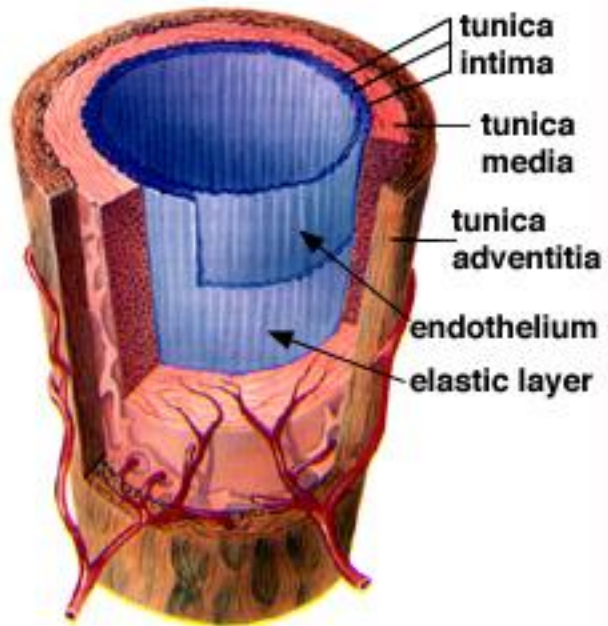


# **Физиология гладких мышц сосудов.**

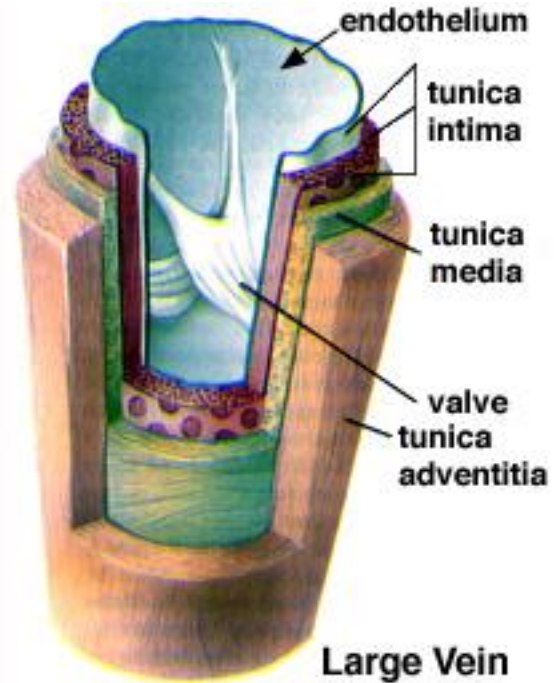
**Медведева Н.А.**

*Кафедра физиологии человека и животных Биологического факультета  
МГУ*

**Москва 2013**

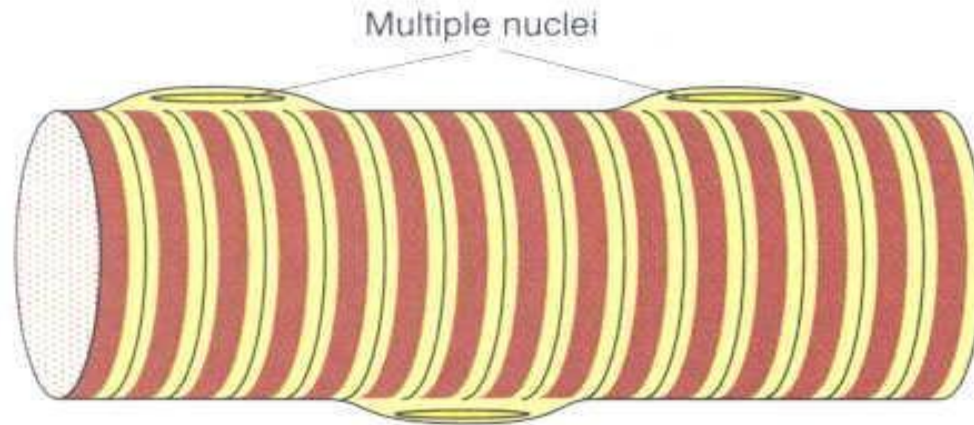


**Muscular Artery**

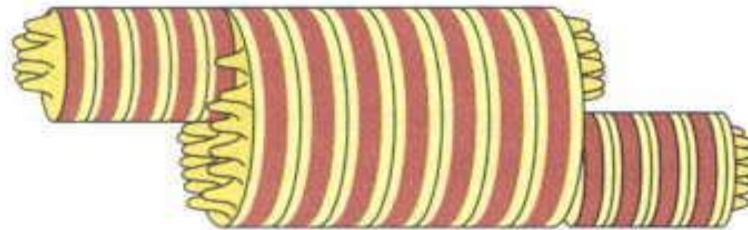


**Large Vein**

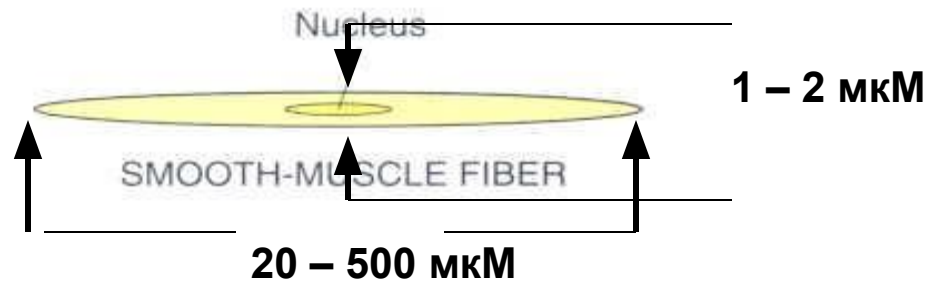
# Типы мышечных волокон



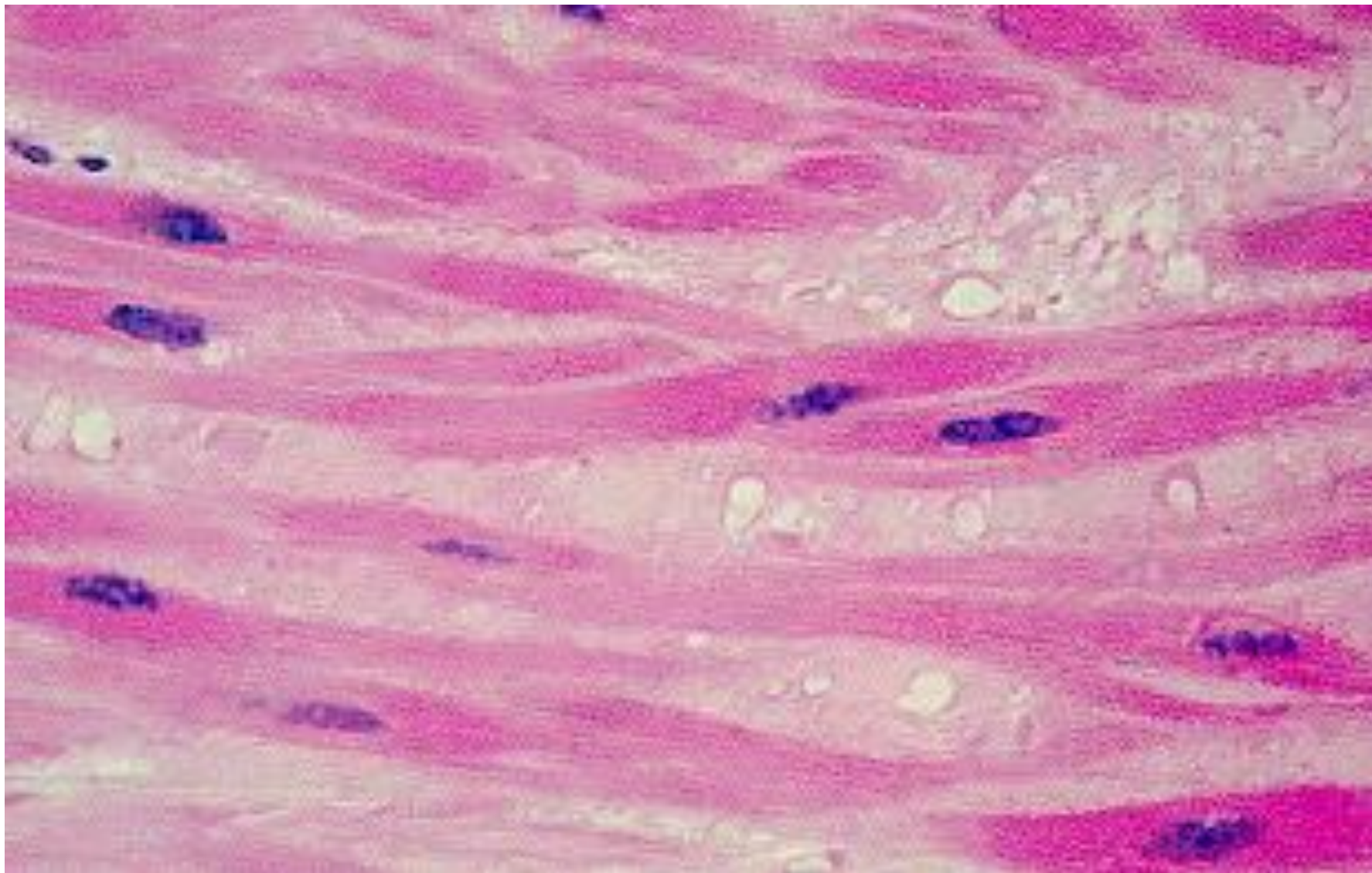
SKELETAL-MUSCLE FIBER



CARDIAC-MUSCLE FIBER

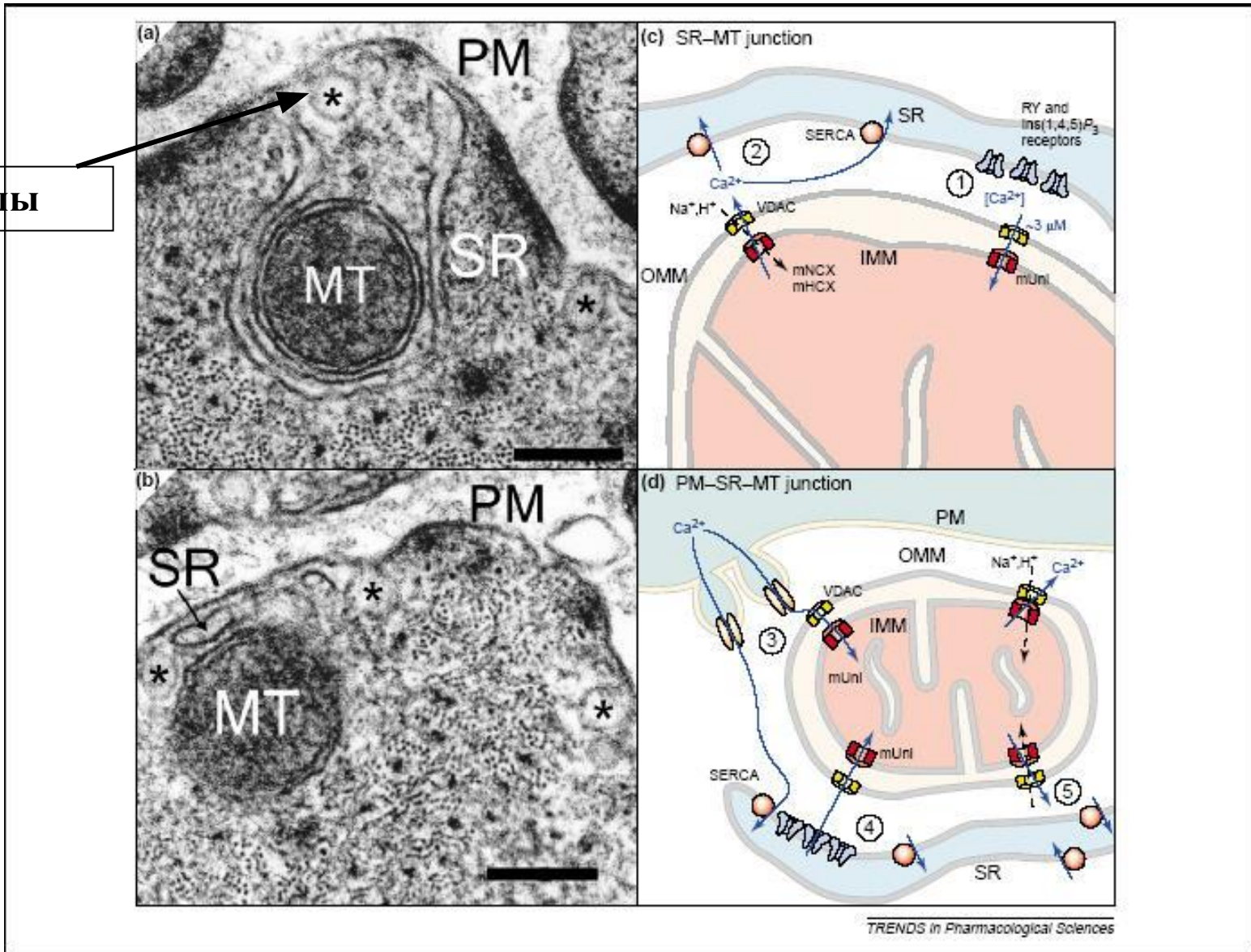


# Фенотип гладкомышечной клетки



# Электронномикроскопическое изображение гладкой МЫШЦЫ

кавеолы



TRENDS in Pharmacological Sciences

Figure 2. Mitochondrial junctions with the sarcoplasmic reticulum (SR) and plasma membrane (PM). (a,b) Smooth muscle electron micrographs (EMs) that are stained with osmium tetroxide and lead citrate to highlight membranes reveal that the SR is in frequent close contact with, and occasionally overlaps, with the outer and inner mitochondrial membranes throughout the

# Сравнительное изображение трех типов мышц

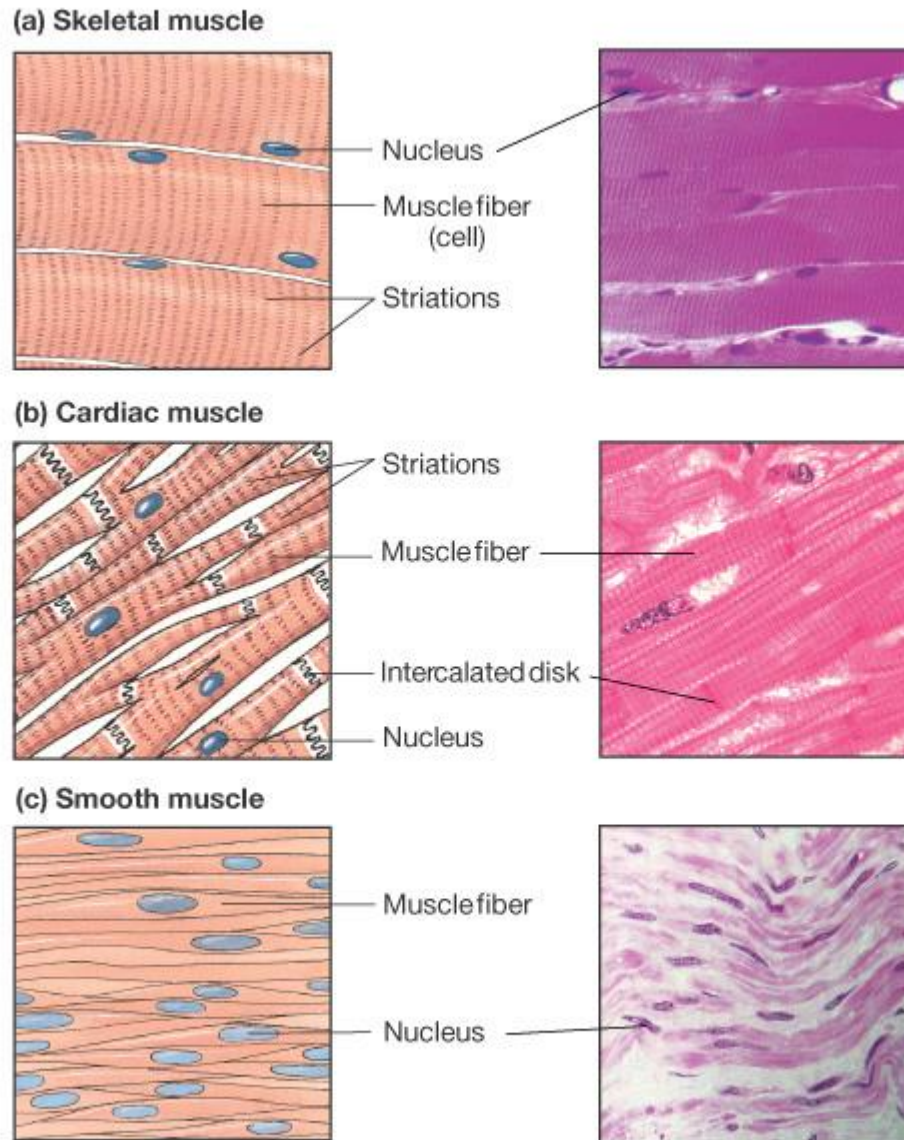
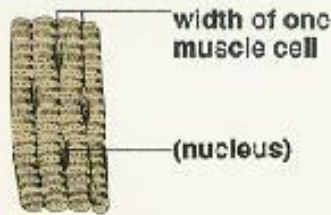
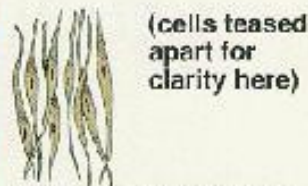
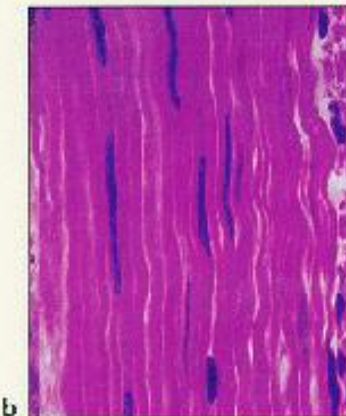


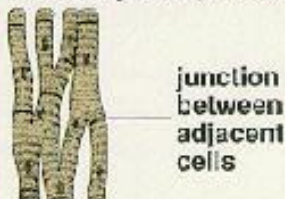
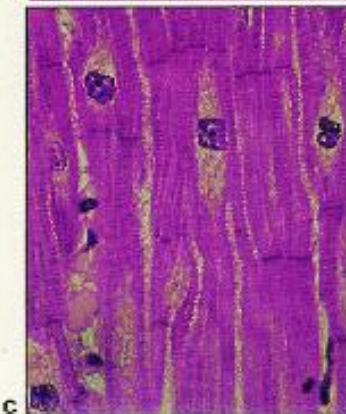
Figure 12-1: Three types of muscles



**TYPE:** Skeletal muscle  
**DESCRIPTION:** Long, striated cells with multiple nuclei  
**COMMON LOCATIONS:** In skeletal muscles  
**FUNCTION:** Contraction for voluntary movements



**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



**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

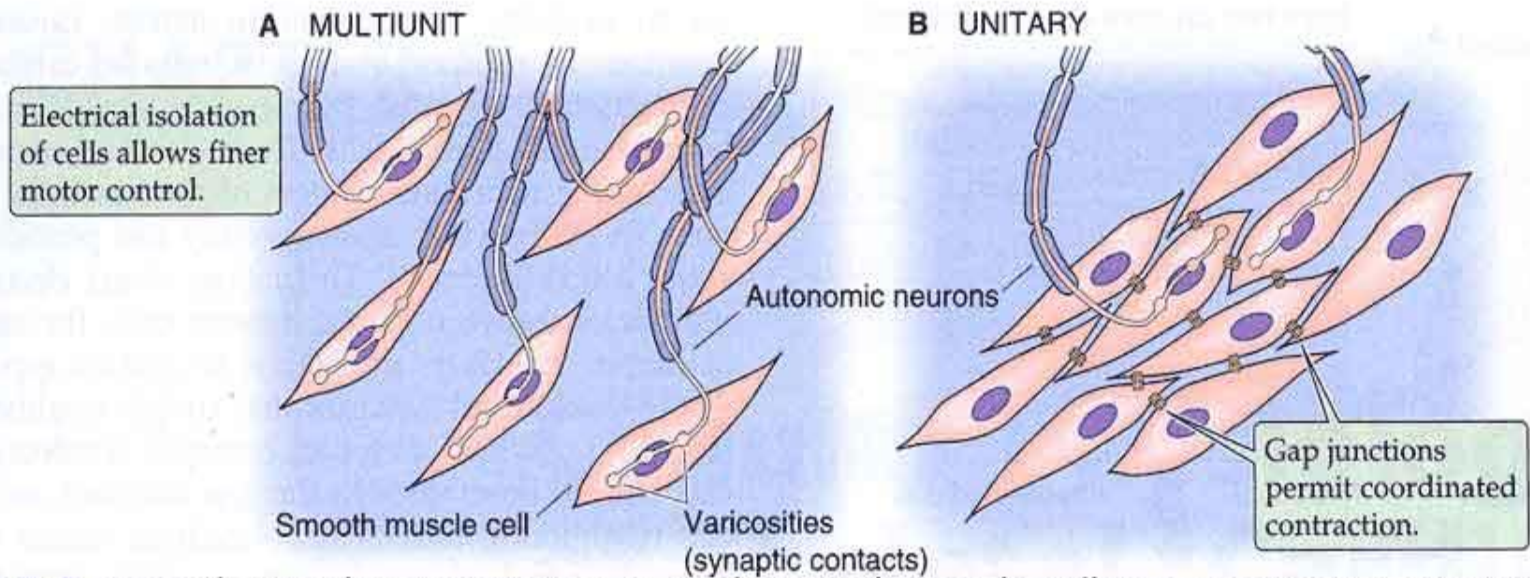


FIGURE 9-2. Smooth-muscle organization. A, Each smooth muscle cell receives its own synaptic input. B, only a few of the smooth muscle cells receive direct synaptic input.



# Распространение сократительной активности в гладкой мышце

(a) Single-unit smooth muscle is connected by gap junctions and the cells contract as a single unit.

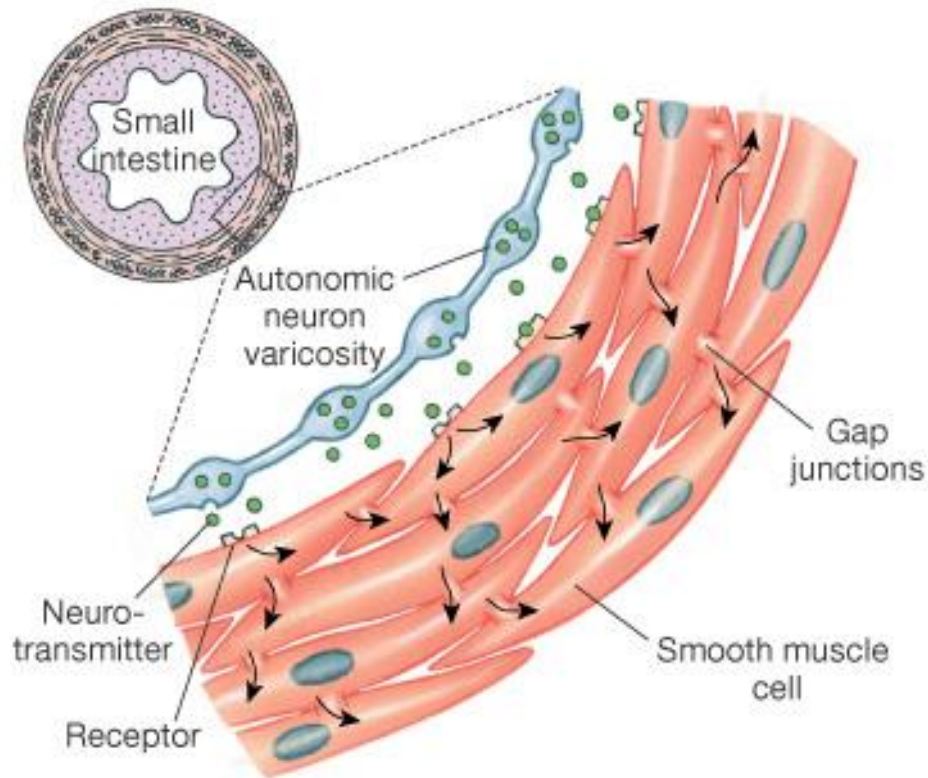
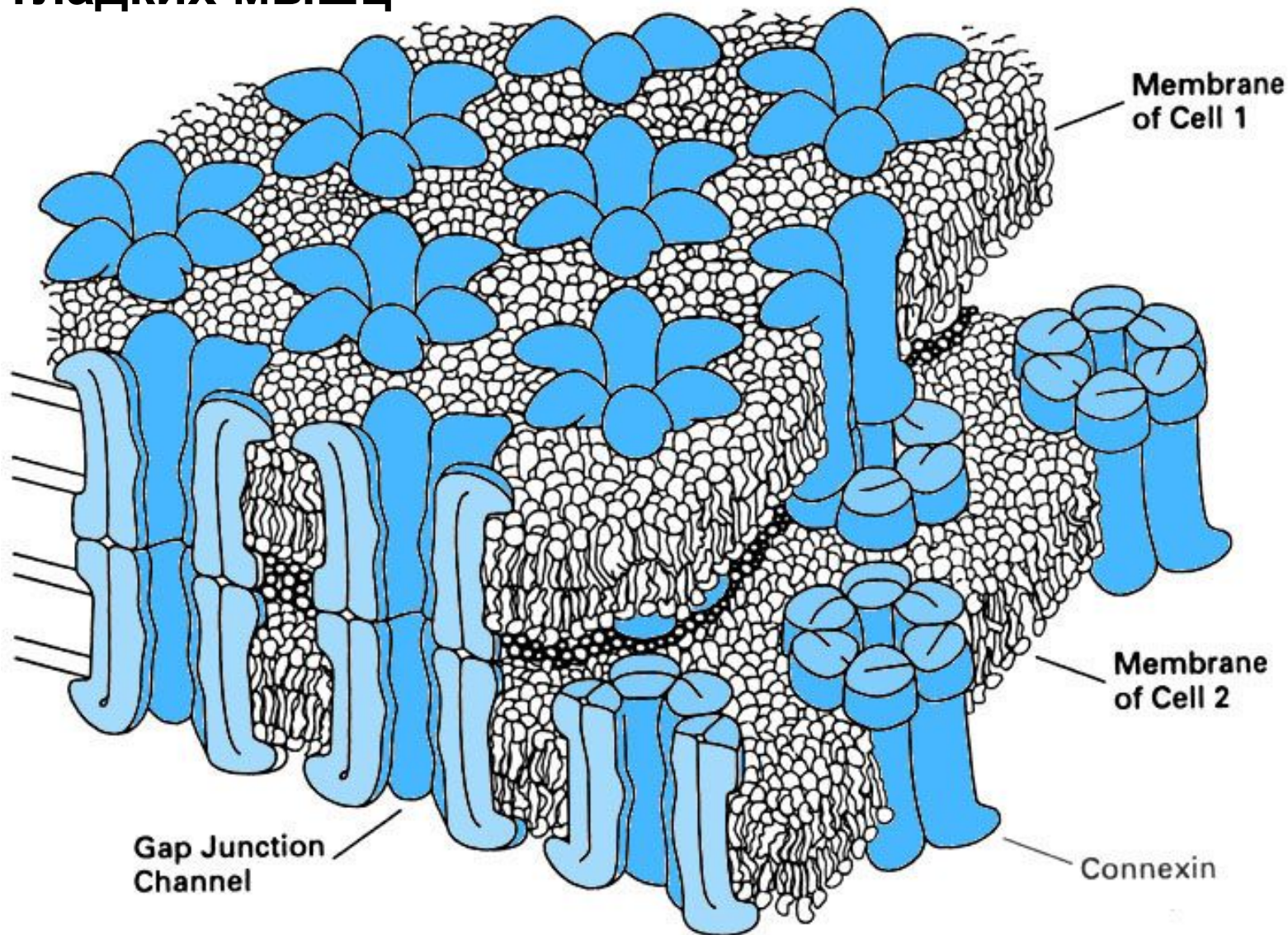
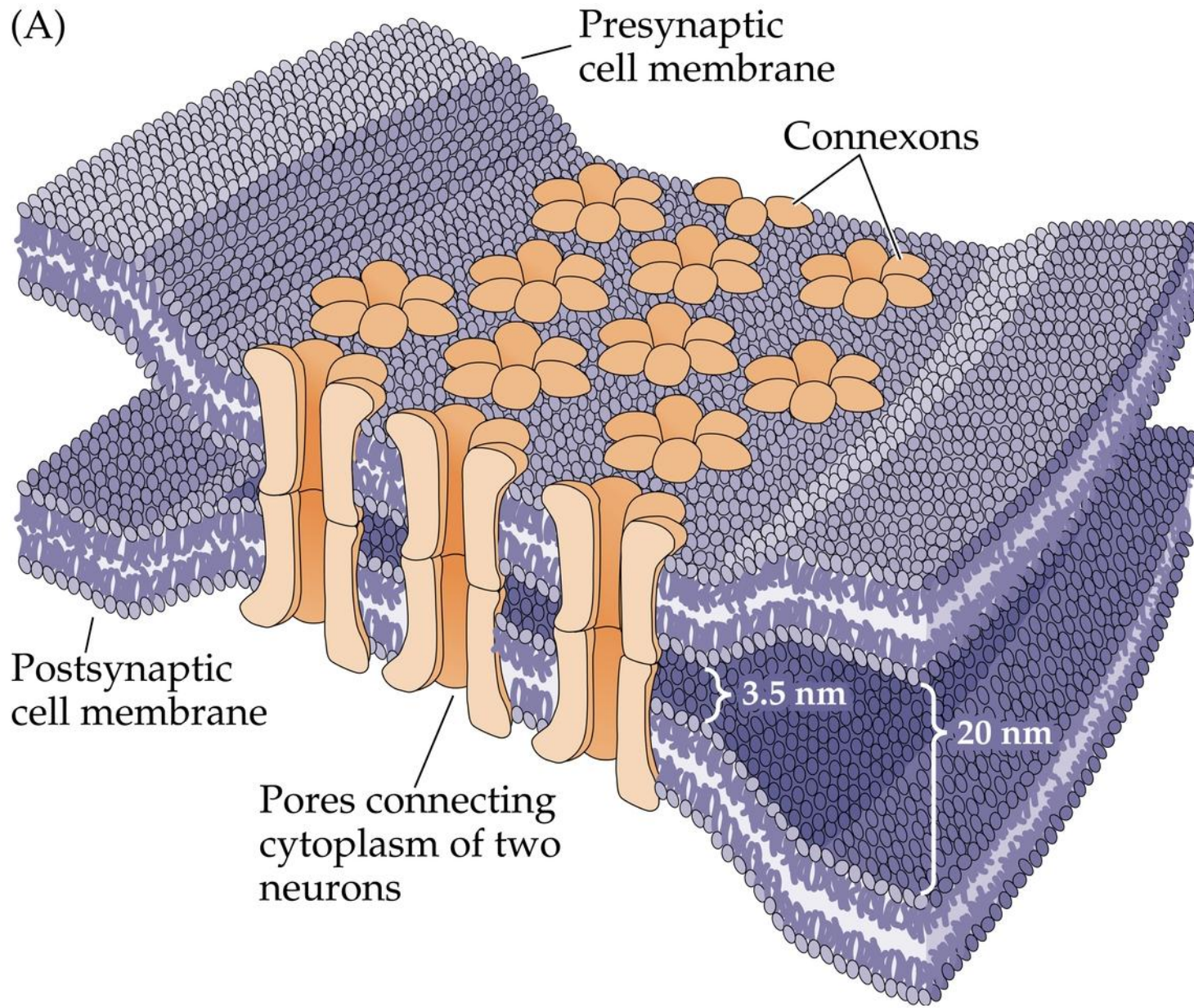


Figure 12-25a: Types of smooth muscle

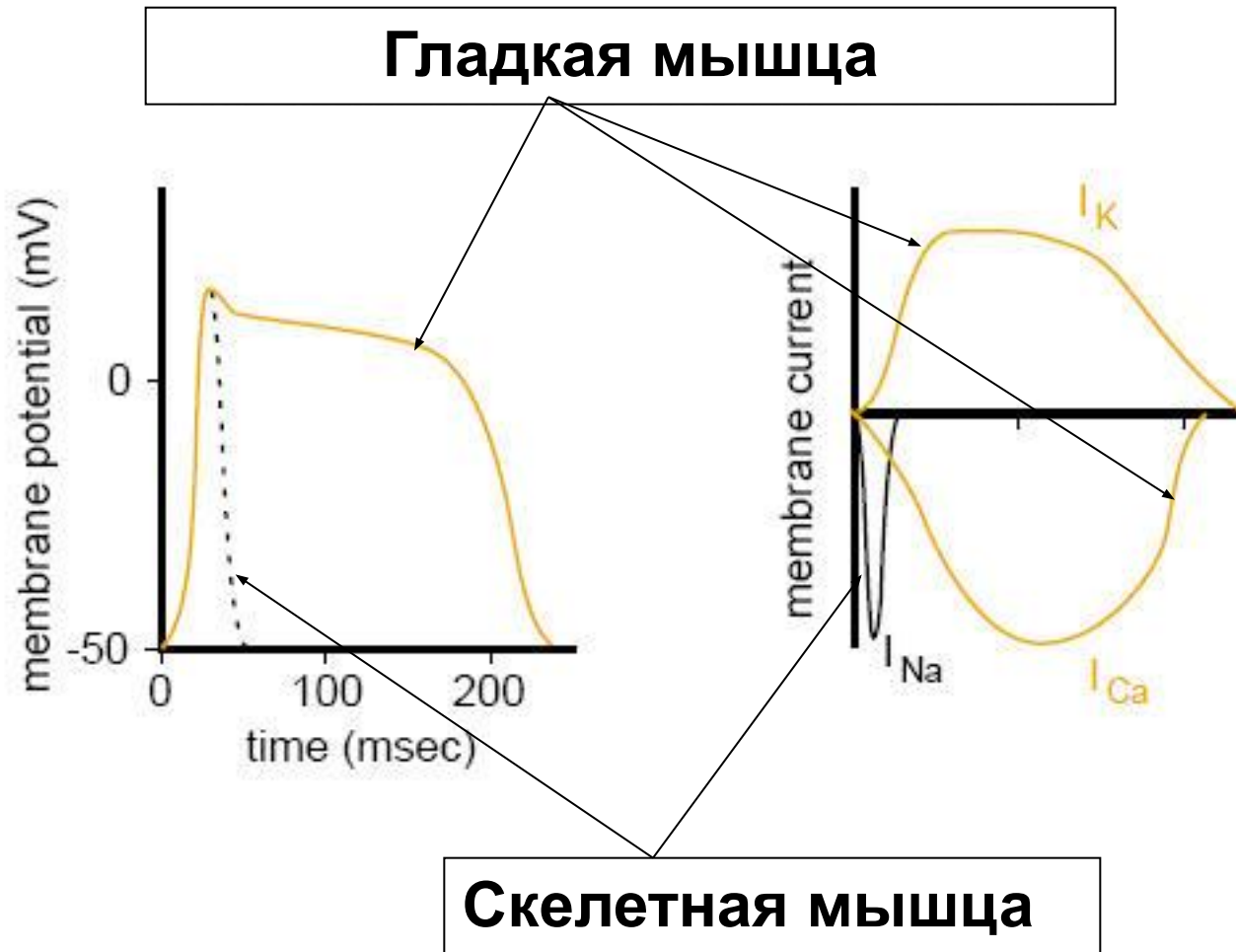
# Щелевые контакты в гладкой мышце осуществляют передачу возбуждения от клетки к клетке в унитарном типе гладких мышц



(A)

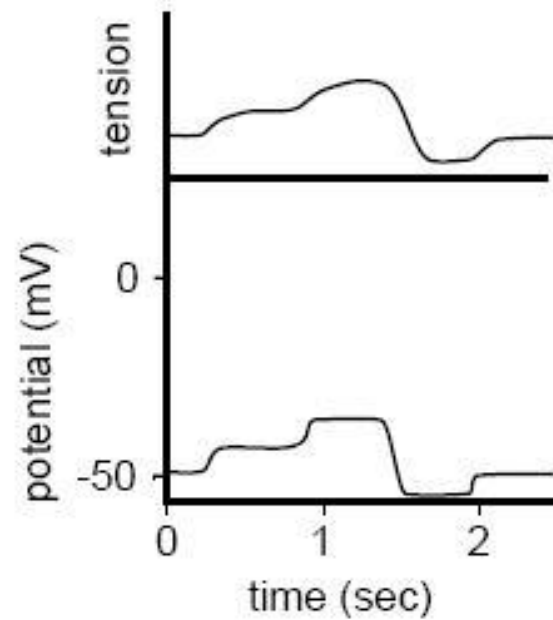
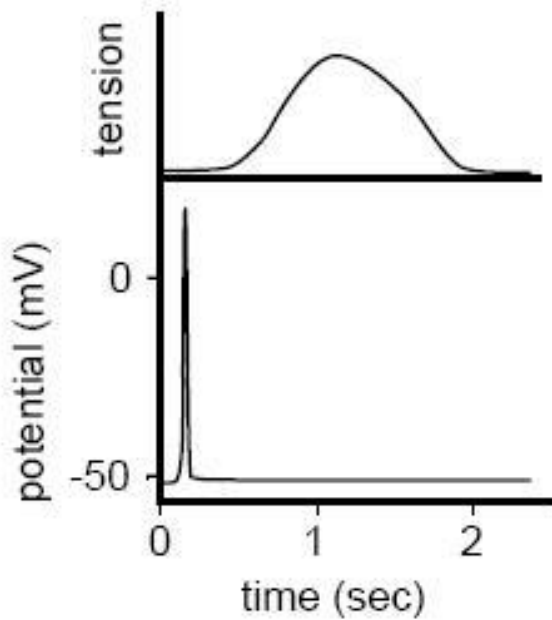


# Потенциал действия гладких мышц сосудов

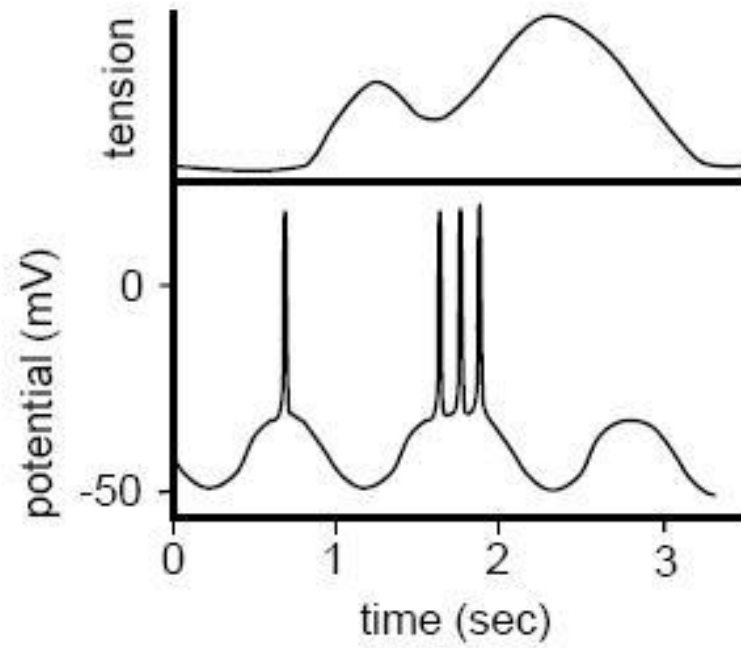


# Тонический и фазический тип сокращений гладких мышц

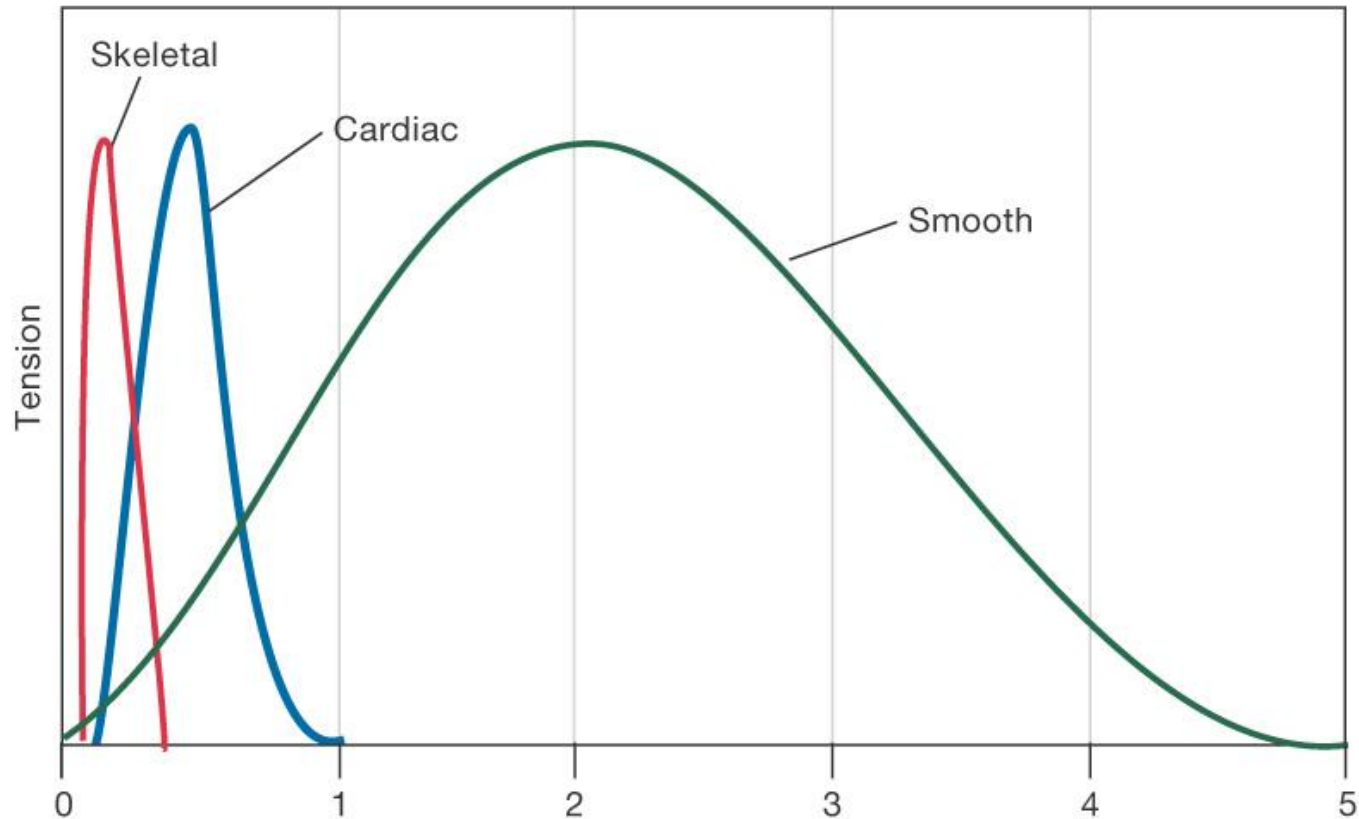
## Smooth Muscle Contraction



## Smooth Muscle Pacemaker Activity



# Кривые сокращений скелетной, сердечной и гладкой мышц



Time (sec) Figure 12-24: Duration of muscle contraction in three types of muscle

# Механизм сокращений скелетных мышц

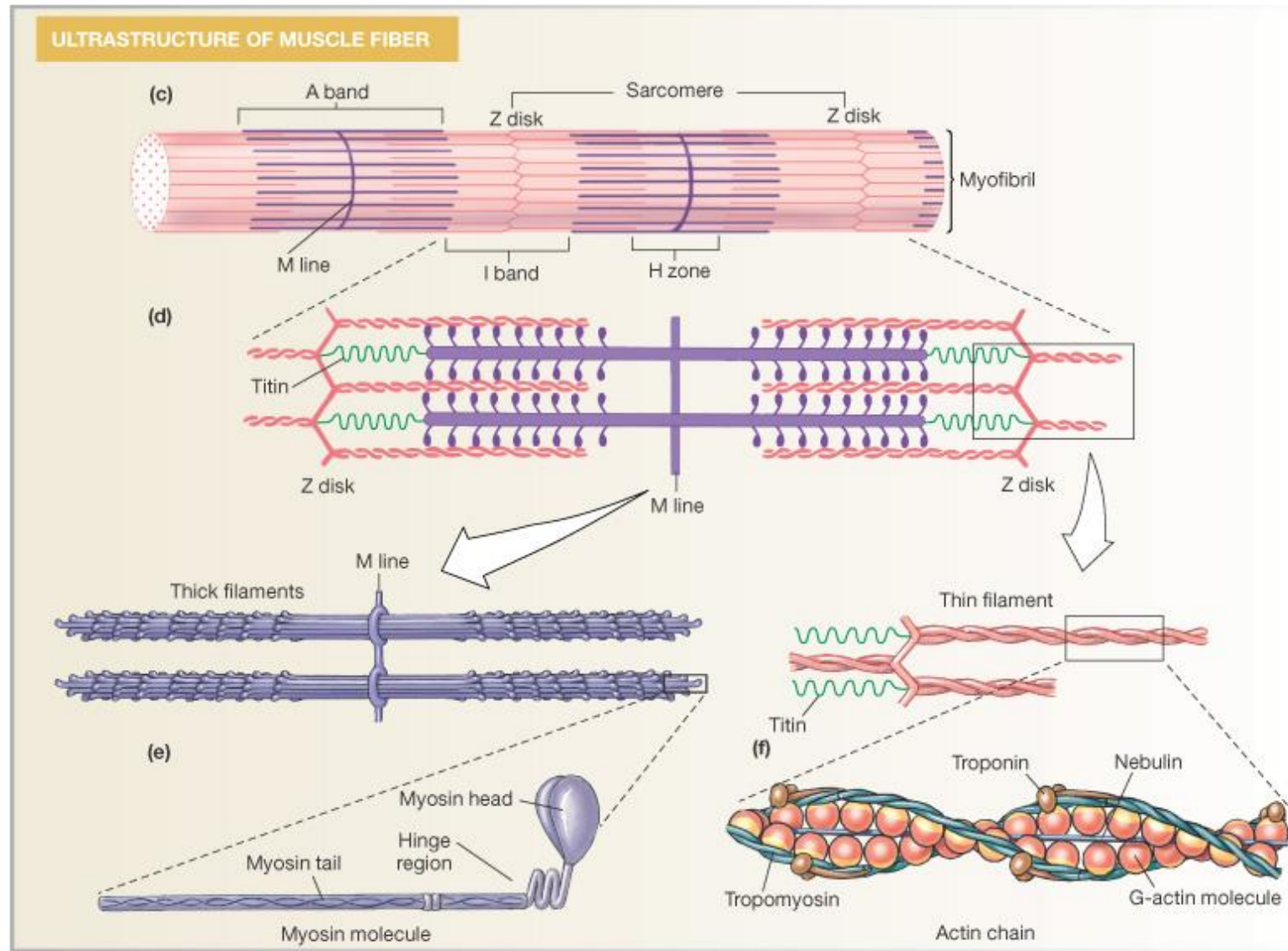
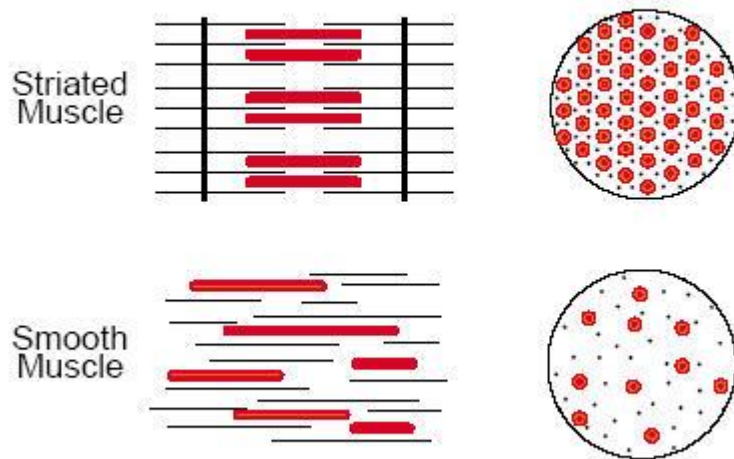


Figure 12-3c-f: ANATOMY SUMMARY: Skeletal Muscle

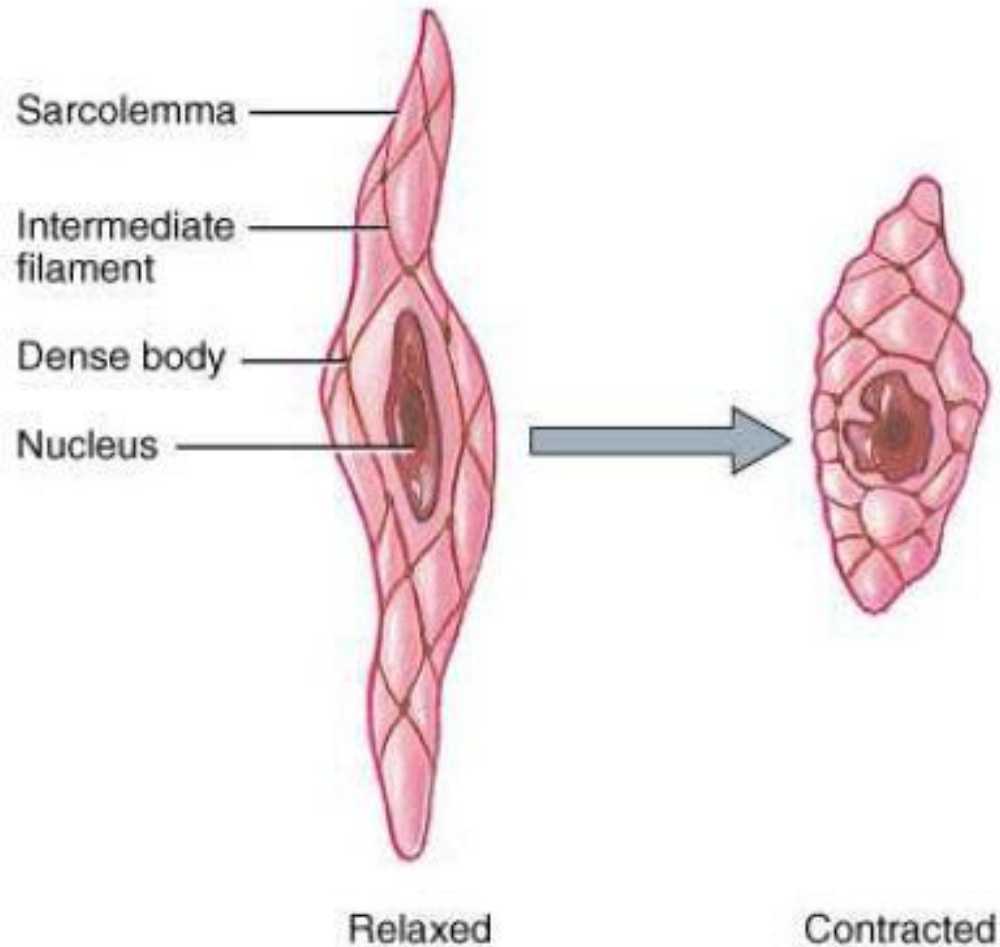


# Сравнительная организация сократительных элементов в скелетной и гладкой мышцах

## Muscle Fiber Organization



# Вид гладкомышечной клетки в покое и при сокращении

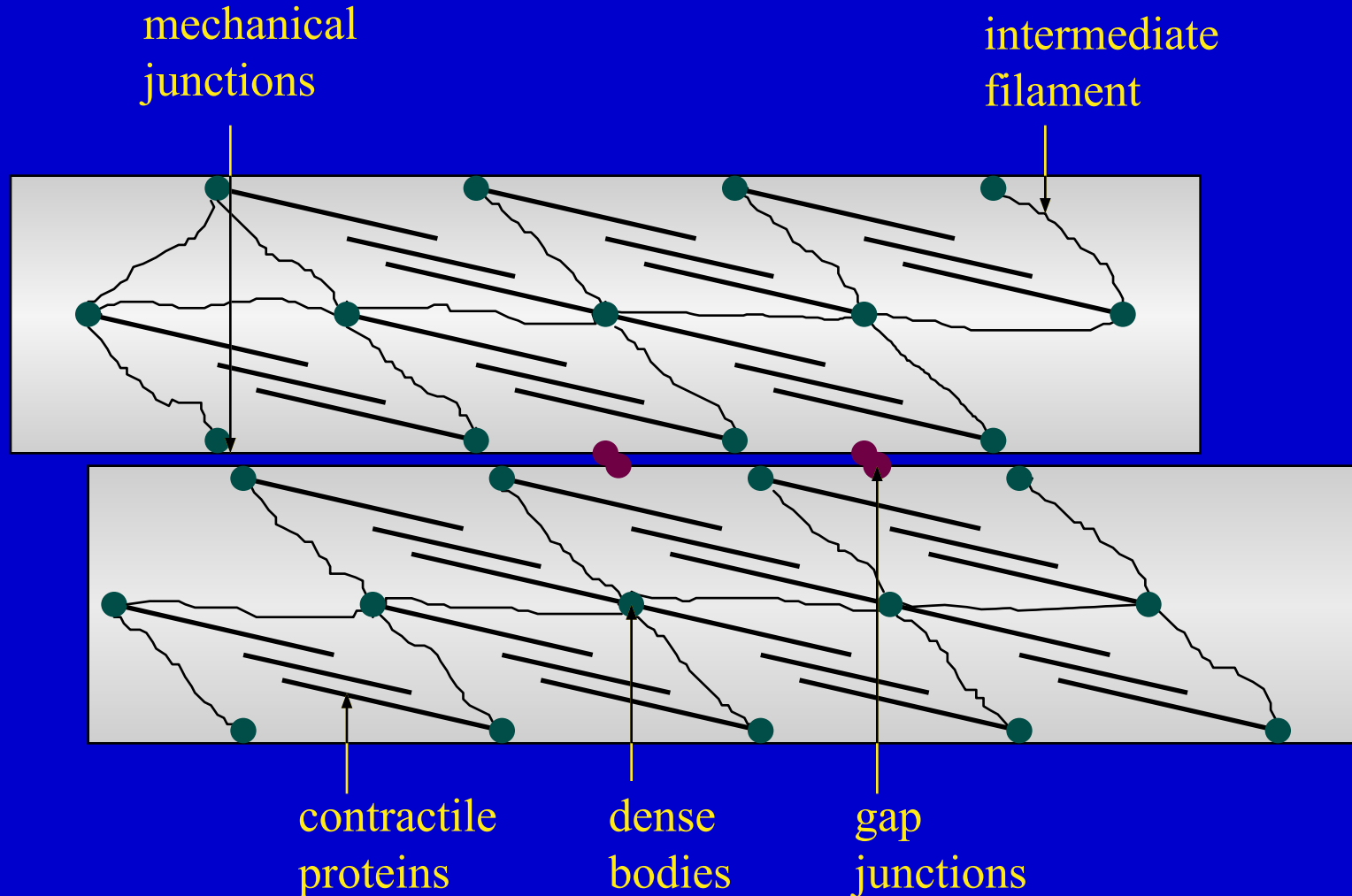


(a) Details of a smooth muscle fiber

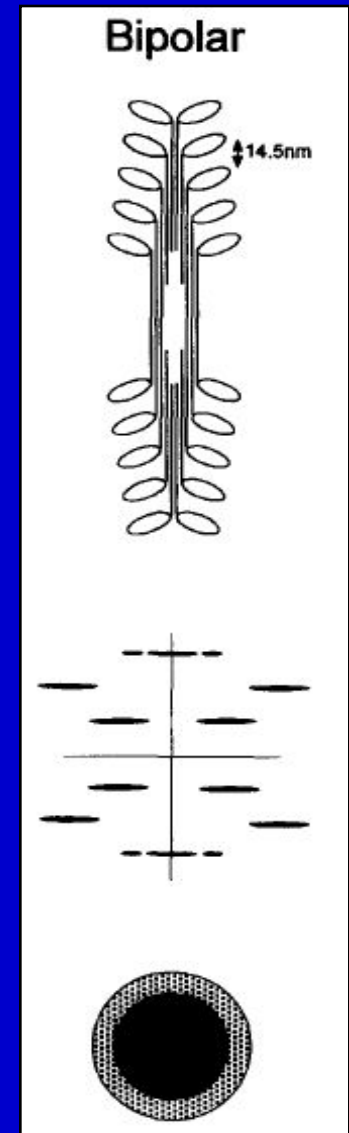
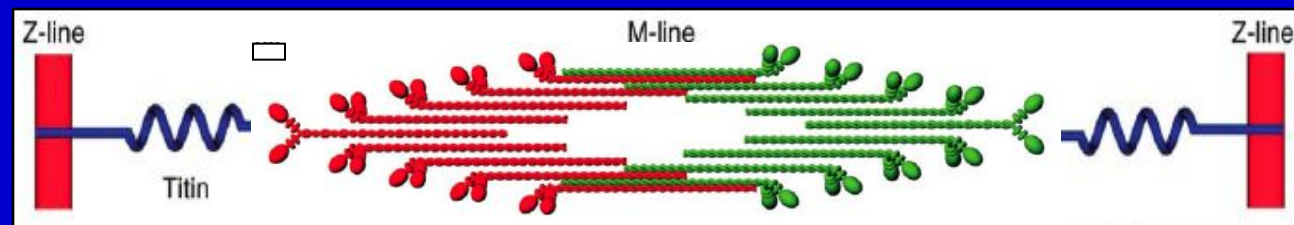
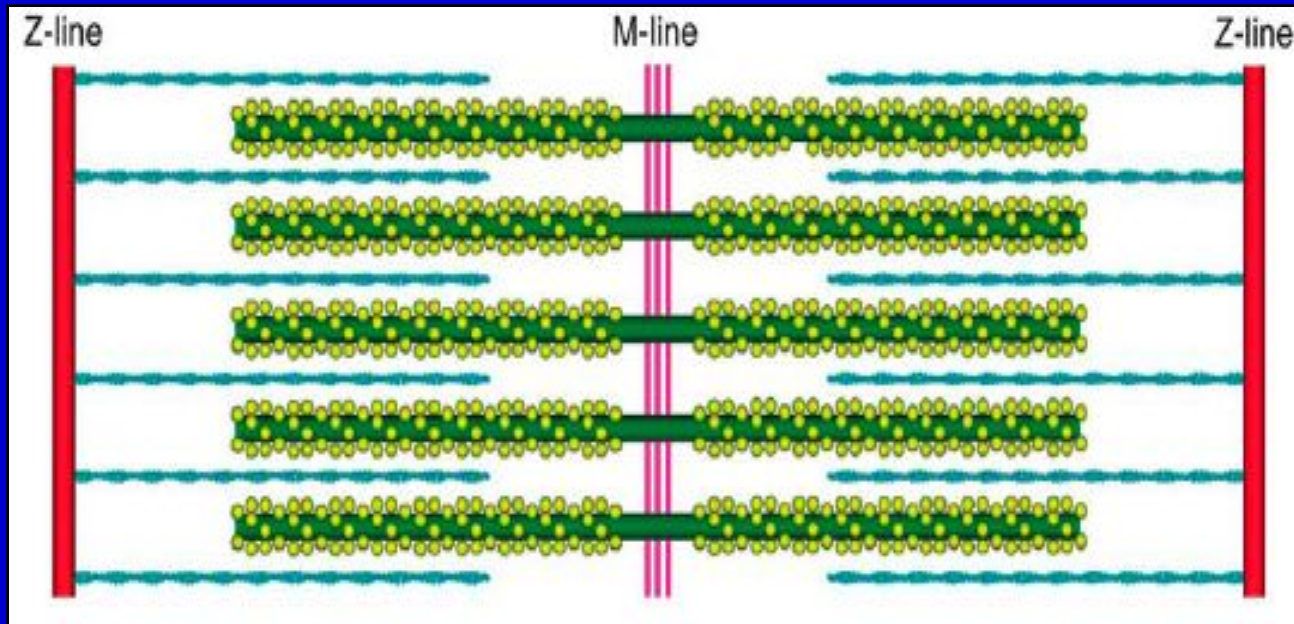
# The fibrillar contractile apparatus

Dense bodies serve as attachment points for the thin filaments

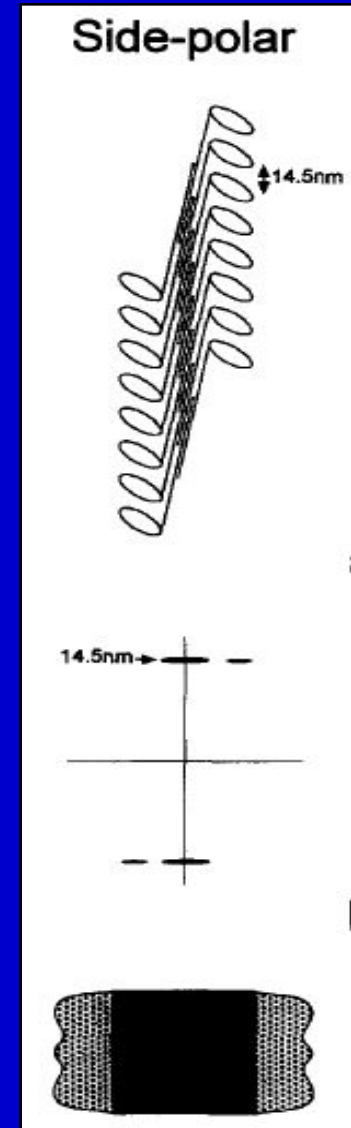
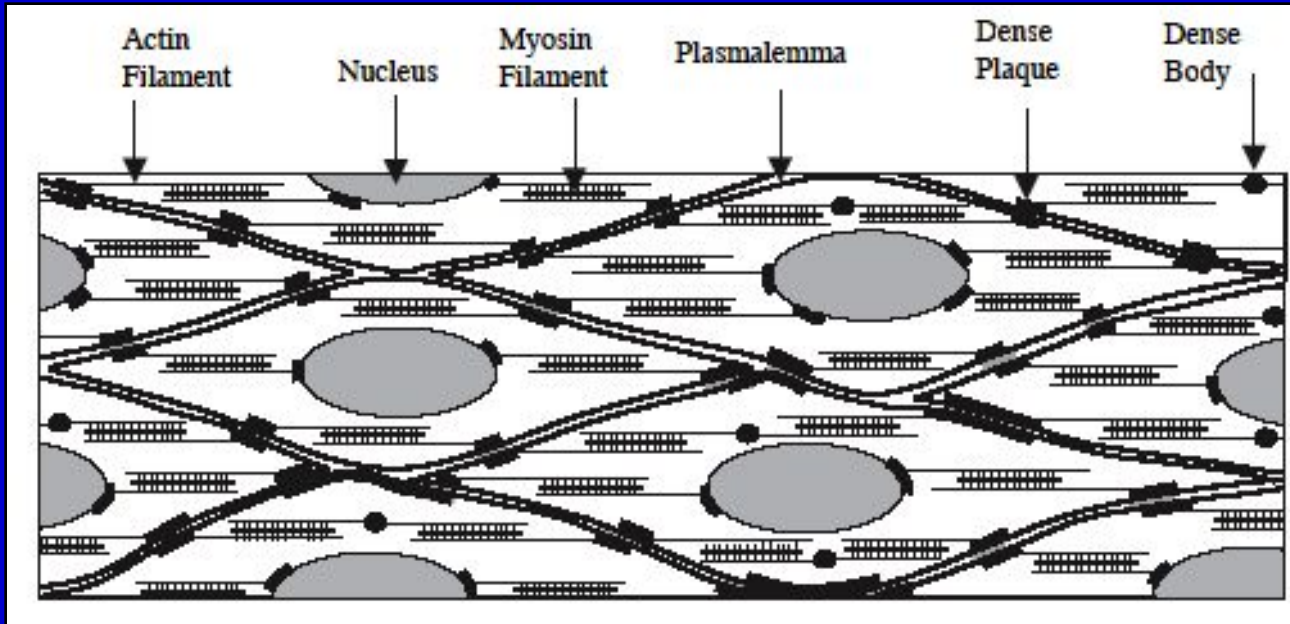
Intermediate filaments form a cytoskeletal network between dense bodies



# Структурная композиция сократительного аппарата (поперечнополосатая мускулатура)



# Структурная композиция сократительного аппарата (гладкая мускулатура)



# Механизм сокращений в гладкой мышце

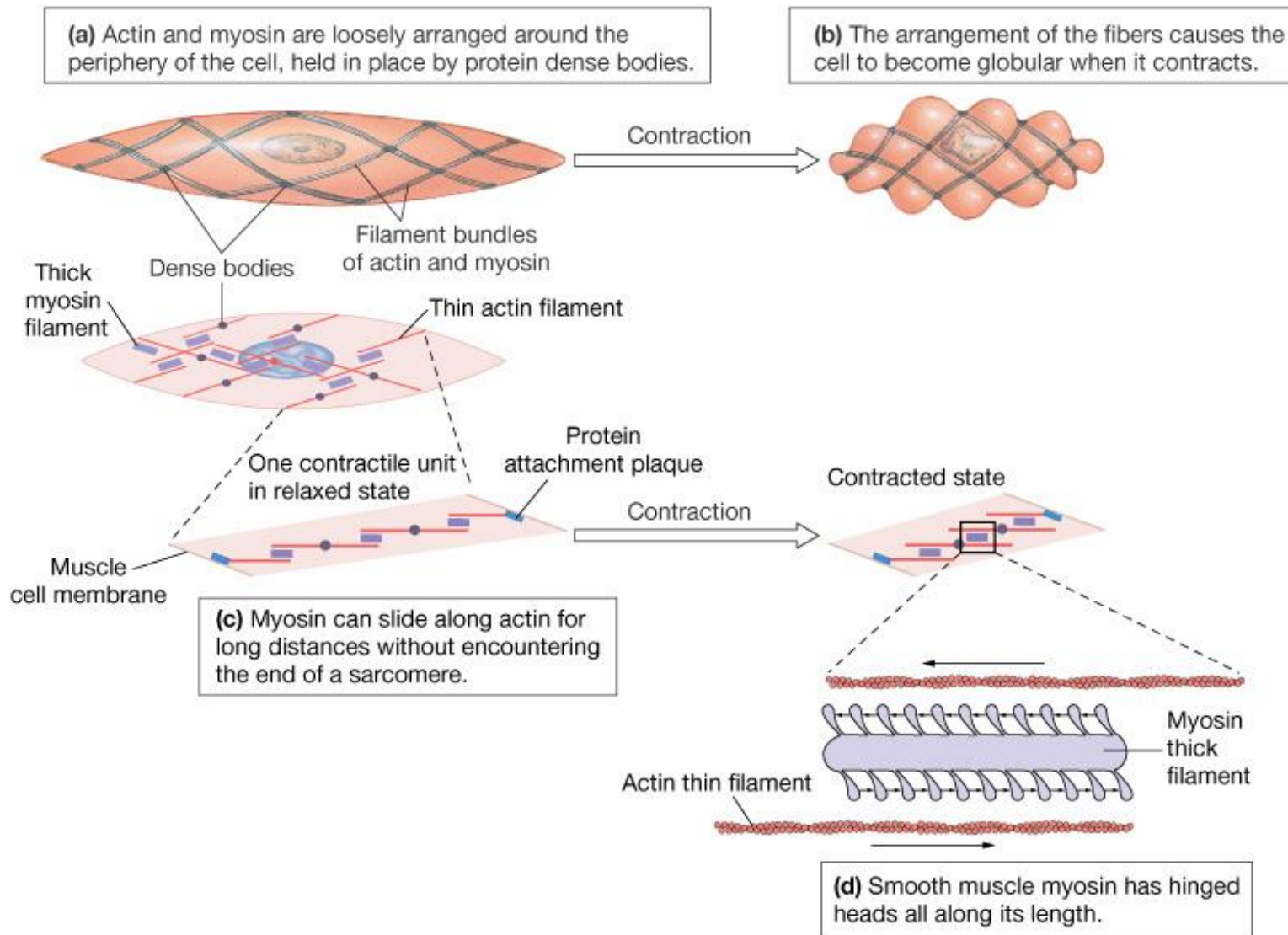
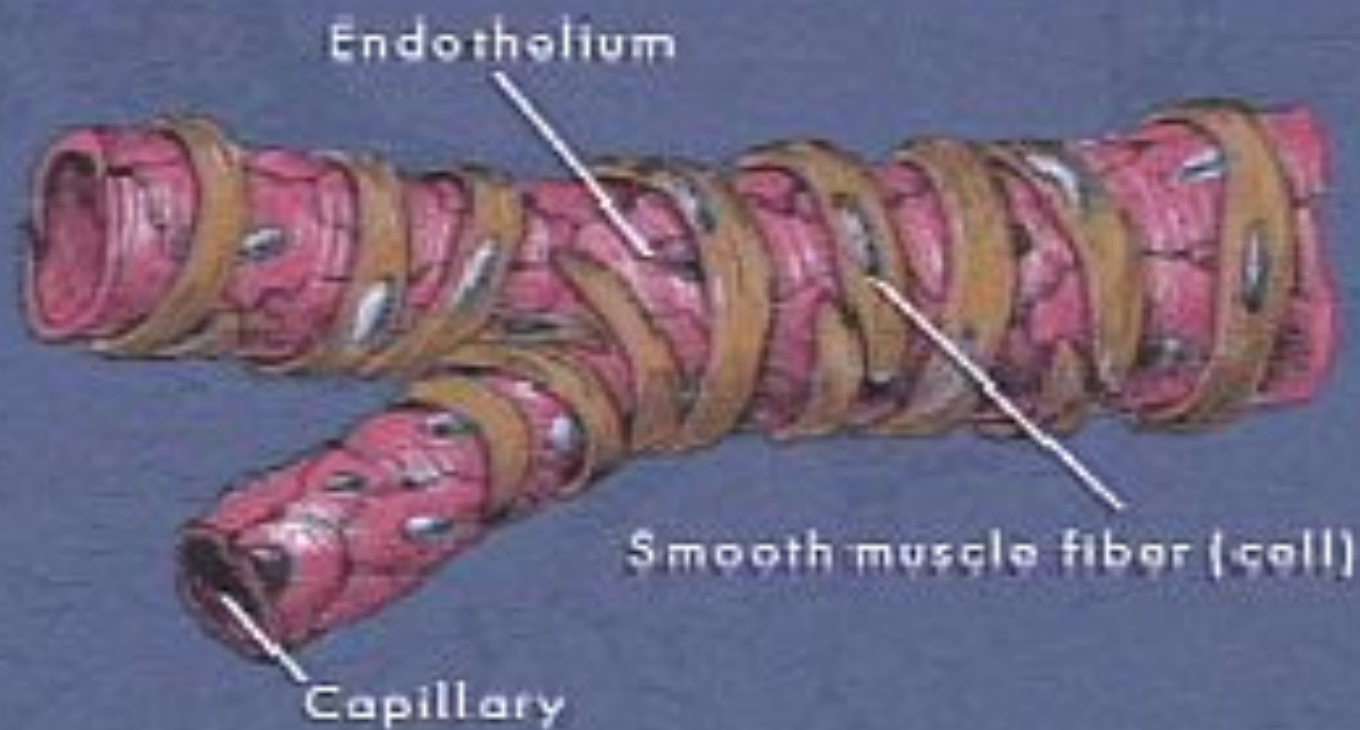
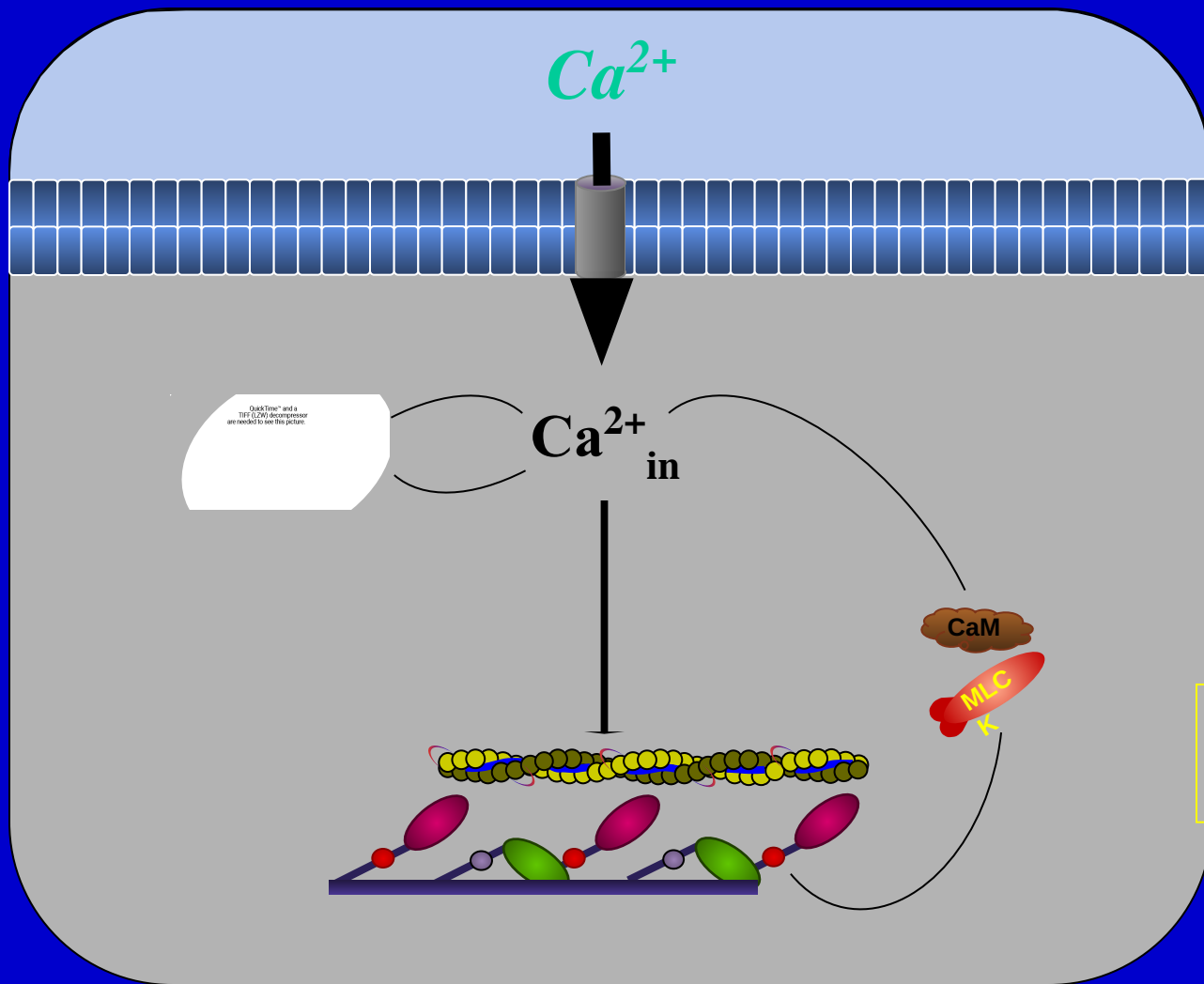


Figure 12-27: Anatomy of smooth muscle

## Structure of an Arteriole



# Регуляция сократительного аппарата скелетных мышц (excitation-contraction coupling)



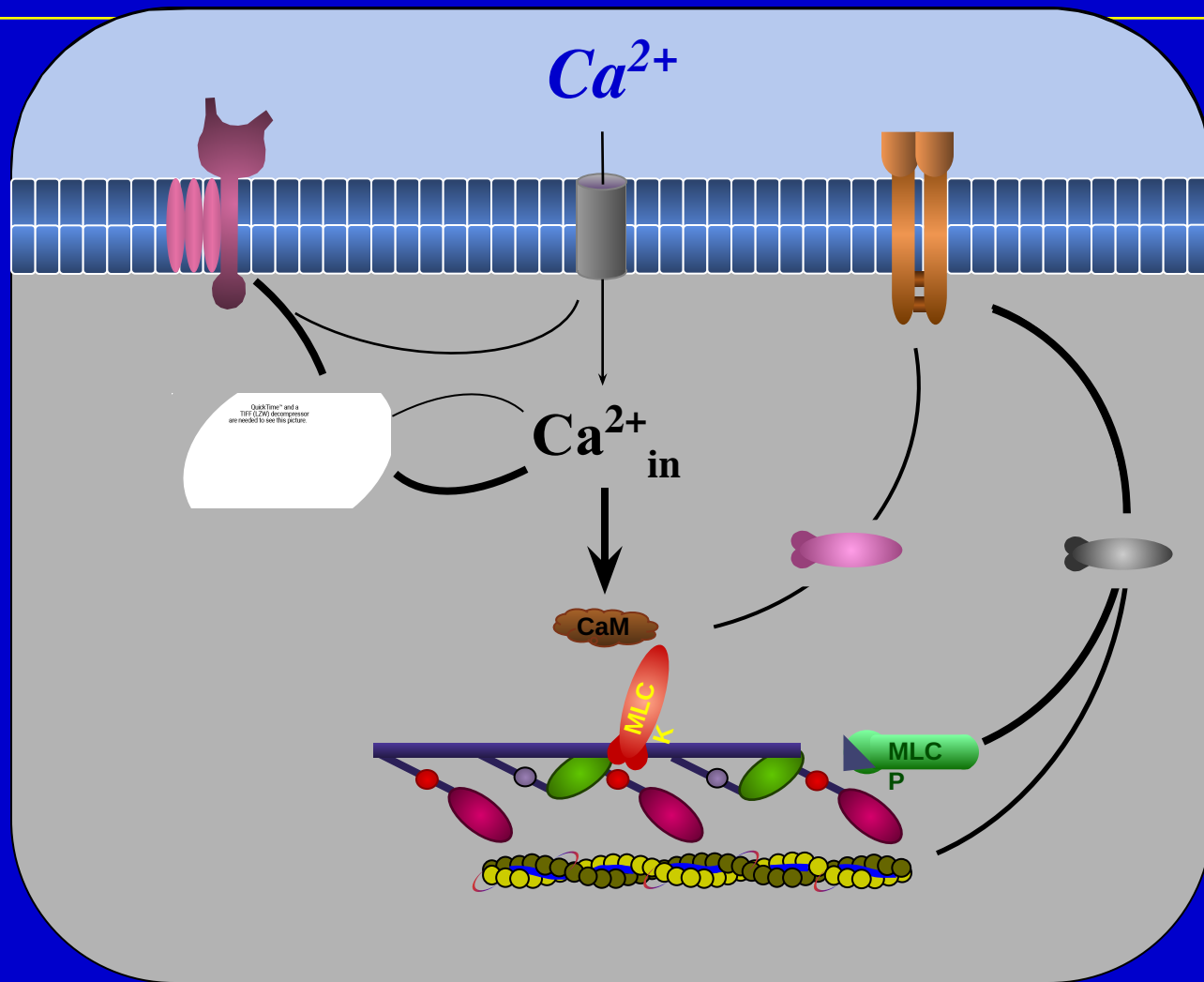
ПОТЕНЦИАЛ  
ДЕЙСТВИЯ  
**VDCC**

ЭЛЕКТРОМЕХАНИЧЕСКОЕ  
СОПРЯЖЕНИЕ

ПРЯМАЯ АКТИВАЦИЯ  
АКТОМИОЗИНА



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

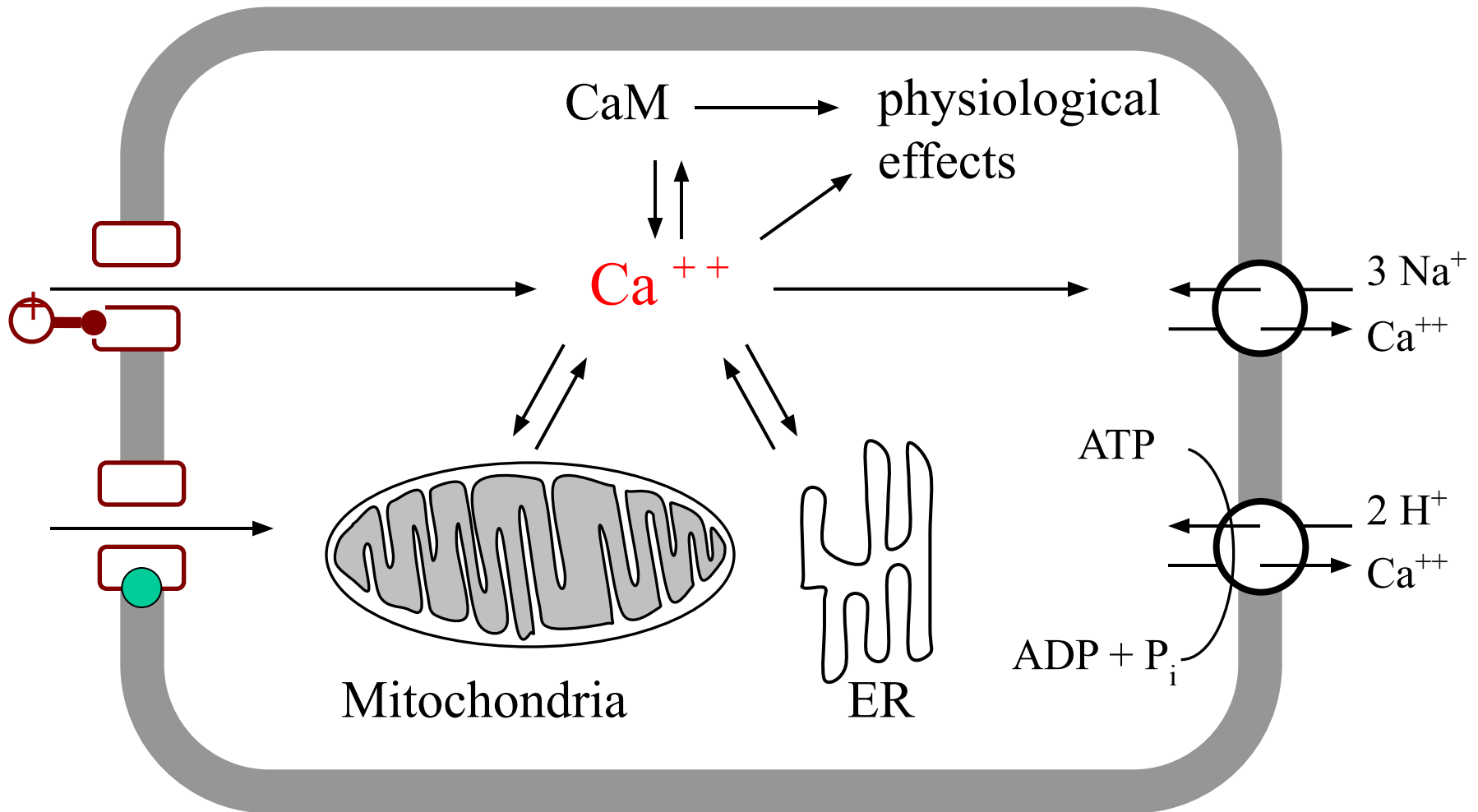


ГОРМОН-РЕЦЕПТОРНОЕ  
МНОГООБРАЗИЕ

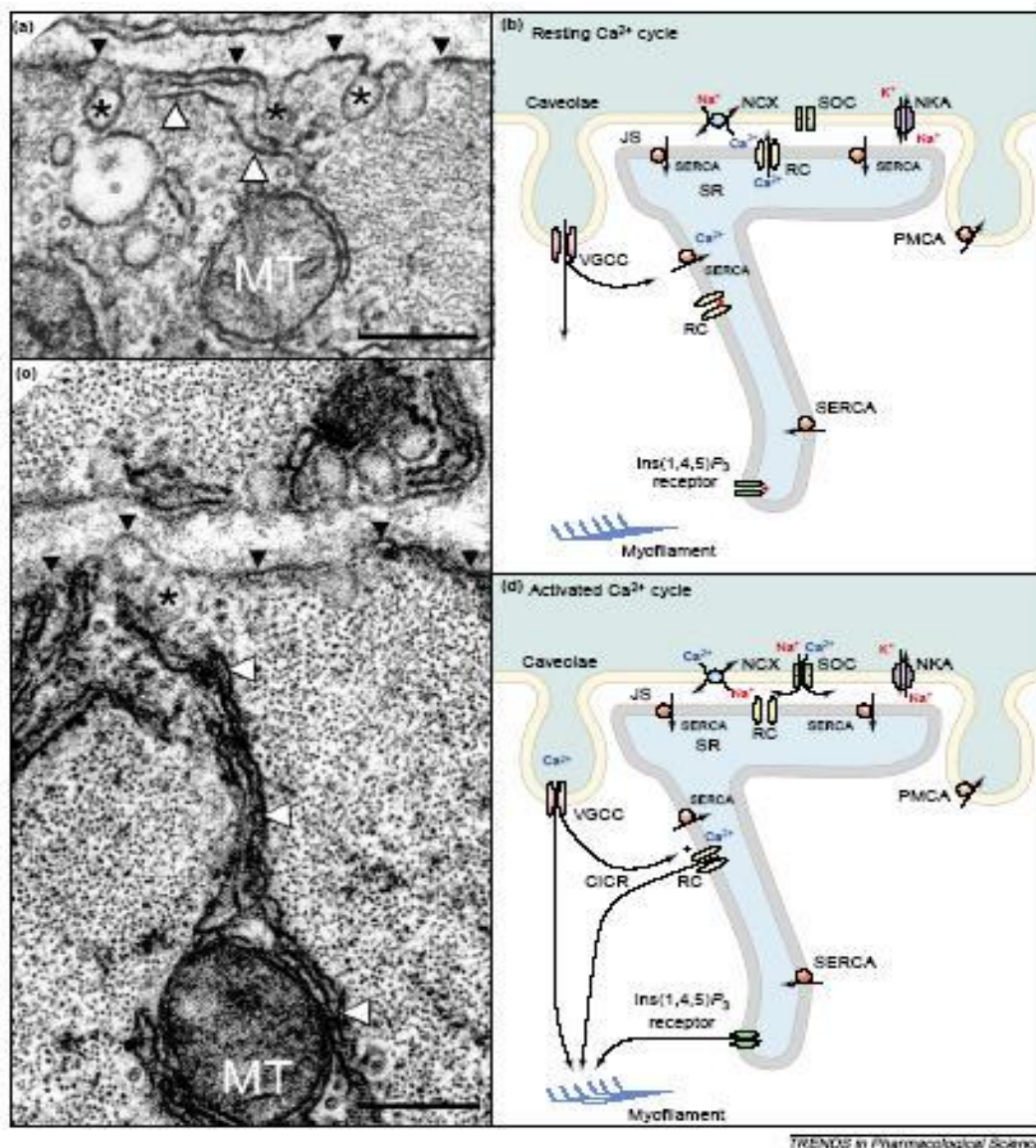
ФАРМАКОМЕХАНИЧЕСКО  
Е  
СОПРЯЖЕНИЕ

$Ca^{2+}$ -ЧУВСТВИТЕЛЬНОСТЬ  
( $Ca^{2+}$ -SENSITIZATION)

# Транспорт ионов кальция в гладкомышечную клетку и из клетки



# Локализация ионов Са в клетке гладкой мышцы



TRENDS in Pharmacological Sciences

V2,N1,2004

Figure 1.  $\text{Ca}^{2+}$  cycling at plasma membrane (PM)-saroplasmic 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  $\text{Ca}^{2+}$  cycling in non-stimulated vascular smooth muscle. At rest, the superficial SR buffers the entry of extracellular  $\text{Ca}^{2+}$  as a result of the low open probability of excitable  $\text{Ca}^{2+}$  channels and putative 'leak' channels, and cycles it, via release channels (RCs) (inositol (1,4,5)-triphosphate [Ins(1,4,5)P<sub>3</sub>] and ryanodine (RY) receptors) to the Na<sup>+</sup>-Ca<sup>2+</sup> exchanger (NCX) in the junctional space (JS) to be

# Calcium activates calmodulin

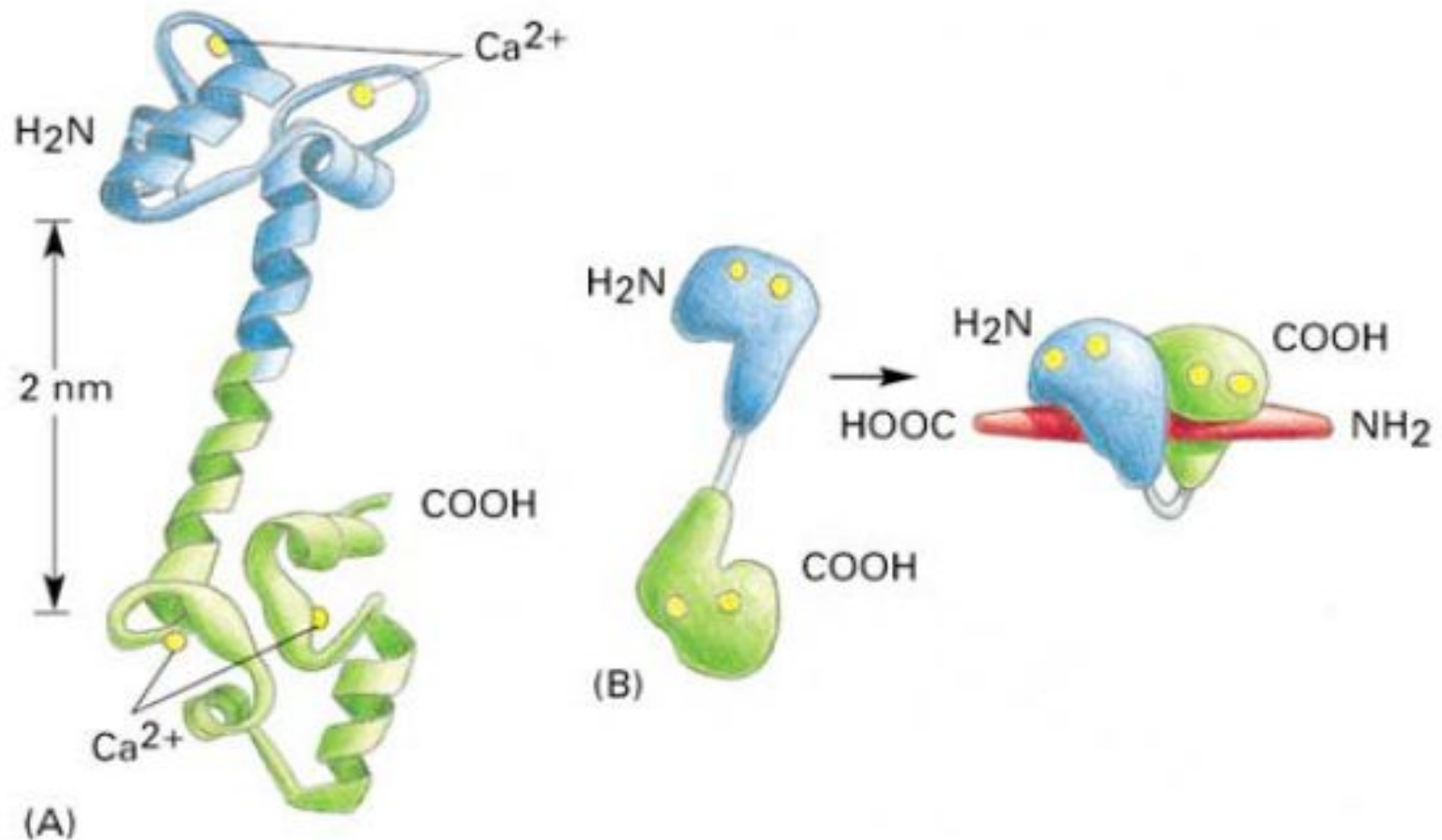
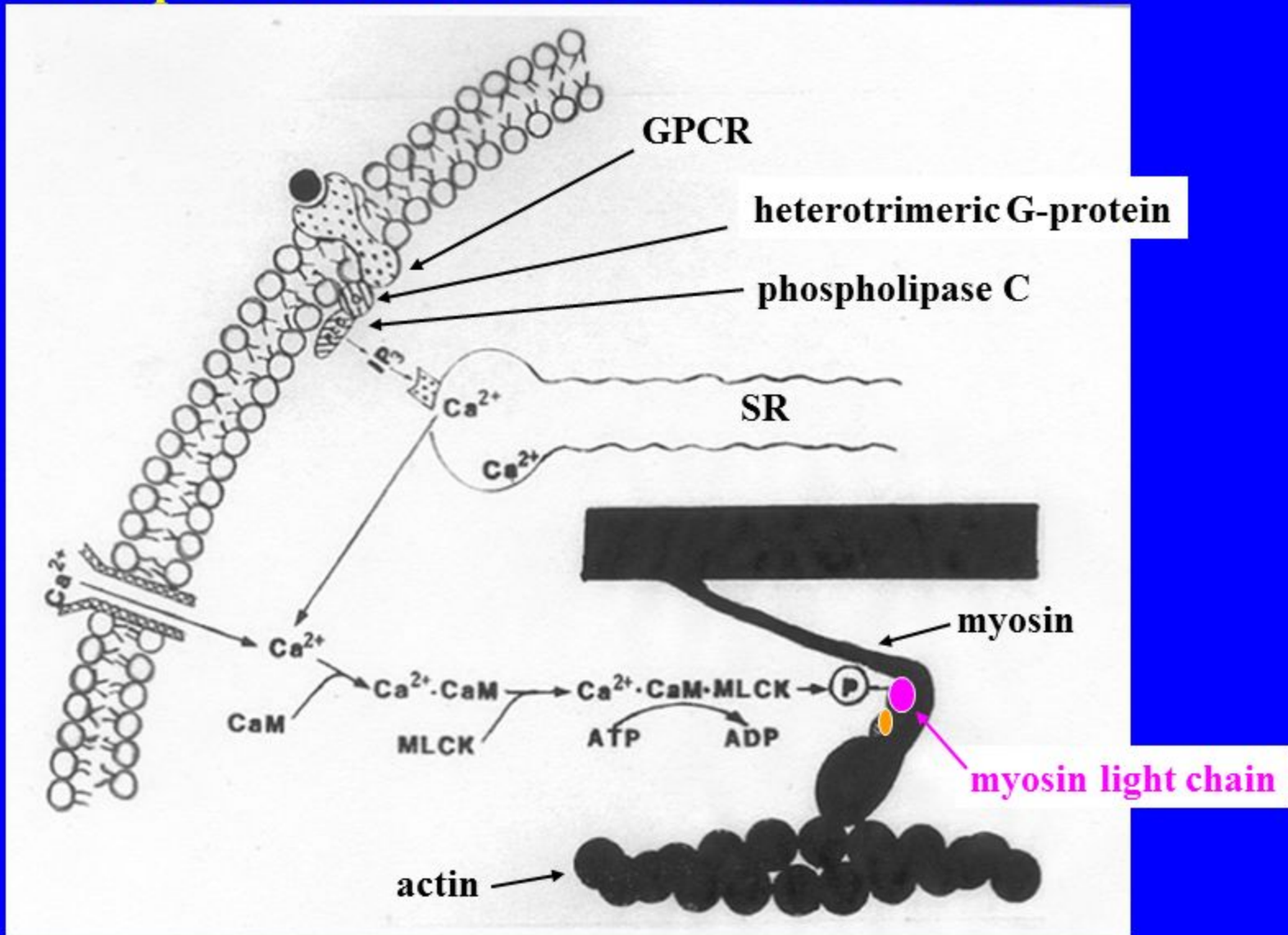


Figure 15-40. Molecular Biology of the Cell, 4th Edition.

# A Simplified View of Smooth Muscle Contraction



**CaM = Calmodulin**

**MLCK = myosin light chain kinase**

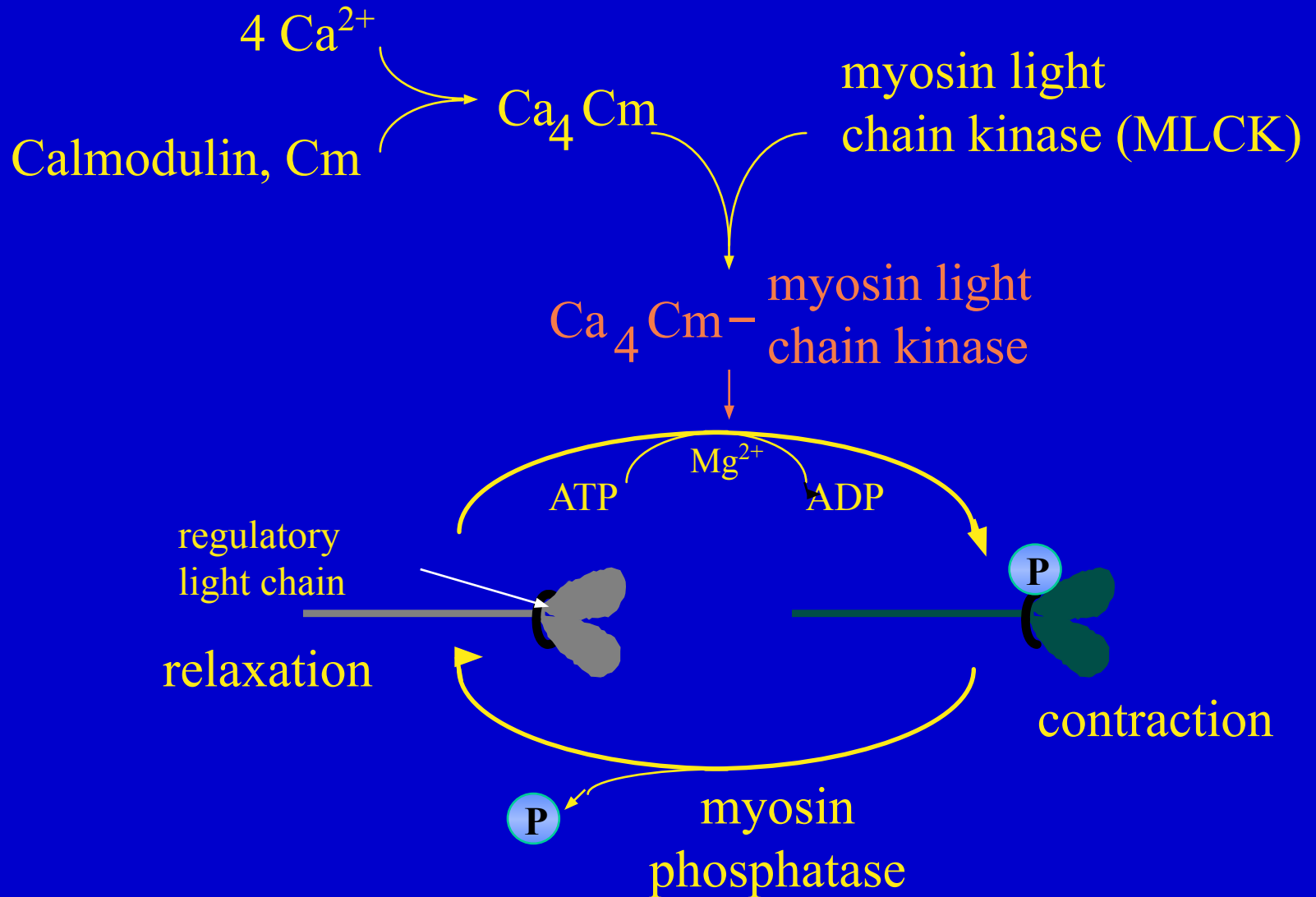
**IP<sub>3</sub> = inositol trisphosphate**

Bárány, K. and Bárány, M. (1996). Myosin light chains.

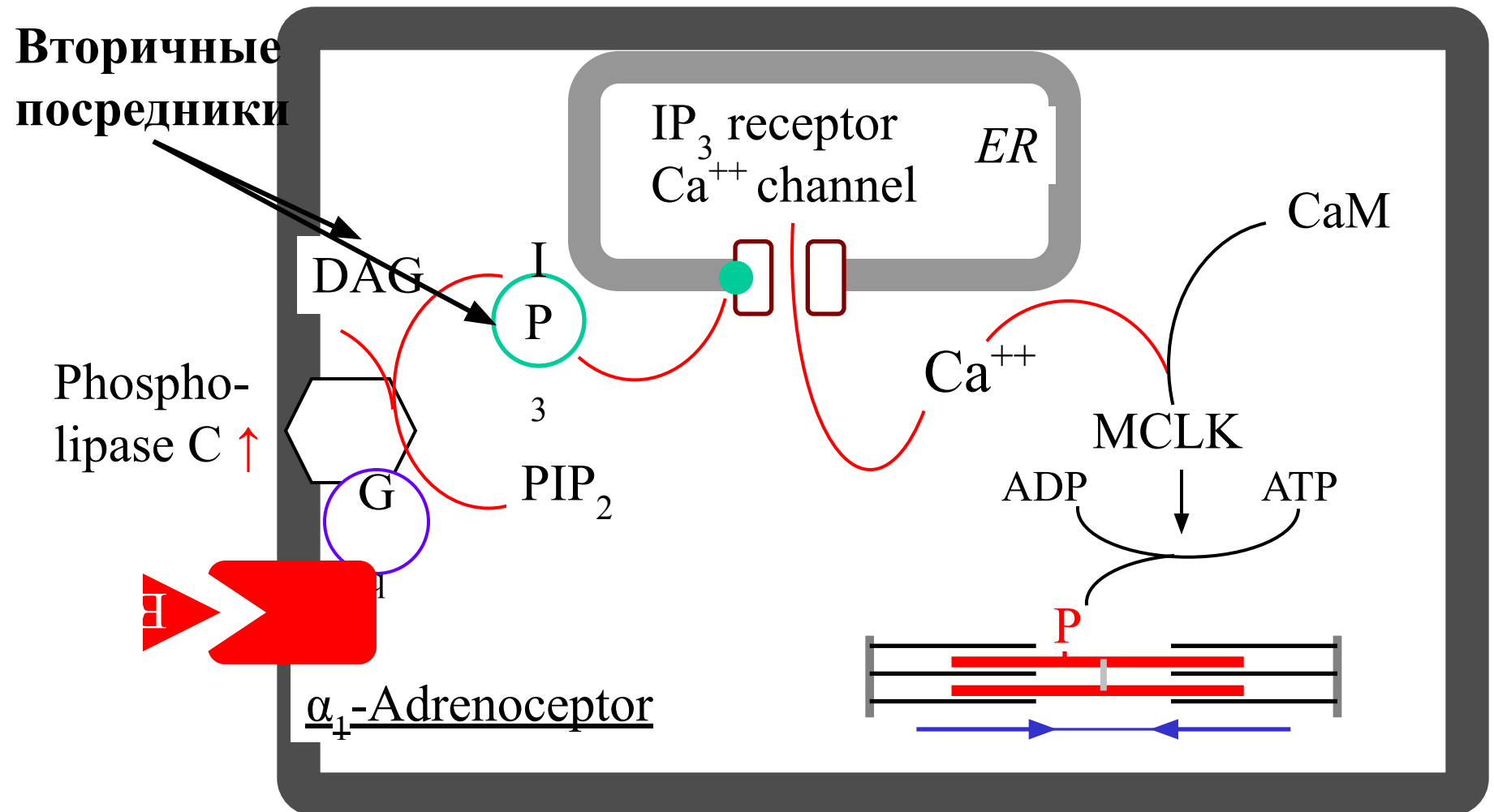
*In Biochemistry of Smooth Muscle Contraction* (M. Bárány, Ed.), pp. 21-35, Academic Press.

# Cross-bridge activation in smooth muscle

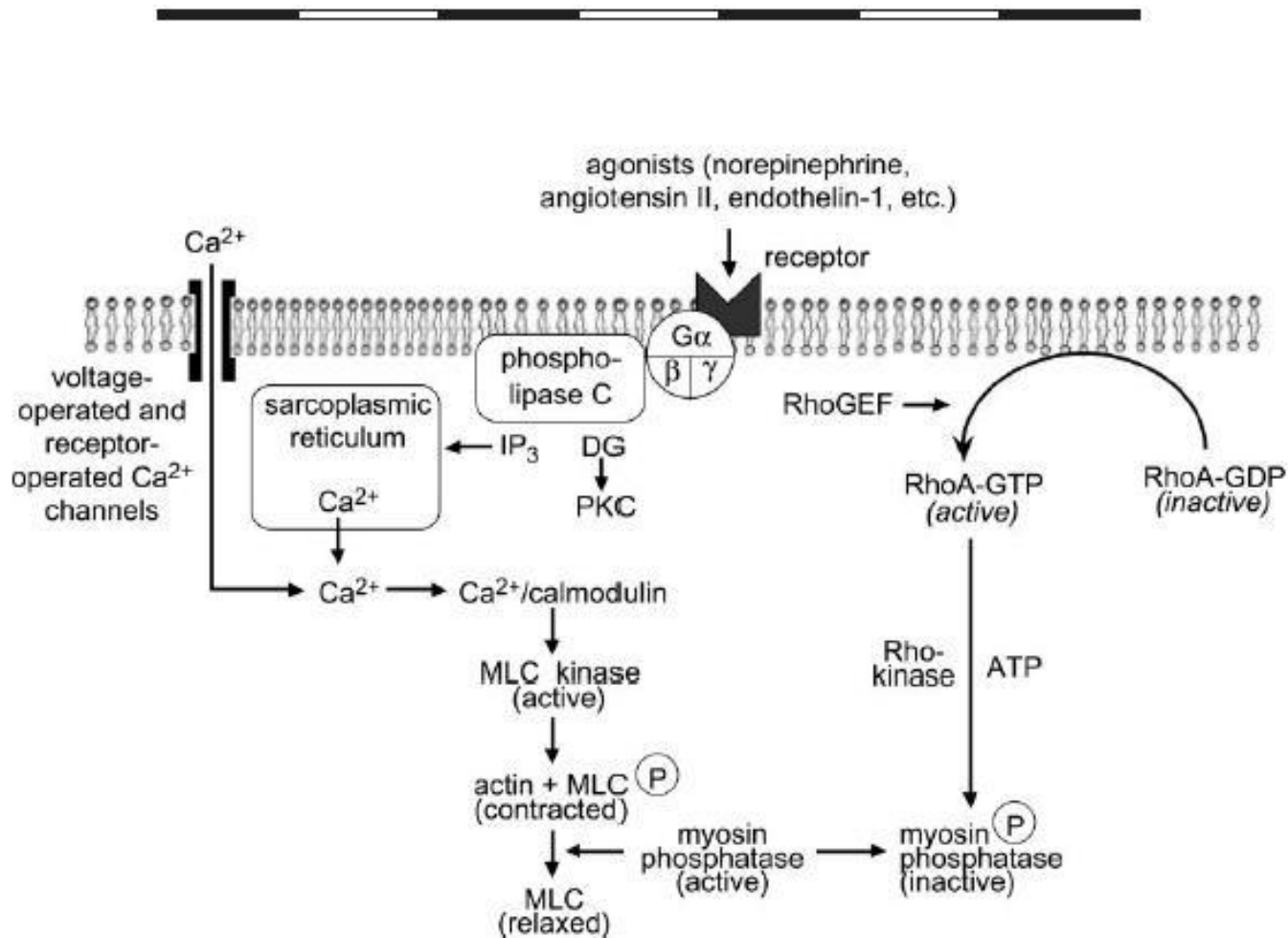
## Ca<sup>2+</sup>-stimulated myosin phosphorylation



# Сокращение гладких мышц сосудов при активации альфа-1 адренорецепторов

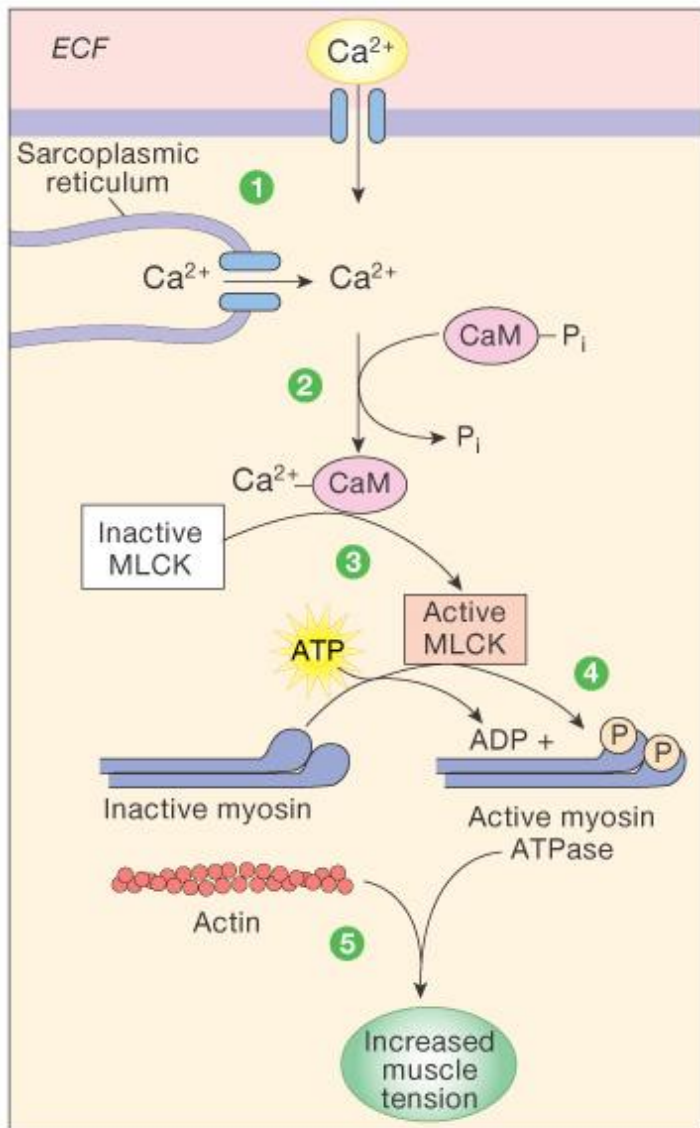


# Механизм рецепторно (гормон)-механического сопряжения





# Основные этапы сокращения гладких мышц



1 Увеличение внутриклеточной концентрации иона кальция

2 Ca связывается с калмодулином (CaM)

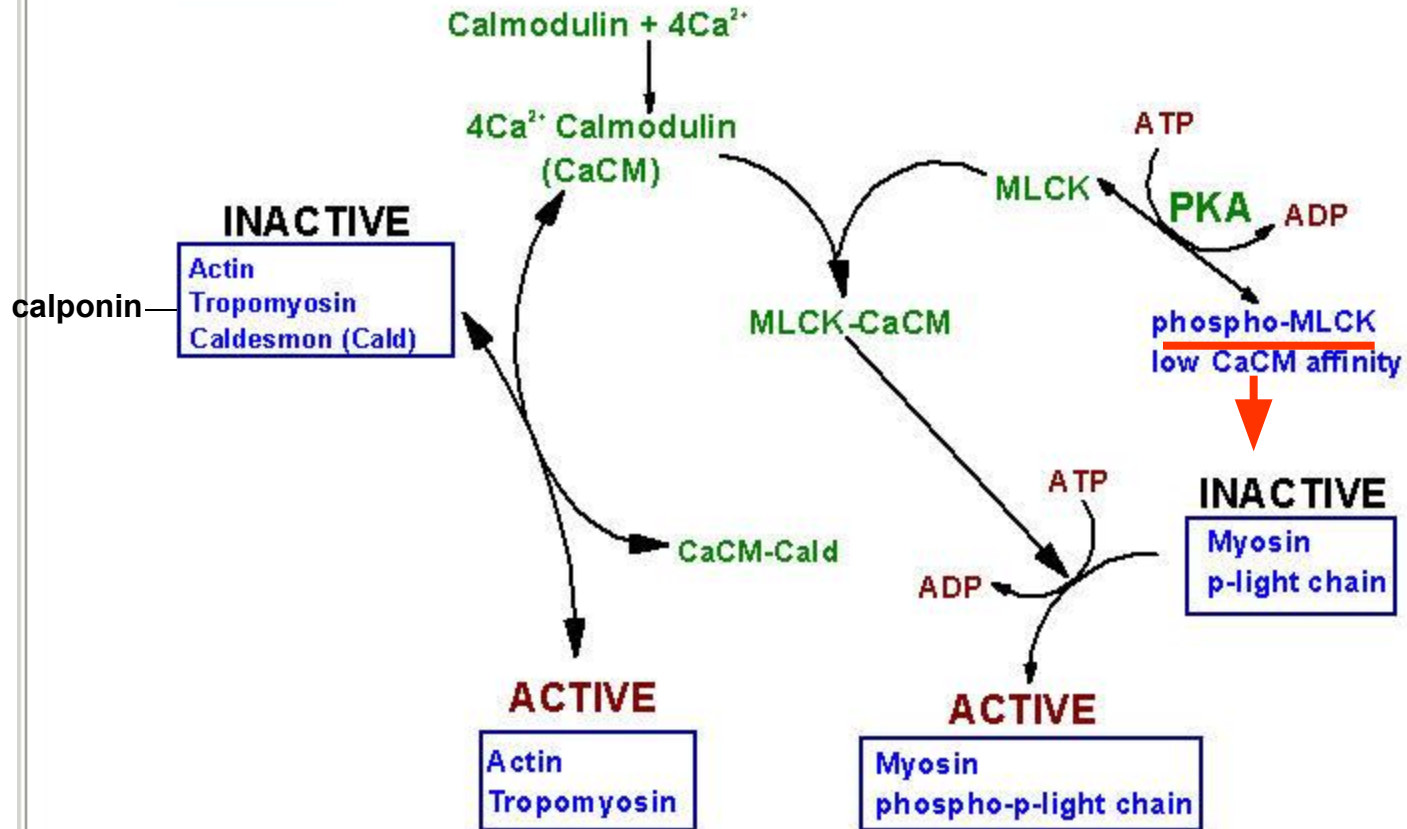
3 CaM активирует киназу легких цепей миозина (MLCK)

4 MLCK фосфорилирует легкие цепи миозиновых головок и увеличивает активность миозин АТФазы

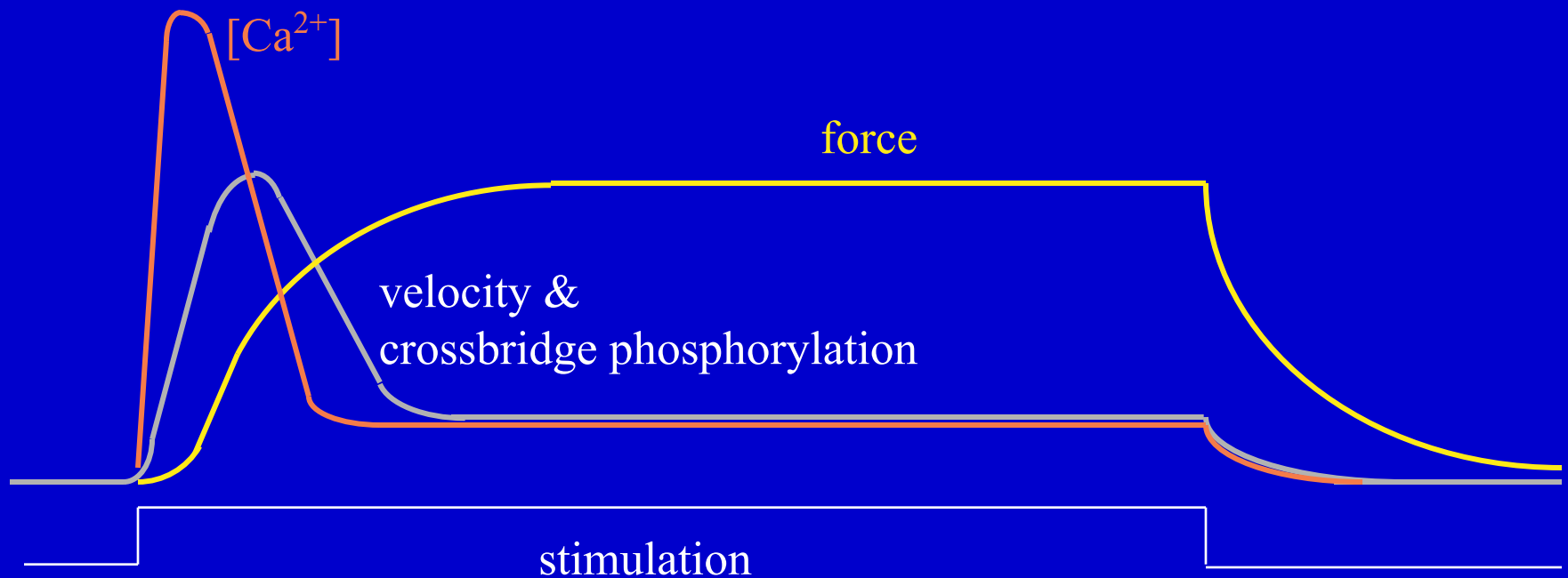
5 Происходит образование поперечных мостиков и скольжение миозина по актину



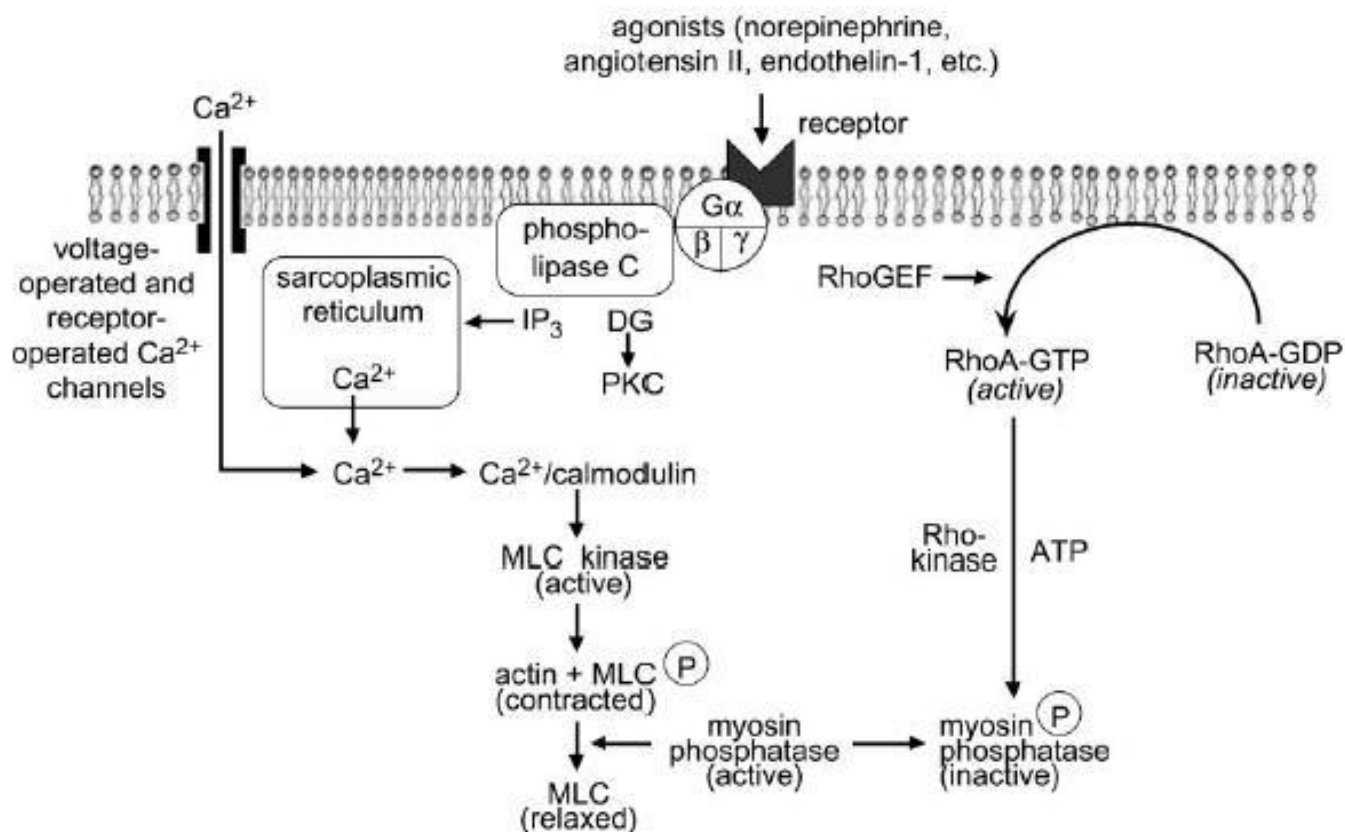
# Smooth Muscle Contraction



# Тоническое сокращение гладких мышц сосудов при низкой концентрации ионов Ca

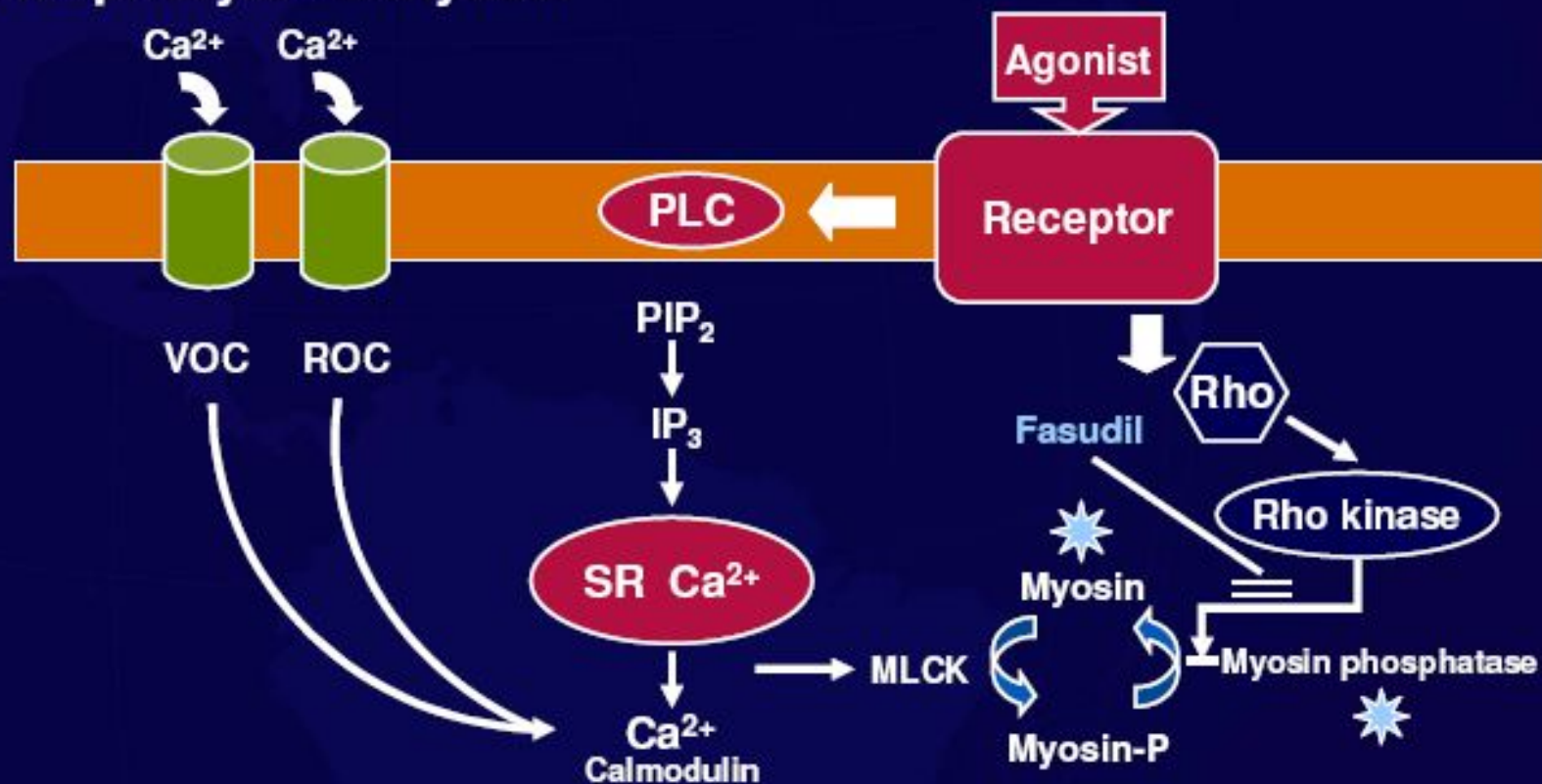


# Механизм рецепторно-механического сопряжения



## 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

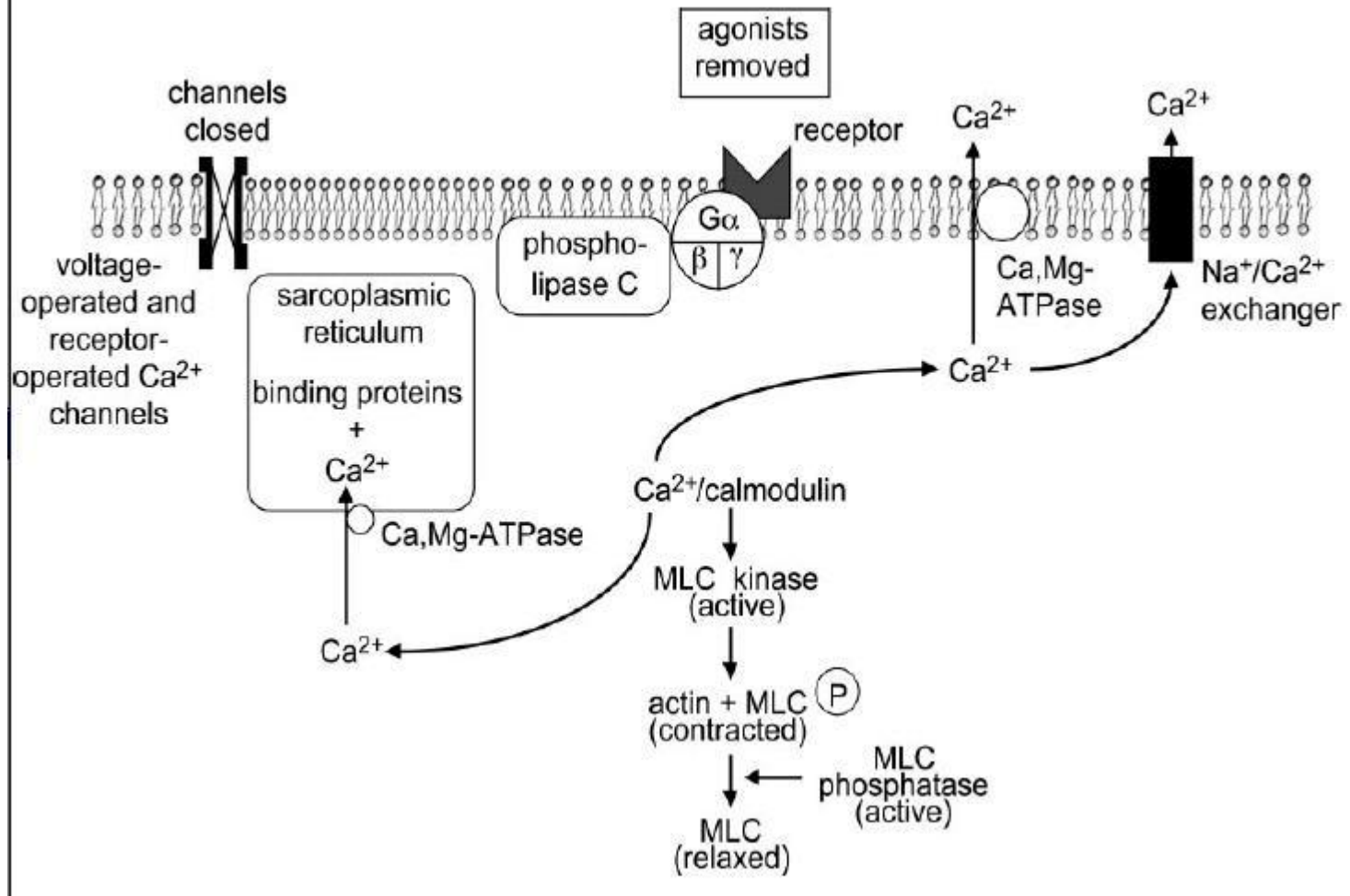
## (2) Функционально отличные изоформы сократительных белков

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

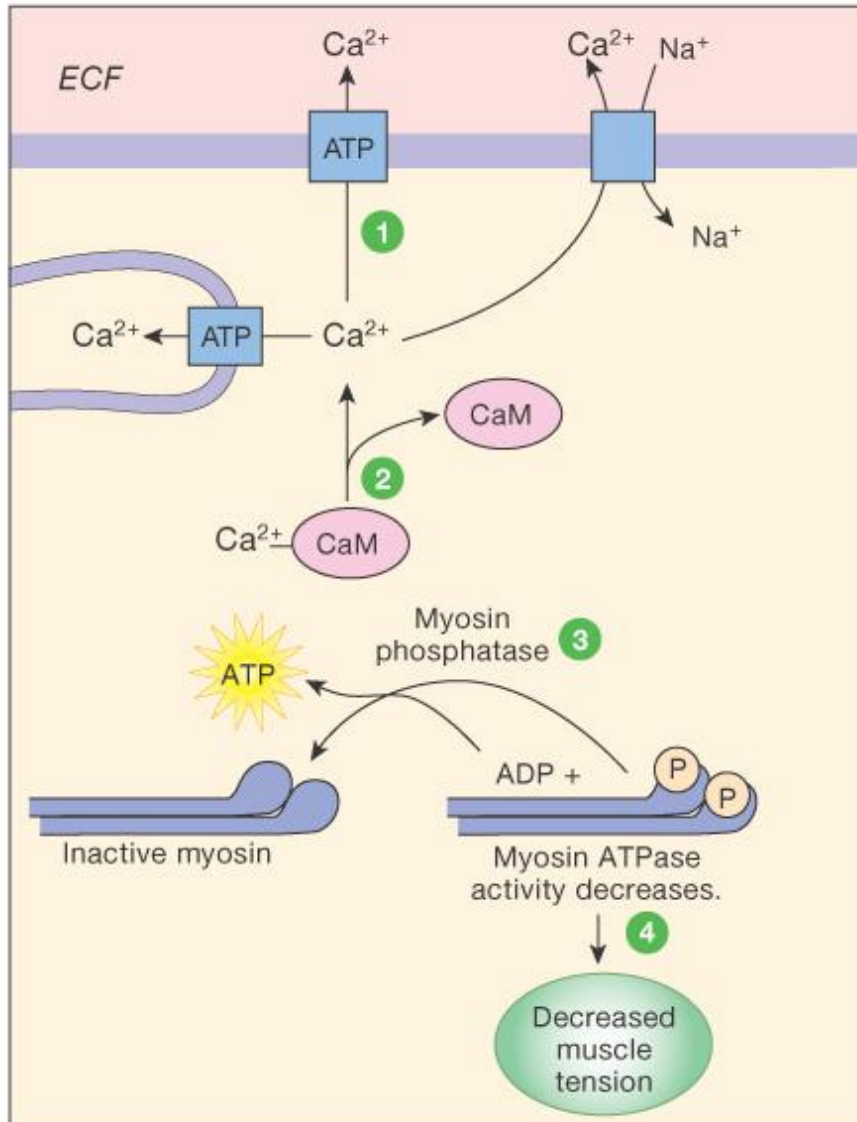
## (3) Физиология сокращения

- гуморальная регуляция (многообразие рецепторных систем)
- фармфармакомеханическое 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  $\text{Ca}^{2+}$  in cytosol decreases when  $\text{Ca}^{2+}$  is pumped out of the cell or back into the sarcoplasmic reticulum.

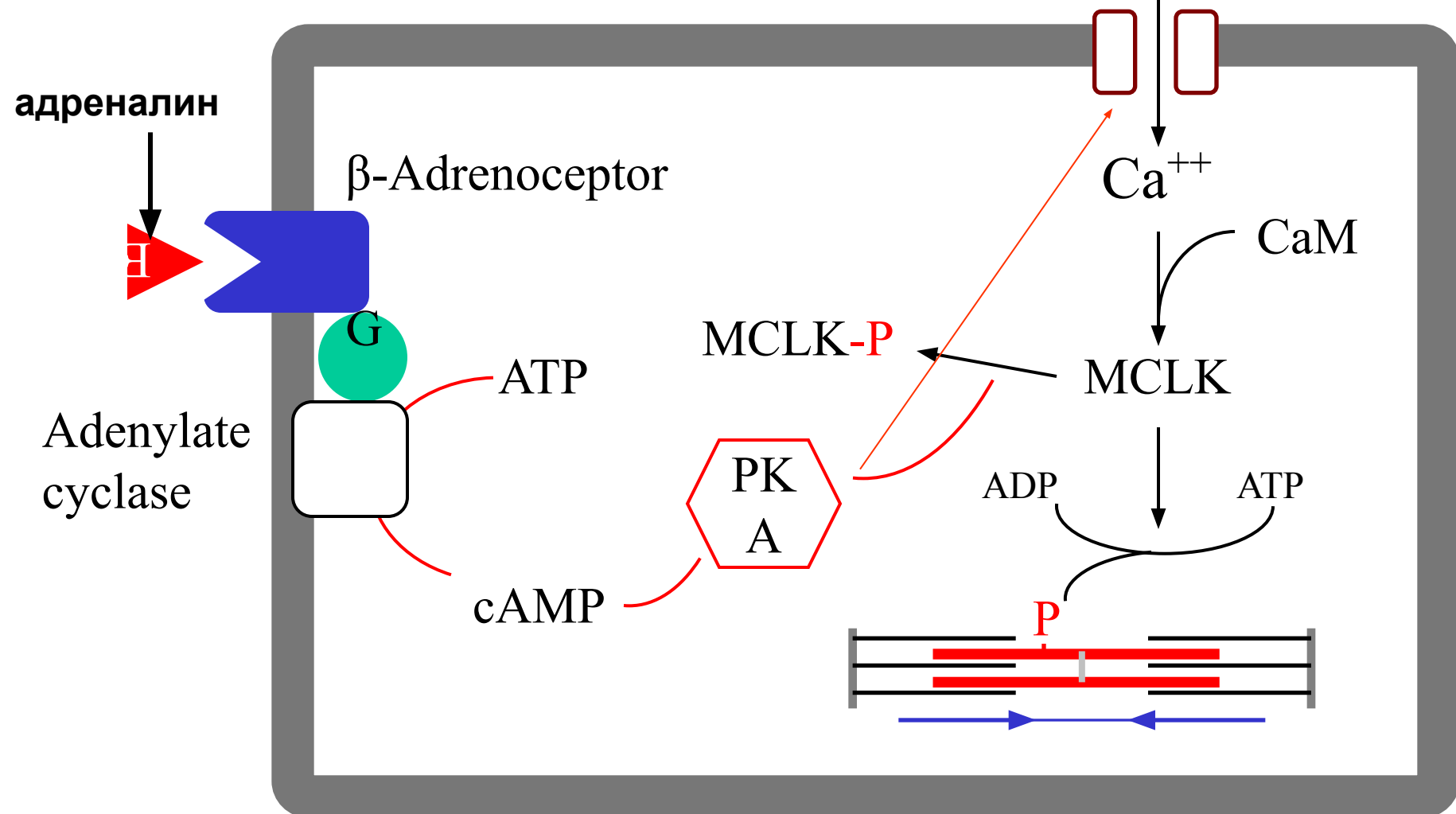
2  $\text{Ca}^{2+}$  unbinds from calmodulin (CaM).

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

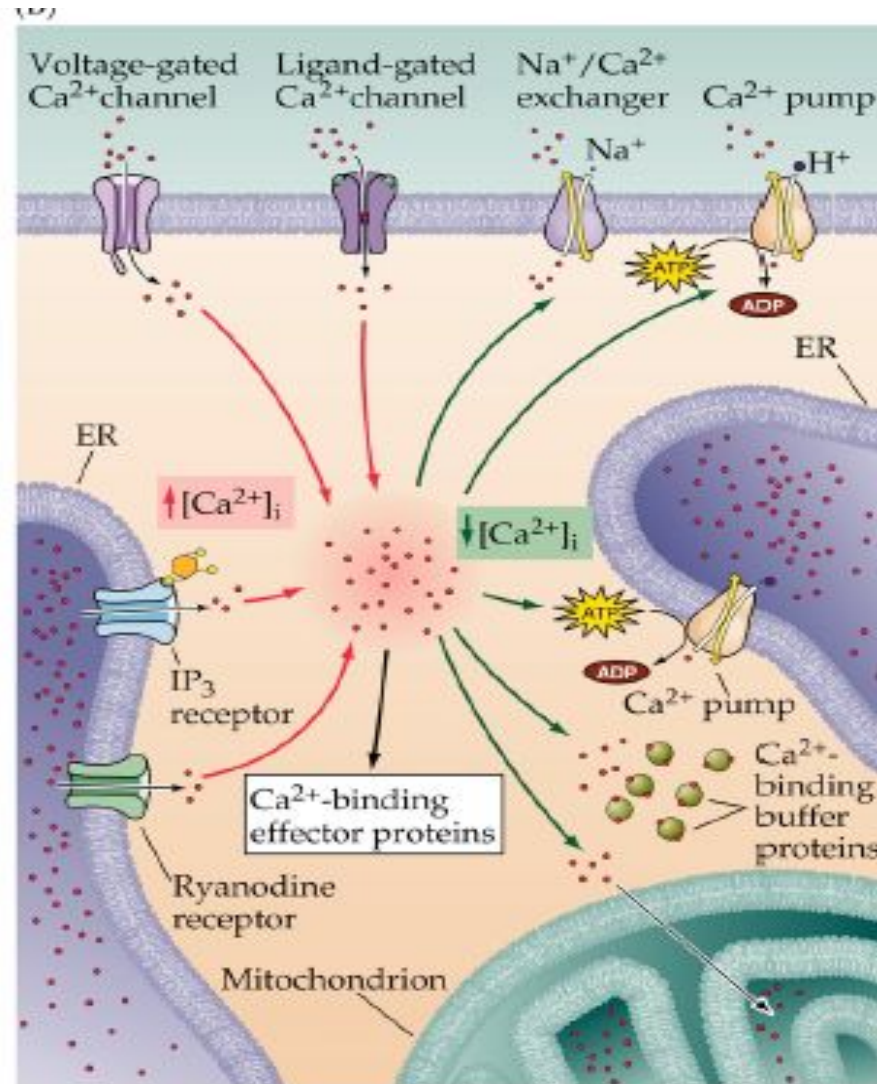
4 Less myosin ATPase results in decreased muscle tension.



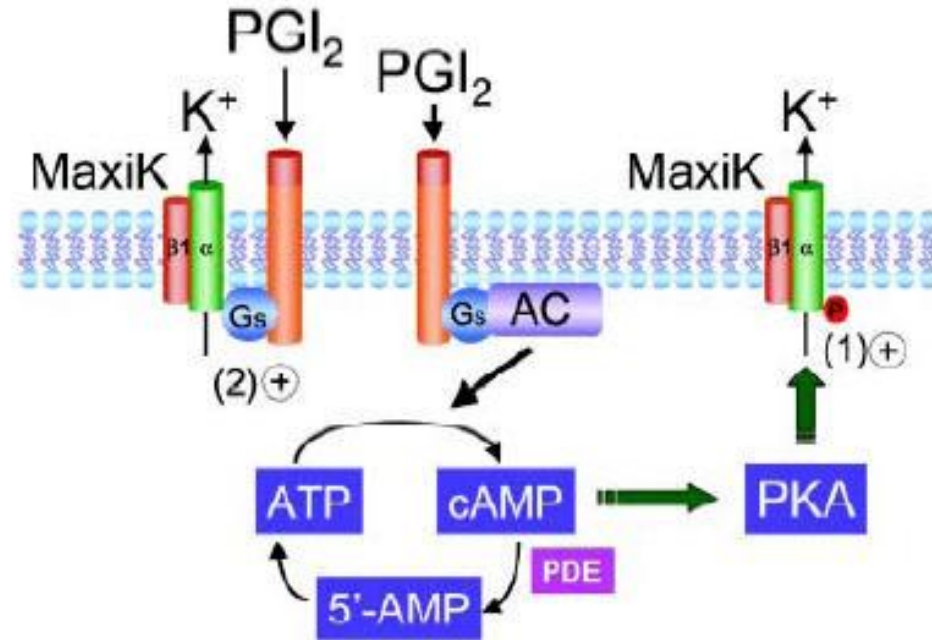
# Бета-адренергический расширительный эффект в гладкой мышце сосудов путем инактивации киназы легких цепей миозина при действии цАМФ-зависимой протеинкиназы



# Механизмы регуляции внутриклеточной концентрации кальция

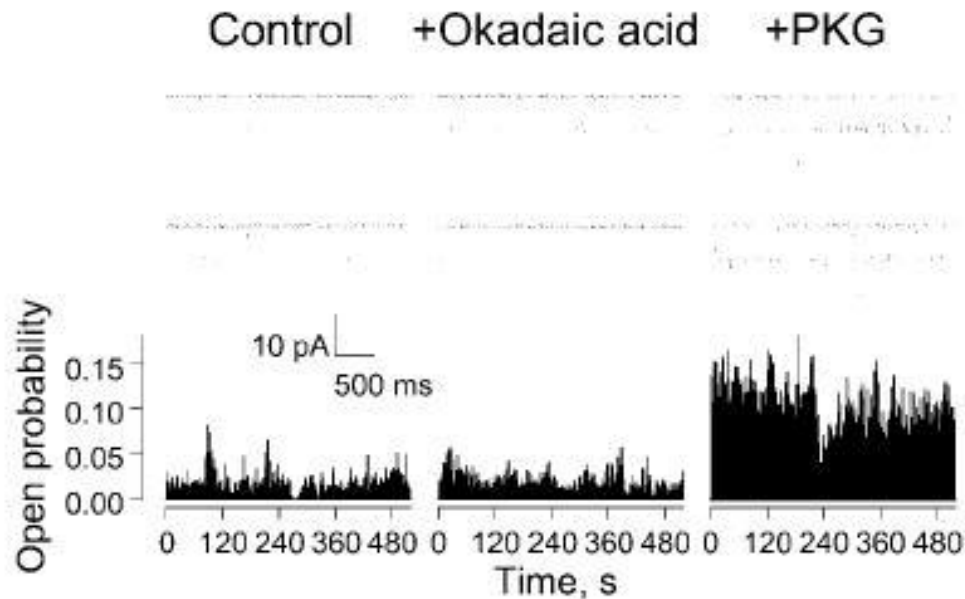


# Активация калиевых каналов в гладкой мышце при действии простаглицина ( $\text{PGI}_2$ )

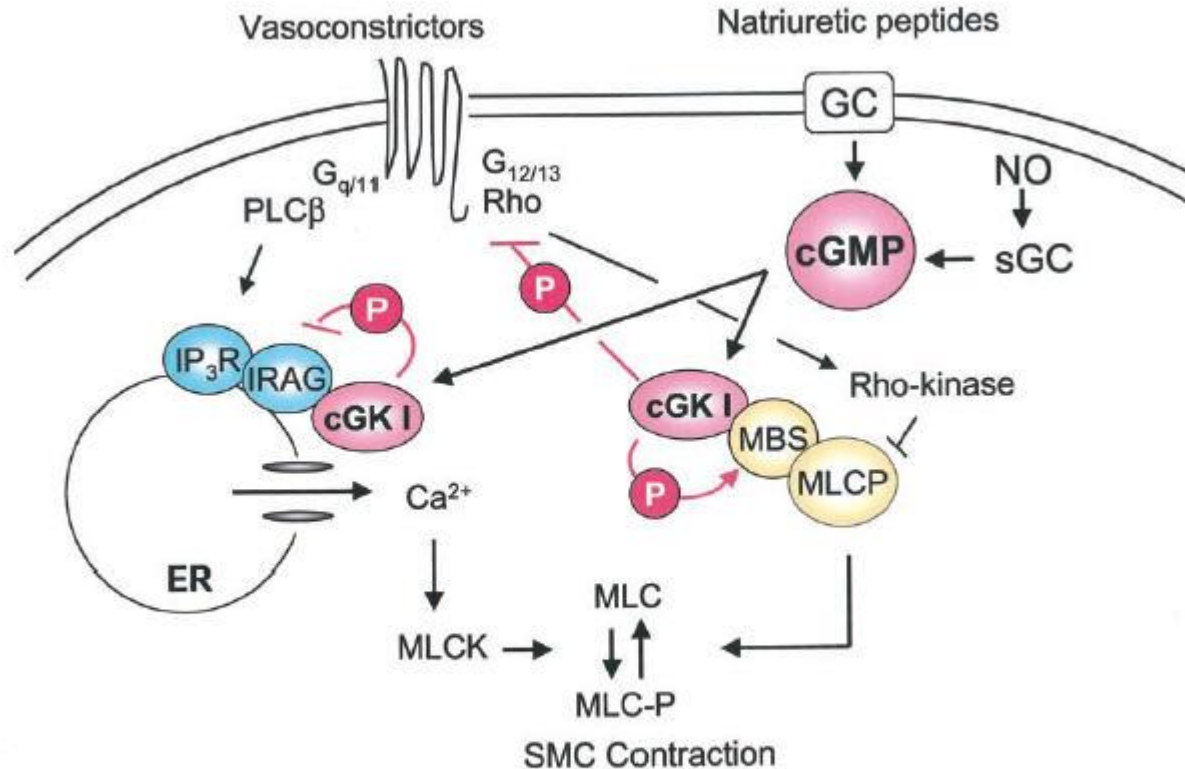


**Fig. 5.** Potential mechanisms of  $\text{PGI}_2$ -mediated activation of vascular smooth muscle MaxiK channel. At least two pathways are possible: (1) direct phosphorylation of the channel  $\alpha$ -subunit by cAMP-dependent protein kinase (PKA); (2) direct channel activation by  $G_s$  ( $G_s\alpha$ ), which is coupled with  $\text{PGI}_2$  receptor (IPR). Serine-869 is likely to be the most significant and functional residue subject to phosphorylation by PKA. A potential role for the  $\beta_1$ -subunit remains to be established.

# цГМФ-зависимая активация калиевых каналов

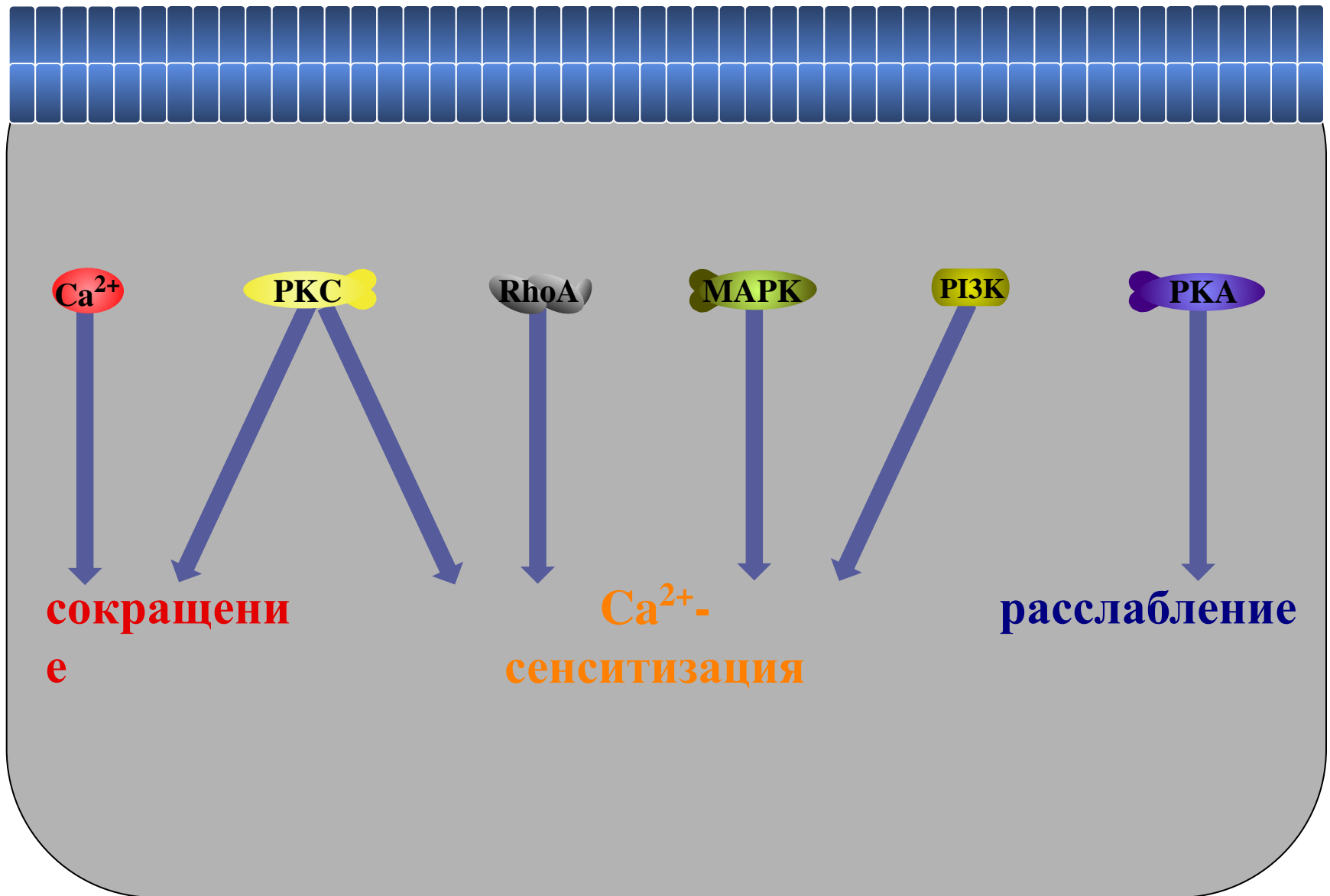


**Fig. 4.** Evidence for MaxiK channel  $\alpha$ -subunit being directly activated by PKG. *HSlo* channels were expressed in oocytes and incorporated into planar lipid bilayers. MaxiK channel currents were recorded in the presence of 0.5 mM cGMP and 1 mM MgATP facing the channel internal side. MaxiK channel  $P_o$  was not affected by the addition of a phosphatase inhibitor, okadaic acid (100 nM) (middle panels). However, stimulation with PKG-I $\alpha$  (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.  $V_{\text{hold}}$  was  $-30$  mV, and  $[Ca^{2+}]_i = 29 \mu\text{M}$ . 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<sup>2+</sup> release (left) and Ca<sup>2+</sup> sensitization (right) to inhibit myosin light chain (MLC) phosphorylation and SMC contraction. cGKI phosphorylation (P) of IRAG inhibits IP<sub>3</sub>/IRAG-mediated Ca<sup>2+</sup> 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<sub>3</sub>R, IP<sub>3</sub> 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	<ul style="list-style-type: none"> <li>■ Voluntary</li> <li>■ Ca<sup>2+</sup> and troponin</li> <li>■ Fibers independent</li> </ul>	<ul style="list-style-type: none"> <li>■ Involuntary</li> <li>■ Ca<sup>2+</sup> and calmodulin</li> <li>■ Fibers electrically linked via gap junctions</li> </ul>	<ul style="list-style-type: none"> <li>■ Involuntary</li> <li>■ Ca<sup>2+</sup> and troponin</li> <li>■ Fibers electrically linked via gap junctions</li> </ul>
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

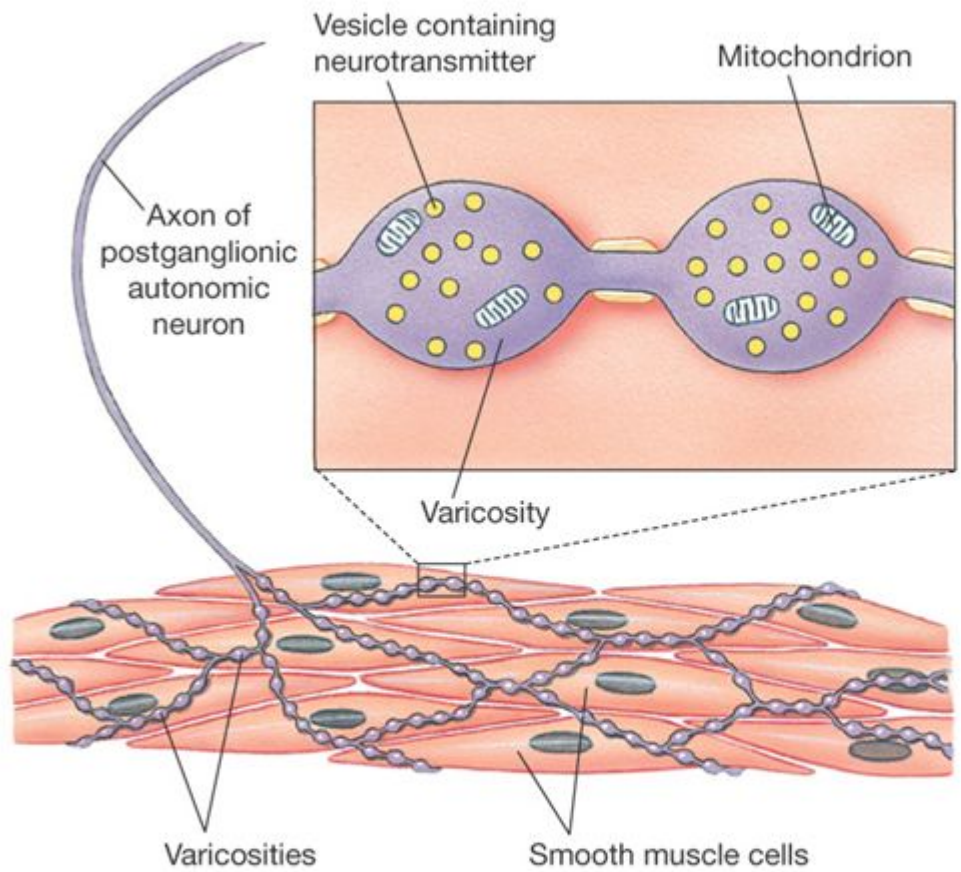
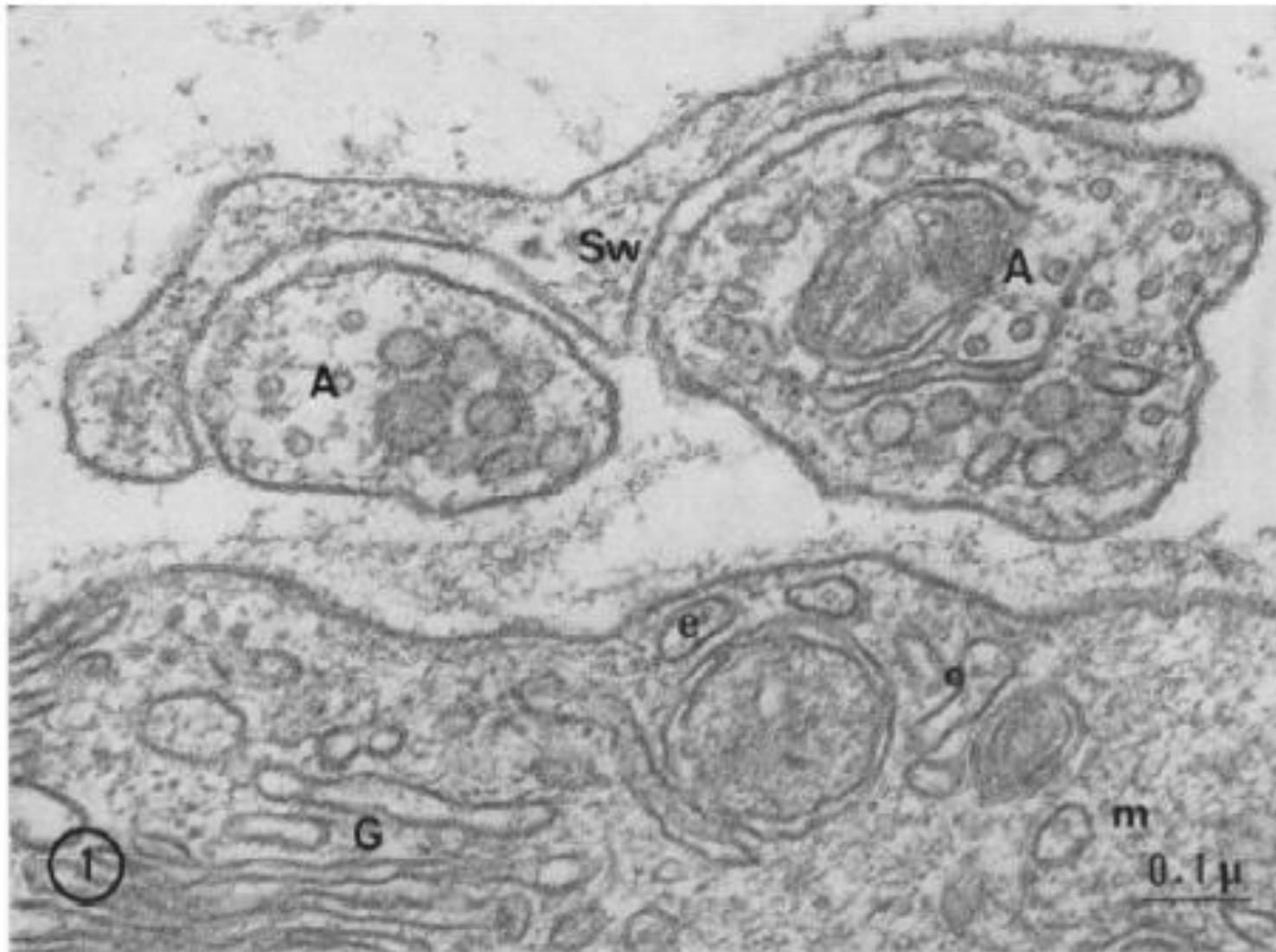
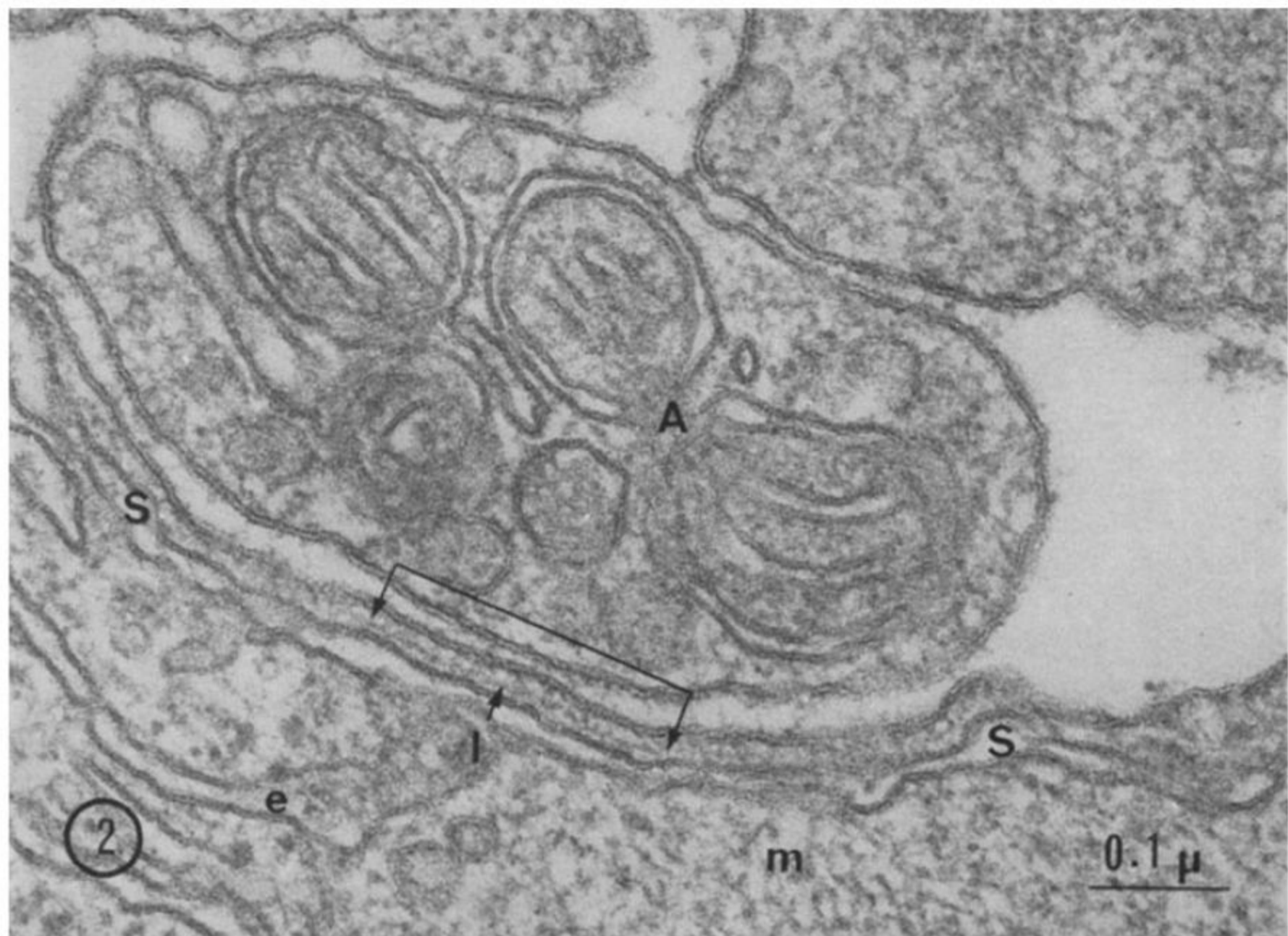


Figure 11-8: Varicosities of autonomic neurons

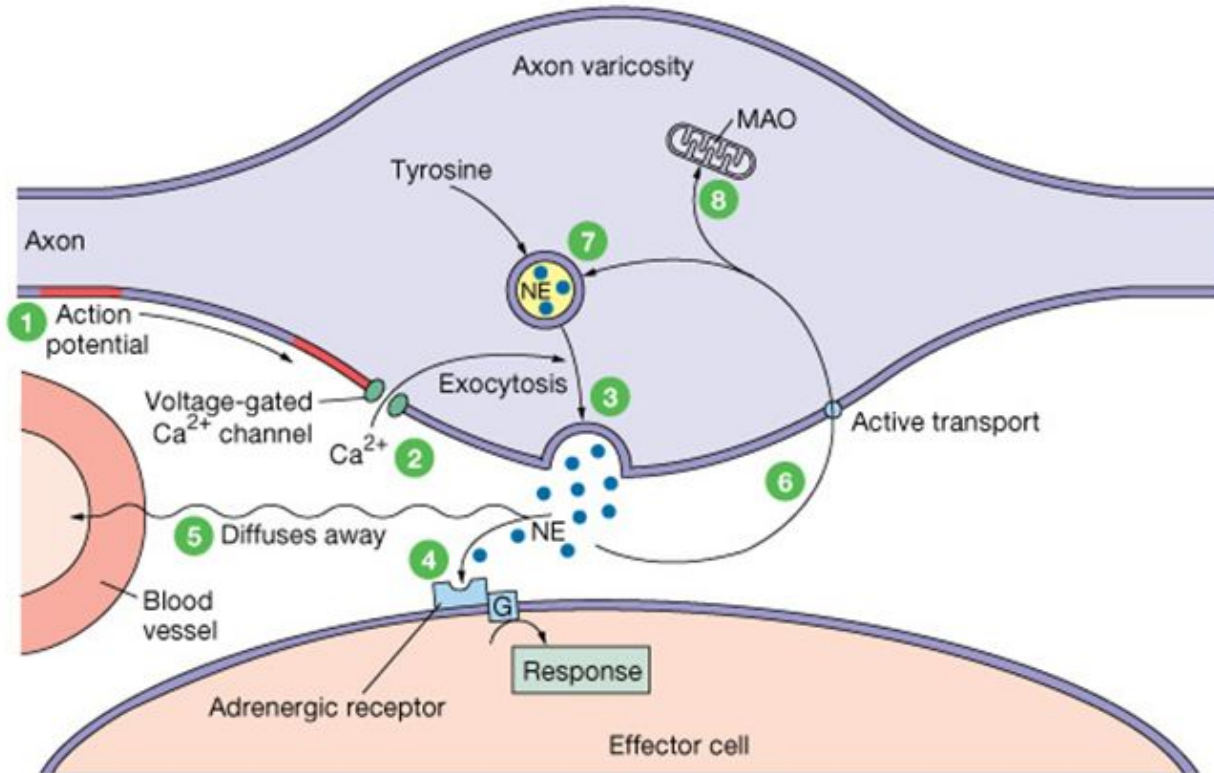


# Электронное изображение симпатического окончания на гладкой мышце сосуда





# Mechanism: Norepinephrine Release and Recycling



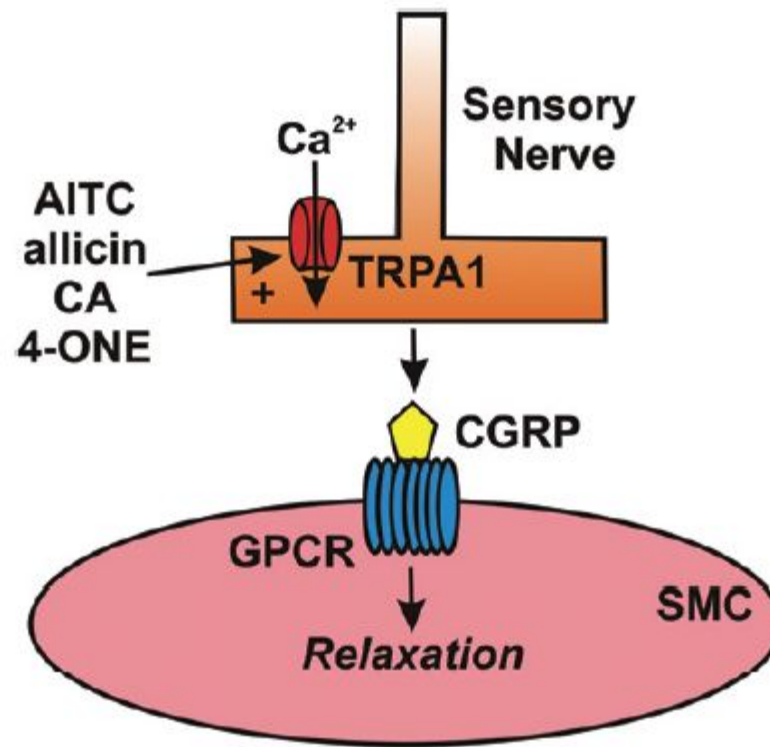
## KEY

- NE (norepinephrine)

- 1** Action potential arrives at the varicosity.
- 2** Depolarization opens voltage-gated  $\text{Ca}^{2+}$  channels.
- 3**  $\text{Ca}^{2+}$  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).

# 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  $\text{Ca}^{2+}$  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.