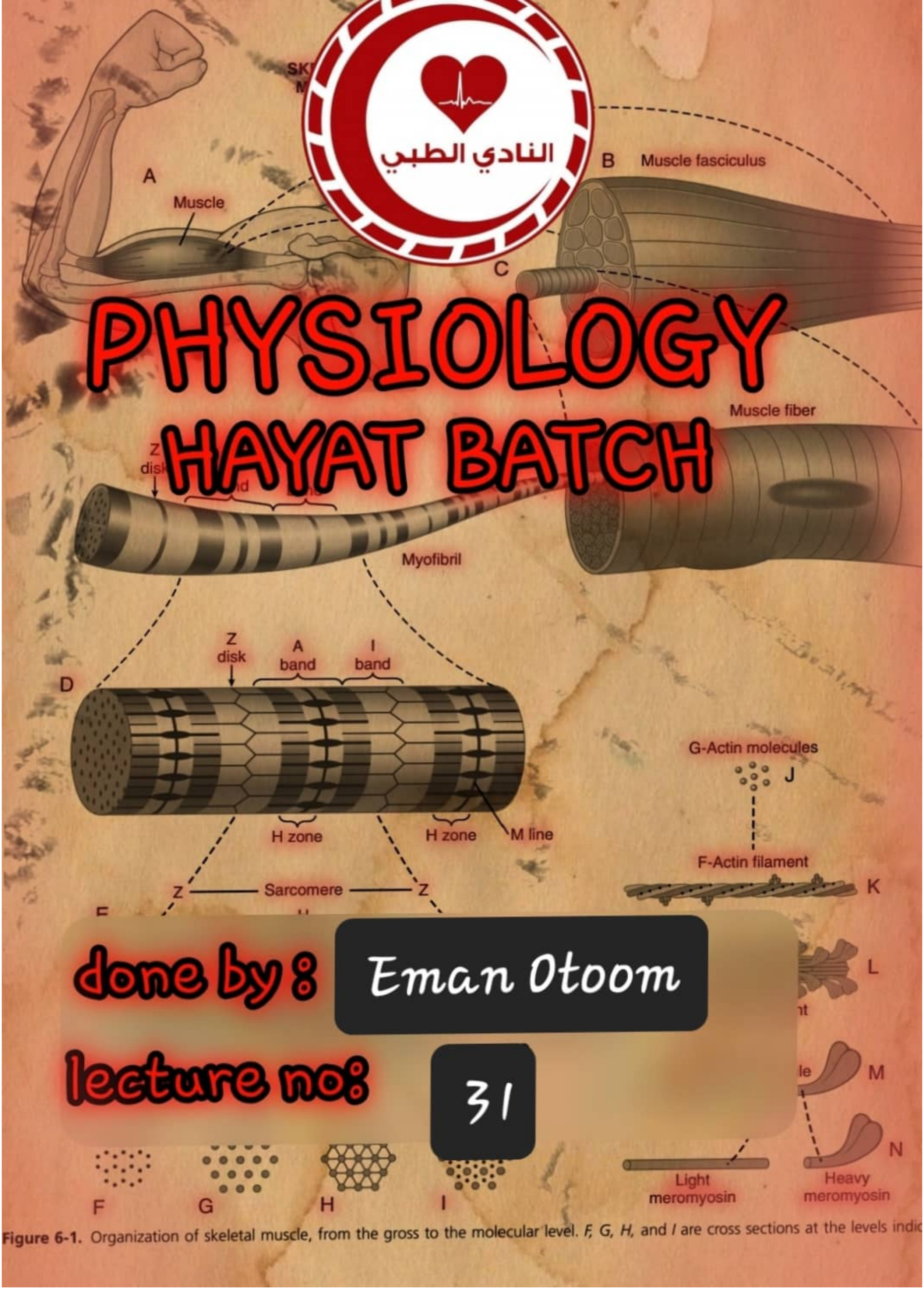
PHYSIOLOGY
HAYAT BATCH



done by : Eman Otoom

lecture no: 31

Figure 6-1. Organization of skeletal muscle, from the gross to the molecular level. *F, G, H,* and *I* are cross sections at the levels indic

General physiology
Second semester 20222023
Lecture 31
Excitation and Contraction in smooth muscle and properties of smooth muscle contraction

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Lecture objectives

- Explain the contraction process in smooth muscle and compare it to those of skeletal and cardiac muscle.
- Describe how smooth muscle can be activated to induce a contraction or to change the strength of a contraction.
- Explain the relationship between vascular smooth muscle membrane
- potential, voltage-gated calcium channels, and strength of contraction.
- Describe the difference between multiunit and unitary smooth muscle.
- Explain the following terms and their role in smooth muscle function:
- calmodulin, myosin light chain kinase, and myosin light chain phosphatase
- Define the Stress relaxation and latch state and describe their physiological importance.

Smooth Muscle Anatomical features

- Spindle shape
- Cells are not striated
- Fibers smaller than those in skeletal muscle 1 to micrometers in diameter and only 20 to 500 micrometers in length.
- single, centrally-placed nucleus central nucleus
- More actin than myosin →**but they are not arranged in the typical as how we see it in the skeletal muscle**
- No sarcomeres
  - Not arranged as symmetrically as in skeletal muscle, thus no striations.
- Dense bodies instead of Z disks **Proteins but they are not like the z discs (orientation and structure)**
- Contraction is non-voluntary **Either spontaneous or by the action of NS**
- Contraction is modulated in a neuroendocrine (neurotransmitter and hormones) **There is lots of hormones as well as neurotransmitters that will affect the activity and contraction of smooth muscles**
- Types of smooth muscles
  - Unitary (single) smooth muscles
  - Multiunit unit smooth muscles

الشرح بالسلايد الي تحت

1-unitary : when they contract, they are excited they contract all together

معظم الي بالجسم من هذا النوع

Exhibit spontaneous depolarization and their activity is affected by hormones and neurotransmitters e.g.(blood vessels , airways, uterus, GI)

2-Multiunit : best example is retina the muscle which don’t exhibit spontaneous activity However, their activity is controlled by the actions of the ANS either sympathetic or parasympathetic

Multiunit Smooth Muscles الخصائص تبعتهم

هذول ما بصيرلهم contract الا إذا وصلهم inputمن ال ANS

- Composed of discrete, separate smooth muscle fibers
- Each fiber operates and contract independently of the others, thus independent motor units
- No coupling, no gap junctions.
- Muscle fibers are heavily innervated by postganglionic fibers of the parasympathetic and sympathetic nervous systems, and it is these innervations that initiates their contraction and relaxation
- Contract only in response to its innervation and their control is exerted mainly by nerve autonomic signals
- The outer surfaces of these fibers, fibers, are covered by a thin layer of basement membrane–like substance, a mixture of fine collagen and glycoprotein that helps insulate the separate fibers from one another.
- Examples of multi-unit smooth muscle
  - are the ciliary muscle of the eye, the iris muscle of the eye
  - Piloerector muscles that cause erection of the hairs when stimulated by the sympathetic nervous system

No gap junctions , no coupling

They are innervated by postganglionic of SANS,PSANS

It helps in isolate fibers from one another , so they contract independently

Smooth muscle present in the skin

بتخلي الشعر الي على الجلد يوقف

Presence of Gap Junctions

Unitary or Single Smooth Muscles

(Syncytial Smooth Muscle, Visceral Smooth Muscle)

Because they are present in visceral organs

A muscle sense to contract a bunch of them or large group of them to generate enough force E.G (the food in the intestine the contraction has to be strong enough to move the the food from one place to another

- Single units means :a mass of hundreds to thousands of smooth muscle fibers that contract together as a single unit.
- The fibers usually are arranged in sheets or bundles, and their cell membranes are adherent to one another at multiple points so that force generated in one muscle fiber can be transmitted to the next.
- Gap junctions :
  - Impulse (action potentials) spreads through gap junctions
- ** Often muscle cells are autorhythmic and exhibit spontaneous pacemaker activity, or slow waves.

الشرح عليها بالسلايد الي بعده

- The frequency of slow waves sets the pattern of action potentials within an organ, which then determines the frequency of contractions
- Is innervated by autonomic nervous system (ANS).
- Muscle cells activity is modulated by ANS or hormones
- This type of smooth muscle is also known as syncytial smooth muscle because of its syncytial interconnections among fibers.
- Also called visceral smooth muscle because it is found in the walls of most viscera of the body, including the gastrointestinal tract, bile ducts, ureters, uterus, and many blood vessels , air ways and bladder

هذول امثلة

**بتشاركها مع خصيصة من خصائص القلب مع اختلاف ال mechanism

طبعا هاي الpacemaker activity

Is modulating by many Hormones and by ANS

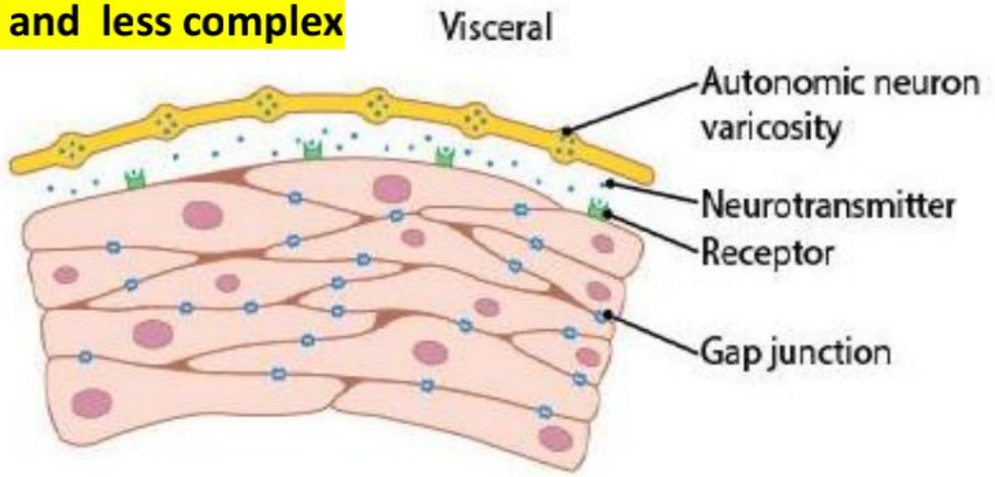
e.g., The pacemaker activity in smooth muscle cells of the GI is increased by Ach where's their activity is declines by the activation of sympathetic NS (which release NE)

Neuromuscular Junction at smooth muscles

Here is different from skeletal muscles NMJ
Here is not well developed and less complex

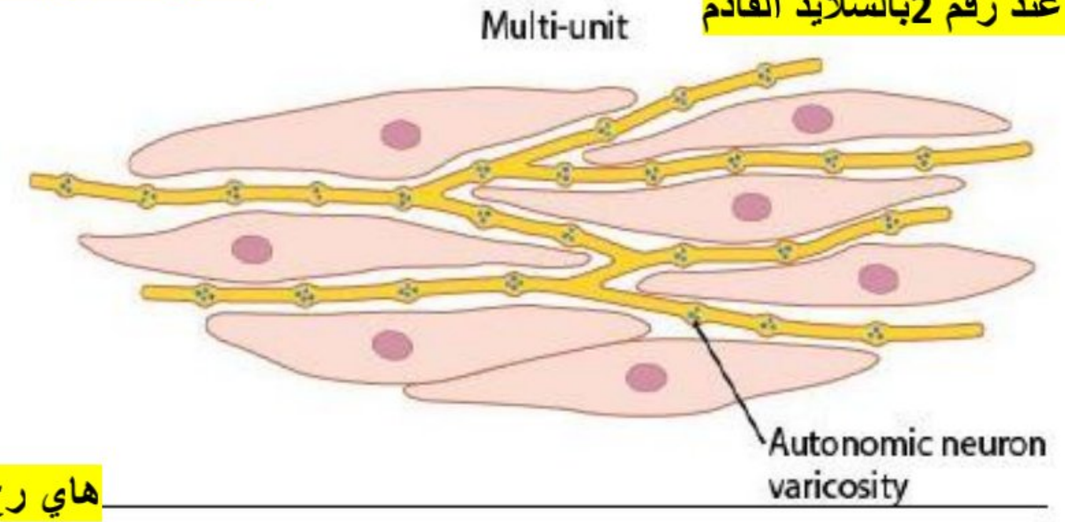
Major points

- Less complex and less well understood compared to Skeletal muscles
- Autonomic nerve fibers branch and form "diffuse junctions" with underlying smooth muscle fibers.
- **Varicosities** in the terminal axons contain neurotransmitter
- Neurotransmitter is secreted into the matrix coating and diffuses to the muscle cells
- Excitation is transmitted by Ca action potential or simple diffusion of Ca into fiber



**** 1 الشرح عند رقم**

الشرح عند رقم 2بالسلايد القادم



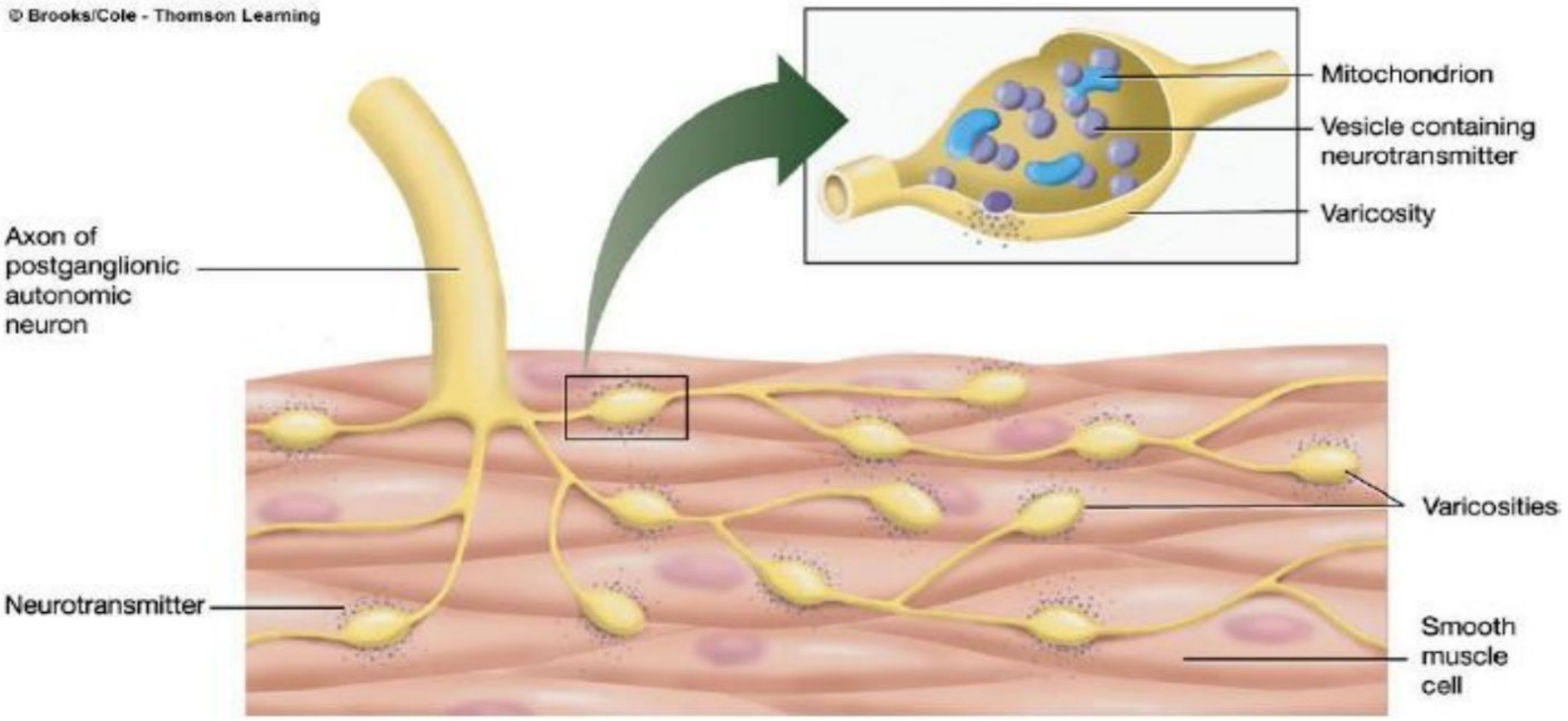
AP هاي رح نحكي عنها بموضوع ال

1** Autonomic neurons come to smooth muscle , within these neurons instead of (making close contact)
They form dilation (varicosities) which release neurotransmitter
Upon excitation by stretch or by electrical excitation when they activate ANS → the AP will arrive this Autonomic nerves and it will cause the release of neurotransmitter from varicosities → the neurotransmitter going to to diffuse and reach the muscle cells and induce it whether it is excitatory

2***The same arrangement present in the multiunit smooth muscle
-- fibers بس لاحظوا هون انه هذول ال
They receive innervation يعني → A single fiber it will form like a motor unit structure but again here the neuromuscular
Junctions is not very well developed and Again the autonomic fibers instead of causing these nice presynaptic terminals they cause
(varicosities again) that will release neurotransmitter → that will go to the muscle cell "receptor"

Innervation of smooth muscle by autonomic postganglionic nerve terminals.

هاي الصورة بتوضح ال varicosities الي فيها زي ما حكينا ال neurotransmitter
الي رح يعمل تأثير على العضلة

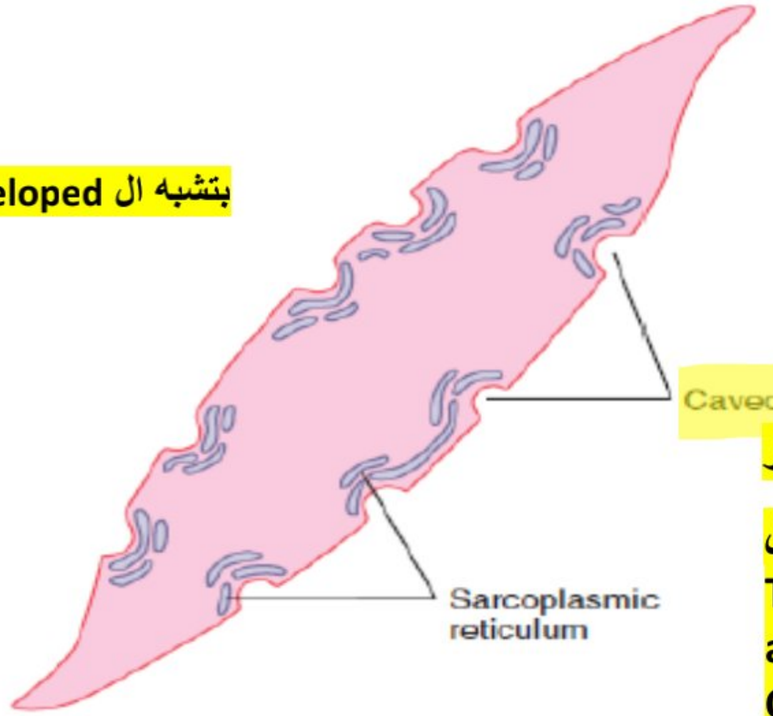


Smooth Muscle Sarcoplasmic Reticulum

- A few slightly developed
- sarcoplasmic tubules that lie near the cell membrane in some larger smooth muscle cel
- No T tubule

T tubule function but not very well developed بتشبه ال

- Caveolae : Small invaginations of the cell membrane, called *caveolae, neighboring* the surfaces of these SR tubules
- Ca $^{+2}$ storage is supplemented by caveolae , small vesicles that cluster close to the cell membrane
- The caveolae suggest a rudimentary analog o the transverse tubule system of skeletal muscle.
- When an action potential is transmitted into the caveolae, is believed to excite calcium ion release from the adjacent sarcoplasmic



زي المغر

خلينا نقول
They help in accumulation of Ca2+ In SR

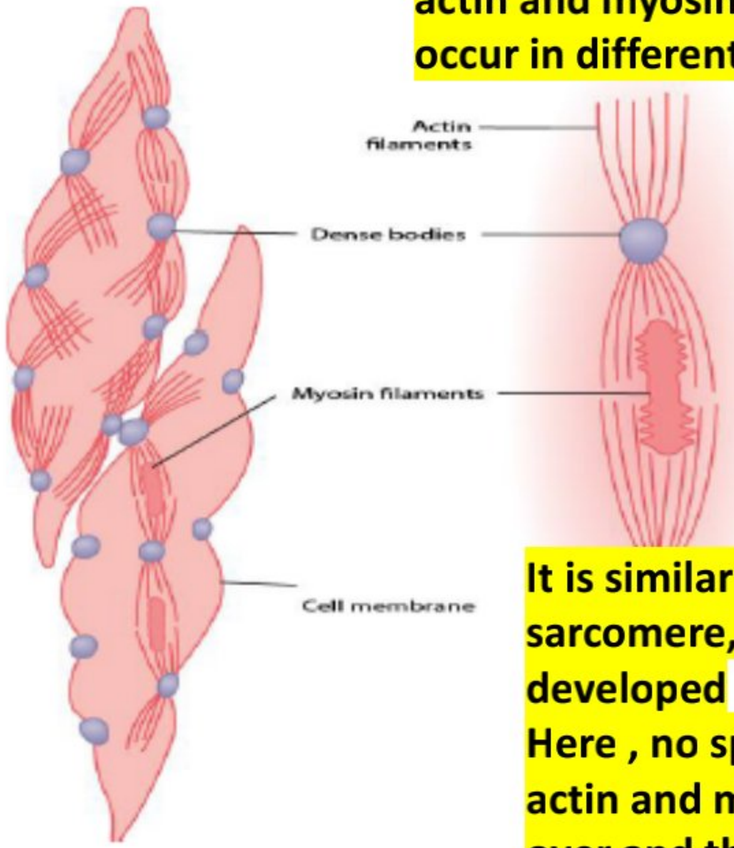
DEPOLARIZATION OF MULTI-UNIT SMOOTH MUSCLE WITHOUT ACTION POTENTIALS

- Multi-unit smooth muscle (examples smooth muscle of iris such as the muscle of the iris of the eye or the piloerector muscle of each hair)
- Normally contract in response to nerve stimuli.
- Autonomic nerve endings secrete acetylcholine smooth muscles and norepinephrine in the case of others.
- Neurotransmitter depolarization of the smooth muscle membrane, and this depolarization in turn elicits contraction.
- Action potentials usually do not develop because the fibers are too small to generate an action potential.
- Thus local depolarization (called the *junctional potential*) caused by neurotransmitter substance itself spreads "electrotonically" over the entire fiber causing muscle.

Contractile elements of smooth muscle

*Actin and myosin with no specific arrangement which will lead to formation of the sarcomere
*The contraction mechanism it is true that is depends on the interaction of the actin and myosin , but there it is still occur in different mechanism

- Contains both *actin* and *myosin filaments,* similar to those of the actin and myosin filaments in skeletal muscle
- No regulatory arrangements in skeletal muscle
- No striation
- No troponin **There is no troponin and tropomyosin**
- membrane associated and cytoplasmic dense bodies containing α actinin (similar to Z lines in skeletal muscles)



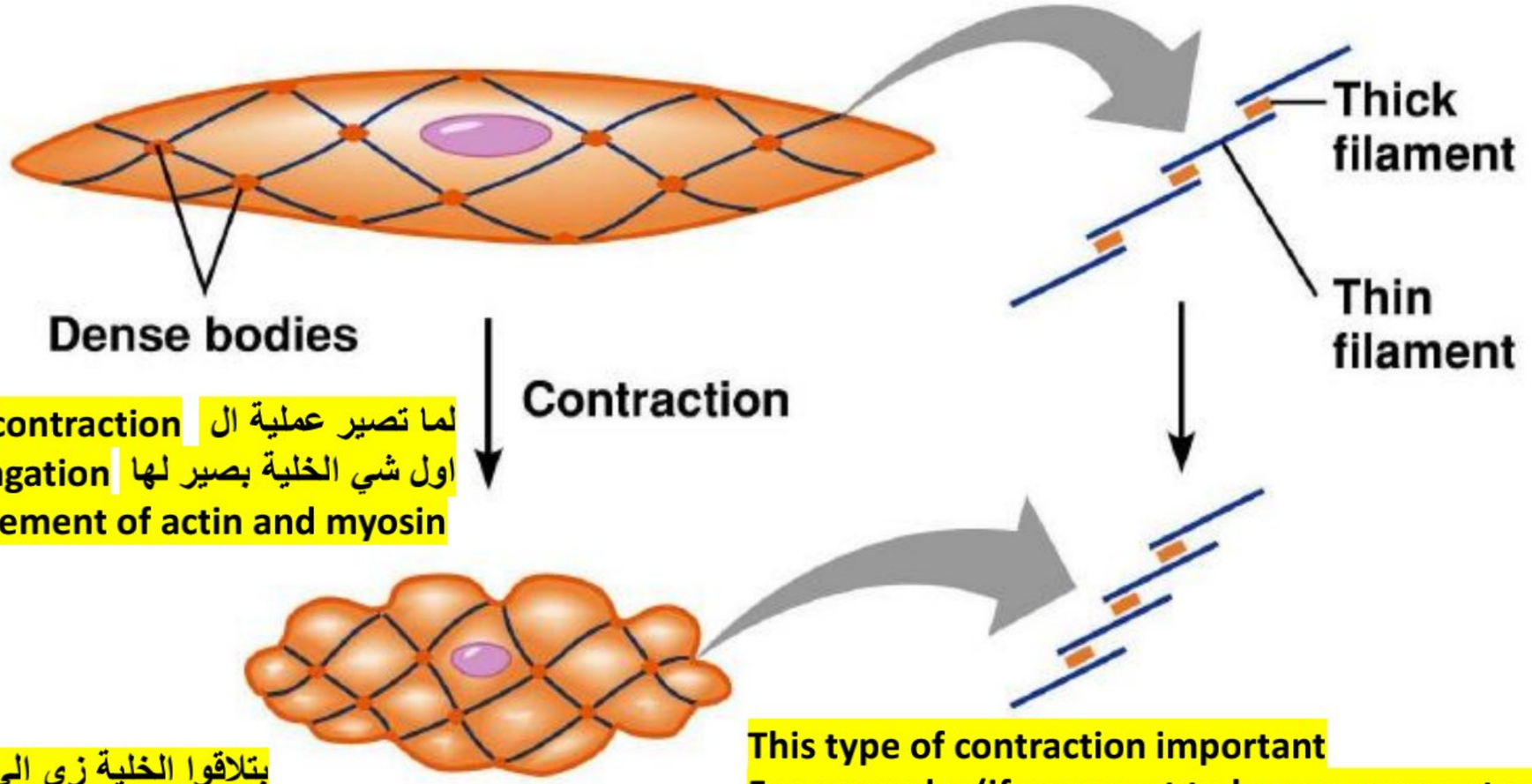
It is similar to the structure of the sarcomere, but it is not very well developed
Here , no specific arrangement the actin and myosin are scattered all over and that's why we don't see the striations

- Different mechanism of contraction , however contraction involve interaction of actin and myosin

Dense is different in the structure from Z line. Dense holds actin filaments in place

Smooth Muscle Cell

Here , when the actin and myosin it pulls over in different directions



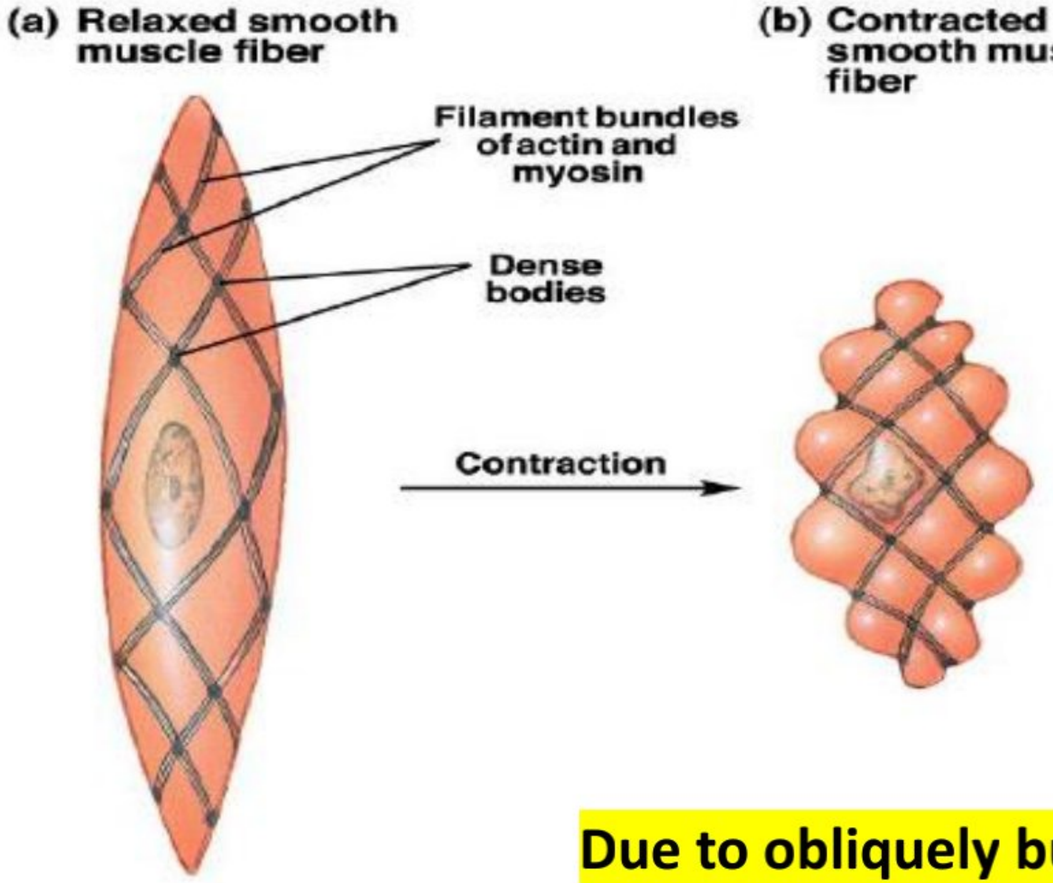
لما تصير عملية ال contraction
اول شي الخلية بصير لها elongation
Due to the arrangement of actin and myosin

بتلاقوا الخلية زي الي بتضب ضب
يعني زي بتتكعبل

This type of contraction important
For example: (if you want to have a segment contraction in the GI)

هذا النوع مهم بعملية الانقباض تبعت ال ل GI

Contractile fibers are arranged in oblique bundles rather than in parallel sarcomeres



Elongated

هون زي تكعبلت

Due to obliquely bundles (actin and myosin)

Myosin of Smooth Muscle contractile elements

- Different isoform than that found in skeletal muscle

Head of myosin is present, but the interaction doesn't occur spontaneously in presence of calcium

لازم يصير في شغله في ال structure تبع الميوسن ونعمل activationلل ATPase

- Smooth muscle myosin ATPase activity is much slower, contraction is longer

بطول وبياخذ وقت

Prolonged action

- Myosin light chain in the myosin head regulates contraction and relaxation

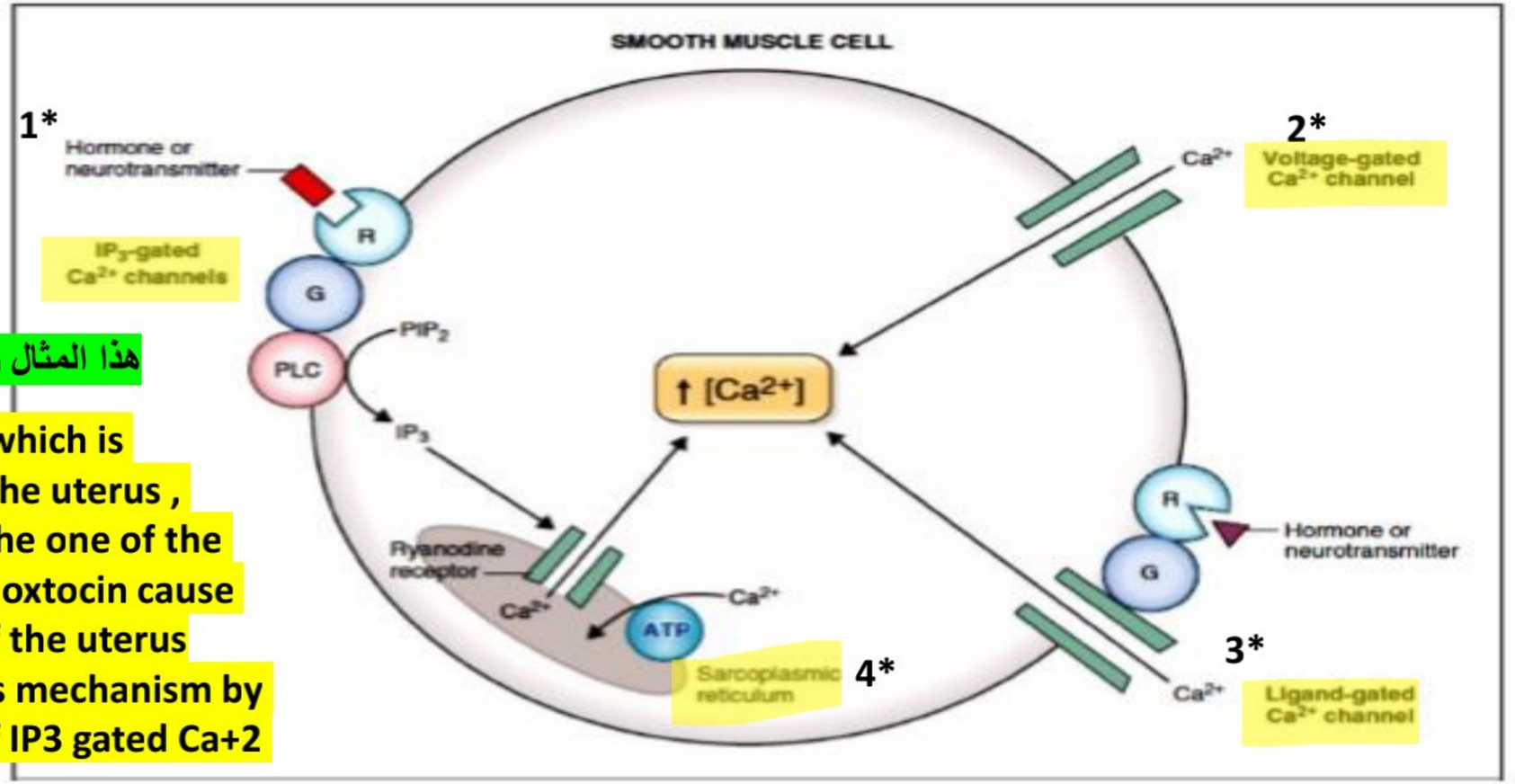
In the skeletal muscles the ATPase activity is present and all
We need calcium to bind with a troponin to exposure of
(myosin active site)

مشان يعملن cross bridge

هون العملية شوي بتختلف لأنه الكالسيوم لما بيتحد ما فيه troponinرح يروح على بروتين ثاني رح نعرفه

كمان شوي الكالسيوم رح يربط مع هذا البروتين رح يعمل activationلل myosin light chain

Mechanisms for increasing intracellular [Ca2+] in smooth muscle. ATP, Adenosine triphosphate; G, GTP-binding protein (G protein); IP3, inositol 1,4,5-triphosphate; PIP2, phosphatidylinositol
4,5-diphosphate; PLC, phospholipase C; R, receptor for hormone or neurotransmitter



هذا المثال ركز عليه الدكتور

**E.G(oxytocin which is important in the uterus , because it is the one of the way by which oxtocin cause contraction of the uterus
Is through this mechanism by stimulation of IP3 gated Ca+2 channels**

**There are multiple ways to increase calcium entry either by AP (activation of ligand gated channels through hormones , neurotransmitters
Or by protein couple receptor (IP3 gated ca+2 channel)
*And from SR بس هنون كمية قليلة**

Contraction of smooth muscles

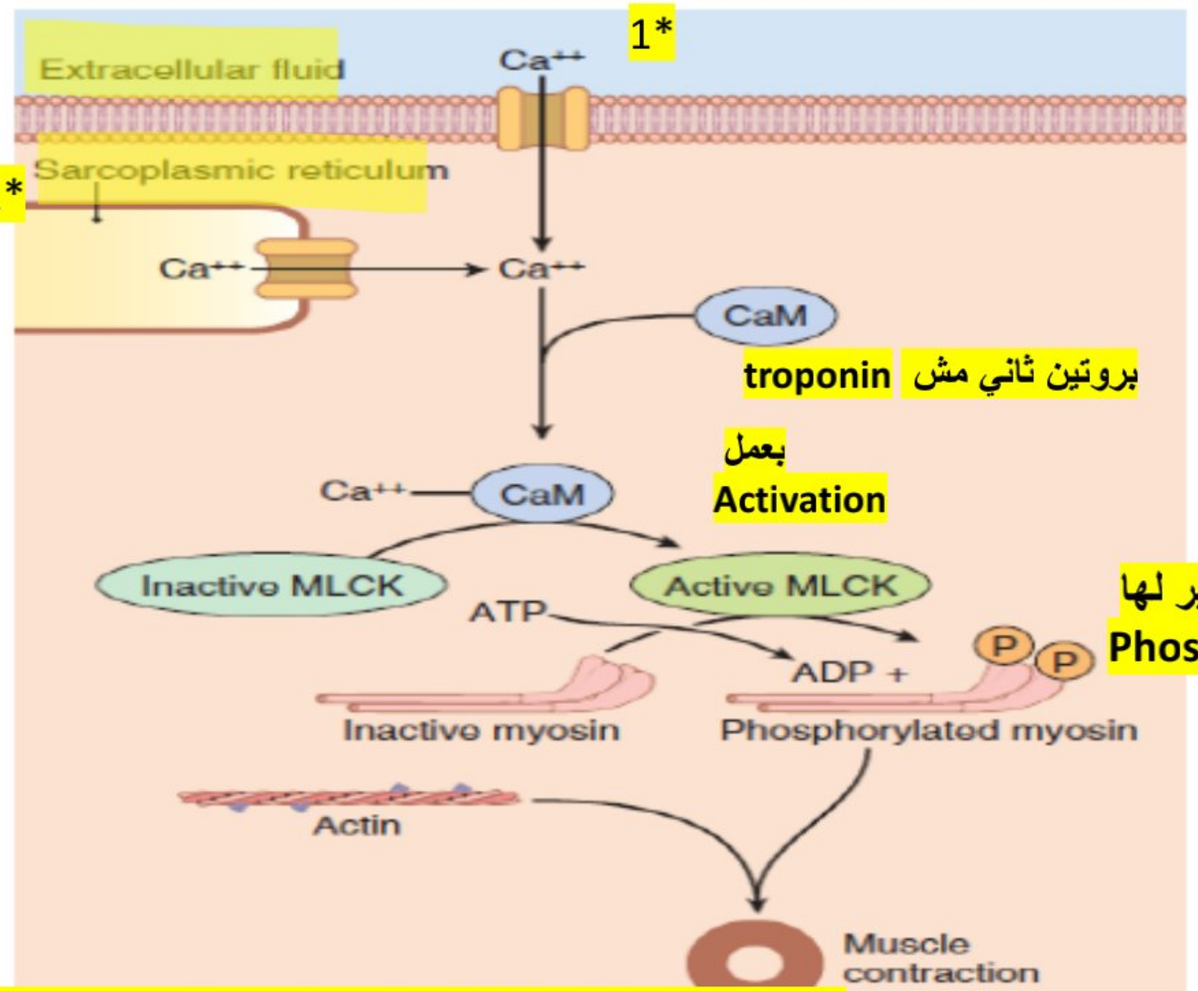
مهمه تتذكروها الدكتور ركز على موضوع فهمها

1* Intracellular calcium ion *(Ca++)* concentration increases when Ca++ enters the cell through calcium channels in the cell membrane or is released form the

2* sarcoplasmic reticulum.

The Ca++ binds to calmodulin *(CaM)* to form a Ca++-CaM complex, which then activates myosin light chain kinase *(MLCK)*.

The active MLCK phosphorylates the myosin light chain leading to attachment of the myosin head with the actin filament and contraction of the smooth muscle



Here, the attachment between myosin and actin will lead by two steps

1-Ca+bindings with CaM

2-Activation of MLCK→ that will lead to phosphorylation of myosin

actin على طول بتفاعلن مع ال

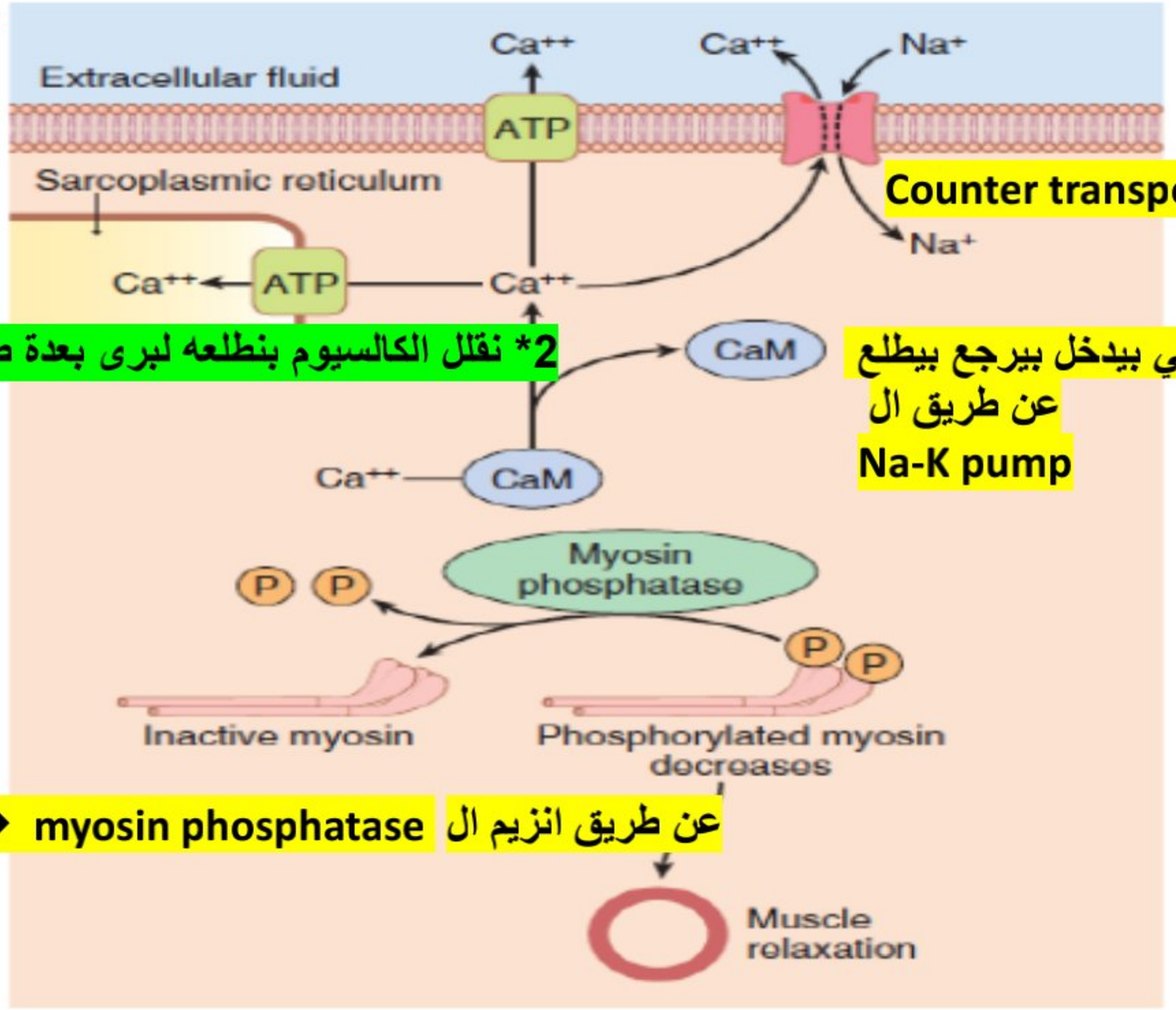
contraction وبتم عنا عملية ال

Relaxation of smooth muscle

العملية هون بالعكس

Relaxation occurs when calcium ion *(Ca++)* concentration decreases below a critical level
Ca++ is pumped out of the cell or into the sarcoplasmic reticulum.

Ca++ is then released from calmodulin *(CaM)* and myosin phosphatase removes phosphate from the myosin light chain, causing detachment of the myosin head from the actin filament and relaxation of the smooth muscle.



2* نقلل الكالسيوم بنطلعه لبرى بعدة طرق

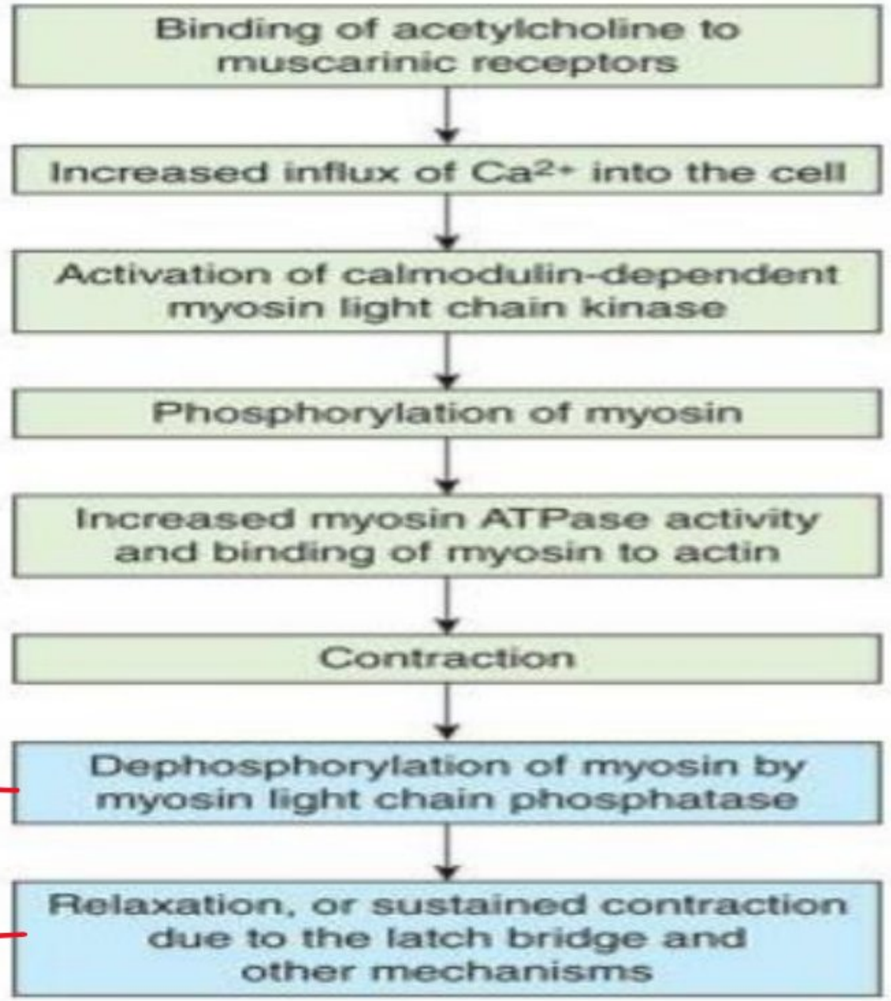
الصوديوم الي بيدخل بيرجع بيطلع عن طريق ال Na-K pump

1*Dephosphorylation → myosin phosphatase عن طريق انزيم ال

Sequence of events in contraction and relaxation of smooth muscle.

هون تلخيص للسلايدين القبل

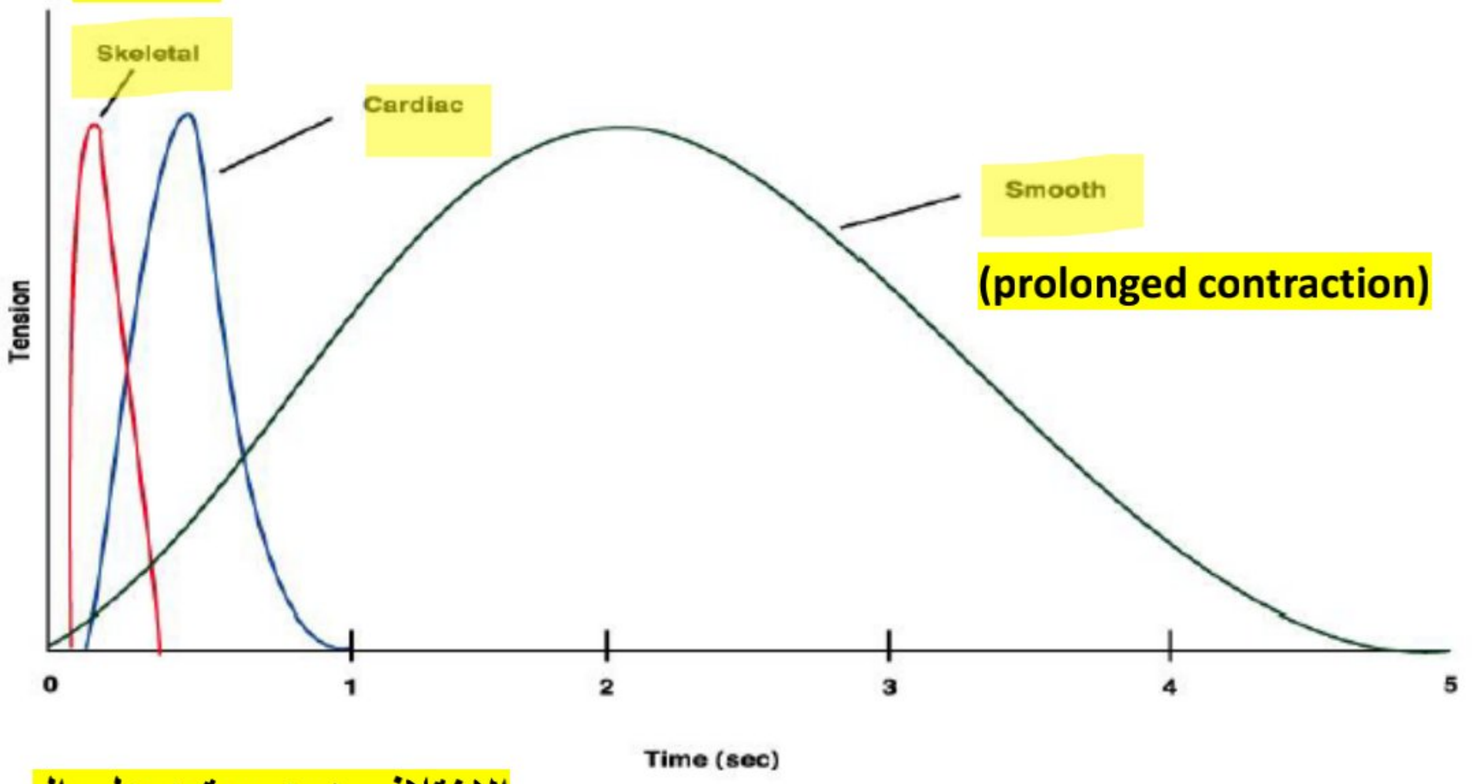
Acetylcholine is given as a sources of stimulus in this example



Relaxation

Comparison of muscle twitch in different types of muscle

Fastest



(prolonged contraction)

الاختلاف هون بيعتمد على ال
ATPase activity

Characteristics of smooth muscle contraction

The time between the electrical stimulus and the appearance of twitch of mechanical response

Slow muscle contraction

Slow ATPase activity →
كمية ال ATPالي بتحتاجها قليلة

- Slow contraction due to slow cycling of cross bridges
- degradation of the ATP that energizes the movements of the cross-bridge heads is greatly reduced, with corresponding slowing of the rate of cycling.
- longer latency to respond to stimulus
- Latency : begins to contract 50 to 100 milliseconds after it is excited
- initiation of contraction in response to calcium ions is much slower than in skeletal muscle
- Reaches full contraction about 0.5 second later, and then declines in contractile force in another 1 to 2 seconds
- Total contraction time of 1 to 3 seconds. **Prolonged is due to (slow ATPase , Poor SR, slow entry of Ca+2)**
- This is about 30 times as long as a single contraction of an average skeletal muscle fiber.
- Other types of muscle contraction could be as short as (O.2 sec - 30 sec)

skeletal muscles **ما في داعي لحفظ الأرقام بس نعرف انها بتوخذ وقت أطول مقارنه بال**

Properties of smooth muscle contraction

- Low Energy Requirement to sustain smooth muscle Contraction
- Is very energy efficient *(O_2 consumption is ~ 1 % of same weight of skeletal muscle at same tension*
- Can operate over large range of lengths *(60 - 75% shortening possible)*
- *length tension relation ship is over a wide range*
- Can be **myogenic** (spontaneously active)
- Has **Ca^{2+} action potentials**. Ca entering through channels is a very important source of calcium for contraction
- Smooth muscles exhibits sustained prolonged tonic contraction which may last for hours or even days
- Grading of muscle contraction

  Depends on intracellular Ca Ions concentration ,

  No recruitment, specially in visceral smooth muscles

Properties of smooth muscle contraction

- Can operate over large range of lengths *(60 - 75% shortening possible)*
- *length tension relation ship is over a wide range*
- Is very energy efficient *(O_2 consumption is ~ 1 % of same weight of skeletal muscle at same tension!)*
- Can maintain force for long periods (hours, days, weeks)
- Can be **myogenic** (spontaneously active)
- Has **Ca^{2+} action potentials**. Ca entering through channels is a very important source of calcium
- Ca $^{+2}$ storage is supplemented by caveolae , small vesicles that cluster close to the cell membrane.

Once the muscle contracts in the sense , it remains in long contracticle state without needing further excitation , Without additional stimulation

Characteristics of smooth muscle contraction.

يعني بس بصيرلها انقباض (لها القدرة تضل منقبضة فترة طويلة قبل ما يصيرلها) relaxation

- Latch state and Latch mechanism in smooth muscles Depend on 1,2,3

1 • Higley dependent on oxidative for ATP availability

2 • Glucose and fatty acids are provided in the blood and mitochondrial oxidative processes produce adequate energy for the slower contractions that occur in smooth muscle

3 • This is due to the lower rate of the myosin ATPase enzyme the lower rate of the myosin ATPase enzyme.

Contraction بضل فترة قبل ما يصير Relaxation

- **The "Latch" Mechanism Facilitates Prolonged Holding of Contractions of Smooth Muscle** (Smooth muscle can maintain tension for long periods)
- The latch state seems to occur because the cross bridges do not dissociate very rapidly in spite of the fact that the myosin light chain is dephosphorylated ;
- Accordingly energy expenditure is minimal
- This is thought to be important in sphincter muscles where tension development must occur for long periods of time. بضلن مسكرات وقت طويل

Stress-Relaxation in Smooth Muscle

أحسن مثال ال Bladder

- Mainly occurs in visceral unitary type of smooth muscle of many hollow organs
- is its ability to return to nearly its original *force* of contraction seconds or minutes after it has been elongated or shortened.

**الشرح بالتفصيل بالسلايد القادم

- Response to stress briefly, then return to their normal state of tension and daapt to new length
- For example, a sudden increase in fluid volume in the urinary bladder, thus stretching the smooth muscle in the bladder wall, causes an immediate large increase in pressure in the bladder.
- However, during the next 15 seconds to a minute or so, despite continued stretch of the bladder wall, the pressure returns almost exactly back to the original level.
- Then, when the volume is increased by another step, the same effect occurs again.
- Conversely, when the volume is suddenly decreased, the pressure falls drastically at first but then rises in another few seconds or minutes to or near to the original level.
- These phenomena are importance in that they allow a hollow organ to maintain about the same amount of pressure inside its lumen despite sustained, large changes in volume.

It is important on the visceral organs particularly on the bladder
If you take the bladder wall (which has smooth muscle) the contraction of these smooth muscles will empty the bladder
Usually, the maturation (which is an autonomic reflex) is caused by stretching of the bladder wall
The stretching somehow causes excitation of the muscles in the bladder wall → entry of Ca+2 → contraction of the smooth
Muscle in the bladder wall → (Emptying of the bladder)
Human urinary bladder tolerate around (400ml) of urine , bladder tolerate this amount of urine before urination this is basically
Due to (stress relaxation mechanism)
Urine increased→ stretch increased→ excitation and contraction increased → Tension will increase
If tension increased and still, → we will have an emergency to go to bathroom
To make us capable to store more and more urine in the bladder

بعد ما يزيد ال tension

Due to the contraction → suddenly tension will drop

ولو هاي العملية مش موجودة رح يصير في مشاكل بصير الواحد كل شوي بده يروح على الحمام
وهاي العملية السبب بوجودها يمكن يضل الواحد خمس او ست ساعات بدون ما يروح على الحمام

Effect of Local Tissue Factors and Hormones on smooth muscle

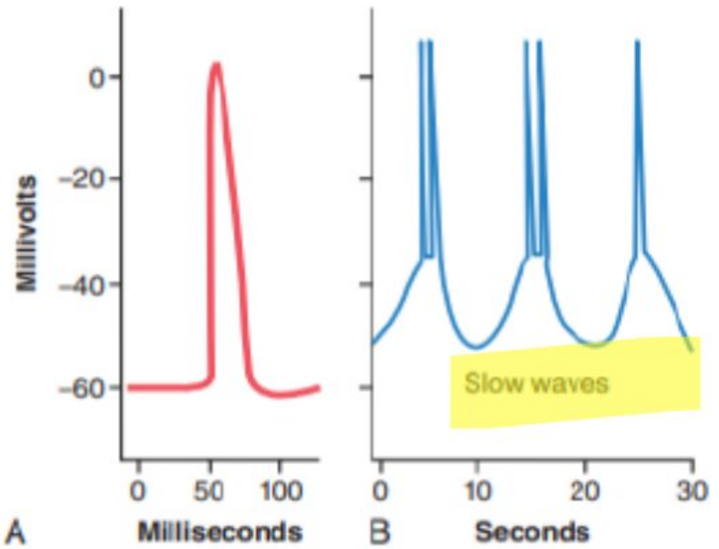
- local tissue chemical factors effects on arteriole smooth muscles
  - Lack of oxygen in the local tissues causes smooth muscle relaxation and, therefore, vasodilation.
  - Excess CO2 causes vasodilations.
- Increased hydrogen ion concentration causes vasodilation.
  - Adenosine, lactic acid, increased potassium ions, diminished calcium ion concentration
- various hormones
- *norepinephrine, epinephrine, angiotensin II, endothelin, vasopressin, oxytocin, serotonin,* and *histamine.*

MEMBRANE POTENTIALS AND ACTION POTENTIALS IN VISCERAL SMOOTH MUSCLE

- In the normal resting state, the intracellular potential is usually about −50 to −60 millivolts
- The action potentials of visceral smooth muscle occur in one of two forms
  - spike potentials
  - action potentials with plateaus.
- Such action potentials can be elicited in many ways
  - Electrical stimulation.
  - Spontaneous generation in the muscle fiber
  - Hormones
  - transmitter substances from nerve fibers
  - Stretch

Spike potentials

- Typical smooth muscle action potential (spike potential) elicited by an external stimulus.
- Observed in GT and in most types of unitary smooth muscle.
- The duration of this type of action potential is 10 to 50 milliseconds,
- Such action potentials can be elicited in many ways—for example, by electrical stimulation, by the action of hormones on the smooth muscle, by the action of transmitter substances from nerve fibers, by stretch, or slow waves depolarization
- Sodium participates little in the generation of the action potential in most smooth muscle.
- Instead, flow of calcium ions to the interior of the fiber is mainly responsible for the action potential
- Depolarization phase is mainly due to activation of L type Ca channel
- Receptive spike potentials generated by slow wave depolarization



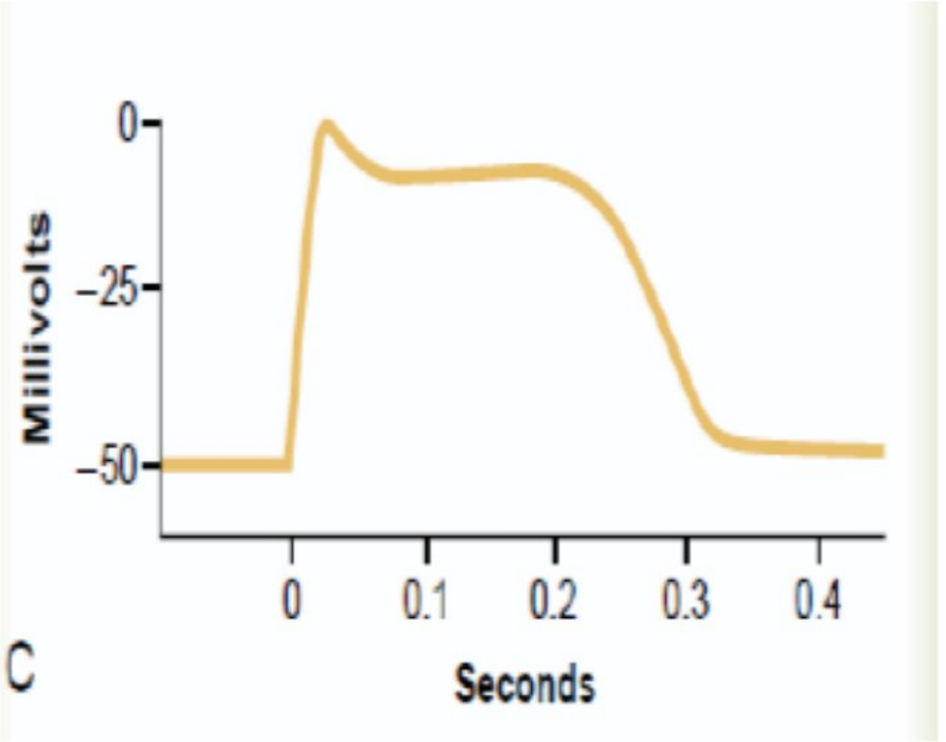
ببين شرح عنها أكثر باخر سلايد

Action potential with a plateau, recorded from a smooth muscle fiber of the uterus

The onset of this action potential is similar to that of the typical spike potential.

However, instead of rapid repolarization of the muscle fiber membrane, the repolarization is delayed for several hundred to as much as 1000 milliseconds (1 second).

The importance of the plateau is that it can account for the prolonged contraction that occurs in some types of smooth muscle, such as the ureter, the uterus under some conditions, and certain types of vascular smooth muscle.

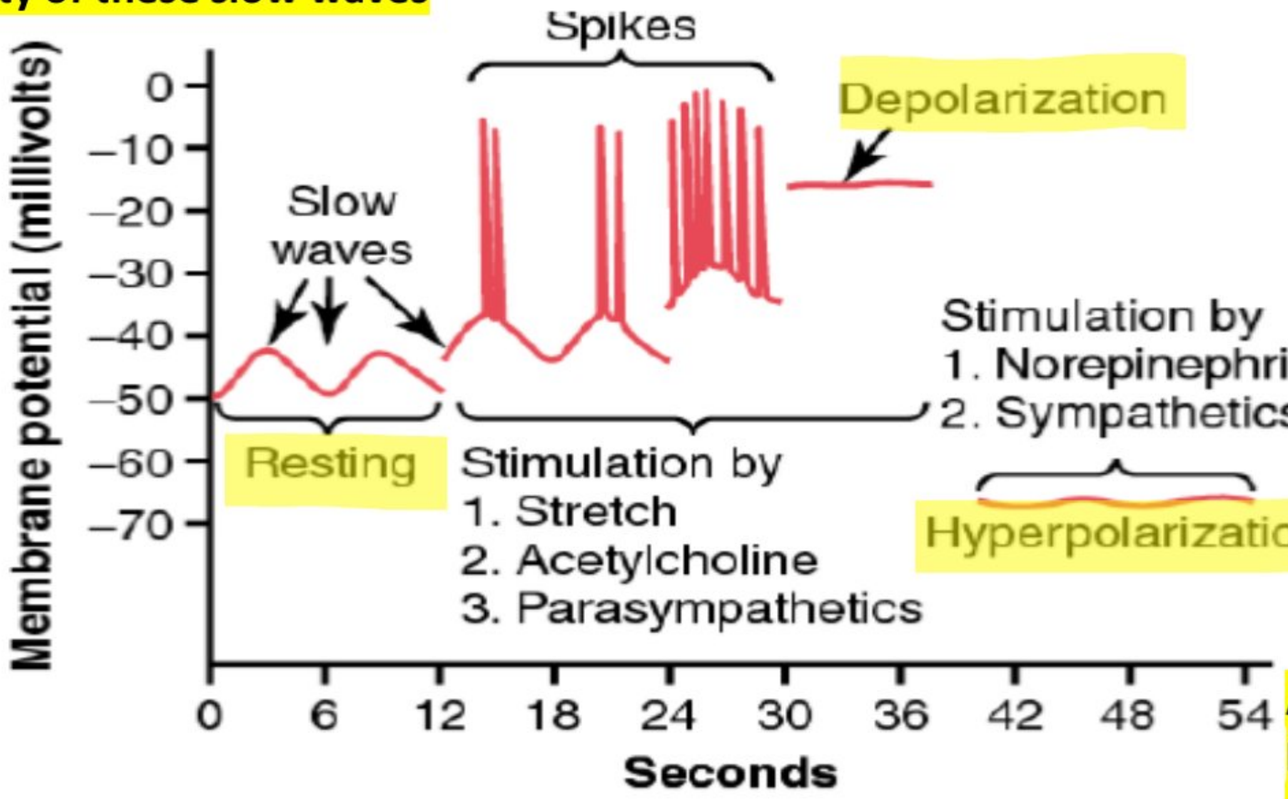


Slow Wave Potentials
(*pacemaker waves) in* Unitary Smooth Muscle Can

- action potentials arise within the smooth muscle cells without an extrinsic stimulus
- action potentials arise within the smooth muscle cells without an extrinsic stimulus
- Slow wave depolarization Leads to Spontaneous Generation of Action Potentials.
- the slow waves are caused by waxing and waning of the pumping of Na pump.
- This type of pacemaker activity for example in the gut
- Controls the rhythmical contractions of the gut.
- Slope of depolarization is influenced by ANS

Slow wave and spikes potentials in visceral smooth muscles
Effects of sympathetic and parasympathetic stimulation

Some how if you stretch smooth muscle or activate of parasympathetics
The rate of rise and the activity of these slow waves will be increased and once the cell membrane potential goes from like -60 to -40 we will reach the threshold and generate AP



There will not be AP

And that's why the GI of Parasympathetic is → excitatory

The effect of the sympathetic Is → inhibitory

(وقل ربِّ زدني علما)