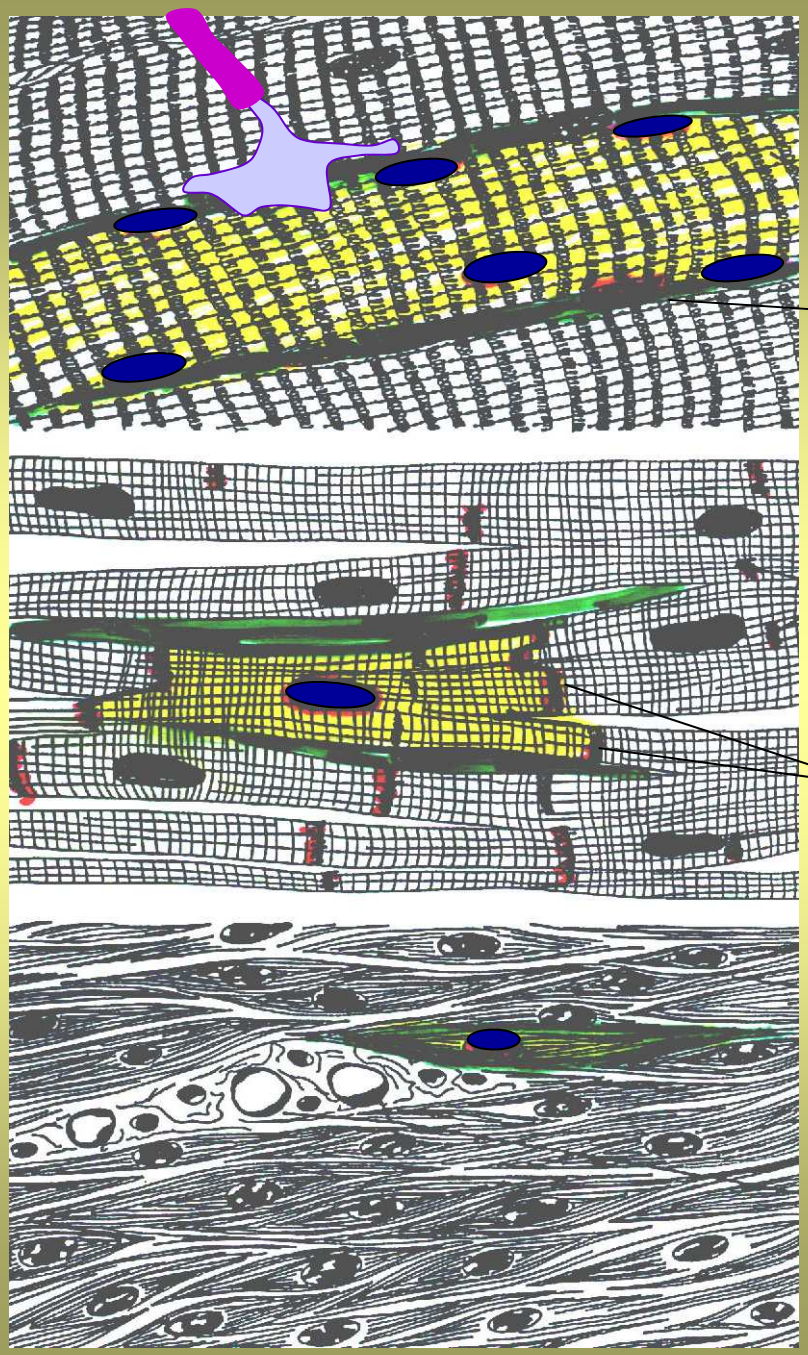
SKELETAL, CARDIAC, AND SMOOTH MUSCLES

SKELETAL, CARDIAC, AND SMOOTH MUSCLES

- Structural characteristics
- Electrical and mechanical activities
- Molecular mechanisms of contraction
- Biophysical properties of muscle as a whole
- Mechanisms of gradation/modulation of contraction

- Overview of characteristic properties of skeletal, cardiac, and smooth muscles



SKELETAL MUSCLE

sarcolemma

CARDIAC MUSCLE

intercalated discs

SMOOTH MUSCLE

(**vascular system**, **airways**, **gastrointestinal** and **urogenital** systems)

ELECTRICAL CONNECTIONS „GAP JUNCTIONS“

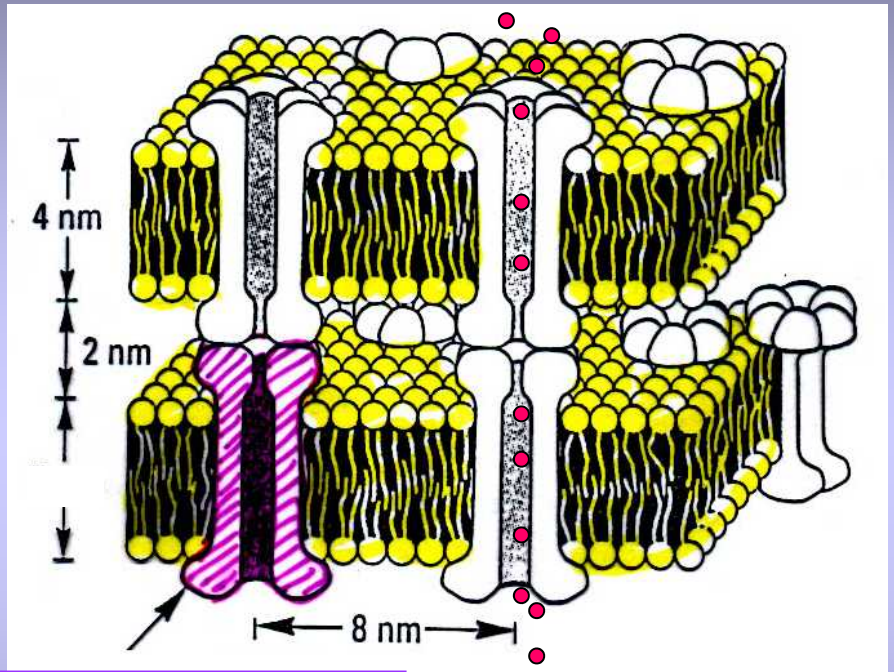
BASIC STRUCTURAL ELEMENTS OF FUNCTIONAL SYNCYTIUM

GAP JUNCTION UNIT

CONNEXON 1

„gap“
(extracellular space)

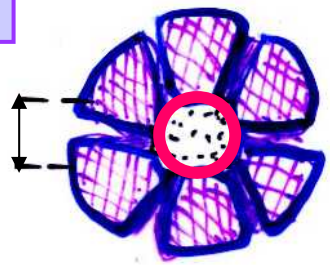
CONNEXON 2



MYOCARDIUM

SMOOTH MUSCLE

pH
$[Ca^{2+}]_i$
membrane voltage



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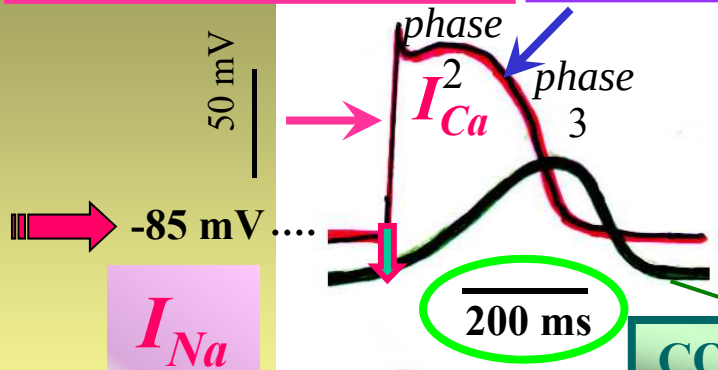
DEPOLARIZATION

REPOLARIZATION

HEART



I_{Na}

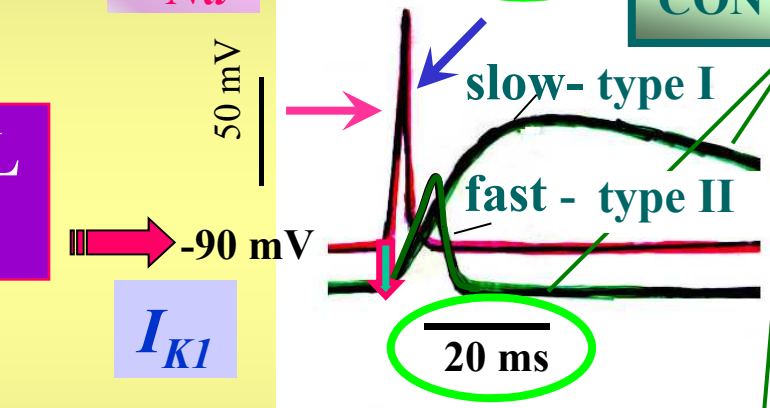
$I_{Ca}inact$

family of K currents

regular pacemaker activity (SA, AV nodes)

CONTRACTION

SKELETAL MUSCLE



I_{K1}

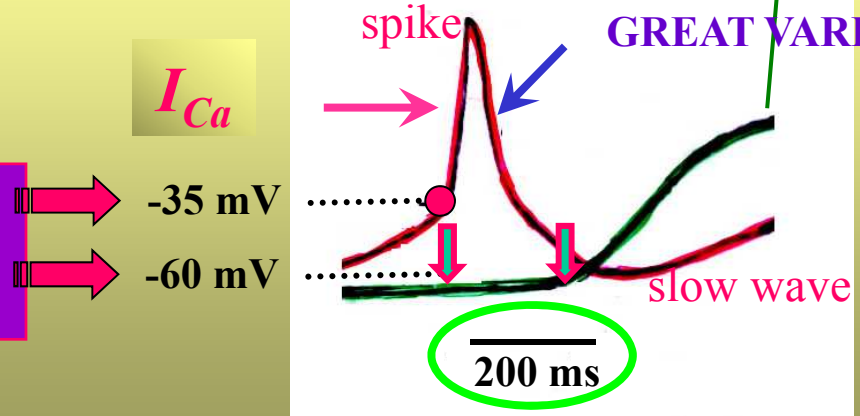
$I_{Na}inact$

I_{K}

GREAT VARIETY IN REPOLARIZATION

I_{Ca}

SMOOTH MUSCLE



$I_{Ca}inact$

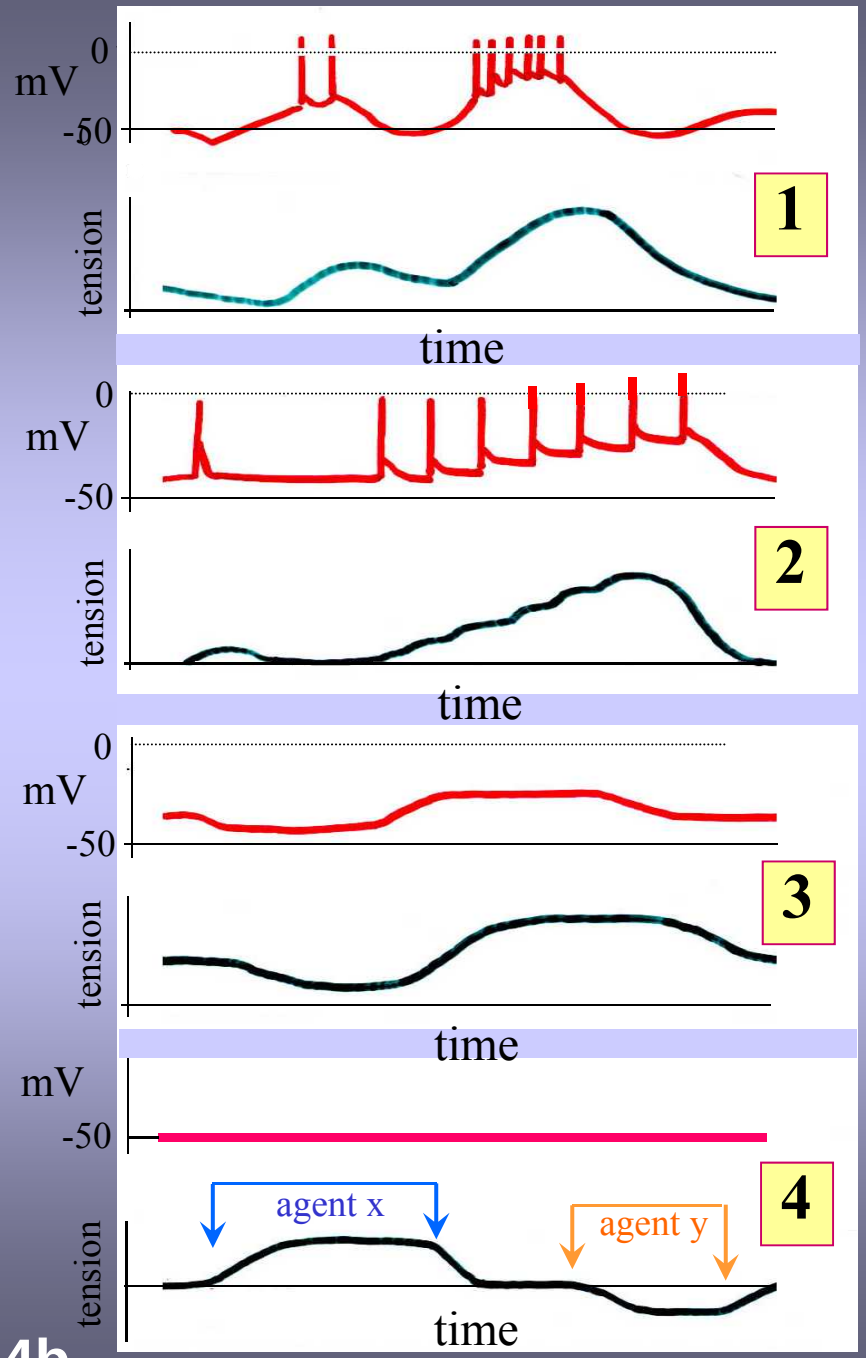
$I_{K(Ca)}$

irregular pacemaker activities of unstable foci

SMOOTH MUSCLE CELL

TRIGGERING AND MODULATION OF MECHANICAL RESPONSES

GREAT VARIETY IN
ELECTRO-MECHANICAL RELATIONS



4b

ELECTRO-MECHANICAL COUPLING

SLOW IRREGULAR WAVES in membrane voltage with APs

↓

SLOW WAVES IN CONTRACTION

(GIT)

↑ **frequency of APs**

↓

TETANIC CONTRACTION

(ureter, gall duct, uterus)

SLOW CHANGES in membrane voltage

↓

SLOW CHANGES IN TONE

(smooth muscles of eye, arterioles)

CONSTANT MEMBRANE VOLTAGE

SLOW CHANGES IN TONE

(vascular smooth muscle)

NEUROHUMORAL STIMULATION

e.g. via **LIGAND-RECEPTOR activation pathways**

SMOOTH MUSCLE CELL

MECHANICAL RESPONSES can be triggered/modulated

- **by different patterns of ELECTRICAL ACTIVITY**
  ELECTRO-MECHANICAL COUPLING

  ELECTRICAL STIMULATION

- **by different NEUROHUMORAL STIMULATION**

  NEUROTRANSMITTERS (acetylcholine, noradrenaline, …)

  NEURAL STIMULATION

  HORMONES (e.g. progesterone, oxytocin, angiotensin II, …)

  LOCAL TISSUE FACTORS (NO, adenosine, P_{CO2}, P_{O2}, pH, …)

  HUMORAL STIMULATION

- **by STRETCH of the smooth muscle cell (STRETCH-ACTIVATED CHANNELS)**

  MECHANICAL STIMULATION

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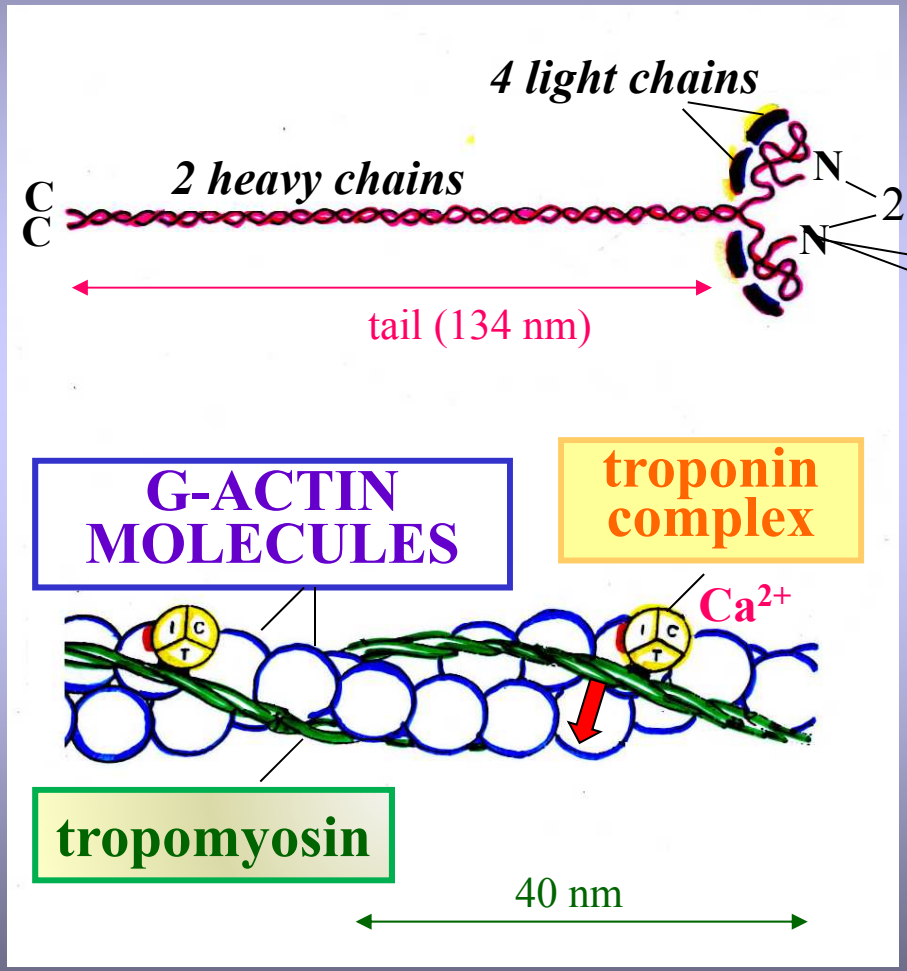
CROSS STRIATED MUSCLES

CONTRACTILE ELEMENTS



THICK MYOSIN FILAMENT

MOLECULE OF MYOSIN II ~300

- **ACTIN binding site**
- **ATP binding site**

(**ATP** → **ADP + P_i**)

THIN ACTIN FILAMENT

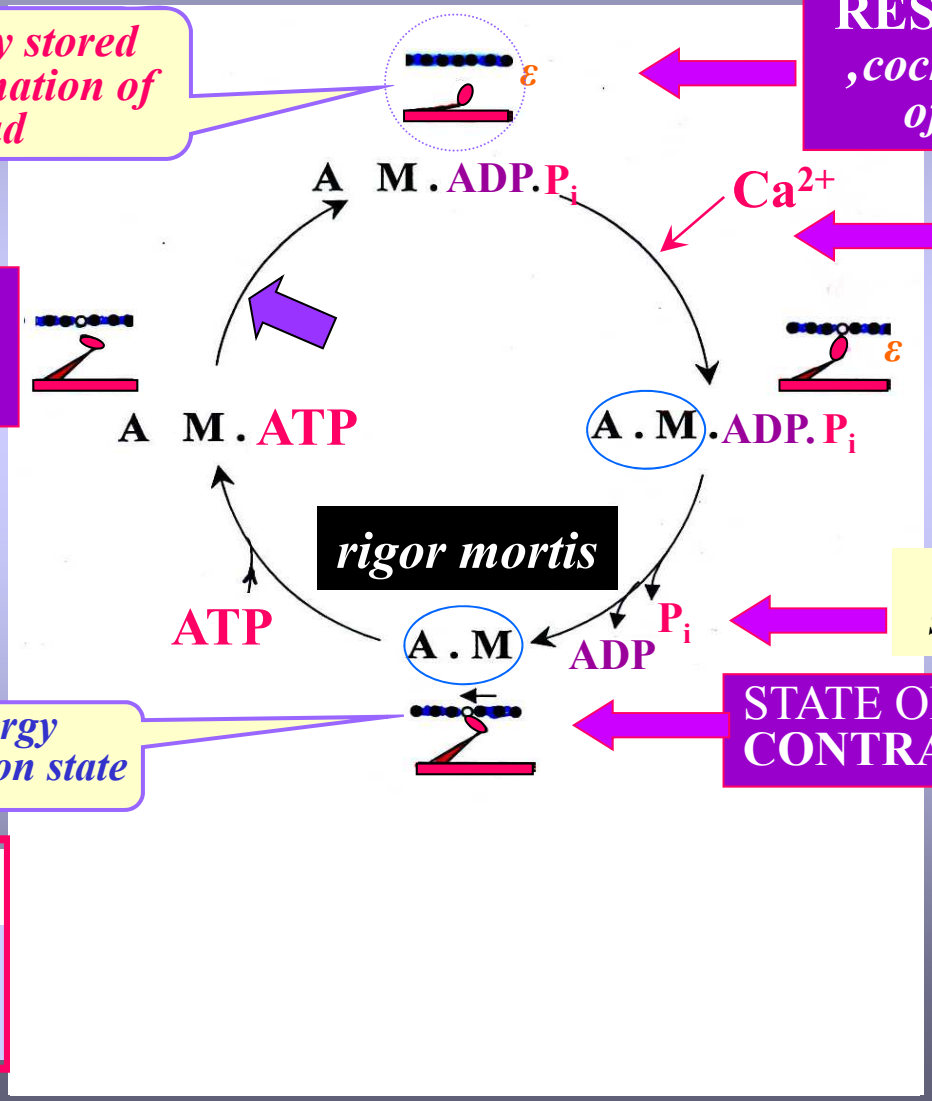
REGULATORY PROTEINS

TROPOMYOSIN –TROPONIN COMPLEX

CROSS-STRIATED MUSCLE

ONE ELEMENTARY CYCLE OF CONTRACTION AND RELAXATION

MOLECULAR LEVEL



high energy stored in conformation of myosin head

RESTING state *‚cocked' position of the head*

Ca^{2+}

Ca^{2+}- troponin C complex

DISSOCIATION of actin–myosin complex

CROSS BRIDGE *weak cross-bridge state*

release of P_i *strong cross-bridge state*

low energy conformation state

STATE OF CONTRACTION

HUXLEY´S sliding model

CONTRACTION

- presence of ATP
- ↑ $[Ca^{2+}]_i$

RELAXATION

- presence of ATP
- ↓ $[Ca^{2+}]_i$

CROSS-STRIATED MUSCLE

MOLECULAR MECHANISM OF CONTRACTION

- **Binding of Ca^{2+} to TROPONIN C ⇒ shift of troponin-tropomyosin complex → actin binding sites for myosin heads are uncovered**

- **Formation of CROSS BRIDGES between actin and myosin (weak cross-bridge state)**

  $A . M^{\varepsilon} . ADP . P_i$

- Release of **P_i (strong cross-bridge state) ⇒ conformational changes in myosin head-neck junction → tilt of the myosin head (power stroke) → sliding of thin on thick filaments ⇒ SHORTENING OF SARCOMERE**

- **ADP** is released → ***actomyosin complex*** is left in a ***rigid 'attached' state***

  $A . M$

- **Binding of ATP to myosin head ⇒ low affinity of myosin for actin → dissociation of ACTIN–MYOSIN complex**

  A M . ATP

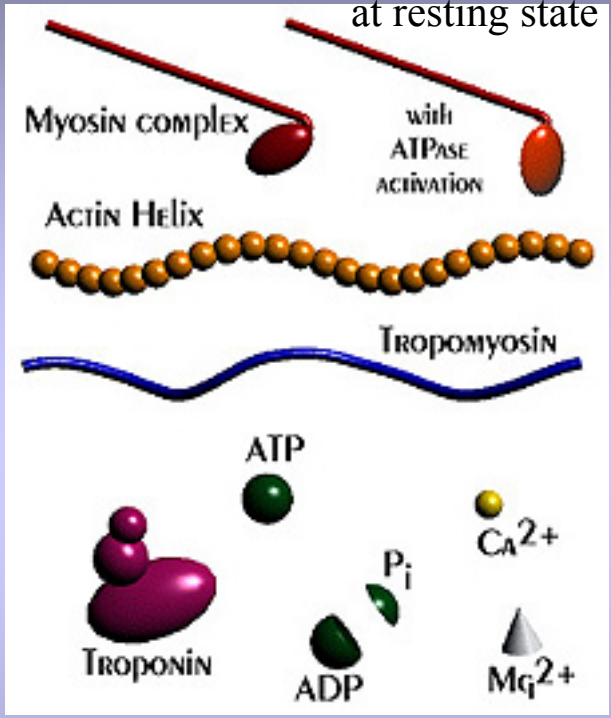
- **ATP-ase activity of myosin head ⇒ partial hydrolysis of ATP,** the **gained energy is used for re-cocking of the myosin head** *(analogy of the stretched spiral spring).* ***Affinity of myosin for actin is high but the forming of the bonds is disabled***

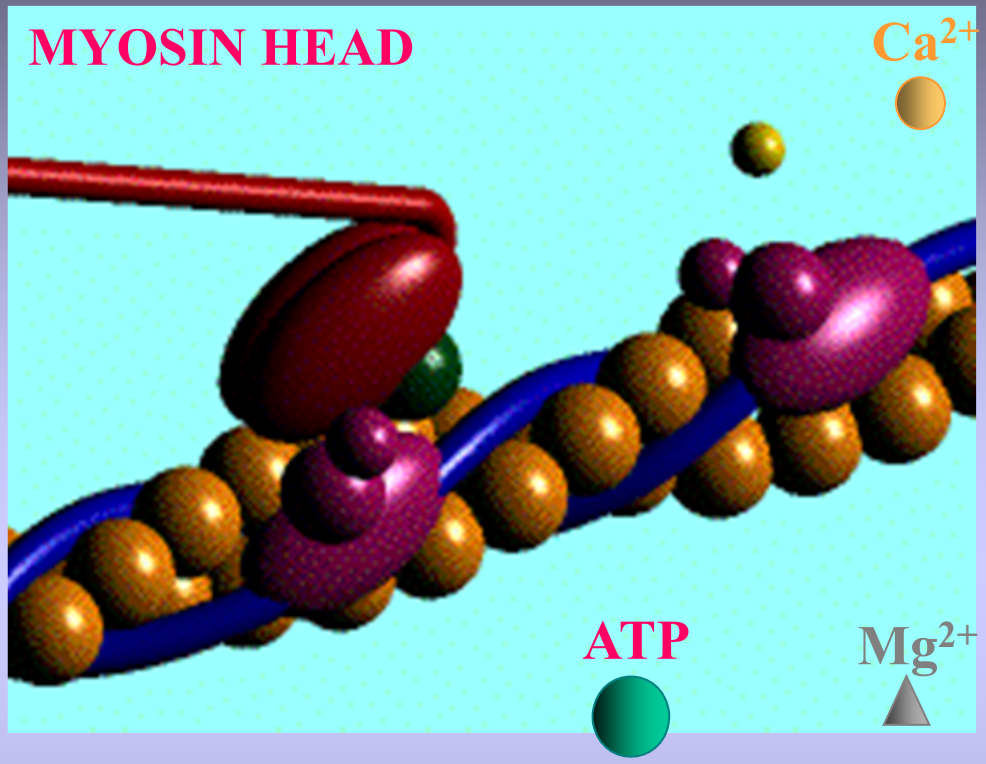
  A M^{ε} . ADP . P_i

- **CONTINUING CONTRACTION** results from the **repeated cycling** due to **maintained** ↑$[Ca^{2+}]_i$ in the **presence of ATP**
- **RELAXATION of the muscle cell** results from the **presence of ATP** and ↓$[Ca^{2+}]_i$ *(Ca^{2+} is pumped back into SR and pumped out of the cell)*

CROSS-STRIATED MUSCLE

vertical position
at resting state





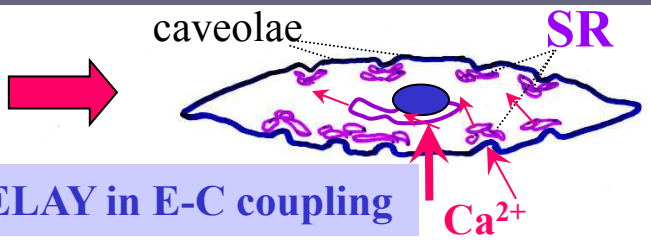
Animated model of interaction of myosin head with actin filament („ paddling “)

Myosin – MOLECULAR MOTOR

It consumes chemical energy released from ***hydrolysis of ATP*** and converts it into the motion (***mechanical work***)

troponin – tropomyosin complex

SMOOTH MUSCLE

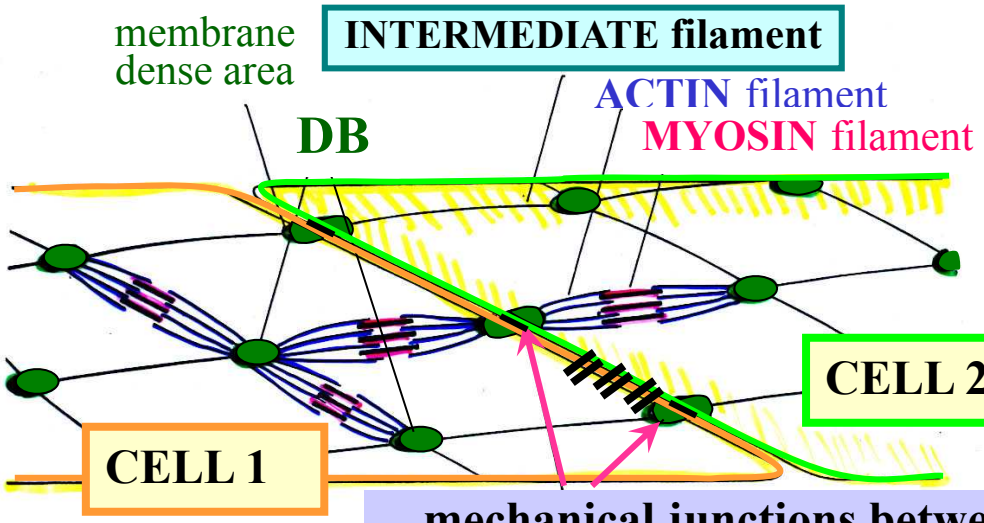


DELAY in E-C coupling

SLOW DEVELOPMENT of **contraction** and **relaxation** ?

SLOW ISOFORMS OF
- myosin ATP-ase
- Ca^{2+} transport systems

ORGANIZATION OF CYTOSKELETON AND MYOFILAMENTS



mechanical junctions between cells

DB - DENSE BODIES

II gap junctions

TROPONIN IS ABSENT !!

REGULATORY PROTEINS

TROPOMYOSIN

CALMODULIN (TNC)

CALPONIN

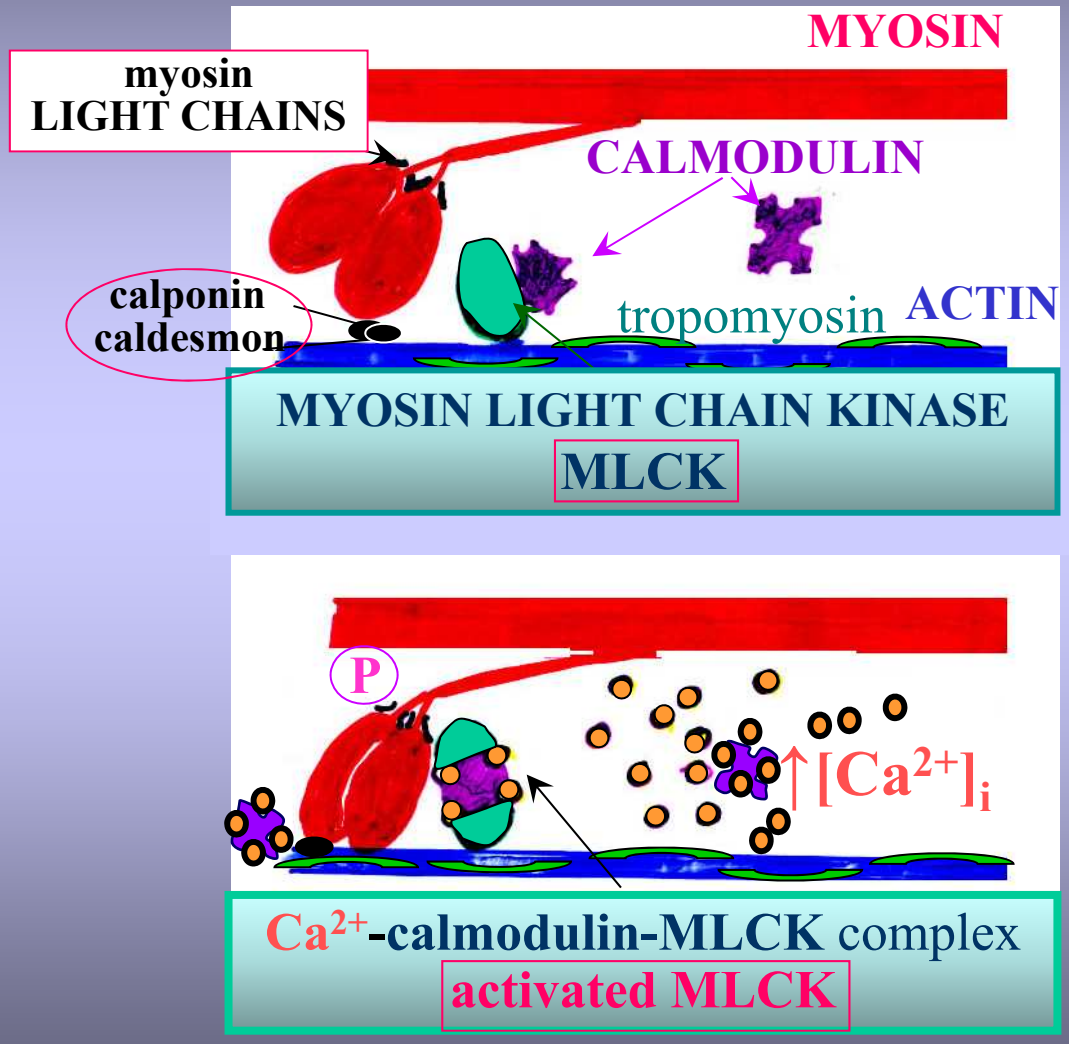
CALDESMON

SMOOTH MUSCLE

TROPONIN COMPLEX is not present

CALMODULIN

2 ROLES OF Ca^{2+}-CALMODULIN COMPLEX



RESTING STATE

Ca^{2+}-CALMODULIN complex

Ca^{2+}/CALMODULIN–MLCK
activated MLCK

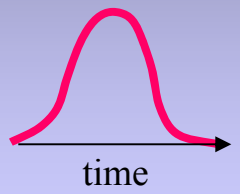
P myosin LIGHT CHAINS

Ca^{2+}-CALMODULIN-
calponin-caldesmon complex

MYOSIN-ACTIN
interaction

CONTRACTION VARIANTS OF SMOOTH MUSCLE CELL

1 PHASIC variant of CONTRACTION - mode of CYCLING



- (P) of **myosin light chains (RMLCs)** is a prerequisite of **PHASIC** contraction
- **ATP is consumed**

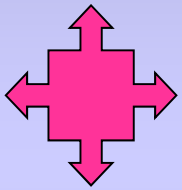
2 TONIC variant of CONTRACTION - LATCH BRIDGES

?

At the state of CONTRACTION RMLCs are dephosphorylated by MLCP → **SLOW dissociation of M.A complex** →

SUSTAINED TONIC CONTRACTION **ATP is spared**

P



SMOOTH MUSCLE

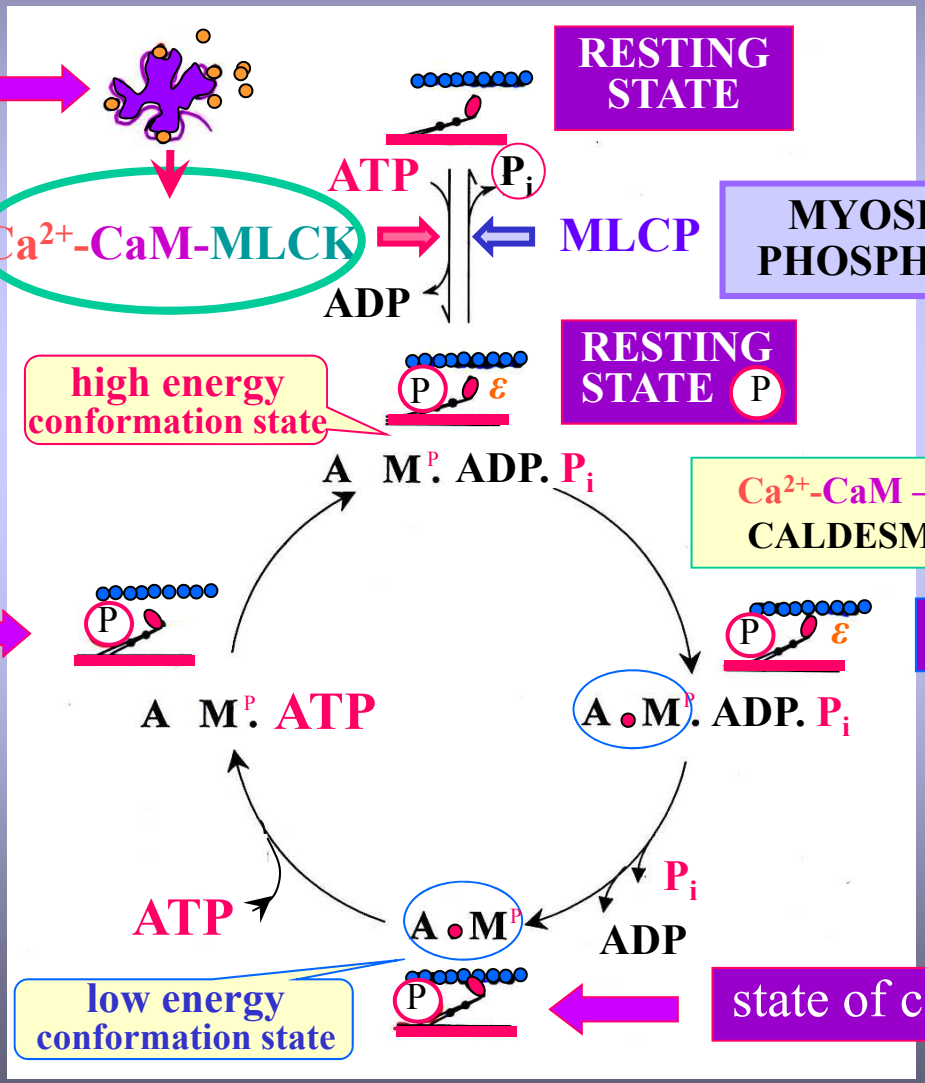
1 PHASIC variant of CONTRACTION - mode of cycling

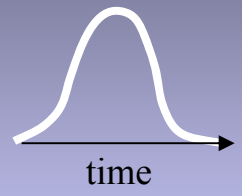
Ca^{2+}-calmodulin complex

MYOSIN-LC KINASE activated

Ca^{2+}-CaM-MLCK

MLCK* / MLCP





dissociation of actin–myosin complex

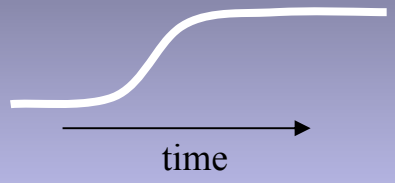
PHOSPHORYLATION of myosin light chains is a prerequisite of PHASIC CONTRACTION

ATP is consumed

Adapted from Berne and Levi (2004)

SMOOTH MUSCLE

2 TONIC variant of CONTRACTION - LATCH BRIDGE



↓ MLCK* / MLCP

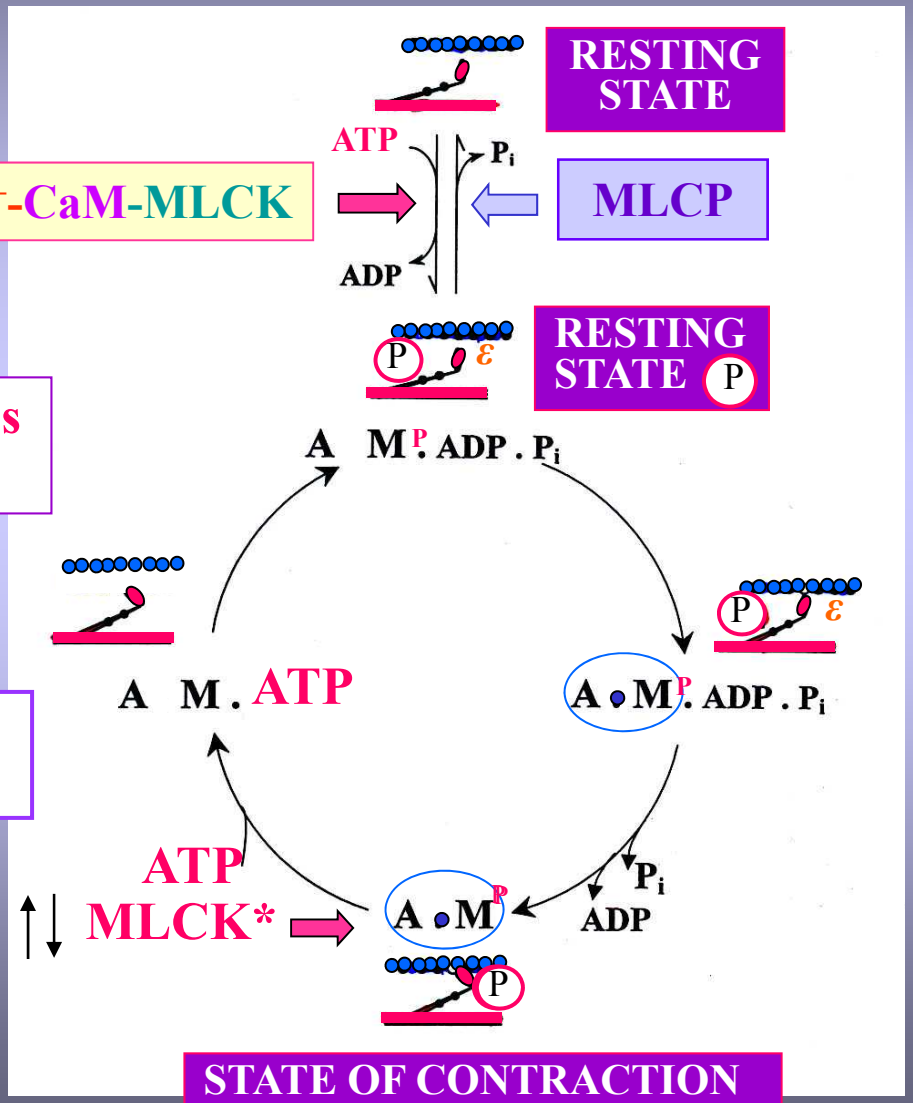
DEPHOSPHORYLATION of **MLCs** at the **STATE OF CONTRACTION**

very slow DISSOCIATION of **M.A** complex

LATCH BRIDGE mechanism of sustained **TONIC CONTRACTION**

ATP is spared

↑ MLCK* / MLCP



Adapted from Berne and Levi (2004)

SMOOTH MUSCLE

Binding of Ca^{2+} to **CALMODULIN** ⇒ **Ca^{2+}-CaM** complex

⇩

Activation of **MYOSIN LIGHT CHAIN KINASE**
Ca^{2+}-CaM-MLCK complex

⇩

Phosphorylation of **MYOSIN LIGHT CHAINS** and simultaneous **conformational changes of** **Ca^{2+}-CaM-calponin-caldesmon-ACTIN-TROPOMYOSIN** complex ⇒ formation of **CROSS BRIDGES**

⇩

Conformational changes in **MYOSIN** molecule ⇒ **TILT** of **MYOSIN HEAD** ⇒ **SLIDING** of **ACTIN** on **MYOSIN** filaments ⇒ **SHORTENING** of the myocyte

⇩ ⇩

REPEATING CYCLING
PHOSPHORYLATION
of ***myosin light chains***
is ***maintained***

SUSTAINED TONIC CONTRACTION
-"LATCH BRIDGE" ***mechanism;***
DEPHOSPHORYLATION of ***myosin light chains*** *at the* ***state of contraction***

ATP is consumed

ATP is spared

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ISOMETRIC AND ISOTONIC CONTRACTION

SKELETAL MUSCLE

RESTING TENSION

IMC → **ISOMETRIC CONTRACTION**

at constant LENGTH

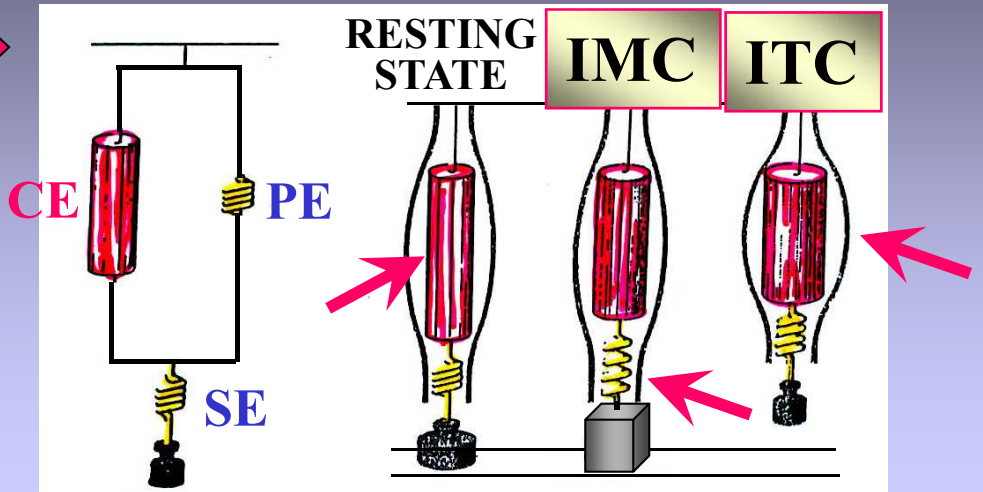
changes in **TENSION** are measured by tensiometer

ITC → **ISOTONIC CONTRACTION**

at constant TENSION

changes in **LENGTH** are measured

AUXOTONIC CONTRACTION



CE – **contractile elements**

PE, SE - **parallel** and **series elasticity** (in relation to contractile elements)

PE – ***extracellular*** and ***intracellular*** elasticity (***titin*** connecting Z and M lines in the sarcomere)

SE – elasticity of fibrous tissue - ***tendon***

HEART

ISOVOLUMIC PHASE (ISOMETRIC)

EJECTION PHASE (ISOTONIC) **AUXOTONIC**

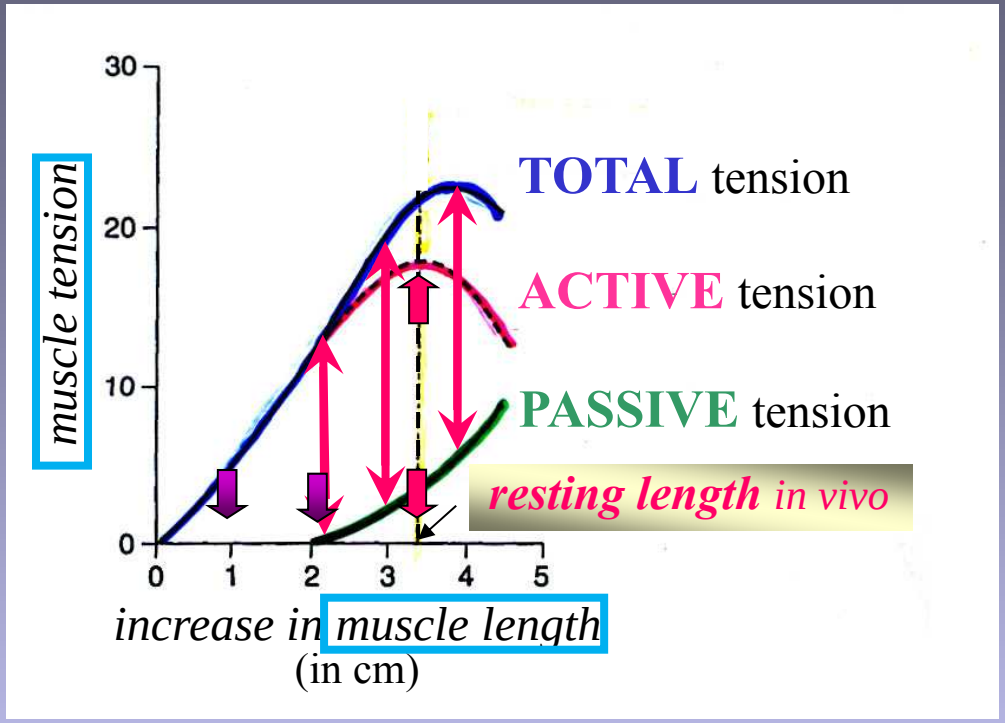
SMOOTH MUSCLE

TONIC CONTRACTION (*tone of blood vessels*)

PHASIC CONTRACTION (*contraction of urinary bladder*)

TENSION-LENGTH RELATIONSHIP

SKELETAL MUSCLE

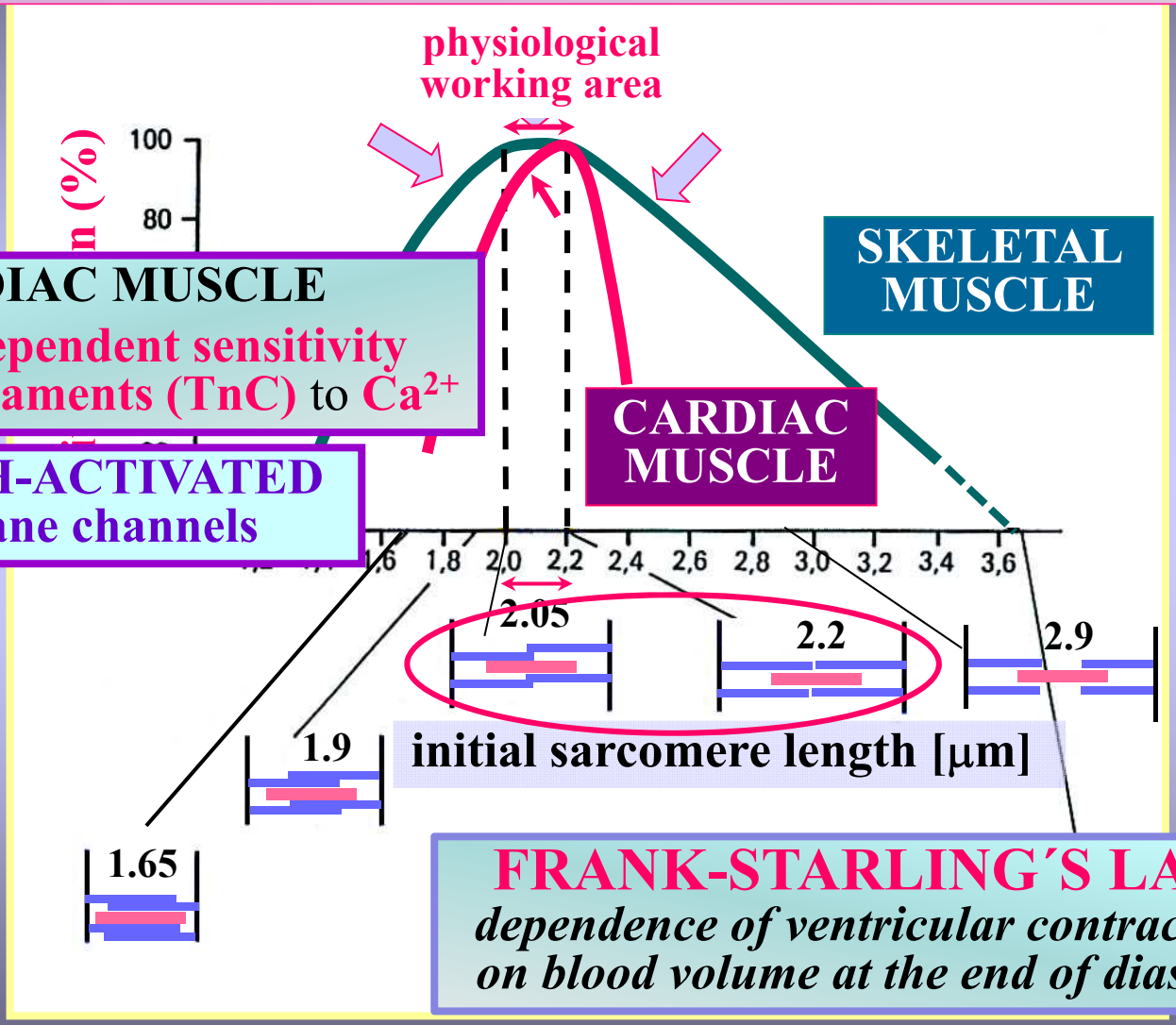


PASSIVE tension — tension of ***unstimulated muscle*** at gradual stretching **(ELASTIC COMPONENTS)**

TOTAL tension — **ISOMETRIC CONTRACTIONS** of ***stimulated muscle*** at gradually increased ***initial (resting) length***

ACTIVE tension — ***difference*** between **TOTAL** and **PASSIVE** tension curves at any length (***tension actually generated by contractile elements***)

ACTIVE TENSION of cross striated muscles as a function of INITIAL LENGTH of SARCOMERE



CARDIAC MUSCLE
stretch-dependent sensitivity of ACTIN filaments (TnC) to Ca^{2+}

STRETCH-ACTIVATED membrane channels

FRANK-STARLING´S LAW
dependence of ventricular contraction on blood volume at the end of diastole

SMOOTH MUSCLE

CHARACTERISTIC FEATURES

- **GREAT EXTENSIBILITY**

  (e.g. **myocytes** of urinary bladder can lengthen up to **200%,** **myocytes** of uterus even up to **1000%** at the end of pregnancy in relation to their original state)

- **PLASTICITY**

No direct relation between the **LENGTH** and **TENSION** in smooth muscle cells. Stretch-induced ***increased tension*** almost ***immediately spontaneously decreases.***

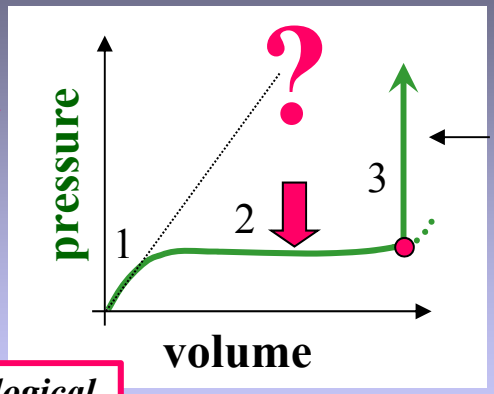
Analogous relation is valid between **VOLUME** and **PRESSURE** in **hollow organs** (*stomach, intestines, urinary bladder, …*).

PLASTICITY OF SMOOTH MUSCLE

CYSTOMETROGRAM

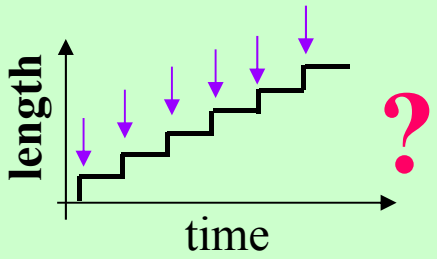
urinary bladder

ISOLATED MYOCYTE
(human jejunum)

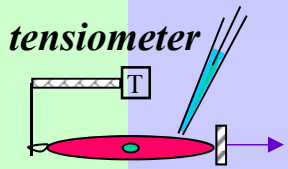


micturition reflex is triggered

P = 2T/r **LAPLACE LAW**



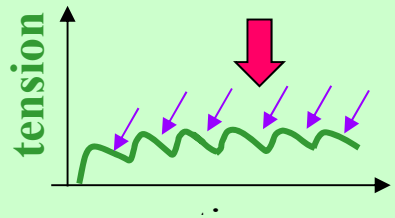
electrophysiological measurements



STRETCH-activated Ca^{2+}-channels (mechano-sensitive channels)

$I_{Ca\ ms}$ **DEPOLARIZATION**

$\uparrow [Ca^{2+}]_i$



PLASTICITY

↑ TENSION

calcium-activated $[Ca^{2+}]_i$-sensitive K^+-channels

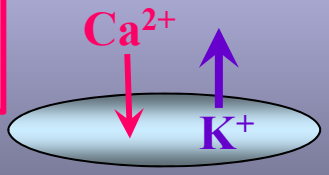
I_{KCa}

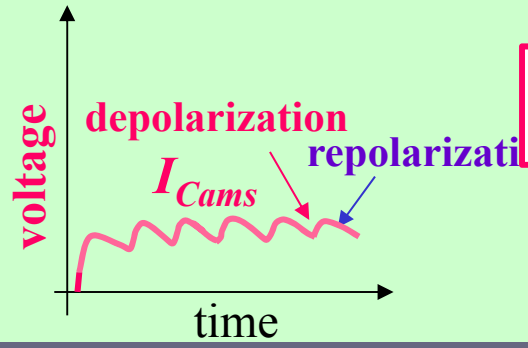
REPOLARIZATION

$\downarrow [Ca^{2+}]_i$

↓ TENSION

VC / PC techniques





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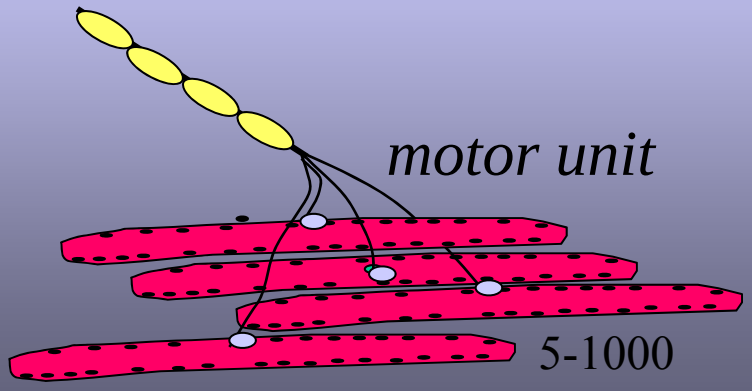
SKELETAL MUSCLE

MAIN FACTORS IN GRADATION OF CONTRACTION

- ↑ ***frequency*** of discharges in ***motor neuron*** ⇒ **FREQUENCY SUMMATION** of contractions in skeletal muscle fibre **(TETANIC CONTRACTION)**

- ↑ ***number*** of activated **MOTOR UNITS** by increasing voluntary effort ⇒ **SPATIAL SUMMATION (multiple fibre summation) - RECRUITMENT OF MOTOR UNITS**



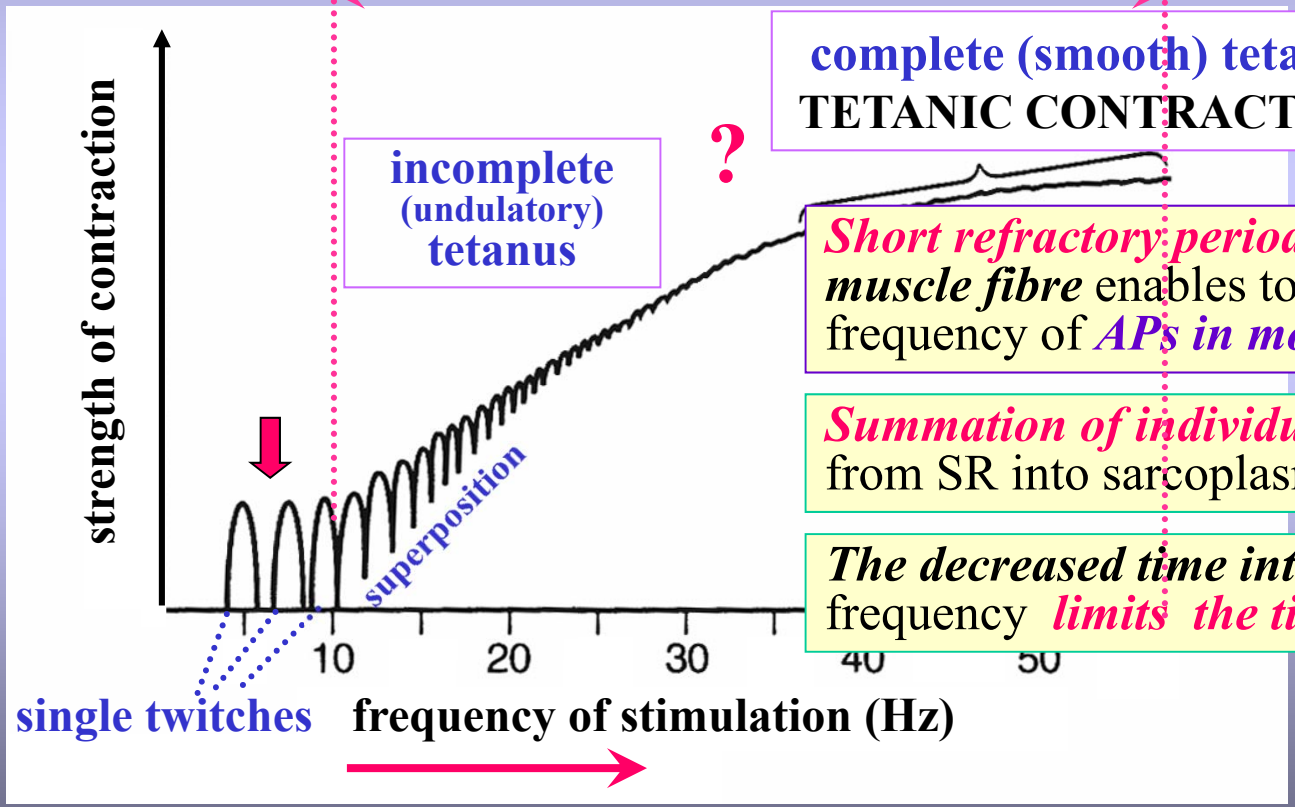
SKELETAL MUSCLE

GRADATION of CONTRACTION by ↑ FREQUENCY of STIMULATION

SINGLE MUSCLE FIBRE

RANGE OF SUMMATION

physiological behaviour of skeletal myocyte



Short refractory period of AP of ***skeletal muscle fibre*** enables to copy the high frequency of ***APs in motor neuron***

Summation of individual releases of Ca^{2+} from SR into sarcoplasm

The decreased time interval at high frequency ***limits the time for relaxation***

$\uparrow[Ca^{2+}]_i$

1 Hz = 1 impulse/sec

CARDIAC MUSCLE

MAIN FACTORS IN GRADATION OF CONTRACTION

- **↑ DIASTOLIC FILLING of ventricles *in vivo* („preload“)**
  ⇒ ↑contraction of ventricles proportionate to the stretching of cardiomyocytes at the end of diastole
  FRANK-STARLING´S LAW
- **↑ FREQUENCY of electrical activity** of cardiac cells *via* modulation of **pacemaker activity of SA node by sympathetic nerves** - positive **FREQUENCY EFFECT**
- **LIGAND-RECEPTOR ACTIVATION CASCADES**
  leading to ↑ **$[Ca^{2+}]_i$** (noradrenalin, adrenalin, thyroxine, …)

⇩

↑ $[Ca^{2+}]_i$

SMOOTH MUSCLE

MAIN FACTORS IN GRADATION OF CONTRACTION / TONUS

- **DEPOLARIZATION of the smooth muscle membrane** with or without triggering of action potentials via opening of the ***voltage dependent calcium channels*** $\Rightarrow \uparrow [Ca^{2+}]_i$
- **FACTORS independent on membrane depolarization**
  - ***Ligand-receptor activation cascades*** leading to $\uparrow [Ca^{2+}]_i$ (e.g. *via* ***activation*** of **PLC** $\Rightarrow \uparrow$ ***IP_3*** releasing **Ca^{2+}** from SR)
  - ***Stretching of the smooth muscle cell*** $\Rightarrow$ opening of the ***stretch-activated*** **channels** $\Rightarrow \uparrow [Ca^{2+}]_i$

⇓

$\uparrow Ca^{2+}$-calmodulin complex

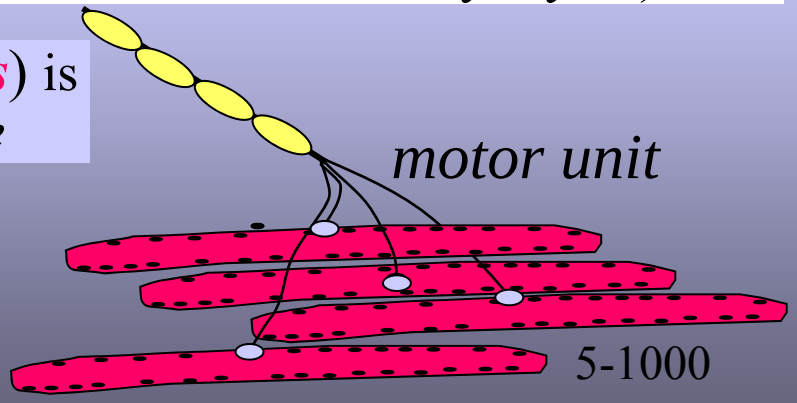
SKELETAL, CARDIAC, AND SMOOTH MUSCLES

- Structural characteristics
- Electrical and mechanical activity
- Molecular mechanisms of contraction
- Biophysical properties of muscle as a whole
- Gradation / modulation of contraction
- Overview of characteristic properties of skeletal, cardiac, and smooth muscles

SKELETAL MUSCLE

MAIN CHARACTERISTIC FEATURES

- ***Multinucleated*** **long cylindrical cells** (max. length up to 20 cm)
- ***Rich*** **sarcoplasmic reticulum**
- ***Regular arrangement*** **of thick and thin filaments in sarcomeres** (***cross striation***)
- **Activity strongly dependent on** ***motor nerve supply*** (excitation transmitted via ***motor end-plate***)
- **Without intercellular connections** (**no** gap junctions between muscle cells)
- **Motor neurons branch to innervate more muscle cells** (***motor unit*** defined as one motor neuron with 5-1000 myocytes)
- ***Summation of contractions*** (***tetanus***) is a ***physiological property of muscle fibre***
- **Activity under** ***voluntary control***



MAIN TYPES OF SKELETAL MUSCLE FIBRES

TYPE I **SLOW - RED** *e.g. muscles of the back, soleus m.*

- ***Slow*** (posture-maintaining) ***contractions***
- ***Motor units*** contain ***slowly conducting motor neurons***

High OXIDATIVE CAPACITY and **high resistance to fatigue**

TYPE II **FAST (RED /WHITE)** *e.g. extraocular muscles, muscles of the hand*

- ***Short*** **twitches** for fine skilled movements
- ***Motor units*** with ***rapidly*** **conducting motor neurons**

TYPE IIa (FAST-RED) and **TYPE IIb (FAST-WHITE)**

Proportion of OXIDATIVE and GLYCOLYTIC metabolism determines the resistance to fatigue

Sport activities cause **gradual transformation** from **IIb** into **IIa**

CARDIAC MUSCLE

MAIN CHARACTERISTIC FEATURES

- ***Branched*** and ***interconnected cells*** with ***one nucleus*** **in the centre** (length ~100 μm)
- ***Well (moderately) developed*** **sarcoplasmic reticulum**
- ***Regular arrangement*** of **thick** and **thin filaments** in sarcomeres (***cross striation***)
- **Excitations (contractions) are independent on nerve supply** (*specialized* ***pacemaker cells***)
- **Functional syncytium** (electrical connections - ***gap junctions***)
- ***Receptors*** for ***neurotransmitters*** (released from neuron endings) and ***hormones*** (brought by circulation); activity is *modulated* by ***local mediators***
- ***Long refractory period*** ***prevents*** cells from **tetanic contraction** (which would be life threatening)
- Activity ís **not** under ***voluntary*** control

SMOOTH MUSCLE

MAIN CHARACTERISTIC FEATURES

- Thin ***spindle-shaped*** **cells** of various length (20-200 μm) with ***one nucleus*** in the centre
- ***Irregular arrangement*** of thick and thin filaments; no cross striation
- ***Poorly developped*** **sarcoplasmic reticulum,** ***TT system*** **is missing**
- **Contractions of** ***visceral muscles*** **can be triggered independently on nerve supply (*slow irregular unstable pacemaker activity*); functional syncytium (*gap junctions*)**
- **Slow** ***phasic,*** often ***tonic,*** even ***tetanic*** **contractions**
- **Numerous** ***receptors*** for ***neurotransmitters*** (released from neuron endings) and ***hormones*** (brought by circulation). Activity is greatly modulated by ***local mediators*** (local tissue factors)
- **Activity can be triggered by stretch (*stretch activated channels*)**
- **Great extensibility and plasticity**
- **Activity without voluntary control**

TYPES OF SMOOTH MUSCLE

VISCERAL „SINGLE UNIT“

e.g. stomach, intestine, uterus, ureter, …

- ***Functional syncytium*** (***gap junctions***)
- Excitation and contraction can be evoked ***in the absence of nerve supply*** (***slow irregular pacemakers in multiple foci*** shifting from place to place, ***gap junctions***)
- Contraction evoked by **stretching** (***stretch-activated channels***)

MULTIUNIT- stimulated by neurons

e.g. arterioles, m. ciliaris, muscle of iris, …

- Myocytes need the stimulation by autonomic “motor” neurons releasing ***acetylcholine / norepinephrine, …*** (**AUTONOMIC „MOTOR UNITS“**)
- Cells are **not** interconnected by **gap junctions**, **APs** are **not** triggered
- **Synapses *„en passant“*** in the course of the neuron endings
- ***Contractions*** are ***finely graded*** and ***localized***