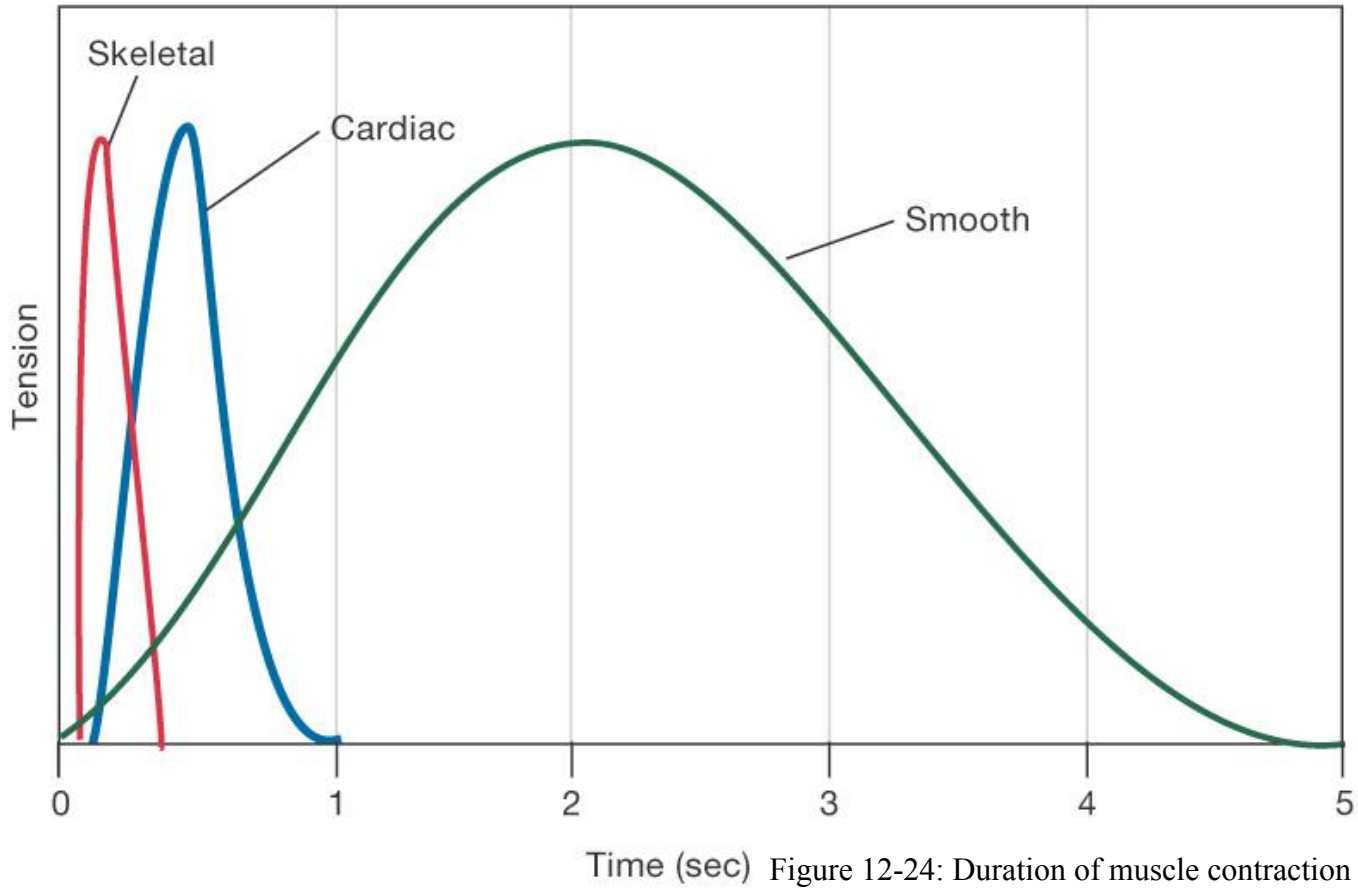


Figure 12-24: Duration of muscle contraction in three types of muscle

Механизм сокращений скелетных мышц

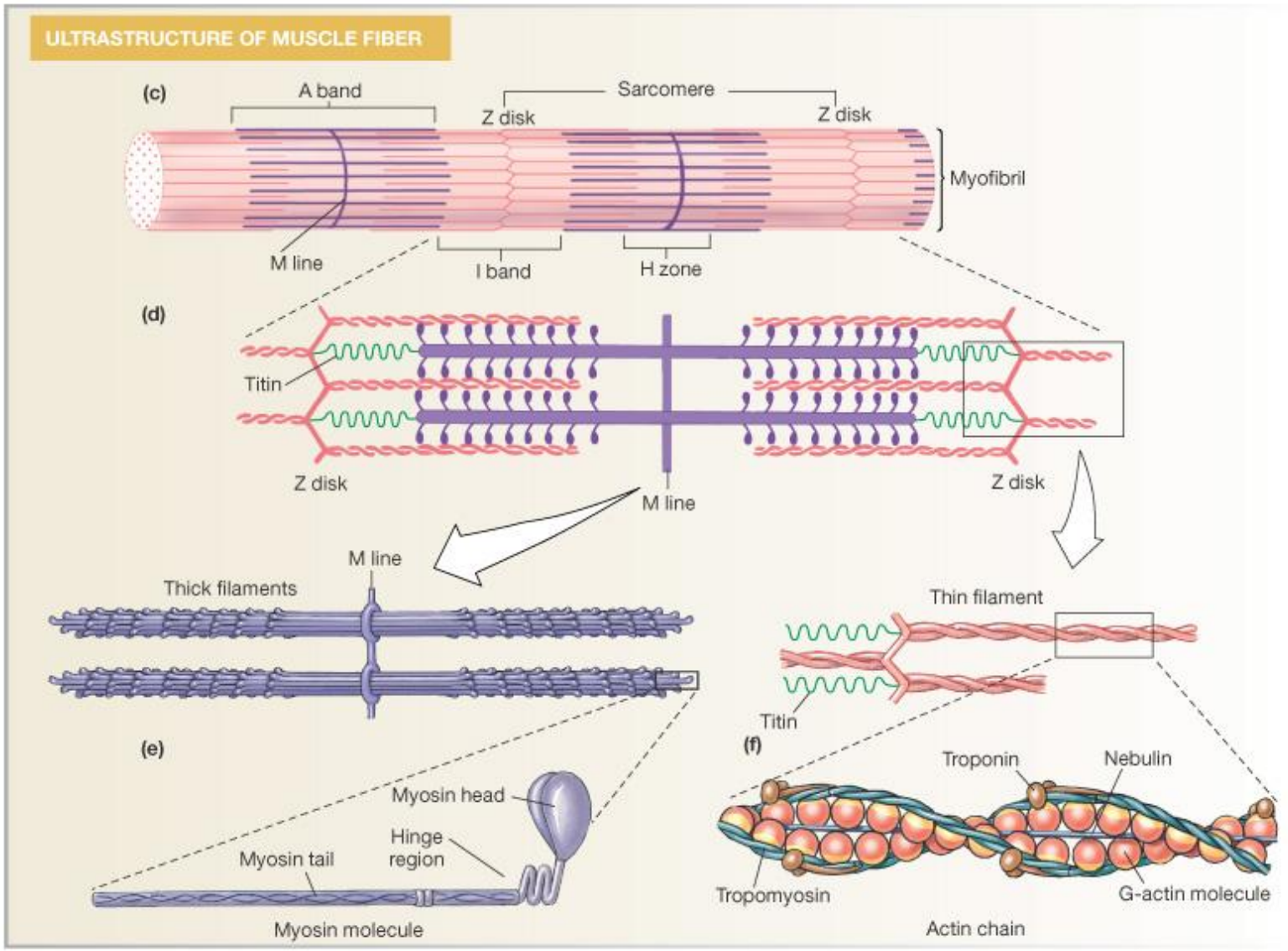
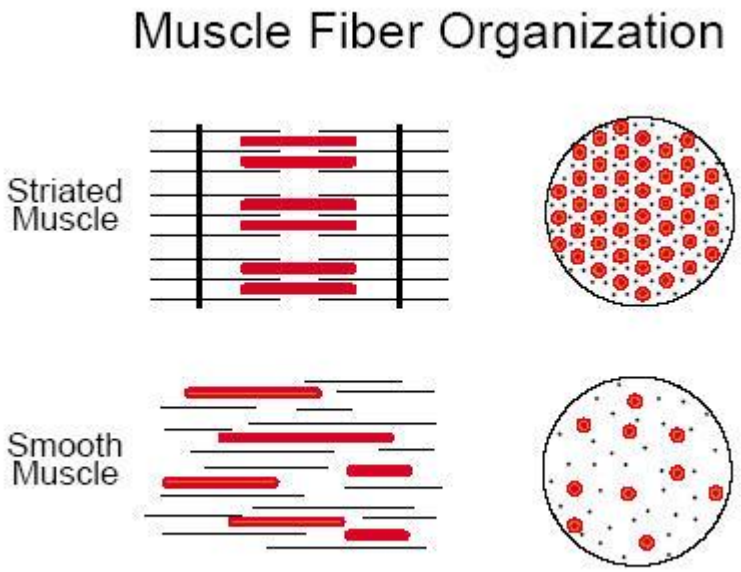
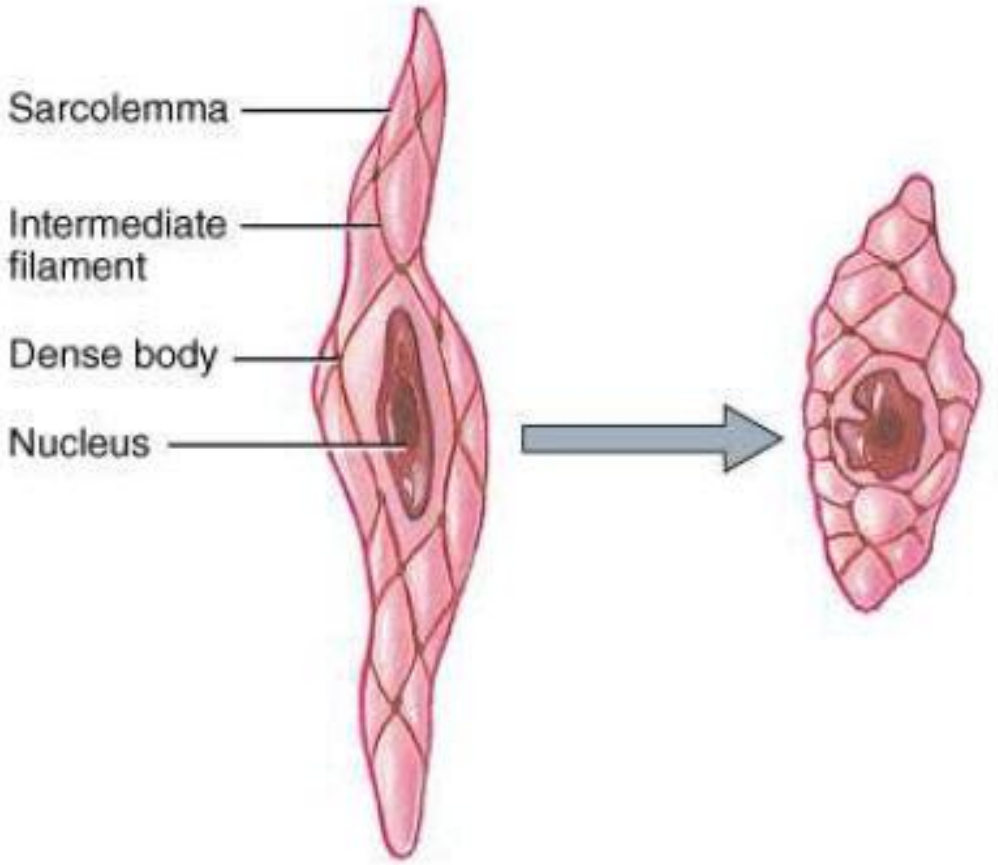


Figure 12-3c-f: ANATOMY SUMMARY: Skeletal Muscle

Сравнительная организация сократительных элементов в скелетной и гладкой мышцах



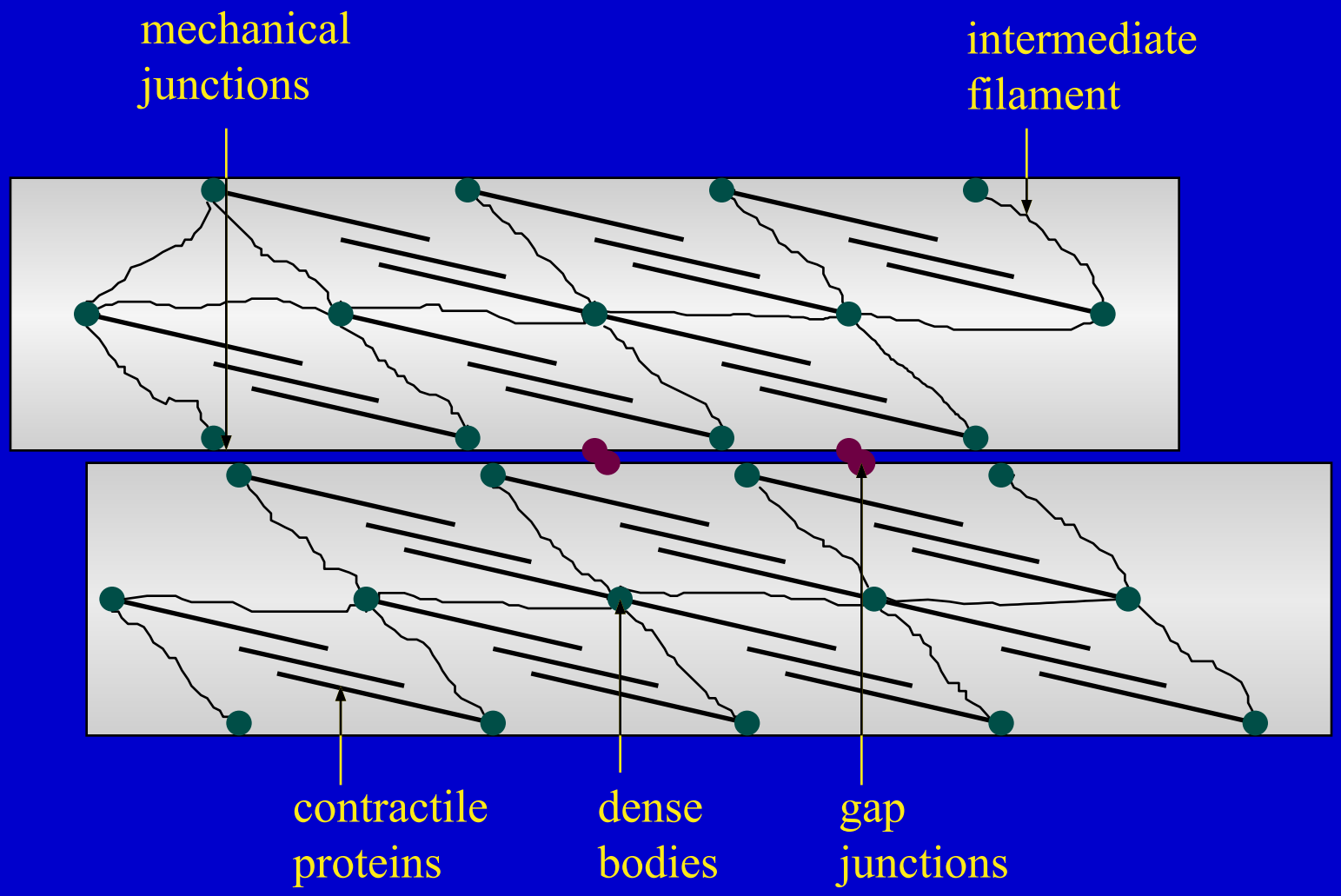
Вид гладкомышечной клетки в покое и при сокращении



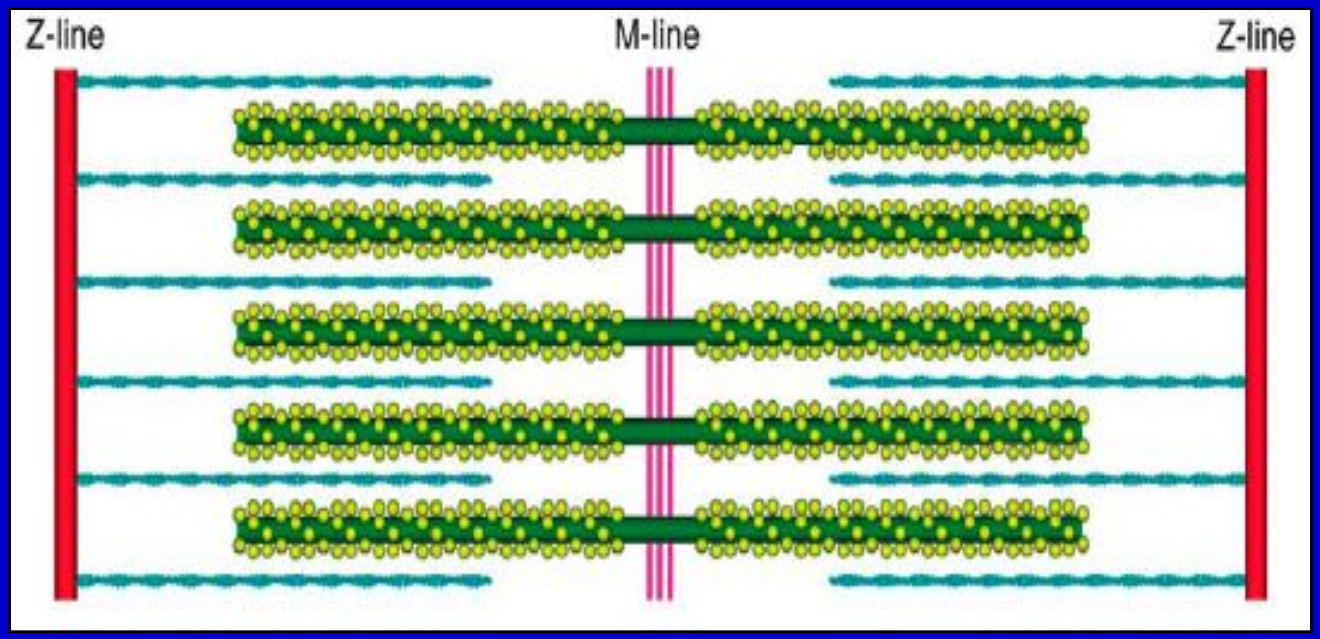
(a) Details of a smooth muscle fiber

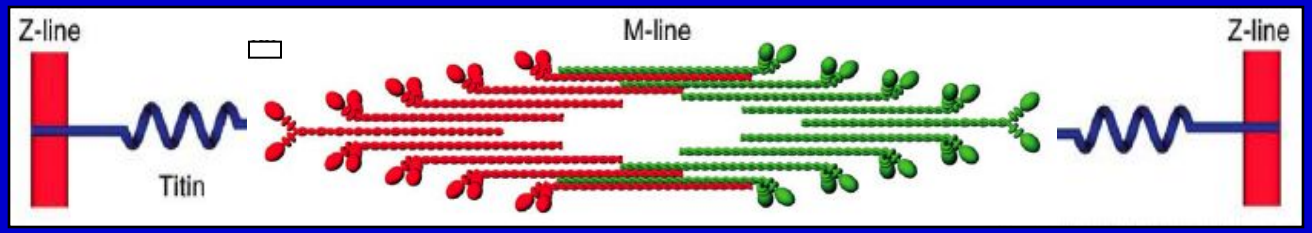
The fibrillar contractile apparatus

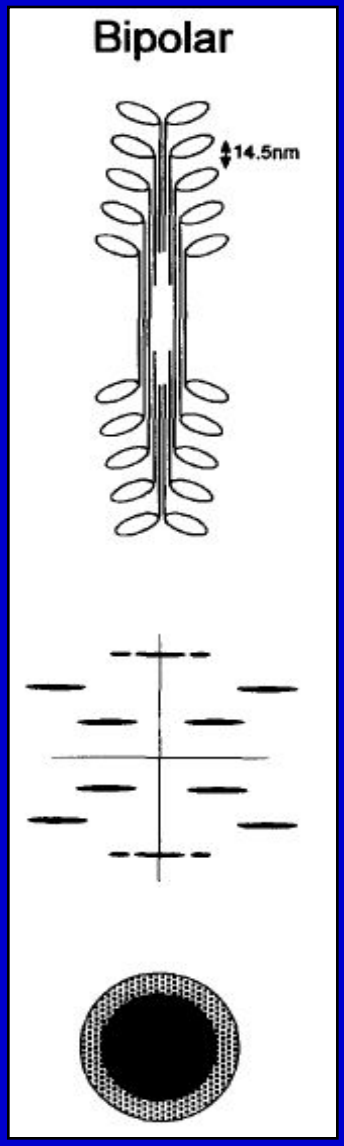
Dense bodies serve as an attachment points for the thin filaments
Intermediate filaments form a cytoskeletal network between dense bodies



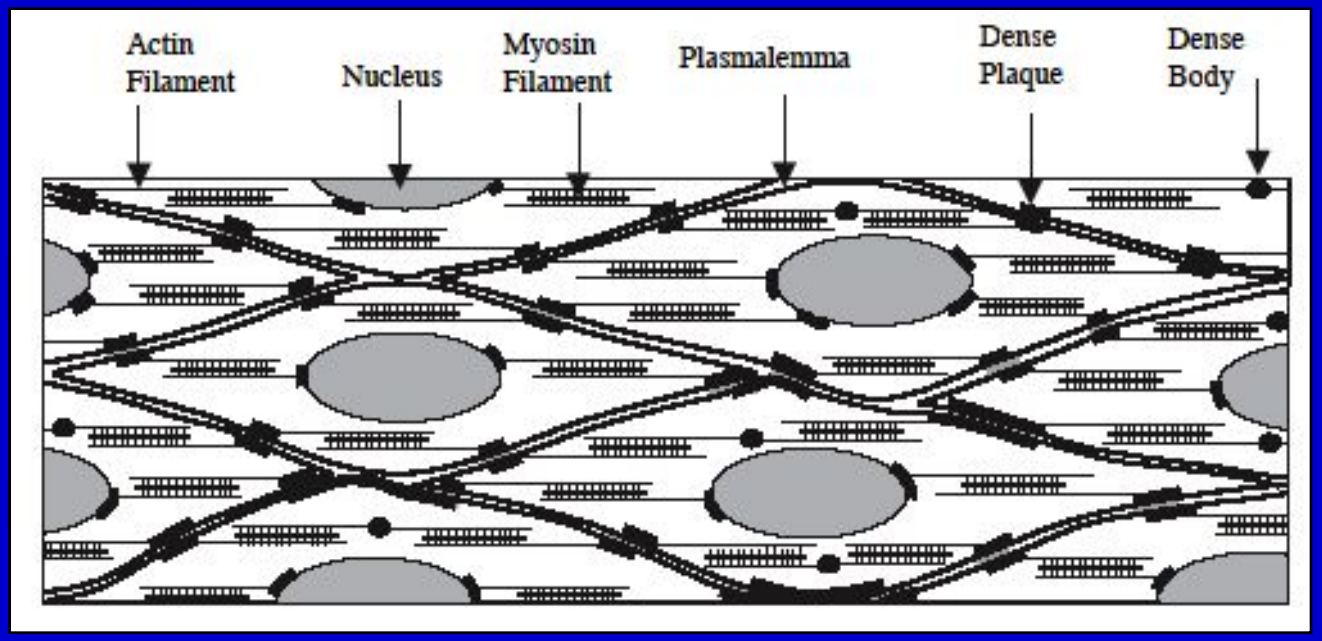
Структурная композиция сократительного аппарата (поперечнополосатая мускулатура)

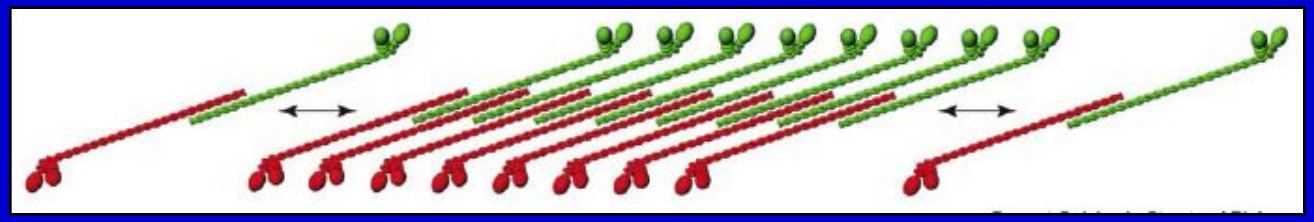


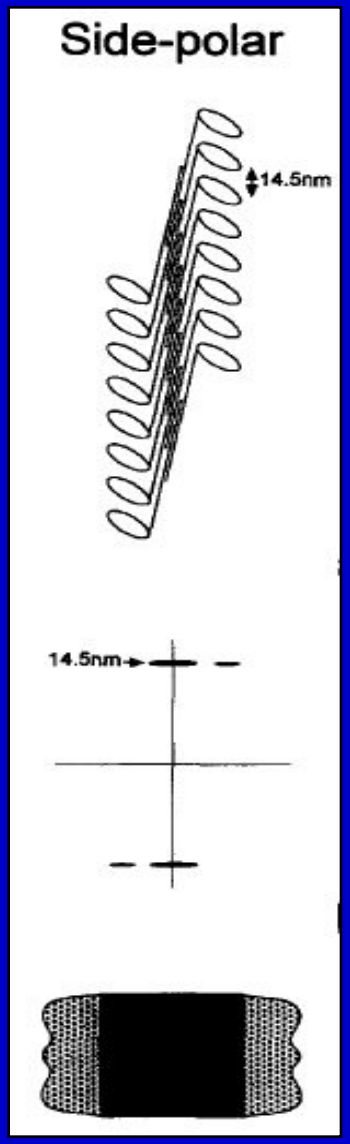




Структурная композиция сократительного аппарата (гладкая мускулатура)







Механизм сокращений в гладкой мышце

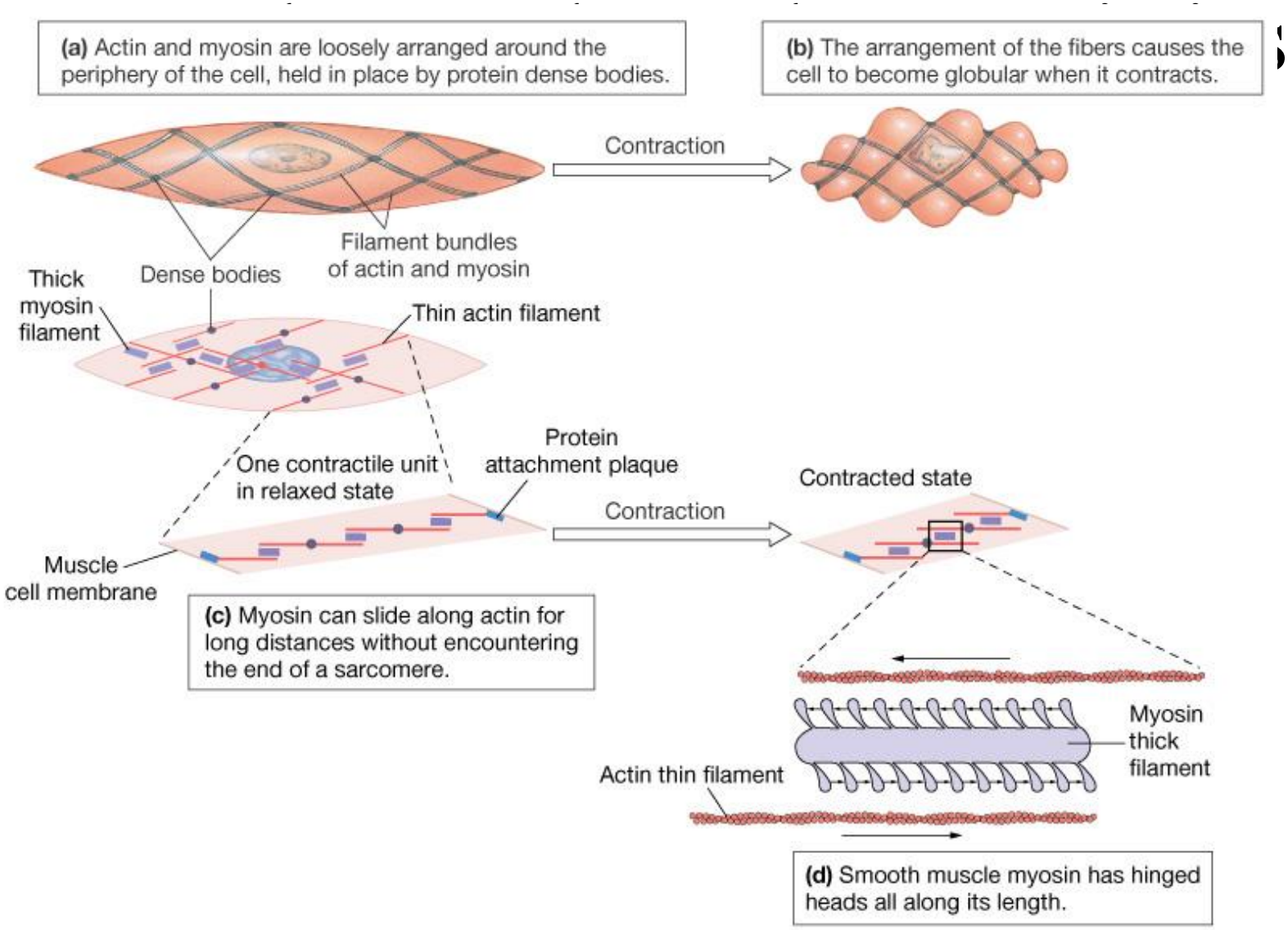
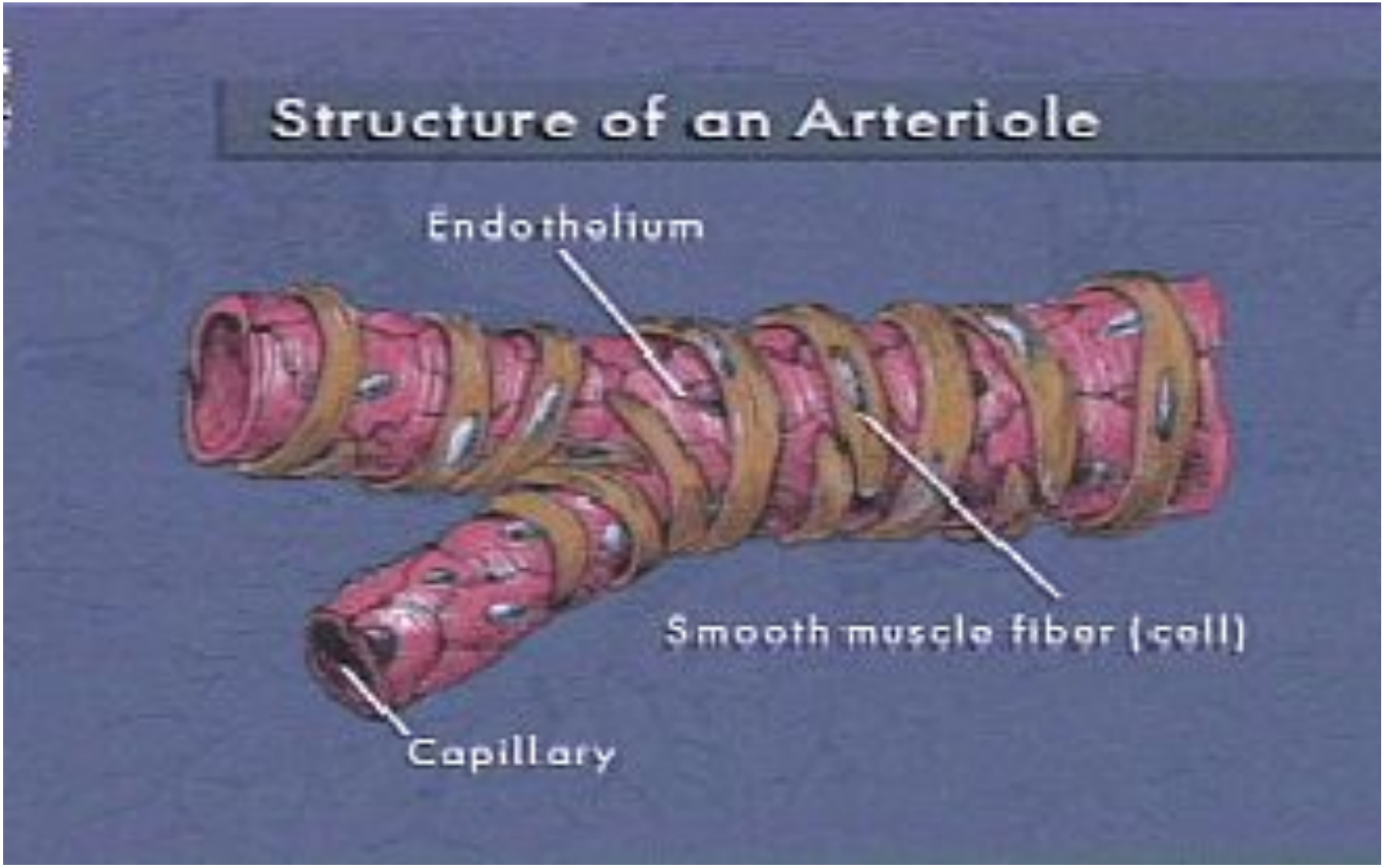
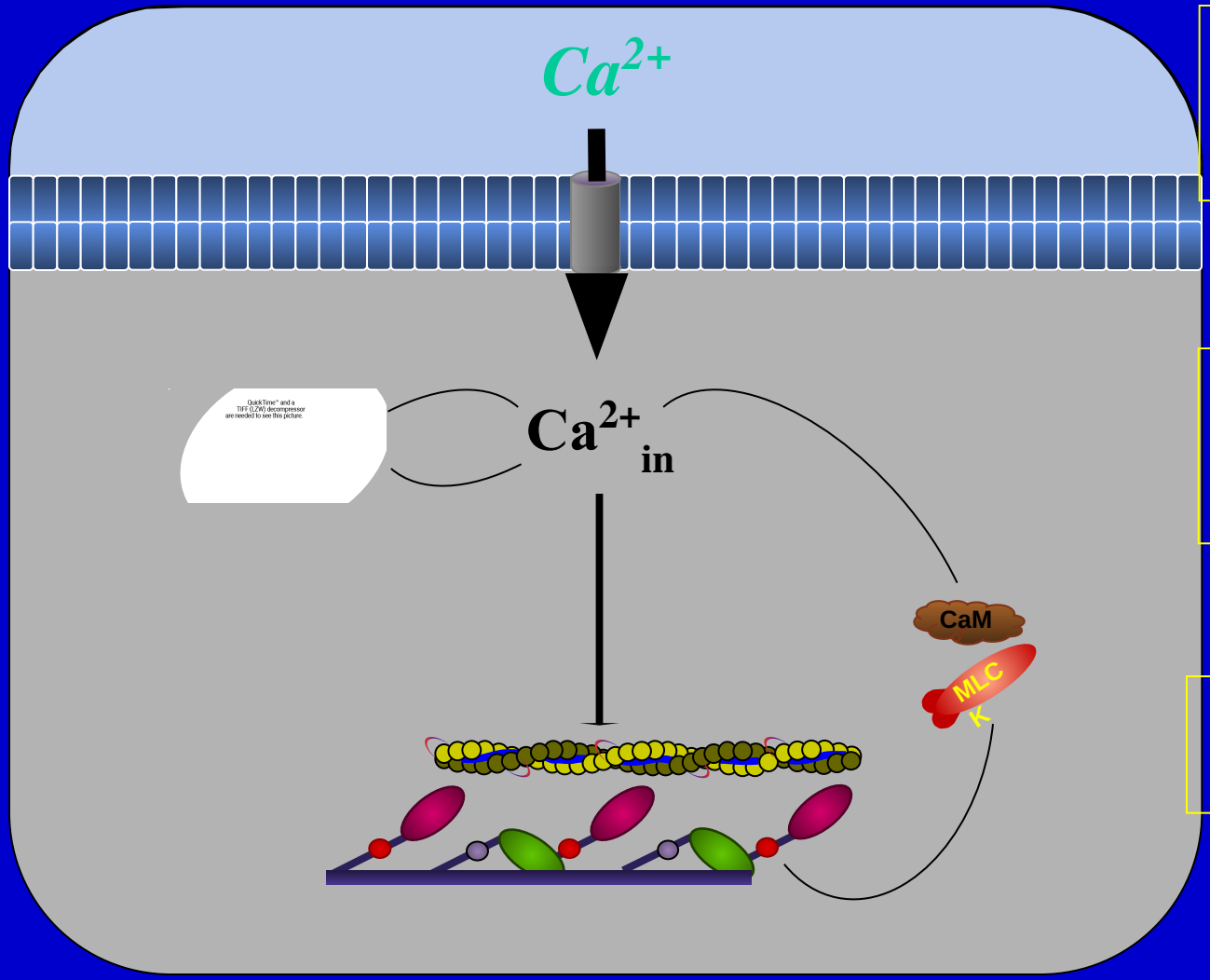


Figure 12-27: Anatomy of smooth muscle


Structure of an Arteriole
Endothelium
Smooth muscle fiber (cell)
Capillary

Регуляция сократительного аппарата скелетных мышц (excitation-contraction coupling)



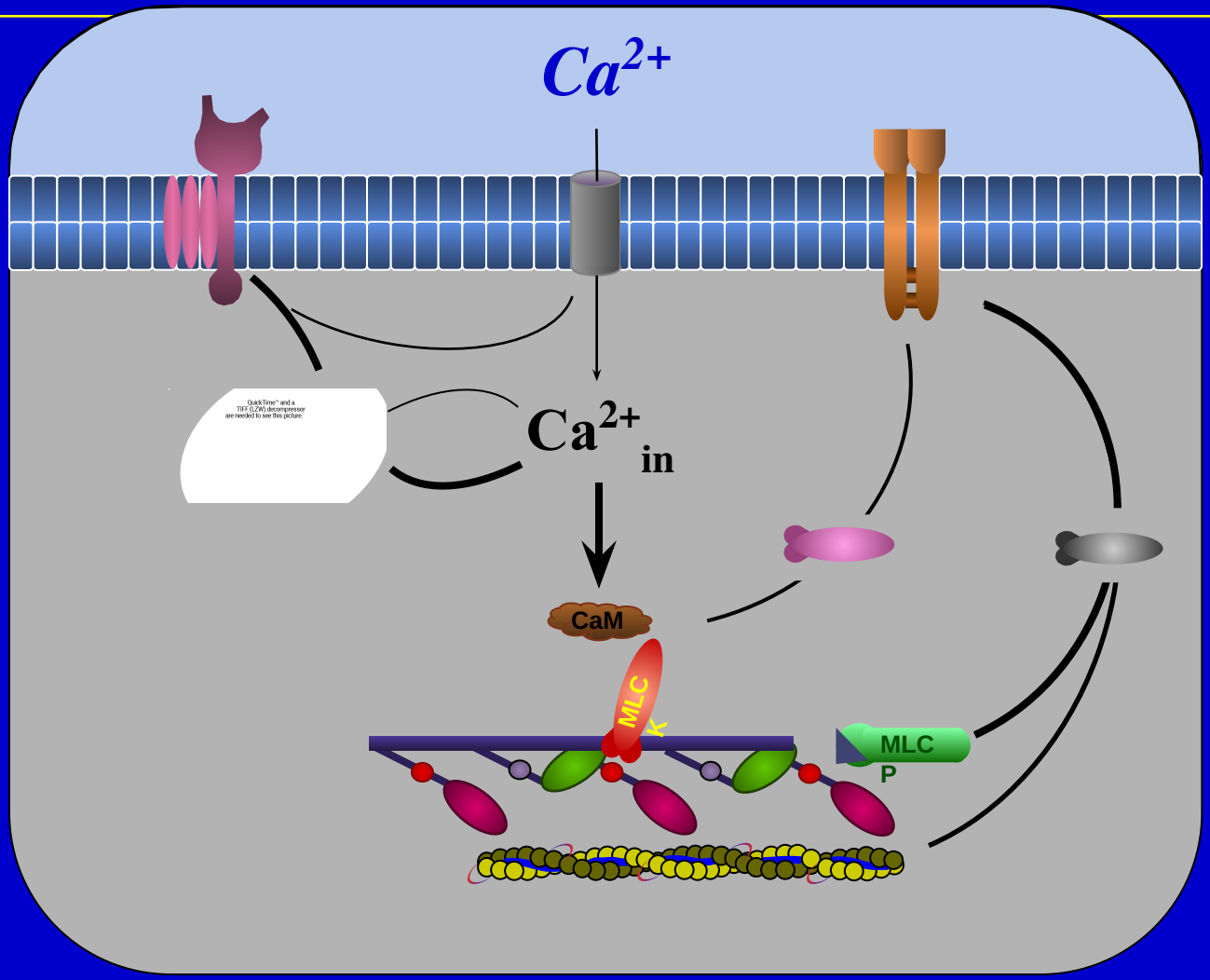
ПОТЕНЦИАЛ ДЕЙСТВИЯ

VDCC

ЭЛЕКТРОМЕХАНИЧЕСКОЕ СОПРЯЖЕНИЕ

ПРЯМАЯ АКТИВАЦИЯ АКТОМИОЗИНА

Регуляция сократительного аппарата гладких мышц сосудов (excitation-contraction coupling)



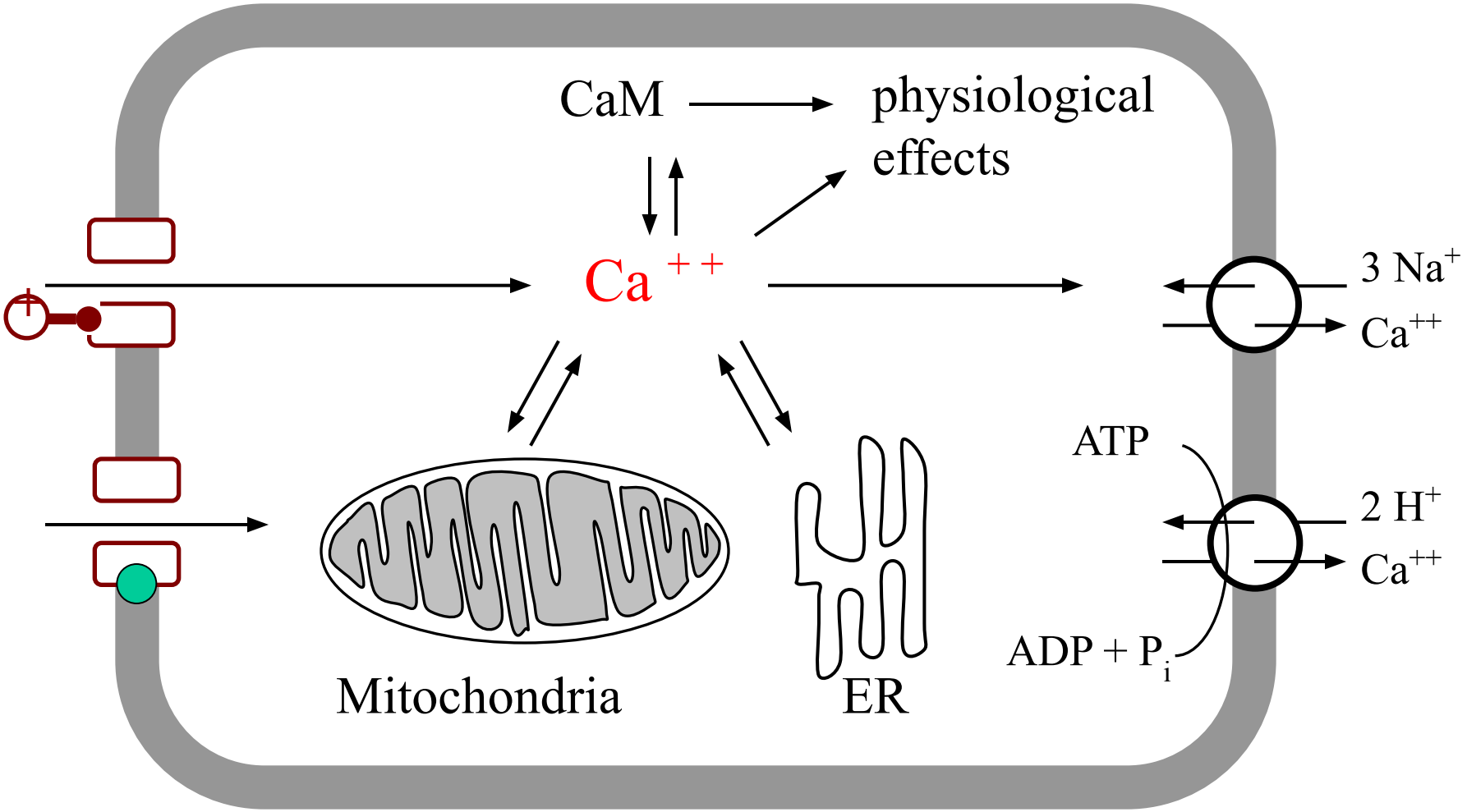
ГОРМОН-РЕЦЕПТОРНОЕ МНОГООБРАЗИЕ

ФАРМАКОМЕХАНИЧЕСКОЕ СОПРЯЖЕНИЕ

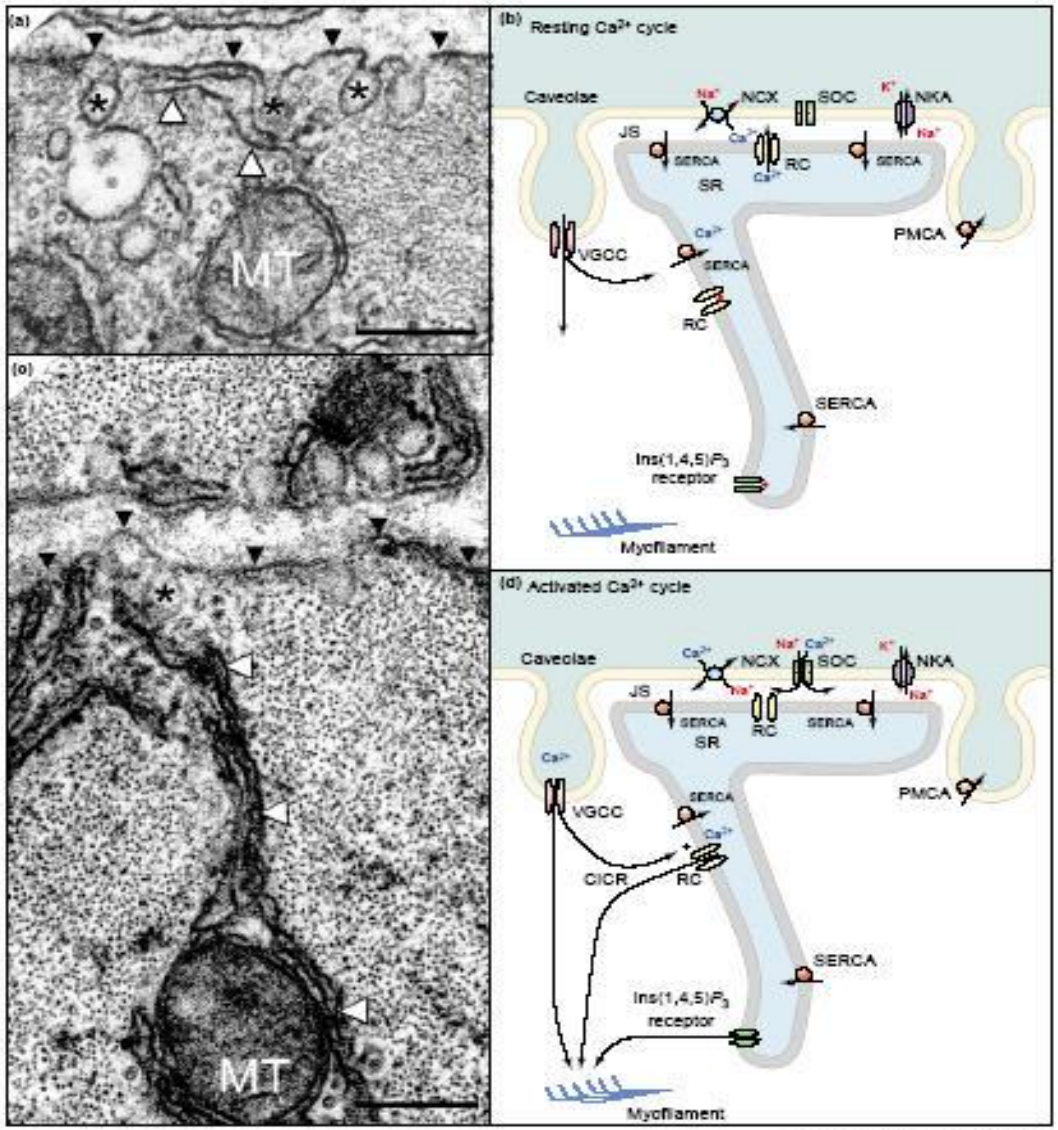
Ca^{2+}-ЧУВСТВИТЕЛЬНОСТЬ

(Ca^{2+}-SENSITIZATION)

Транспорт ионов кальция в гладкомышечную клетку и из клетки



Локализация ионов Ca в клетке гладкой мышцы



V2,N1,2004

Figure 1. Ca^{2+} cycling at plasma membrane (PM)–sarcoplasmic reticulum (SR) junctions in smooth muscle. (a) An electron micrograph (EM) of superficial SR (white arrowheads) associated with the PM (black arrowheads) and caveolae (asterisks). (b) A cartoon to illustrate cellular Ca^{2+} cycling in non-stimulated vascular smooth muscle. At rest, the superficial SR buffers the entry of extracellular Ca^{2+} as a result of the low open probability of excitable Ca^{2+} channels and putative 'leak' channels, and cycles it, via release channels (RCs) (inositol (1,4,5)-triphosphate [Ins(1,4,5)P_3] and ryanodine (RY) receptors) to the Na^+–Ca^{2+} exchanger (NCX) in the junctional space (JS) to be

Calcium activates calmodulin

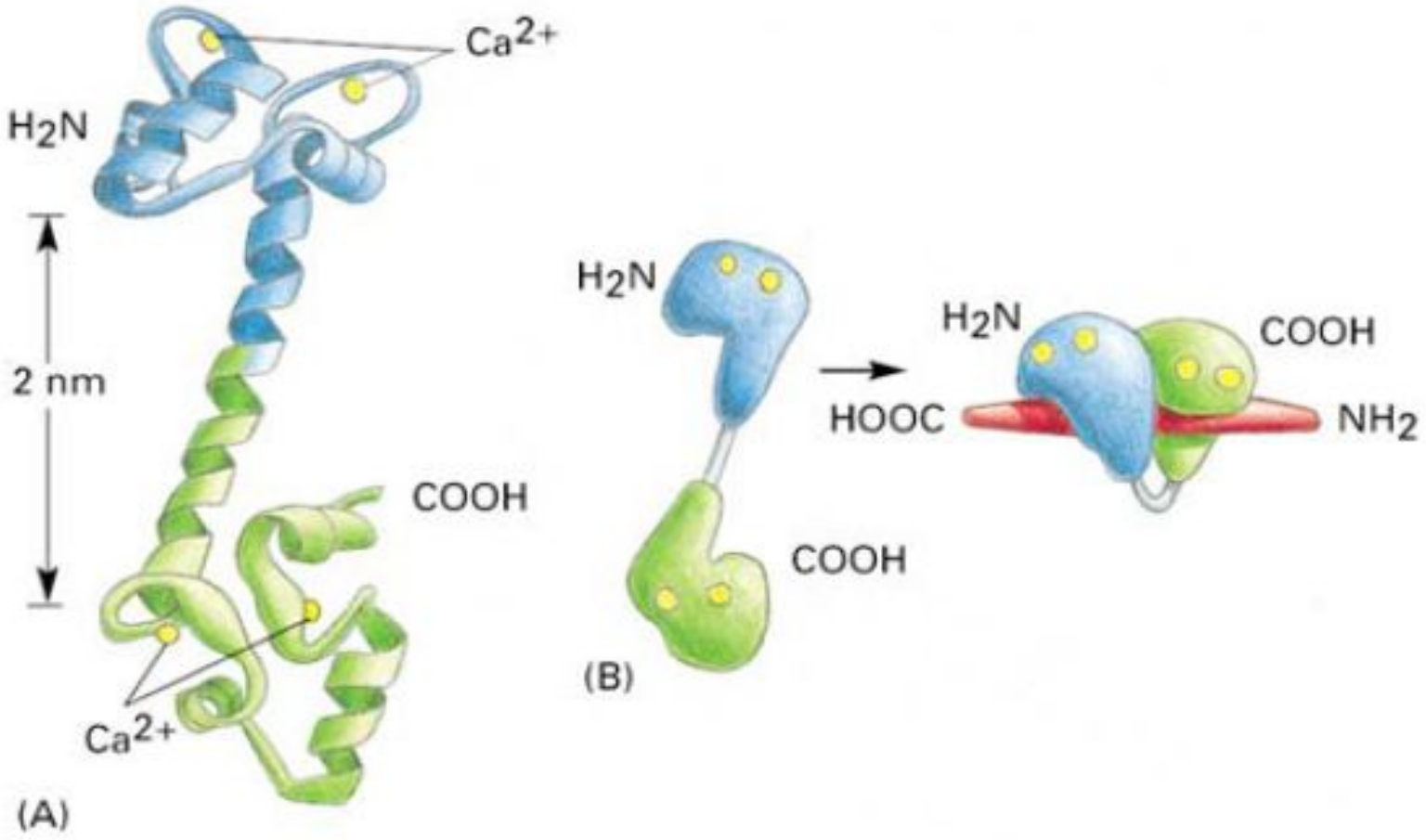
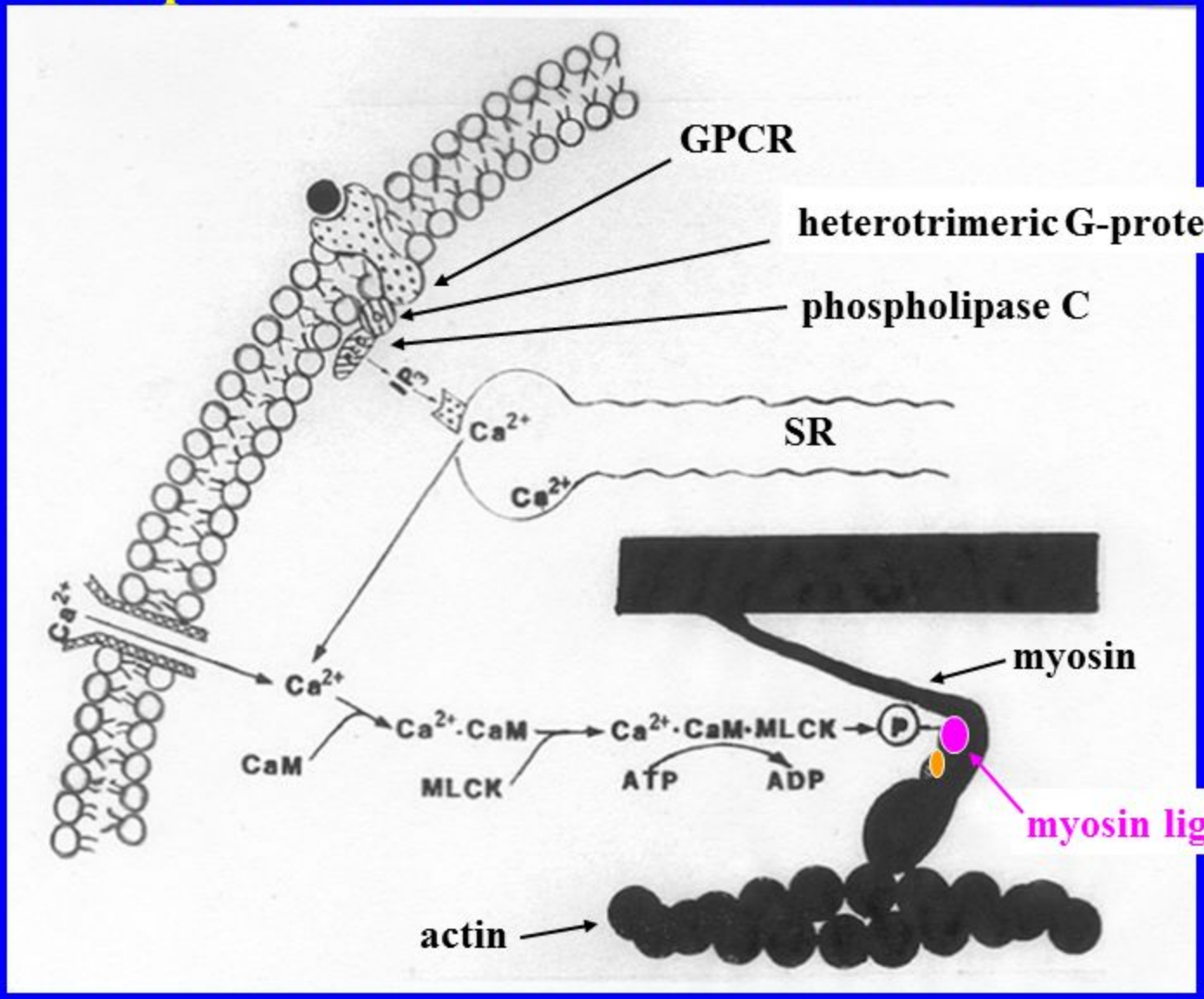


Figure 15–40. Molecular Biology of the Cell, 4th Edition.

A Simplified View of Smooth Muscle Contraction



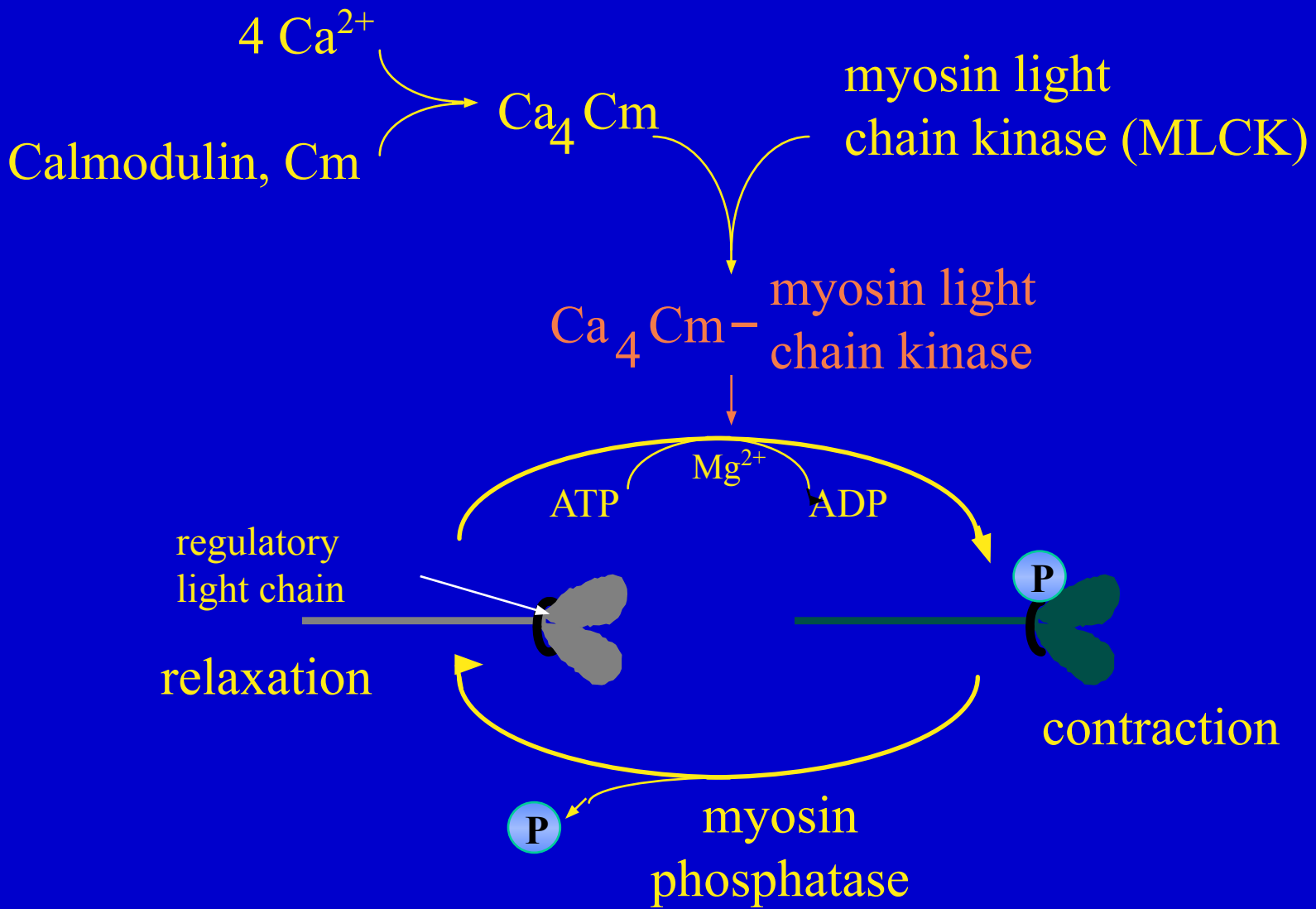
CaM = Calmodulin

MLCK = myosin light chain kinase

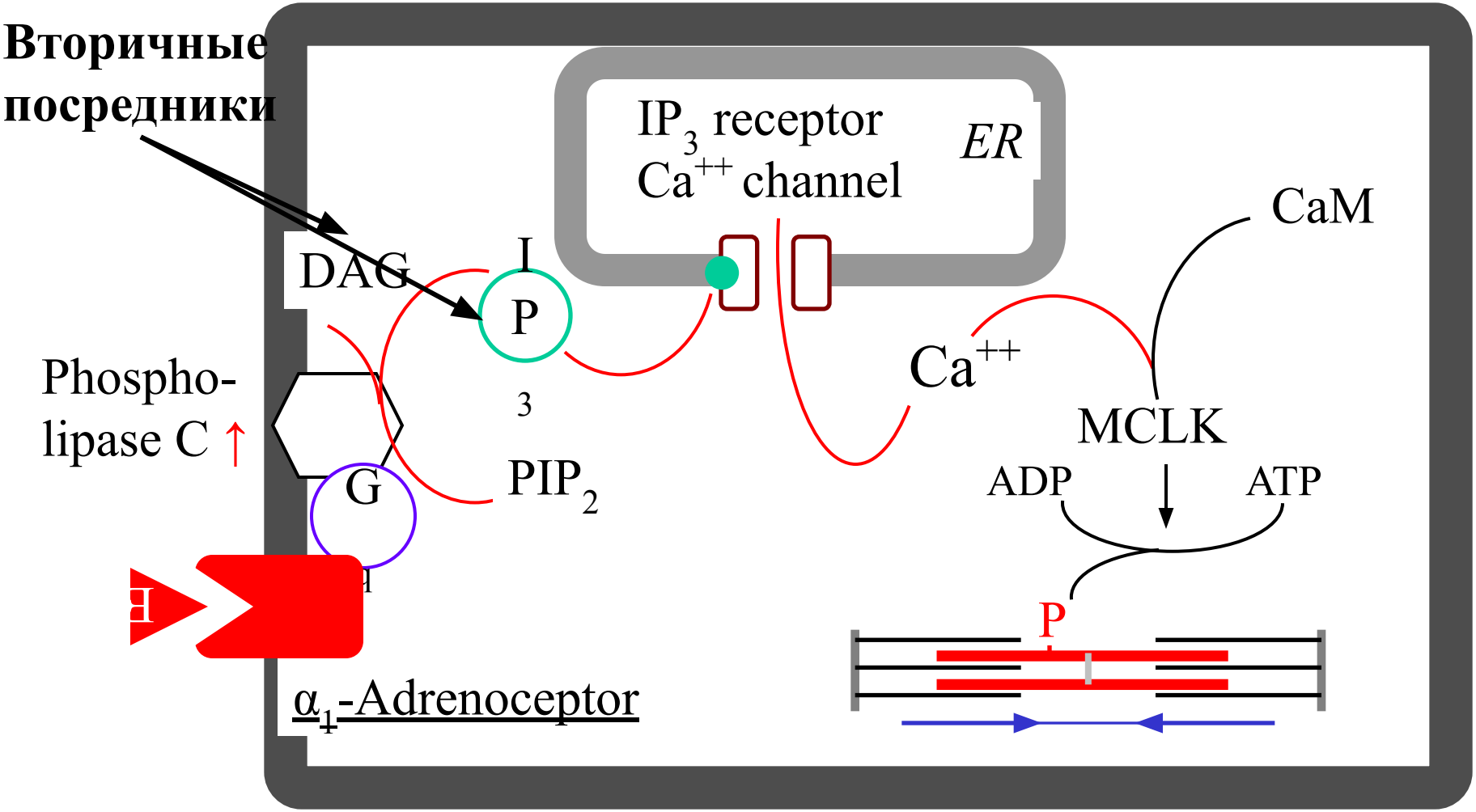
IP_3 = inositol trisphosphate

Bárány, K. and Bárány, M. (1996). Myosin light chains.
In *Biochemistry of Smooth Muscle Contraction* (M. Bárány , Ed.), pp. 21-35, Academic Press.

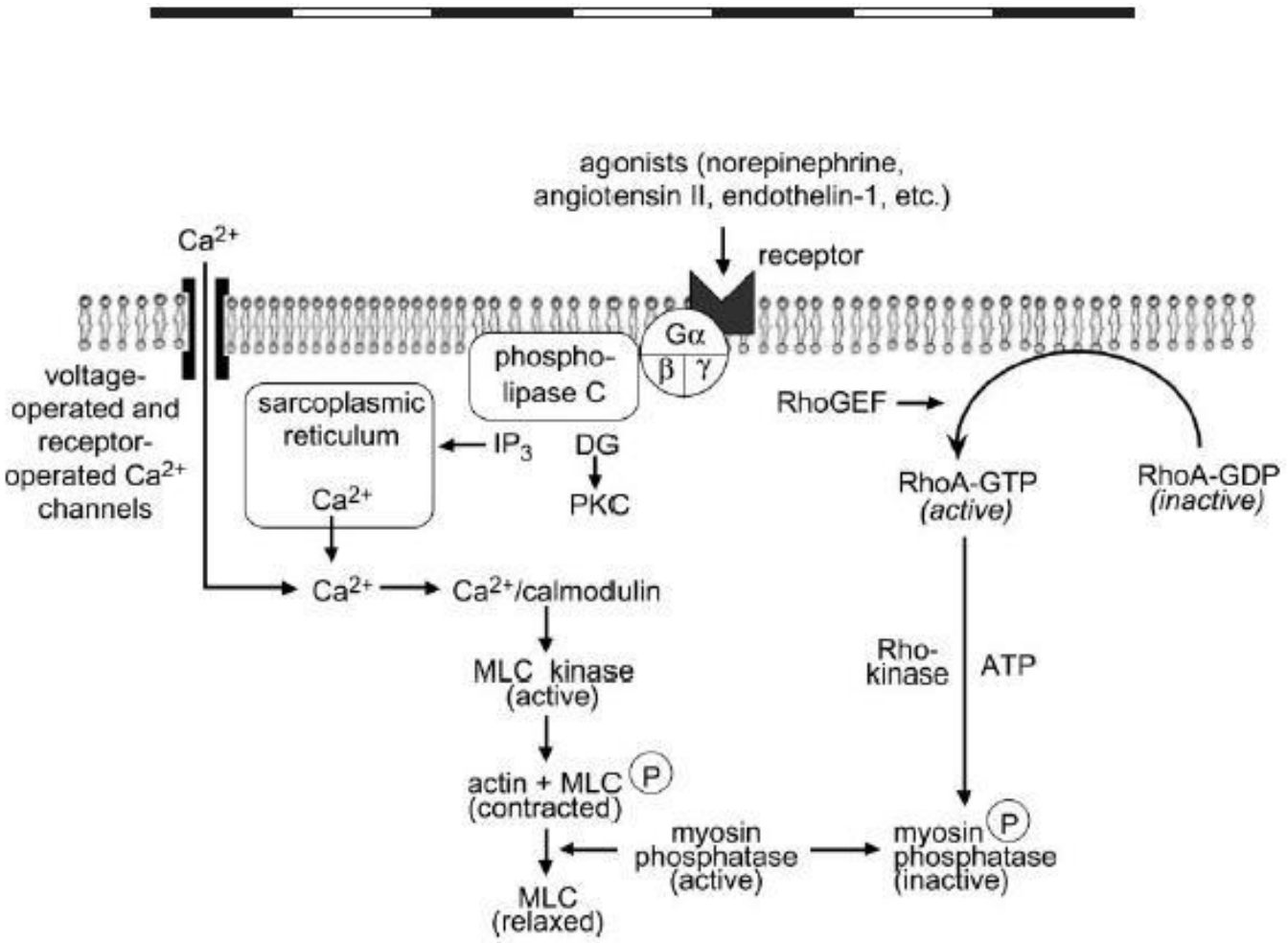
Cross-bridge activation in smooth muscle
Ca^{2+}-stimulated myosin phosphorylation



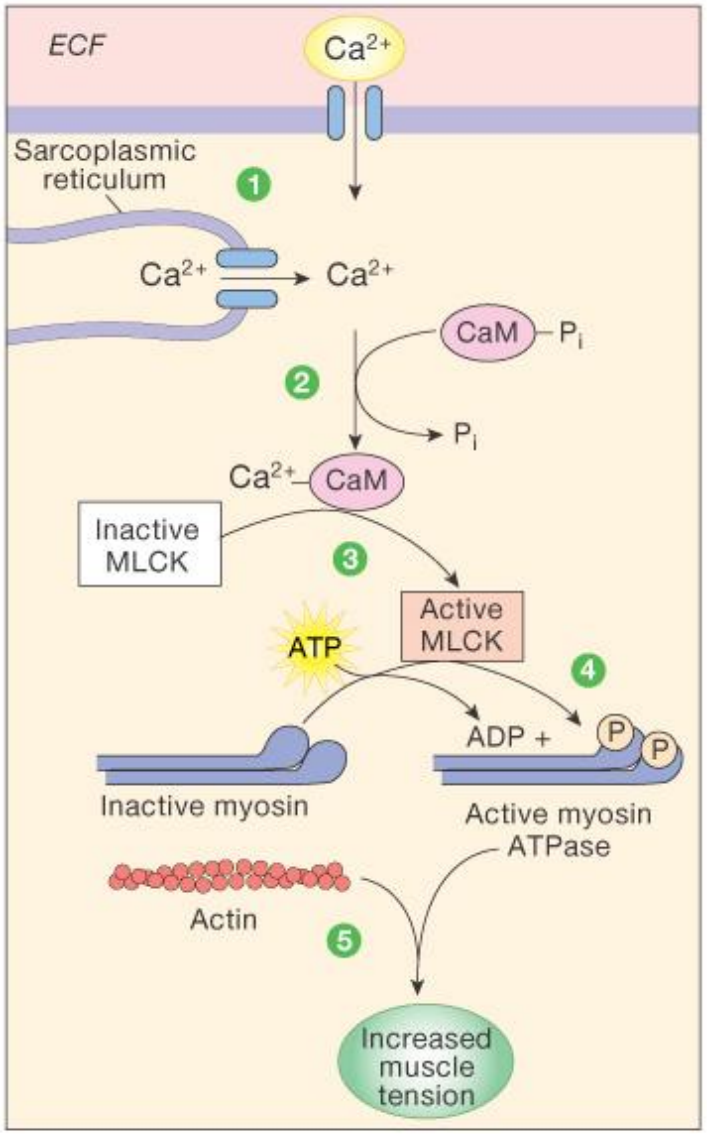
Сокращение гладких мышц сосудов при активации альфа-1 адренорецепторов



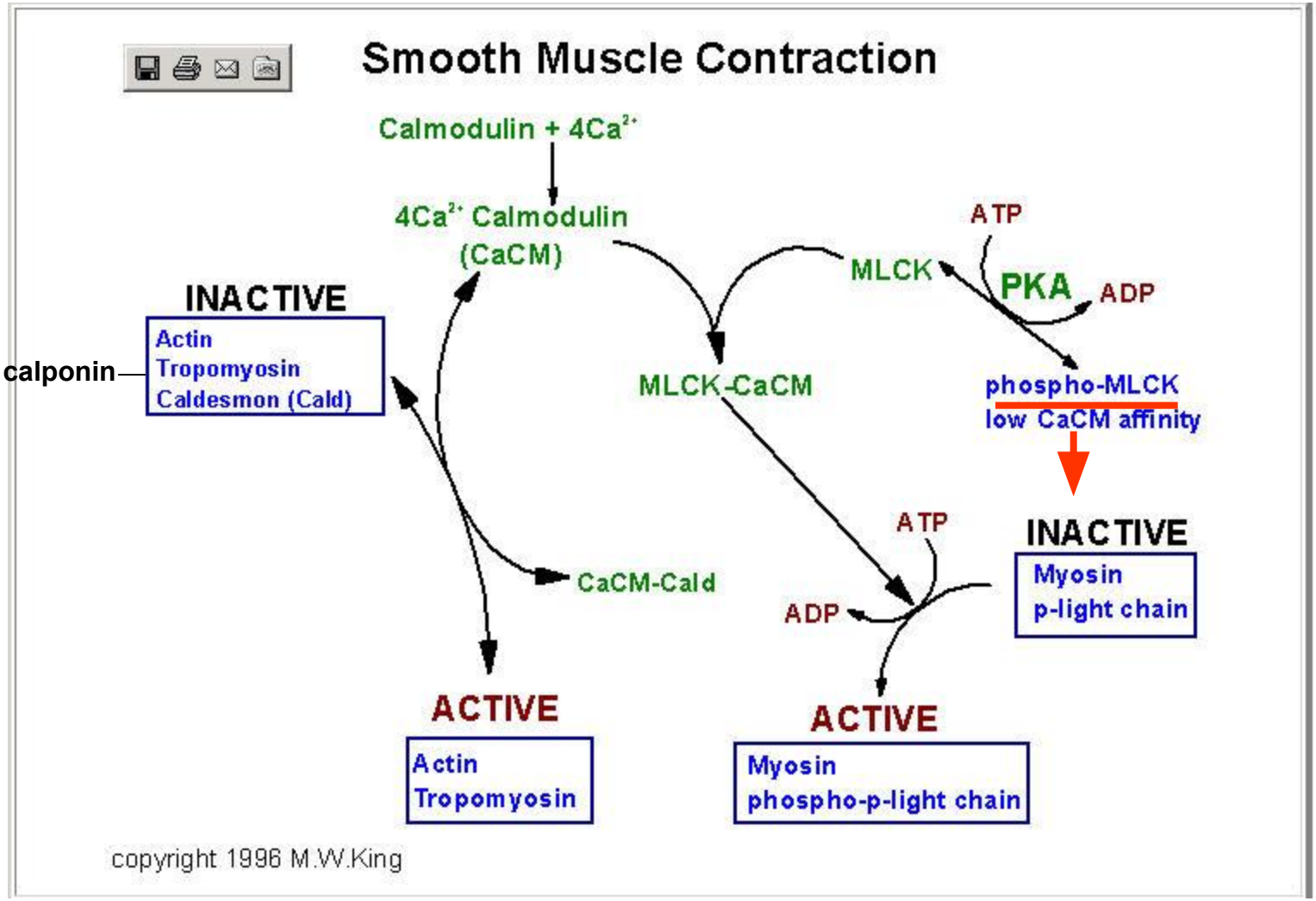
Механизм рецепторно (гормон)-механического сопряжения



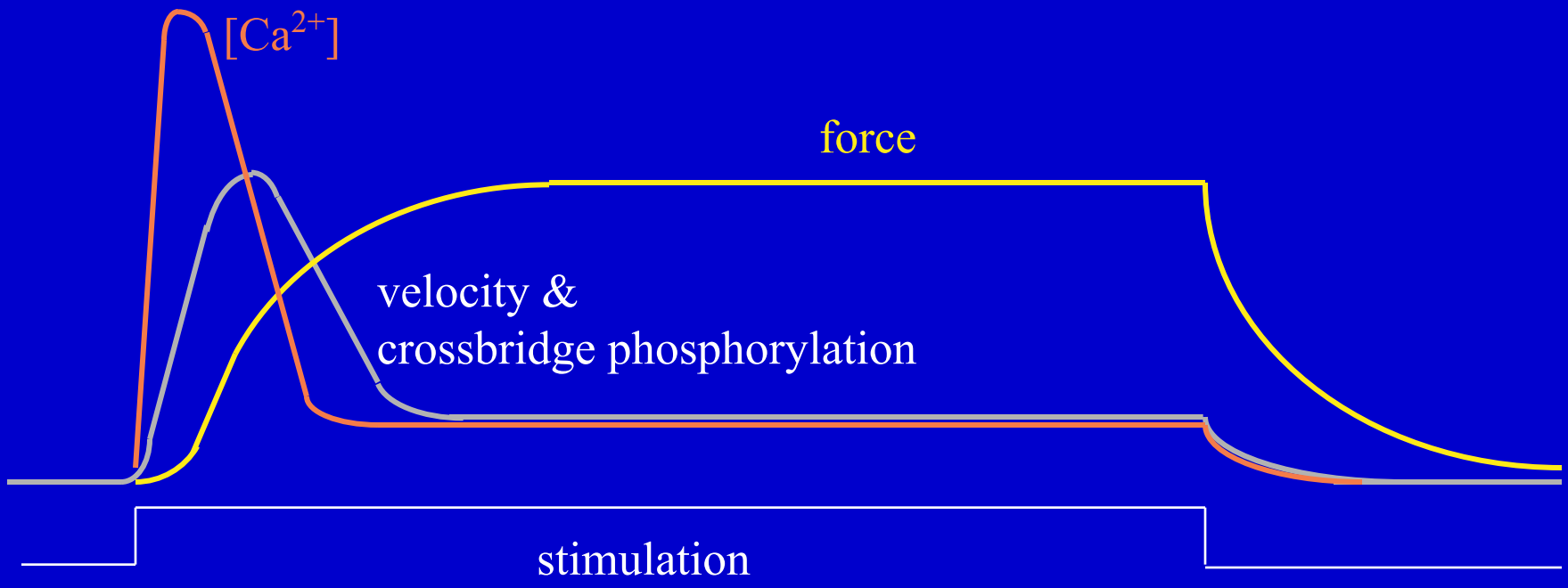
Основные этапы сокращения гладких мышц



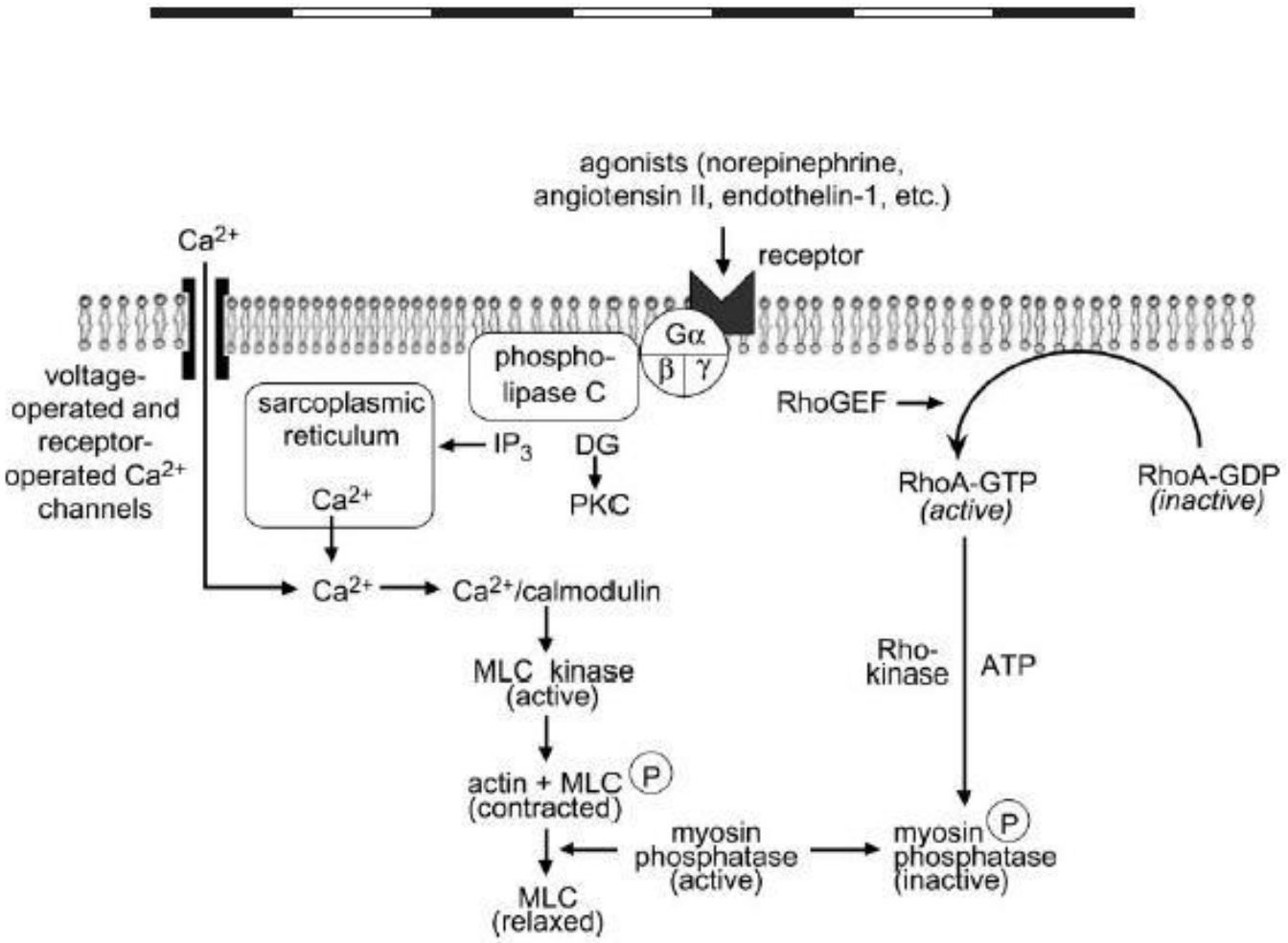
1. **Увеличение внутриклеточной концентрации иона кальция**
2. **Ca связывается с калмодулином (CaM)**
3. **CaM активирует киназу легких цепей миозина (MLCK)**
4. **MLCKфосфорилирует легкие цепи миозиновых головок и увеличивает активность миозин АТРазы**
5. **Происходит образование поперечных мостиков и скольжение миозина по актину**


Smooth Muscle Contraction
Calmodulin + 4Ca2+
4Ca2+ Calmodulin
(CaCM)
ATP
MLCK
PKA
ADP
INACTIVE
Actin
Tropomyosin
Caldesmon (Cald)
calponin
MLCK-CaCM
phospho-MLCK
low CaCM affinity
ATP
INACTIVE
Myosin
p-light chain
CaCM-Cald
ADP
ACTIVE
Actin
Tropomyosin
ACTIVE
Myosin
phospho-p-light chain
copyright 1996 M.W.King

Тоническое сокращение гладких мышц сосудов при низкой концентрации ионов Ca

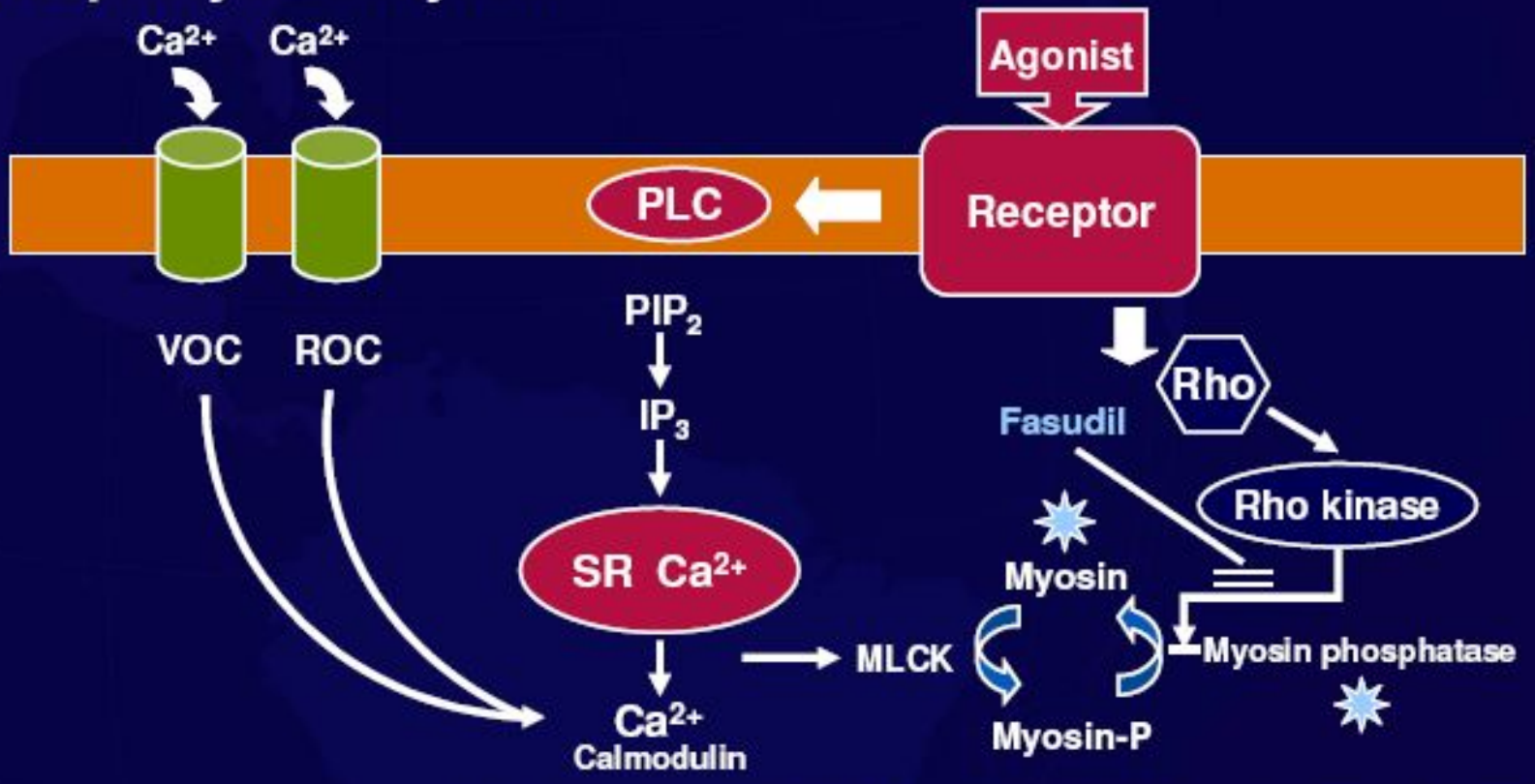


Механизм рецепторно-механического сопряжения



Rho kinase inhibition: Fasudil

Rho kinase triggers vasoconstriction through accumulation of phosphorylated myosin



Adapted from Seasholtz TM. *Am J Physiol Cell Physiol*. 2003;284:C596-8.

ОТЛИЧИТЕЛЬНЫЕ ОСОБЕННОСТИ ГЛАДКИХ МЫШЦ

(1) *Структурная композиция сократительного аппарата*

- миозиновый тип регуляции сокращения
- миозин образует длинные филаменты с боковой полярностью

(2) *Функционально отличные изоформы сократительных белков*

- миозин (требует активации фосфорилированием) → ОСНОВНОЙ ПУТЬ
- отсутствие саркомерной организации
  - кальдесмон-тропомиозин (актиновая регуляция) → второстепенный

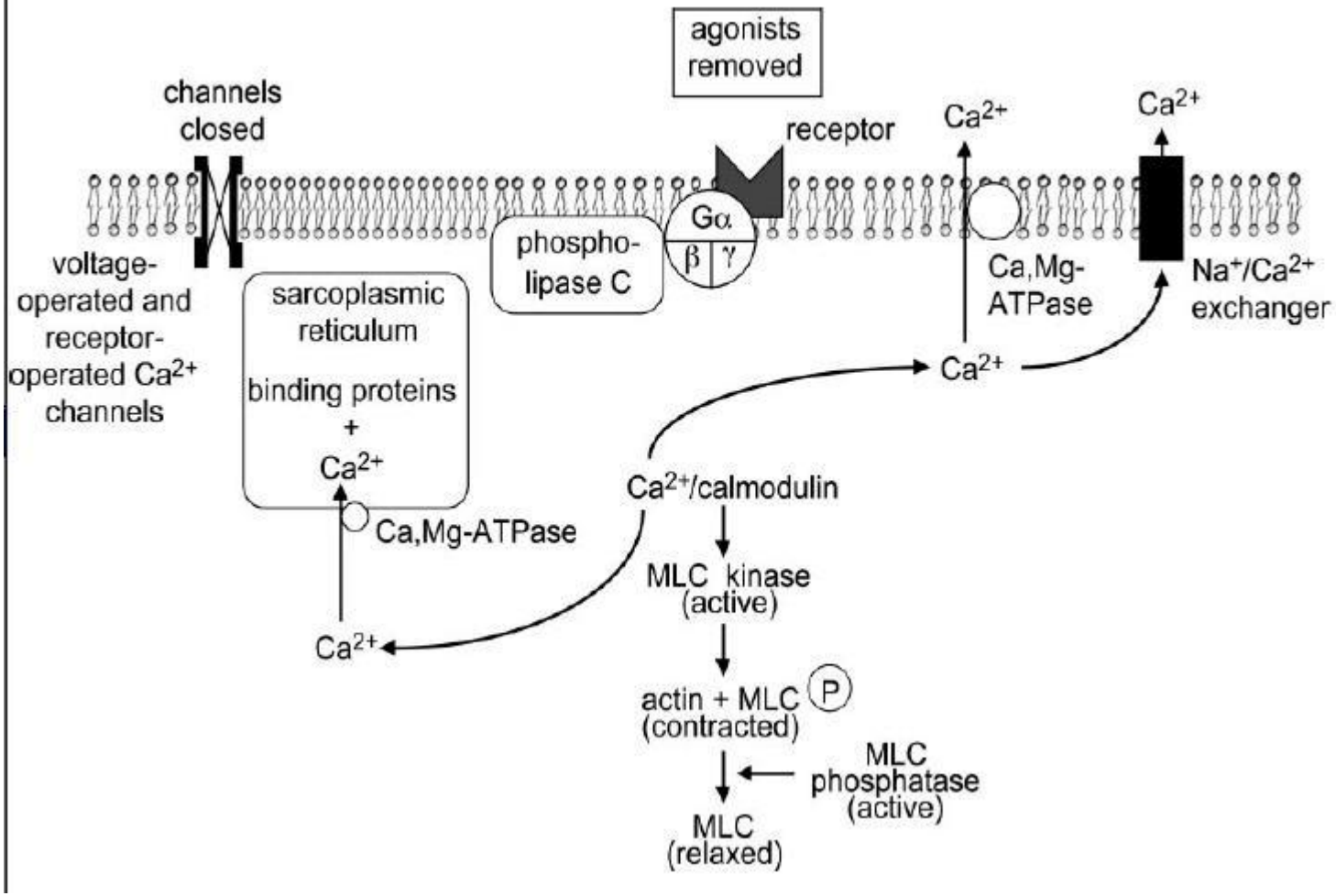
(3) *Физиология сокращения*

- гуморальная регуляция (многообразие рецепторных систем)

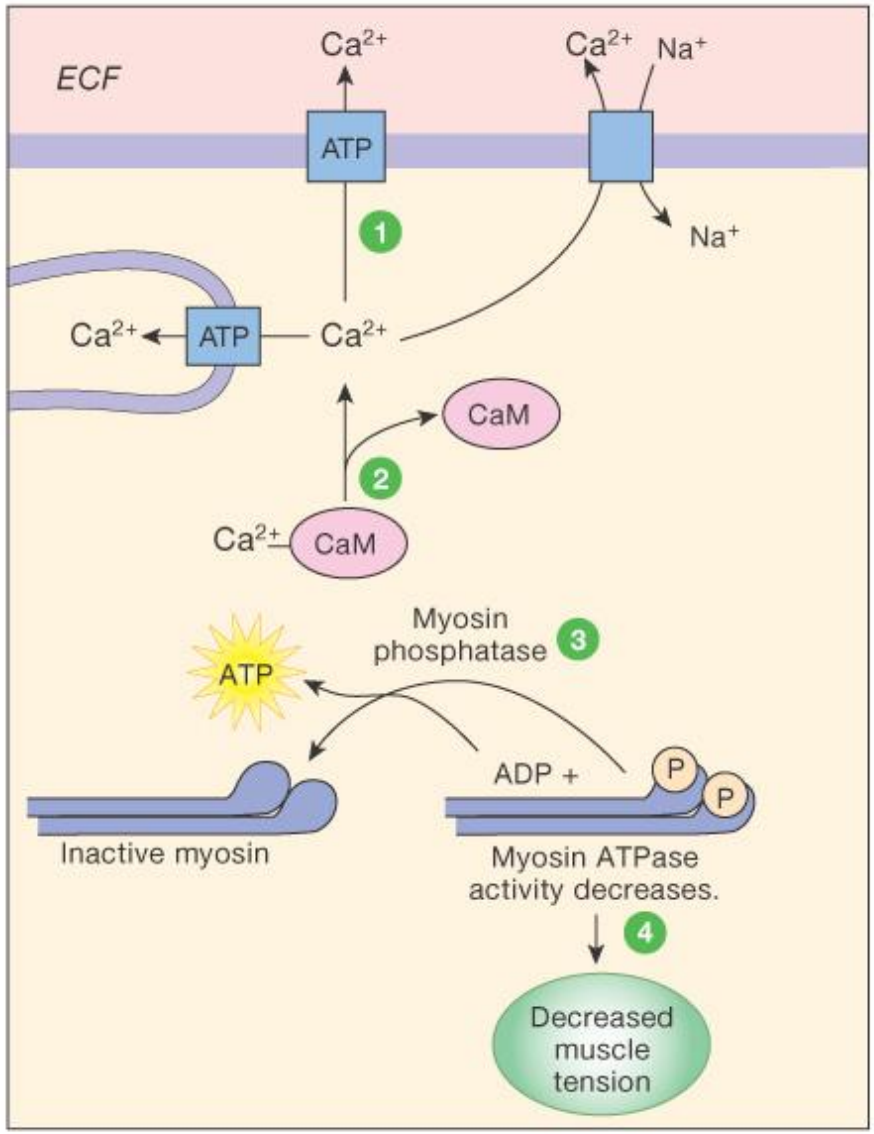
фармармакомеханическое сопряжение и «эстафетная» передача сигнала

- уникальные силовые характеристики (адаптация к длине и Ca^{2+}-чувствительность)

Ионные механизмы процесса расслабления гладких мышц



Механизм расслабления гладких мышц



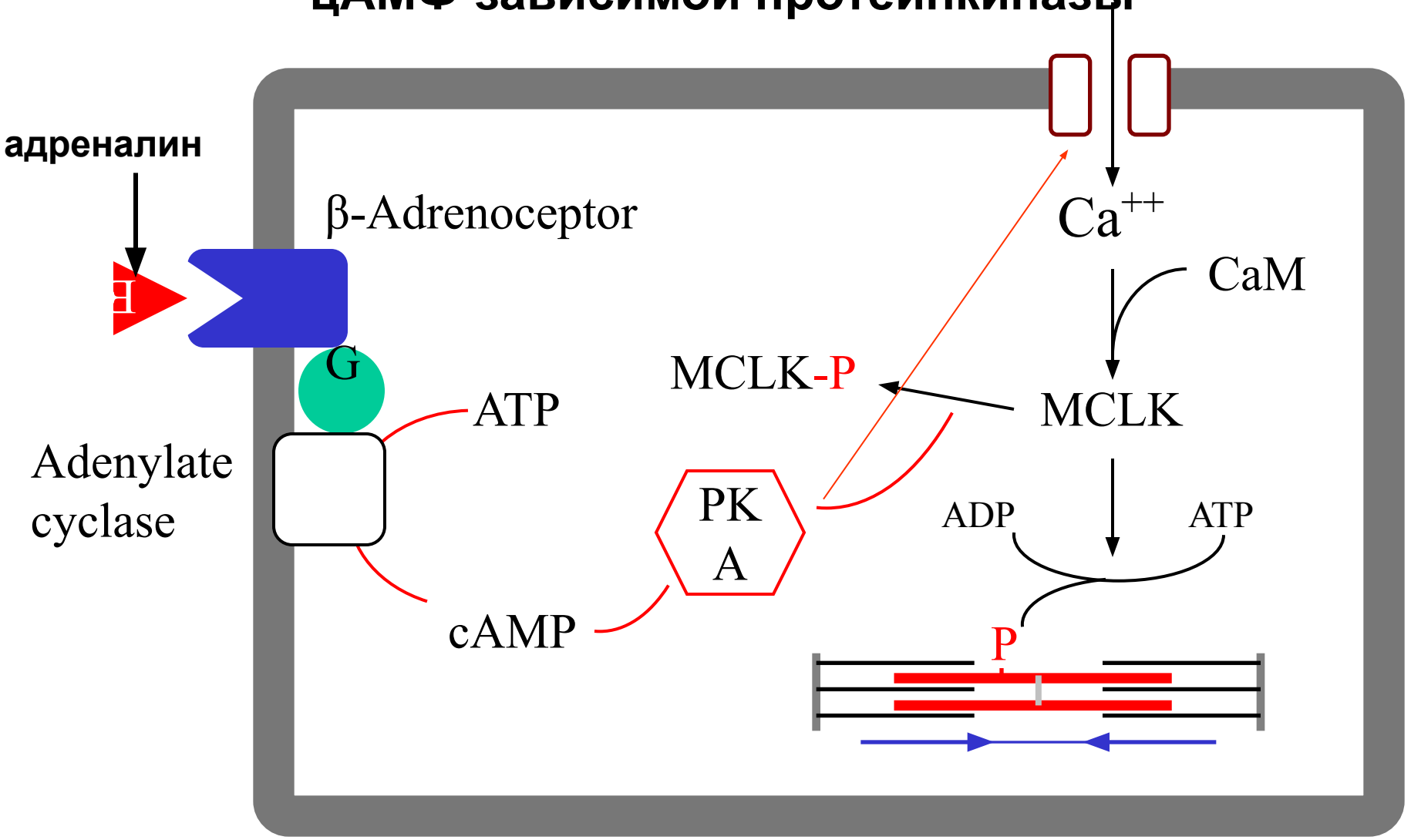
1. Free Ca^{2+} in cytosol decreases when Ca^{2+} is pumped out of the cell or back into the sarcoplasmic reticulum.

2. Ca^{2+} unbinds from calmodulin (CaM).

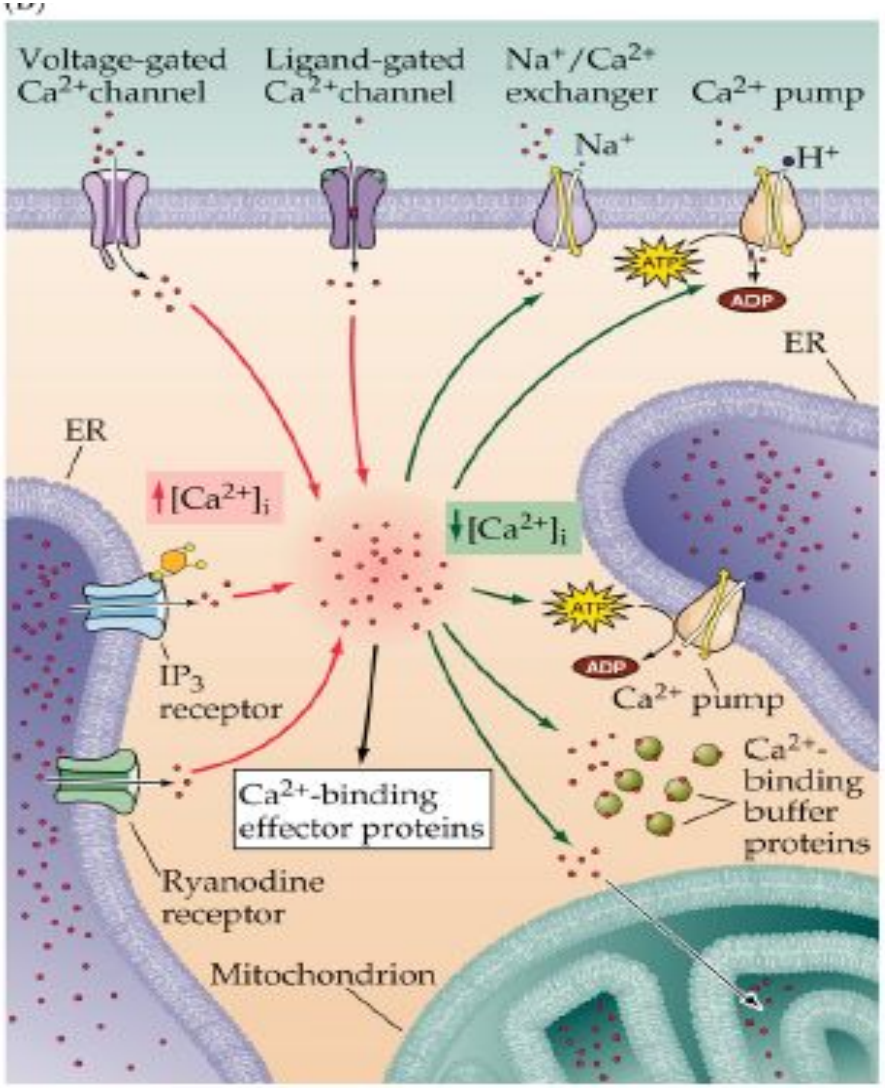
3. Myosin phosphatase removes phosphate from myosin, which decreases myosin ATPase activity.

4. Less myosin ATPase results in decreased muscle tension.

Бета-адренергический расширительный эффект в гладкой мышце сосудов путем инактивации киназы легких цепей миозина при действии цАМФ-зависимой протеинкиназы



Механизмы регуляции внутриклеточной концентрации кальция



Активация калиевых каналов в гладкой мышце при действии простациклина (PGI_2)

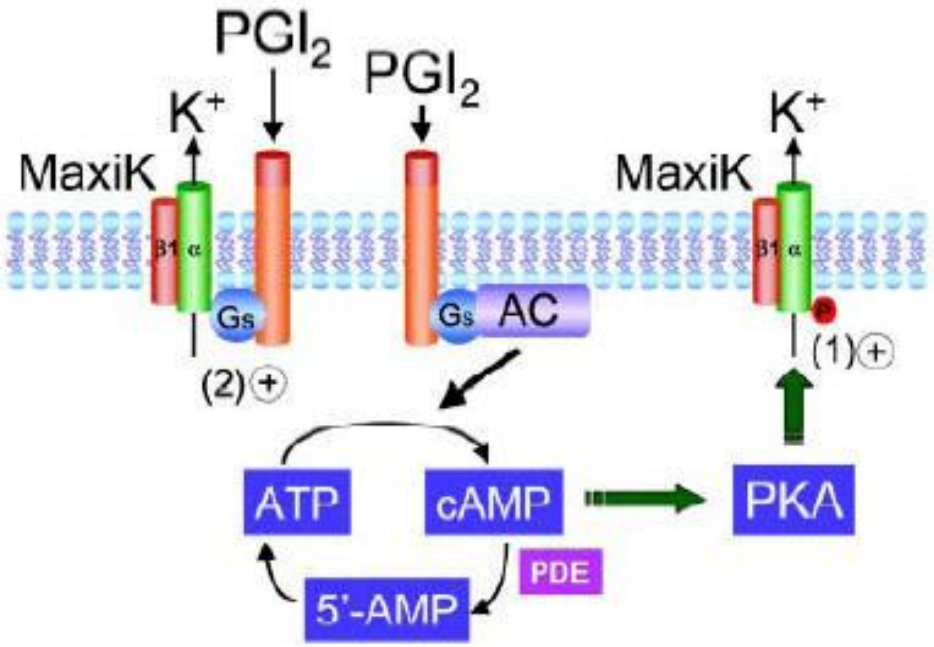


Fig. 5. Potential mechanisms of PGI_2-mediated activation of vascular smooth muscle MaxiK channel. At least two pathways are possible: (1) direct phosphorylation of the channel α-subunit by cAMP-dependent protein kinase (PKA); (2) direct channel activation by G_s ($G_s\alpha$), which is coupled with PGI_2 receptor (IPR). Serine-869 is likely to be the most significant and functional residue subject to phosphorylation by PKA. A potential role for the β1-subunit remains to be established.

цГМФ-зависимая активация калиевых каналов

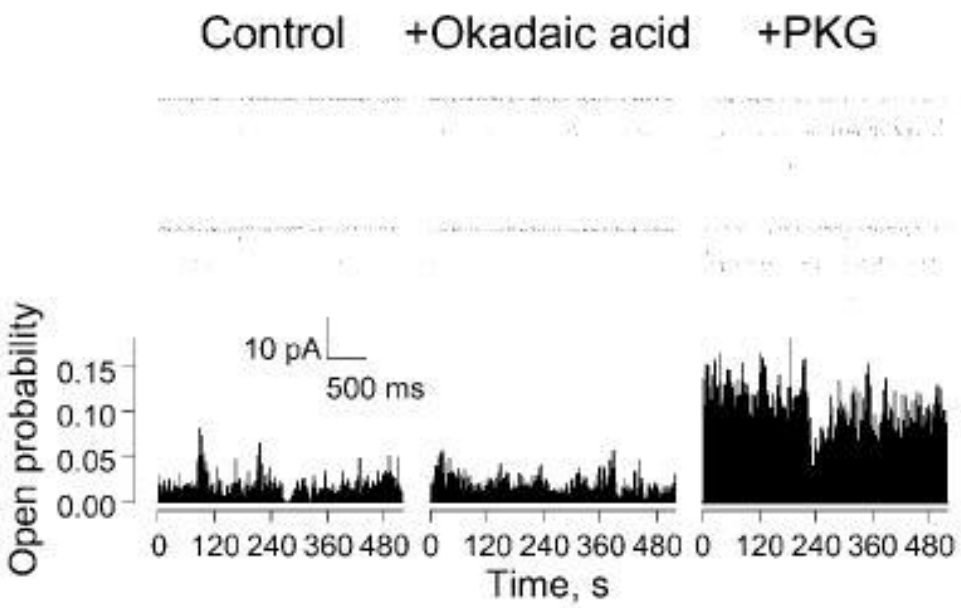


Fig. 4. Evidence for MaxiK channel α-subunit being directly activated by PKG. *HSlo* channels were expressed in oocytes and incorporated into planar lipid bilayers. MaxiK channel currents were recorded in the presence of 0.5 mM cGMP and 1 mM MgATP facing the channel internal side. MaxiK channel P_o was not affected by the addition of a phosphatase inhibitor, okadaic acid (100 nM) (middle panels). However, stimulation with PKG-Iα (80 nM) increased the mean P_o from 0.02 to 0.1. The solution contained equal K^+ concentrations at both sides of the membrane. V_{hold} – was –30 mV, and $[Ca^{2+}]_i$ – 29 μM. Lower traces are the plots showing the alterations in P_o before and after application of PKG. Reproduced from Alioua *et al.* (1998) with permission from The Journal of Biological Chemistry (The American Society for Biochemistry and Molecular Biology, Inc.).

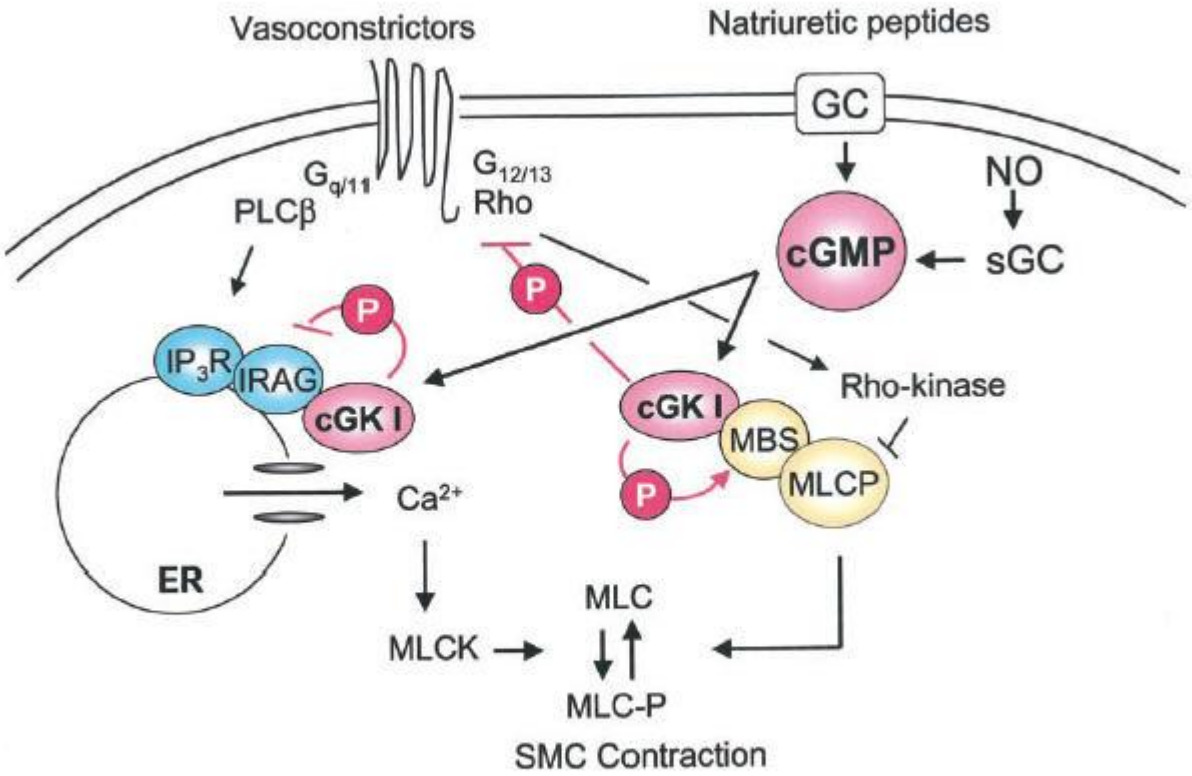
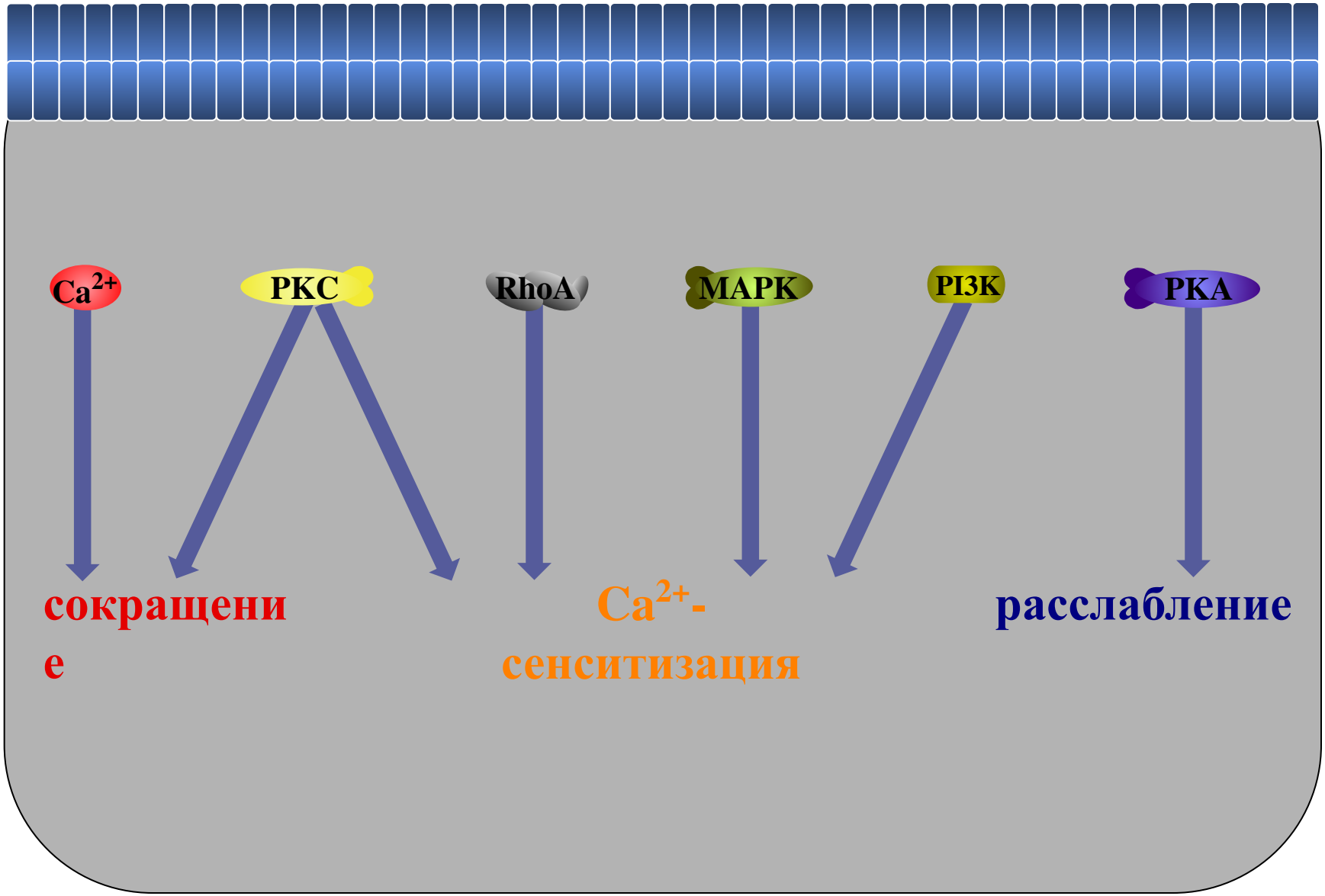


Figure 1. Mechanisms of cGKI inhibition of Ca^{2+} release (left) and Ca^{2+} sensitization (right) to inhibit myosin light chain (MLC) phosphorylation and SMC contraction. cGKI phosphorylation (P) of IRAG inhibits IP_3/IRAG-mediated Ca^{2+} release from the endoplasmic reticulum (ER), thus inhibiting MLC kinase (MLCK) and vasoconstriction. cGKI phosphorylates Rho and interferes with Rho kinase inhibition of MLCP, thus MLCP dephosphorylates MLC and enhances SMC relaxation. Binding of cGKI to substrates (eg, IRAG and the myosin-binding subunit [MBS] of MLCP), which are also members of signaling complexes or scaffolds, could be an important aspect of achieving specificity of cGKI action. G indicates G-protein; IP_3R, IP_3 receptor; NO, nitric oxide; PLC, phospholipase C; and sGC, soluble guanylate cyclase.

Фармакомеханическое сопряжение



Основные характеристики трех типов мышц

Table 12-3: Comparison of Three Muscle Types

	SKELETAL	SMOOTH	CARDIAC
Appearance under light microscope	Striated	Smooth	Striated
Fiber arrangement	Sarcomeres	Longitudinal bundles	Sarcomeres
Fiber proteins	Actin, myosin; troponin and tropomyosin	Actin, myosin, tropomyosin	Actin, myosin; troponin and tropomyosin
Control	■ Voluntary ■ Ca^{2+} and troponin ■ Fibers independent	■ Involuntary ■ Ca^{2+} and calmodulin ■ Fibers electrically linked via gap junctions	■ Involuntary ■ Ca^{2+} and troponin ■ Fibers electrically linked via gap junctions
Nervous control	Somatic motor neuron	Autonomic neurons	Autonomic neurons
Hormonal influence	None	Multiple hormones	Epinephrine
Location	Attached to bones; a few sphincters close off hollow organs	Forms the walls of hollow organs and tubes; some sphincters	Heart muscle
Morphology	Multinucleate; large, cylindrical fibers	Uninucleate; small spindle-shaped fibers	Uninucleate; shorter branching fibers
Internal structure	T-tubule and sarcoplasmic reticulum	No t-tubules; sarcoplasmic reticulum reduced or absent	T-tubule and sarcoplasmic reticulum
Contraction speed	Fastest	Slowest	Intermediate
Contraction force of single fiber	All-or-none	Graded	Graded
Initiation of contraction	Requires input from motor neuron	Can be autorhythmic	Autorhythmic

: Types

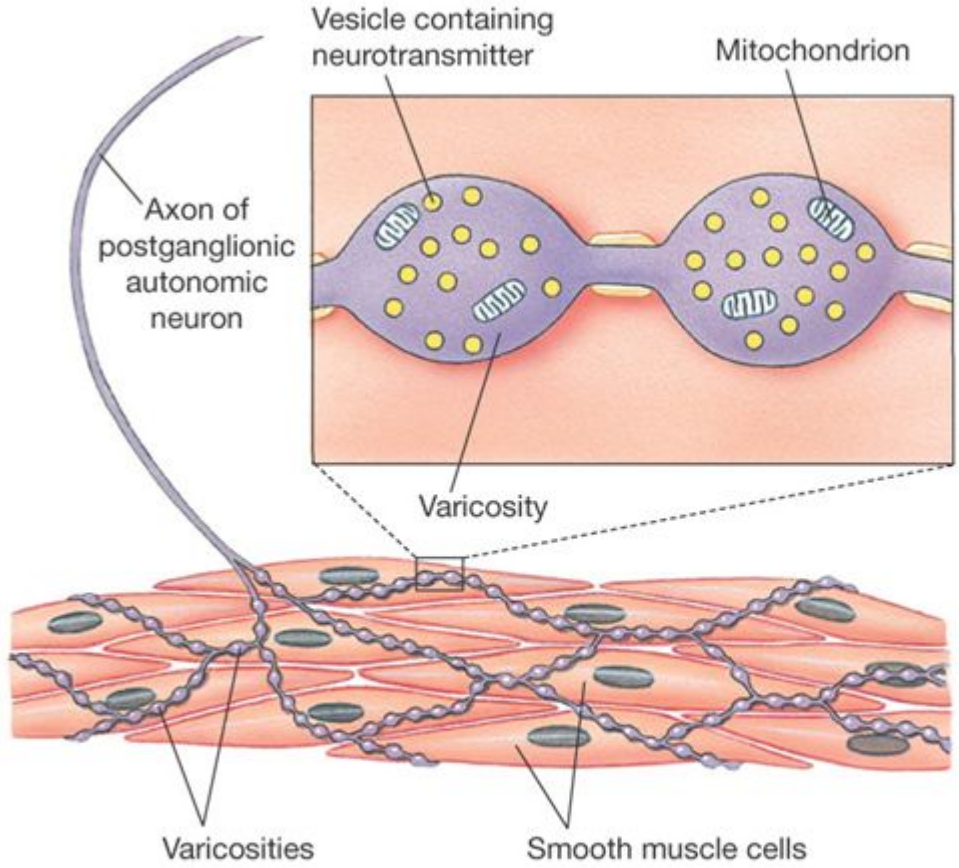
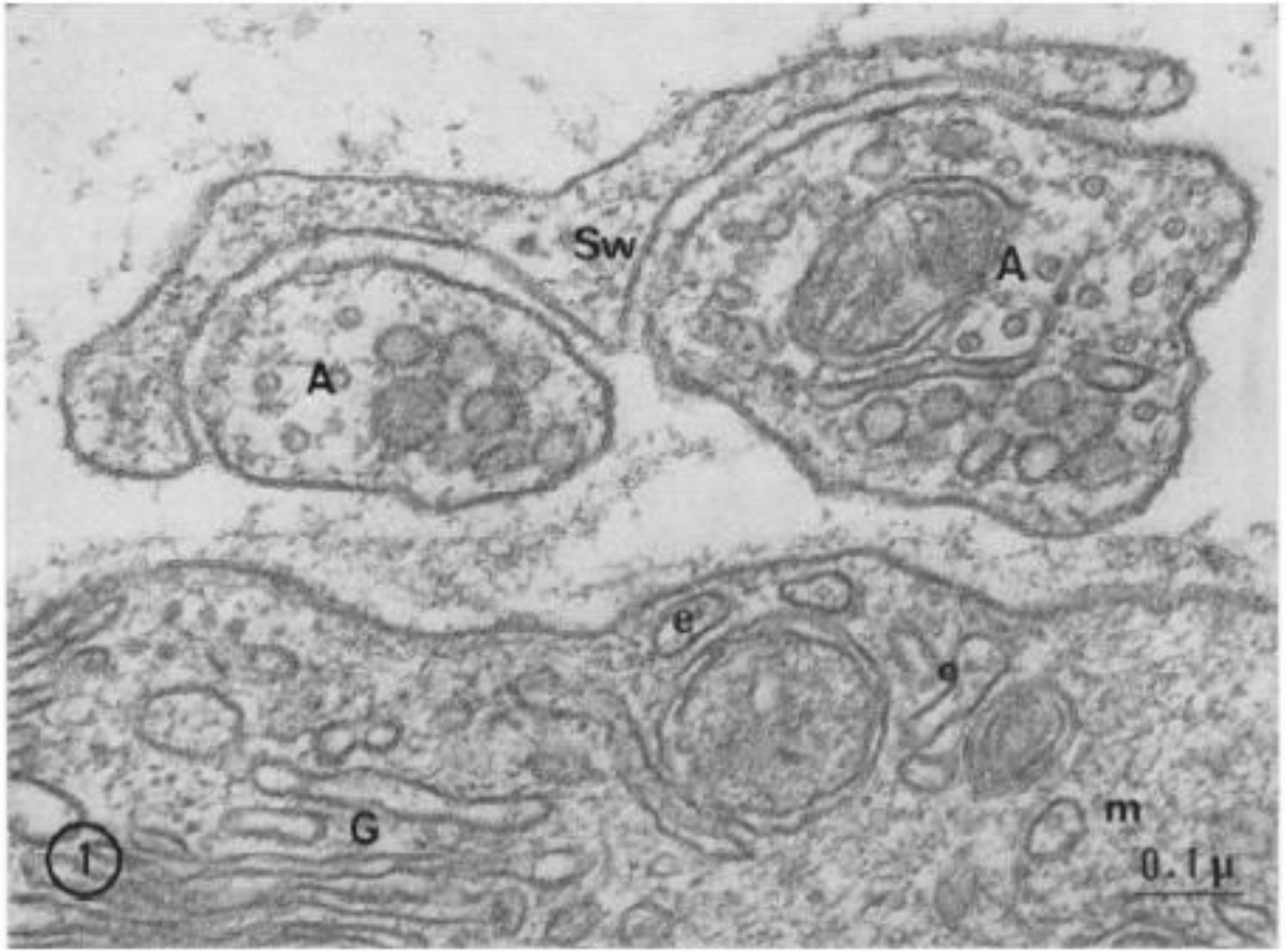
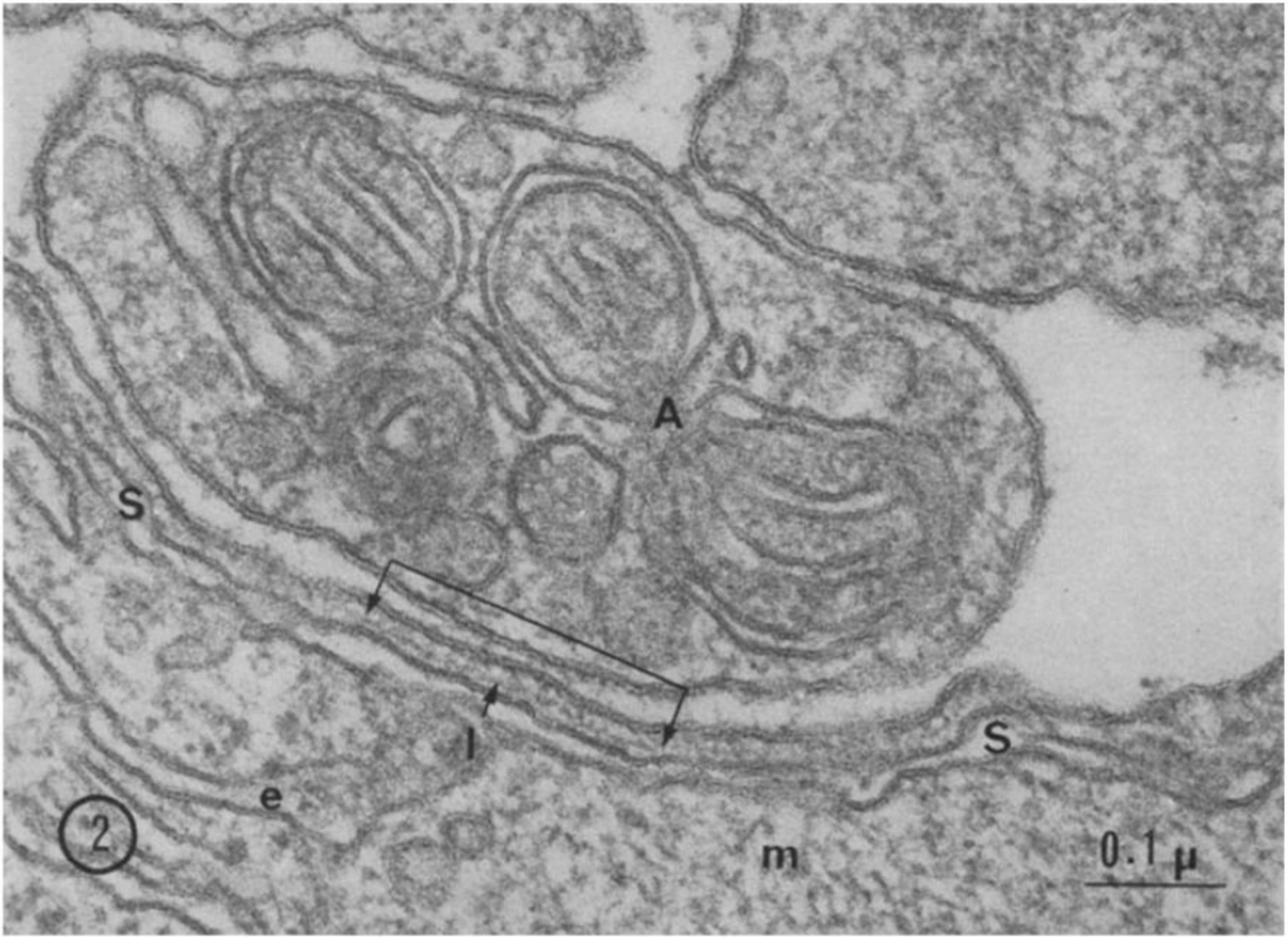


Figure 11-8: Varicosities of autonomic neurons

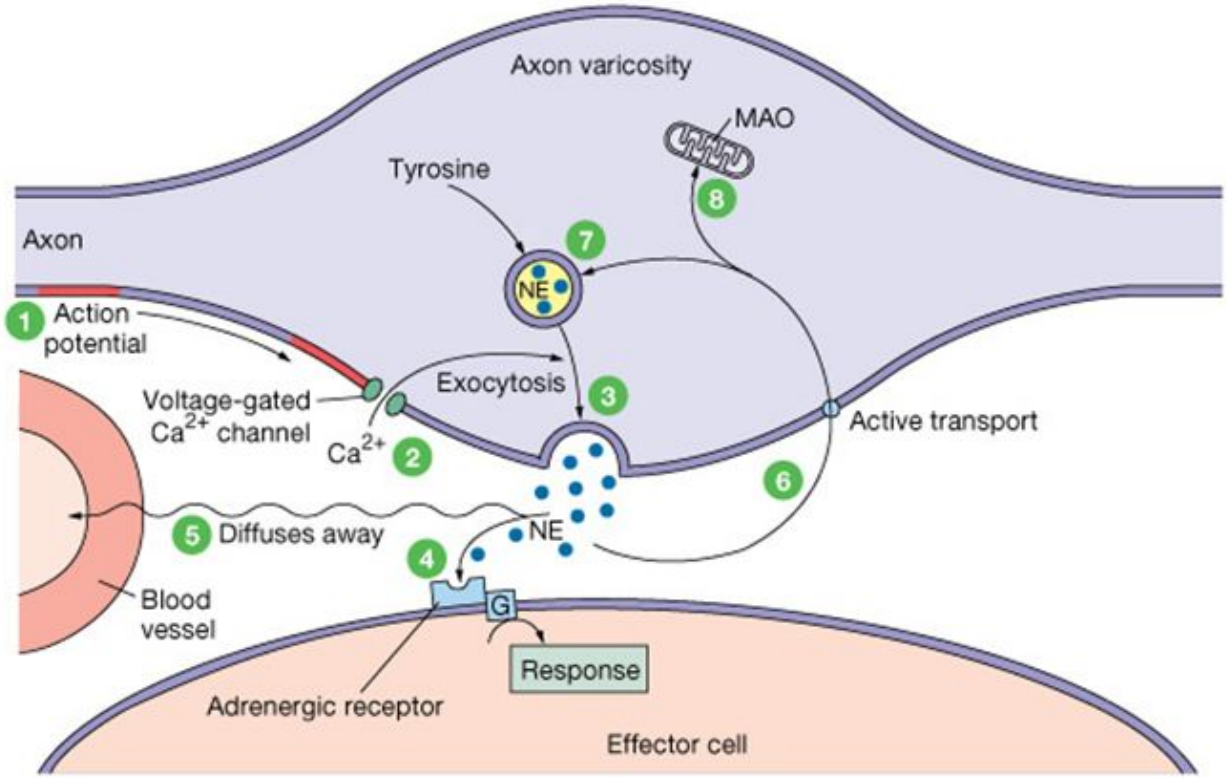
Электронное изображение симпатического окончания на гладкой мышце сосуда





(2)

Mechanism: Norepinephrine Release and Recycling



KEY

- NE (norepinephrine)

1. Action potential arrives at the varicosity.
2. Depolarization opens voltage-gated Ca^{2+} channels.
3. Ca^{2+} entry triggers exocytosis of synaptic vesicles.
4. NE binds to adrenergic receptor on target.
5. Activity ceases when NE diffuses away from the synapse.
6. NE is transported back into the axon.
7. NE can be taken back into synaptic vesicles for re-release.
8. NE is metabolized by monoamine oxidase (MAO).

REVIEW

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TRPA1 channels in the vasculature

Scott Earley

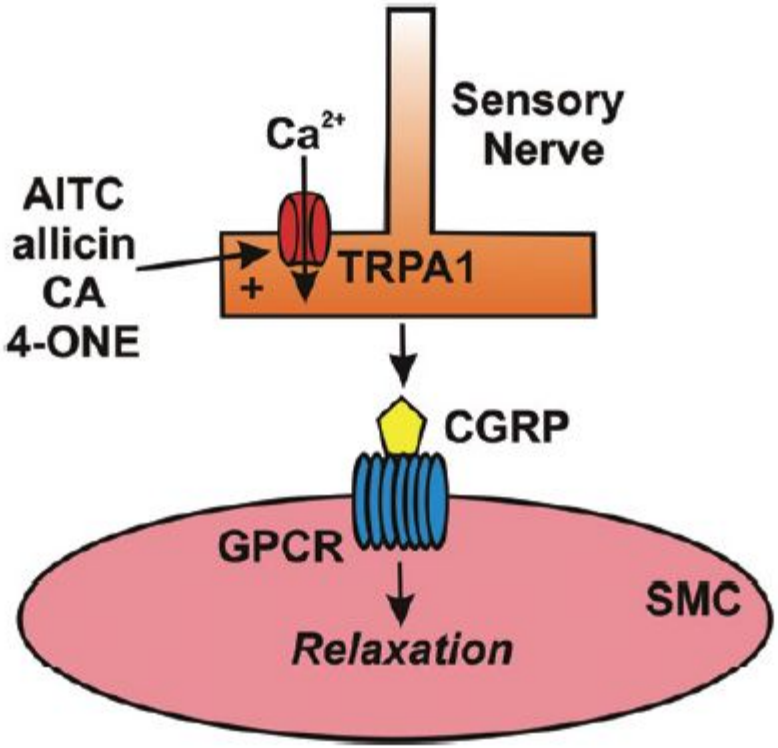

Figure 1

Activation of TRPA1 channels in sensory nerves causes arterial dilation. Allyl isothiocyanate (AITC), allicin, cinnamaldehyde (CA) and 4-oxo-2-nonenal (4-ONE) activate Ca^{2+} influx via TRPA1 channels in sensory nerves, causing release of calcitonin gene-related peptide (CGRP) from perivascular terminals. CGRP binds to its G protein-coupled receptor (GPCR) on the plasma membrane of vascular smooth muscle cells (SMCs) to cause membrane hyperpolarization and myocyte relaxation.