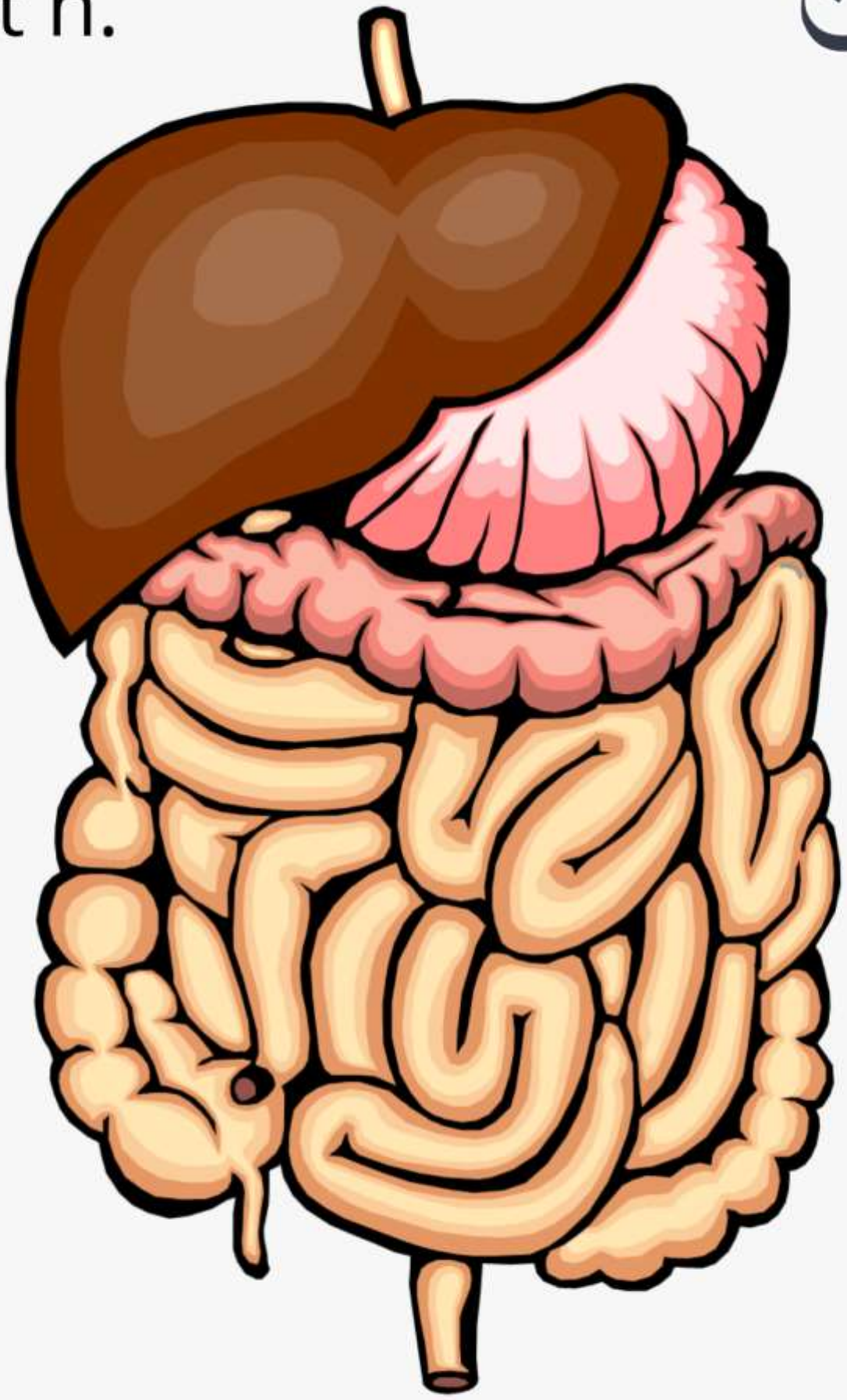
Physiology

Sheet n.



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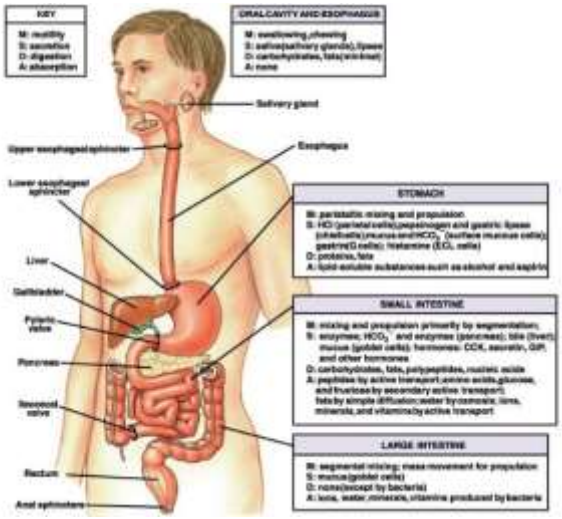
بسم الله الرحمن الرحيم

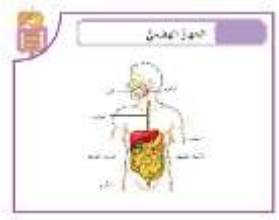
Gastrointestinal physiology

Slides notes
Doctor Additional

This is the largest system in our body, starting from the buccal cavity(mouth) and ending with the anus. We have a lot of organs in this system. We don't care about the details of Anatomy, only know the names of organs ☺



اتعب في التوجيهي،
بترتاح في الجامعة



Physiological processes are taking place along the gastrointestinal (GI) tract.

after processing the food, we use it as a fuel to provide our body with energy .

Four physiological processes are taking place along the gastrointestinal (GI) tract. These include: بالترتيب

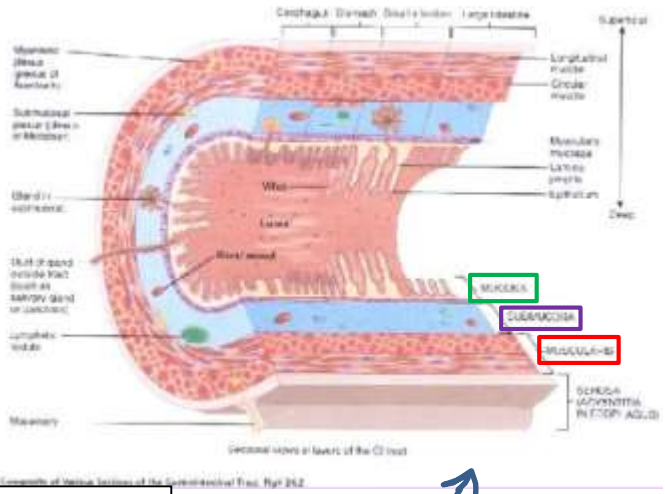
1. **Motility.** (by muscles) تحريك الطعام
2. **Secretion** (by glands) افراز عصارات هاضمة
3. **Digestion.** (we are focusing on the **chemical** digestion **via enzymes**) هضم الطعام
4. **Absorption.** (by specialized cells)امتصاص الطعام

Functional structures in the gastrointestinal tract

we will talk about them in detail
هسا بس اعرف اسماءهم

1- **Smooth muscle cells**
2- **Interstitial cells of Cajal**
3- **Secretory cells**

The GI tract is like a tube from the beginning until the end. **Generally** Is formed by 3 layers (we have some variations between organs ما رح نحكي عن هاي الاختلافات الا اذا كان الها اهمية وظيفية) so we are talking generally.



The outer layer → **smooth muscle cells**
The inner part → **the mucosa**
In between → **submucosa**

Other related structures

ايش الاشياء اللي بتتحكم بالجهاز الهضمي او بتضبطه ؟

Control systems of GI functions.

ENS: one of the main divisions of the peripheral nervous system (PNS), it's a system of neurons that control the function of the gastrointestinal tract

1- Neural control: ضبط عصبي

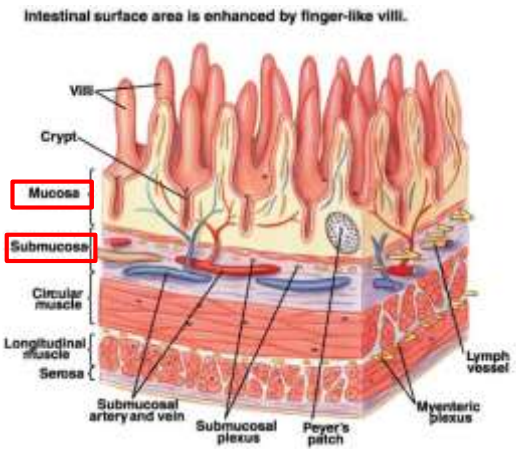
- **Enteric nervous system** (control all the functions of GI tract)
- **Autonomic nervous system**

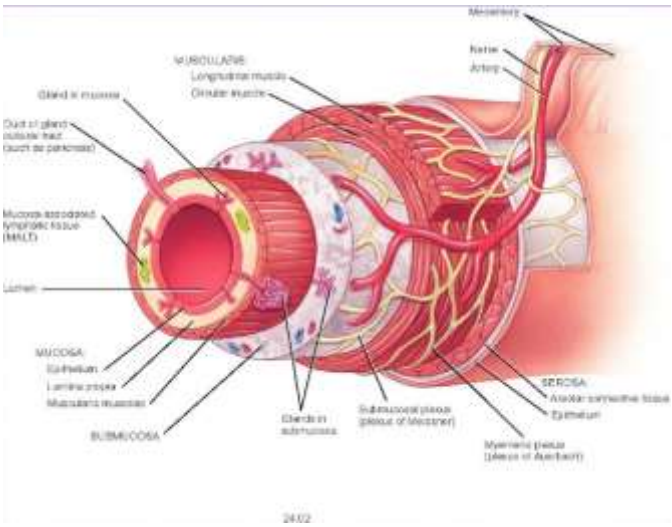
As we know, only the parasympathetic will increase the function of GI tract ..بزيد الانقباضات والهضم والافرازات

2- Hormonal control:ضبط هرموني GI endocrine → we have a lot of endocrine cells dispersed along the GI tract that control the secretion of hormones.

3- Blood flow to the GI. ضبط دموي → important for the process of secretion and absorption (when you need more secretion, you need more fluids which are coming from circulation)

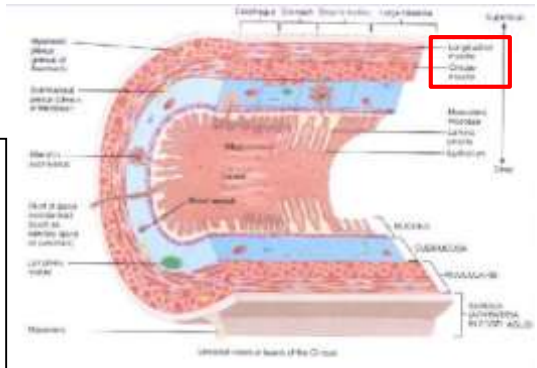
as you see in the picture, we have plenty of blood vessels in the submucosa (highly vascularized). Also, we have capillaries in the mucosa, which are important in the absorption of nutrients ☺





We will start talking about these functional structures:

Functional structures in the gastrointestinal tract



Smooth muscle cells (SMCs)

It has contractile proteins, but the organization of those contractile proteins is different from skeletal muscle (remember in skeletal muscles we have striation because of thick and thin filaments)

Here we have longitudinal and circular layers

2 main layers are generally forming Gastro-intestinal tract with some variations according to organ. These layers are clearly seen in small intestine:

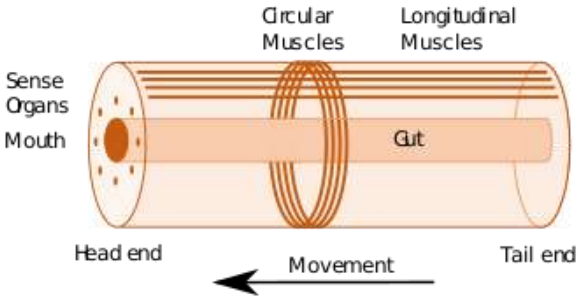
- **Longitudinal layer**: outer layer of smooth muscle cells arranged longitudinally along the digestive tract (the axis of the tube).

- **Circular layer**: extend circumferentially around the gut. Located beneath longitudinal layer.

Additional picture:

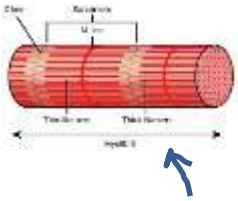
بقصر طول العضلة←العضلات الطولية لما تنقبض

بقصر قطر العضلة ← العضلات الدائرية لما تنقبض

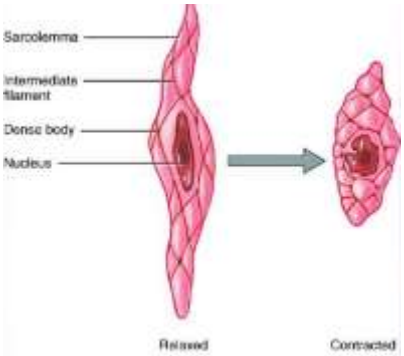


Each layer is forming a bundle like structure. Cells in each bundle are connected together by **gap junctions** with permit these cells to function as **syncytium.** Therefore, by this organization, a group of cells is functioning together to an effective contraction along gastro-intestinal tract.

In addition to these two main layers, a third thin layer of smooth muscle cells is also present at the junction between the mucosa and submucosa which is known as **Muscularis mucosa**. This layer is involved in **the secretion from tubular glands** and **movements of mucosal folds.**

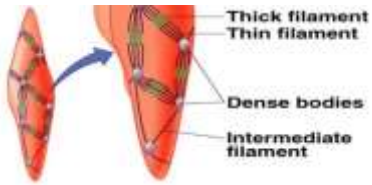


contractile protein of smooth muscles:
they are not organized as skeletal muscle, as you see we have dots called :
dense bodies → holding the thin filaments, similar to z-disk



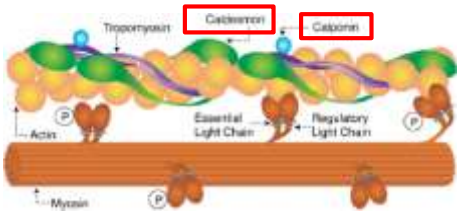
in between thin filaments, we have thick filaments, also we have interaction between thin and thick filaments. By the interaction.. the distance between dense bodies becomes shorter → contraction

additional picture:



NOTE: the structure of thin filaments in smooth muscles is **different** from the structure of thin filaments in skeletal muscles.

Additional picture:
It has calmodulin instead of troponin.



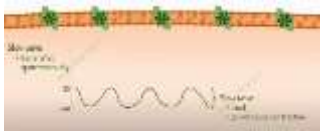
Smooth Muscle Cells Characteristics

Electrical activity
- Slow waves (basic electrical rhythm)

Additional notes from dr:

Slow waves: هي مش جهد فعل حقيقي لانها ما وصلت لجهد العتبة، some smooth muscle cells are self-excitatory. This property is due to rhythmic variations in membrane potential that appear at muscle membrane. These rhythmic variations are known as slow waves. These waves are probably caused by changes in Na+ pump activity, or changes in conductance of ion channels. Slow wave are not action potentials and they cannot induce contraction in smooth muscle. When the peak of these slow waves rises above threshold, they can generate spike potentials, which result in contraction of smooth muscle.

ما بصير انقباض بالعضلة (there is no tension)



Spike potentials:

Fast depolarization and repolarization (have short duration) these can be elicited by external stimulus.

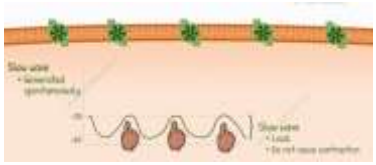
بكل بساطة هو عبارة عن جهد فعل بصير بالعضلات الملساء لما يتحفز اما بهرمون او ناقل عصبي.

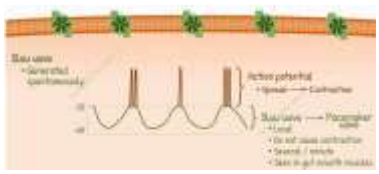
بالتالي بصير انقباض في العضلة

او لما توصل السلو ويفز لجهد العتبة

- when slow waves (at the tip)

reach the threshold, it will generate true action potential (spikes)→ tension

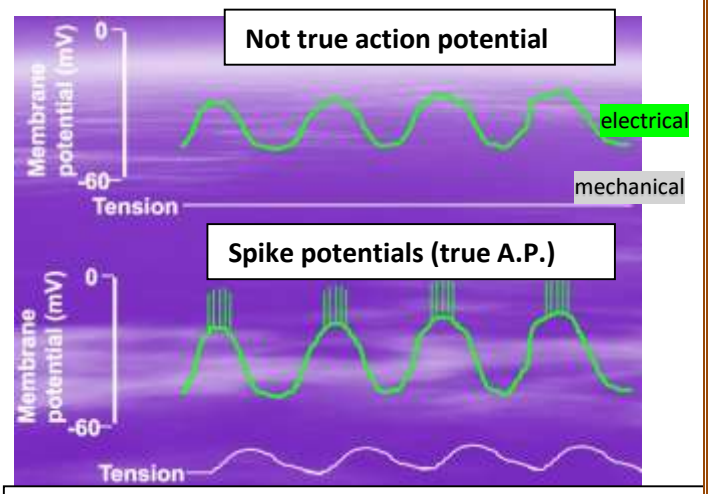




Those slow waves are specific for the smooth muscles of GI tract: they are always → depolarization, repolarization, depolarization, re….. etc

Different from the smooth muscles in uterus → in uterus we have action potential plateau

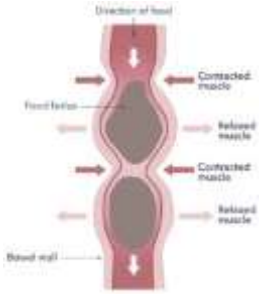
At the tip of slow waves, if they reach the threshold (all the time they reach it)→ we will have spikes (true action potential)



Then the action potential will spread in smooth muscle cells because of gap junction

وبالتالي رح يصيرو الخلايا ينقبضو مع بعض

→ syncytium .. التفاصيل بعد صفحتين ☺



زي ما شايفين بالصورة:

عشان لقمة الاكل تنزل، خلايا العضلات اللي فوق بنقبضو مع بعض واللي تحت بكونو منبسطين عشان ينزل الاكل للاسفل بعدين بعكسو...وهكذا

So **electrical activity:** slow waves + spikes → all the time we have contraction, relaxation, cont, relax…. They follow the same **rhythm** ايقاع

Smooth muscle cells are characterized by the presence of 1-**slow waves** (undulating (move in waves) changes in membrane potential known as **basic electrical rhythm (BER)**) and 2-**spike potentials**. The spike potentials are the true action potentials that appear at the peak of slow waves. (after reaching the threshold, and always they reach threshold)

*** Ca++ in smooth muscle cells contractions:** The role of calcium in smooth muscle contraction is known. The source of Ca++ for contraction is either from extracellular fluid or sarcoplasmic reticulum(intracellular). (while in skeletal muscle the source only from SR)

electrical activity: The entry of Ca++ from the interstitial fluid appears by activation of Ca++ channels. This activation is generated by **spike potentials that occur at the peak of slow waves** which represents the true action potentials at smooth muscle cells.

Chemical activity: The release of Ca++ from sarcoplasmic reticulum occurs by formation of IP3 that results during signal transduction mechanisms by activation of phospholipase C3 in **response to binding of ligand (hormone or neurotransmitter)** to its receptor. التفاصيل تحت

بالحالتين سواء الكالسيوم اجا من برا او من جوا:

Ca++ acts via calmodulin to activate myosin filaments which results in developing of attractive forces between actin and myosin.

1- Once you have spikes (true action potential), then we have activation of Ca channels on the sarcolemma

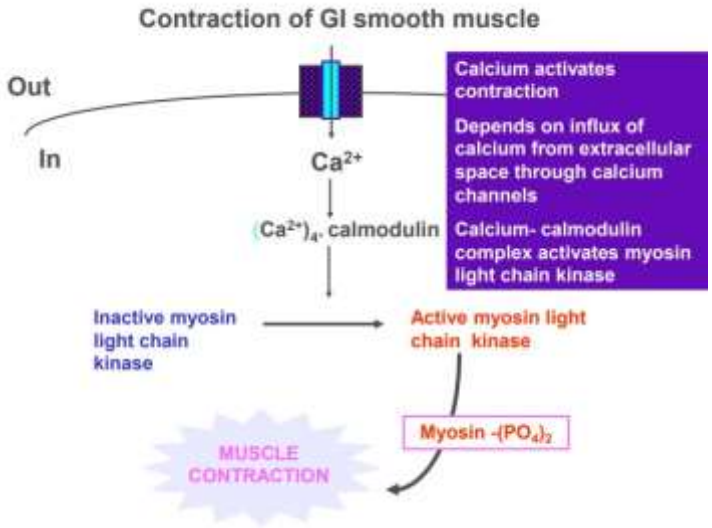
2- entry of Ca ions

3- ca binds with calmodulin (we need 4 Ca ions to bind with one calmodulin)

4- Ca-calmodulin complex will activate myosin kinase

5- phosphorylation of Myosin head

6- interaction between Myosin and Actin



Remember in skeletal muscle, we have troponin, but here we have calmodulin

7- Then how to get relaxation?

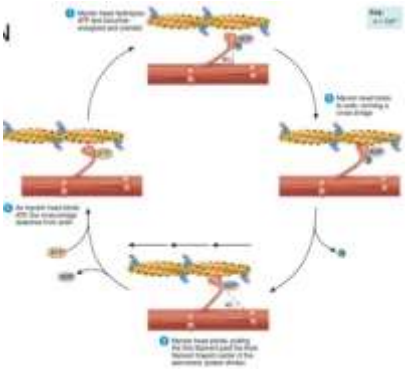
The relaxation of smooth muscle cells also involves a decrease in Ca++ concentration by increased activity of Ca++ pumps located at the plasma membrane and sarcoplasmic reticulum. In addition to that, the mechanism of relaxation also involves dephosphorylation of myosin heads by an enzyme called myosin phosphatase.

Additional notes from dr:

The mechanism of contraction in smooth muscle cells also involves actin-myosin interaction but with a different mechanism than that found in skeletal muscle. When smooth muscle is stimulated, it takes longer time than striated muscle to induce contraction (long latent period), the total contraction time is about 30 times more than that in skeletal muscle. These appear because of the slow attachment and detachment of contractile proteins, which results in slow cycling of cross bridges.

The mechanism of contraction in smooth muscle also involves an increase in Ca++ concentration, but the source could be different than in skeletal muscle. The source in skeletal muscle is only from the endoplasmic reticulum, which has high representation in skeletal muscle, while in smooth muscle the main source is extracellular and some contraction can be induced also by the release of Ca++ from intracellular stores (sarcoplasmic reticulum), which is moderately developed in smooth muscle (not well as in skeletal muscle).

Additional picture to remember the steps:



Video for better understanding:
https://youtu.be/zX1JFj36BkA?si=Ys1ZmdXZiZ5-
بنصحكم فيه☺

Smooth Muscle Cells Characteristics

Gap junctions:

The smooth muscle cells have Gap junctions between them, and it's important because of:

1 - Communication between cells

They can display slow waves together, display spikes together. So they have:

2 - Functional syncytium → Contract and relax together مندمجين كانهم وحدة وحدة

The second type of control is:

Chemical control of SMCs

simply, we have receptors (muscarinic receptor), after activating this receptor, then we will have activation of phospholipase C → then IP3

IP3 will activate the Ca channels → causing the release of Ca from intracellular store → contraction

This type of control is **tonic contraction** because we have tension.

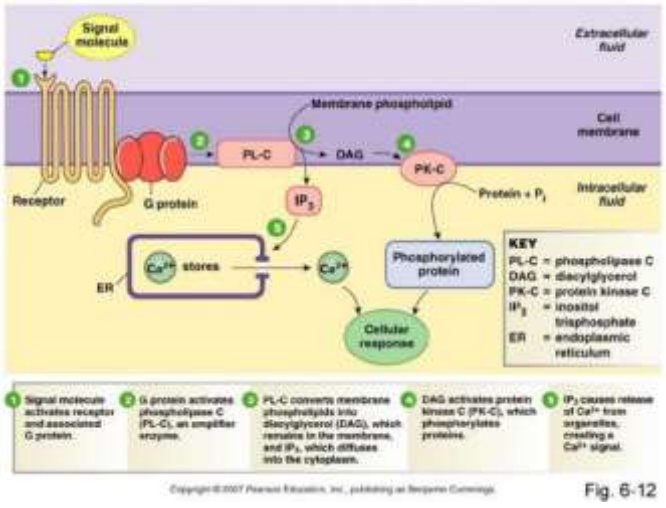


Fig. 6-12

Smooth muscle cells respond to a wide range of stimuli caused by **neurotransmitter** or **hormones**. This activity appears by activation of receptors on smooth muscle cells. These transmitters may induce relaxation or contraction of smooth muscle cells according to the type of transmitter, type of receptor and the transduction mechanism involved in receptor activation.

Finally, integration of responses by smooth muscle cells by binding of ligands to their receptor will result in exhibition of **tonic contraction.** Variations in the tonic contractions by increase or decrease in intensity is seen along gastro-intestinal smooth muscle. In addition to these, also **rhythmic contractions** have been seen along gastro-intestinal tract (known also as phasic or rhythmic contractions). In the later type, a group of smooth muscle cells are exhibiting a rhythmical contractions and relaxations as we will see in small intestinal motilities. These contractile activities are controlled mainly by the electrical rhythm that smooth muscle cells of the GI tract are displaying.

التنين مهمين لوظيفة الجهاز الهضمي، بعض العضلات الملساء المكونة للجهاز بتنقبض بالطريقة الاولى والبعض الاخر تنقبض بالطريقة التانية:

Tonic contraction:

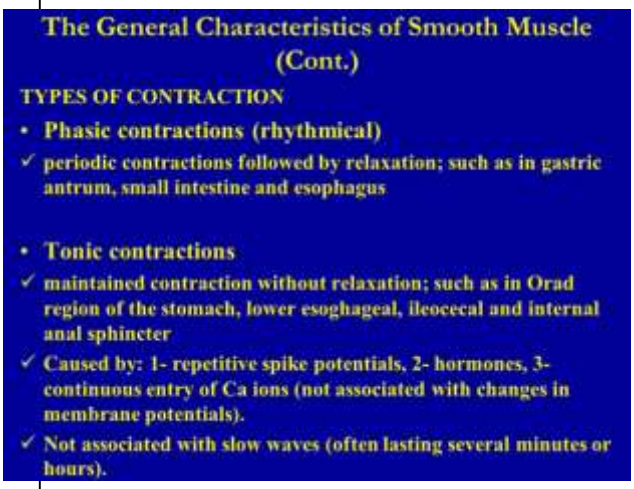
انقباضات مستمرة لمدة دقائق او ساعات بدون انبساط بسبب تحفيز من هرمون او ناقل عصبي و جهود فعل متكررة ومستمرة ودخول الكالسيوم بشكل مستمر. → by repetitive spikes because of external stimuli . Eg. Smooth muscles of sphincter

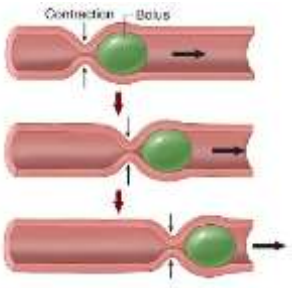
Rhythmic contraction انقباضات ايقاعية:→ by small waves + spikes without external stimuli

Contraction, relaxation, contraction, relaxation → rhythm ايقاع

بصير بدون محفز خارجي وبساعد على نزول لقمة الاكل الى الاسفل

additional:





Control of smooth muscle cells activity

Smooth muscle cells activity is controlled by

Electrical control:

- Rhythm or phasic contractions

Electrical activity of smooth muscle cells: (slow waves and spike potentials).

Chemical control:

- tonic contractions

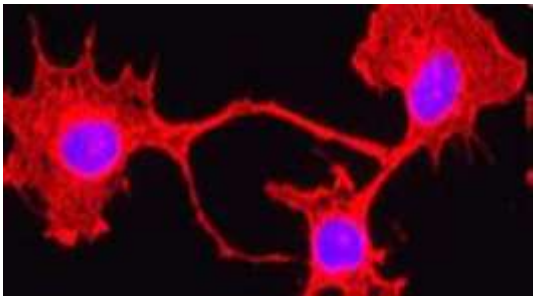
Neurochemical control: represented by the response of smooth muscle cells of the GI to a large number of transmitters that are released by many types of neurons in the ENS.

To have an effective activity by smooth muscle cells of the GI tract, cells are functioning in **syncytium** (the activity is very well synchronized by organized contraction and relaxation at the segmental level which promote an efficient motility of the GI tract). The synchronization in part is provided by the ENS. In addition to these, **the cells of Cajal** play also an important role in the synchronization of this activity.

So by the chemical control we are controlling the tonic contraction and by the electrical control we are controlling what we called the phasic contraction.

How many basic electrical rhythm/ slow waves are generated in smooth muscle cells of the upper part of the GI tract??12 per min, also the phasic contraction following that rhythm=12 contractions per min.
In the lower part of the small intestine the rhythm is 8 per minute (which means the upper part is more active than the lower part with regard to rhythm of slow waves and rhythm of phasic contraction)

Interstitial Cells of Cajal (ICCs):



Explanation of the Dr regarding these pictures:

What are these??

Not neurons as you might think. And not smooth muscle cells. They have lots of spikes connected to each other and to smooth muscle cells by gap junctions.

They all have action potential and plateu in a rhythmic tone. This can be a sudden action potential which is different from conductive tissue of heart

Function: communicating with each other by gap junctions and with smooth muscle cells by also gap junction

They are considered as pacemaker cells of GI tract which means getting errhythemic generation of action potential so depolarizing

Interstitial Cells of Cajal (ICCs):

Interstitial cells are widely spread all over the gastrointestinal tract. These cells have certain characteristics. They have large number of processes. Also, these cells communicate through these processes by gap junction with other ICCs as well as smooth muscle. In addition, these cells can elicit by themselves electrical activity as action potentials. All these have supported the theory of considering these cells as pacemaker cells of the gastrointestinal tract.

Characteristics of ICCs:

Communications:

The ICCs-ICCs and ICCs-smooth muscle cells communication (by a gap junction) provide the basis for the synchronization of the electrical activity of smooth muscle cells as a group and consequently the harmony of contractile responses of smooth muscle cells. This will result in the functional syncytium of gastro-intestinal smooth muscle cells.

Generation of Action Potentials: (pacemaker cells of the GI tract)

ICCs generate slow wave:

ICCs are excitable cells and elicit an electrical activity. These electrical activities have a sudden and periodical appearance of an upstroke from a constant resting potential of about –70mV. The initiation of these activities is believed to be metabolic dependent.

The appearance of the upstroke is believed to cause the slow waves in smooth muscle cells that are in junction with ICCs or to regulate the rhythm of slow waves in smooth muscle cells.

*ICCs also receive inputs from the ENS:

In addition to their communication with smooth muscle cells, ICCs also receive inputs from the ENS. These inputs may give these cells an important role in mediating the activity to smooth muscle cells which promote a regulatory role of smooth muscle cells activity.

Secretory cells:

Mucous secretion and serous secretion

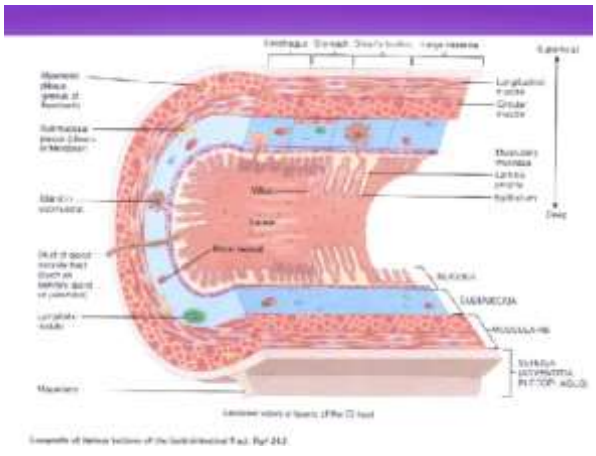
- **Solitary cells**
- **Pits**
- **Compound glands**
- **Secretory organs**

These are represented as solitary cells that line the digestive tube or grouped in functional structures (known as glands). These cells are specialized in synthesis and secretion of organic substances that function as enzymes, hormones, factors or mucus. Some of these structures are secreting only water and electrolytes (this type is known as serous secretions). More details about secretory cells, their functions, and regulation will be given with gastro-intestinal secretion lecture.

Notes regarding the paragraph above:
solitary cells which means individual cells dispersed all over the mucosa and have a secretory functions, in addition you can have a group of cells with secretory function and

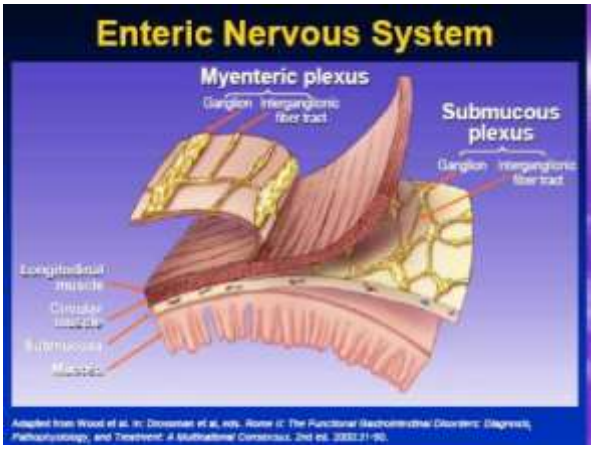
found at level of mucosa only, called simple glands. Finally, there are more complex organization of these secretory structures to form secretory glands at the level of submucosa and these glands are called compound glands or complex glands.

As we said before we have autonomic nervous system and enteric nervous system supplying the GIT.



Beginning from the esophagus and extending along the entire GI tract, there is a neural network known as **Enteric Nervous System**. Neurons in this system are grouped into two main plexuses.

As you see in the picture :



One is located between longitudinal and circular smooth muscle layers known as *myenteric plexus or Auerbach's plexus*. The second plexus lies in submucosa and known as *submucosal or Meissner's plexus*. Neurons within each plexus are connected by nerve fibers that are projecting orally, caudally and circumferentially. Some

And both are interconnected and involved in the control of smooth muscle cells, the secretory cells, blood vessels diameter (increase/decrease blood flow), and a lot of endocrine cells control the activity of these systems.

Neurons from myenteric plexus usually control the activity smooth muscle cells from longitudinal and circular layer, and consequently, gastrointestinal movements. Submucosal plexus usually controls gastrointestinal secretion and local blood flow. Some neurons are considered sensory neurons that transmit signals from gastrointestinal epithelium to both enteric plexuses, prevertebral ganglia of sympathetic, spinal cord, and to brain stems through vagus nerve. These fibers are stimulated by excessive distension of the gut, irritation of the mucosa, or by specific chemical substances in the lumen.

Also there are plenty of neurons at gastrointestinal tract doing all the functions of GI system (organizing all these functions). And these neural structures act as brain of gastrointestinal tract (يعني طلعت صح الجملة اللي منحكيها بالعامي كل عقلك ببطنك)

-**what type of neurons?** Excitatory and Inhibitory …

Characteristics of ENS

- **Enteric Neurons:**Enteric neurons that control gastrointestinal functions contain transmitters that could have inhibitory or excitatory effects on motility, secretion, or vascular blood flow.

–**Excitatory**(increasing contractions, tone)

–**Inhibitory**(reducing tone of muscle).

- **Neurotransmitters** Many types of transmitters have been identified in ENS, such as:

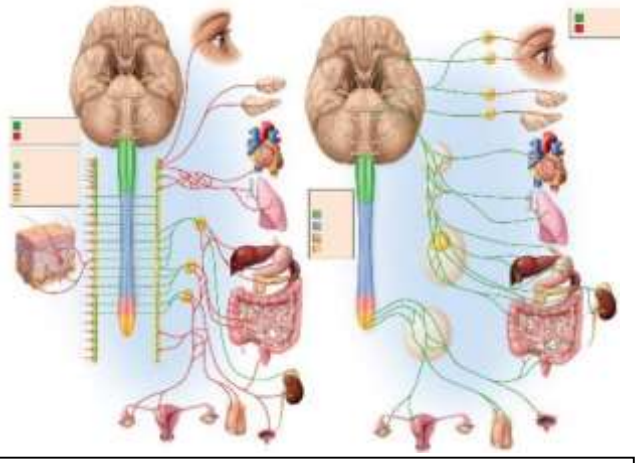
Ach, SP (Substance P), VIP (Vasoactive intestinal peptide), CGRP (Calcitonin gene related peptide), GRP (Gastrin releasing peptide)…etc

In autonomic nervous system we have 2 types of neurotransmitters: acetylcholine and norepinephrine

In contrast to the enteric nervous system more than 50 neurotransmitters which have an effect all over the cells.

Autonomic nervous system(ANS):

Sympathetic → directly over blood vessels and also change activity of neurons of enteric nervous system.



Sympathetic fibers that innervate gastro-intestinal tract originate in the spinal cord (segments T5-L2). These fibers pass through paravertebral ganglia and synapse with the second neuron in celiac, superior mesenteric or inferior mesenteric ganglia.

-in autonomic we have 2 divisions as you know: thoracolumbar for sympathetic and craniosacral for parasympathetic.

Generally, stimulation of the sympathetic system causes a decrease in the activity of the enteric nervous system and GI smooth muscle cells.

Parasympathetic → acts directly over secretory cells and indirectly by changing activity of some neurons of enteric nervous system and modulating the activity of other effector structures.

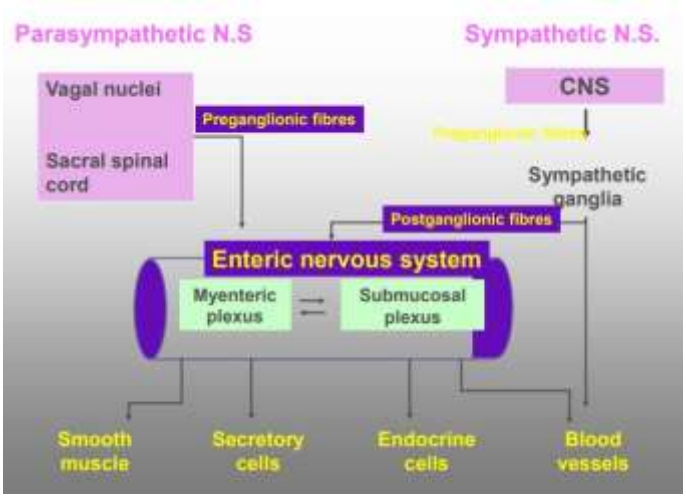
According to the location of neural cell bodies, it is divided into:

- Cranial division: Provide innervations through vagus nerve to esophagus, stomach, pancreas, small intestine and first half of large intestine.

- Sacral division:Provide innervation through pelvic nerves to the distal half of the colon, sigmoidal, rectum and anal region. Fibers in this division have importance in executing defecation reflex.

Generally, stimulation of parasympathetic system causes an increase in the activity of enteric nervous system and consequently, enhances the activity of the gastrointestinal functions. These include motility, secretion and blood flow.

(so all these are harmonized by complex control of gastrointestinal tract changed by nervous system).



Enteric Endocrine System

Endocrine cells and Hormones in the GI. (Largest endocrine system in our body)

Many hormones have been identified at the level of GI tract. Many of these have their function unidentified yet. These hormones include:

- **Gastrin**
- **Chlecystokinin (CCK)**
- **Secretin**
- **GIP (Gastric Inhibitory peptide) or (Glucose dependent Insulinotropic Polypeptide)** Function: release of insulin so deficiency of GIP may cause diabetes mellitis.

Other hormones are also secreted along the Gastrointestinal tract, including: **Glucagon-like peptide-1(GLP-1), Motilin, Ghrelin, Amylin, Enterostatin, Neuropeptide Y (NPY), Pancreatic polypeptide which is closely related to polypeptide YY and NPY. In addition, scattered endocrine cells releasing Somatostatin, Neurotensin, Thyrotropin releasing hormone (TRH), and Adrenocorticotropic hormone (ACTH)** have been described along the GI tract. (most of them we will take them in endocrine)

Functions of Hormones

- **Control of motility**
- **Control of secretion**
- **Control of blood flow**
- **Regulation of food intake**
- **Regulation of metabolic activities in the body**

Intrinsic nervous system: enteric nervous system

Extrinsic nervous system: autonomic nervous system

Hormones released from gastrointestinal gland: involved in controlling the activity of smooth muscle cells, excretory cells, exocrine (directly affecting glands), and endocrine (through the bloodstream).

Blood Flow of the GI

- Related to GI activities:

-Controlled by:

- **Hormones (Secretin, CCK)**
- **ENS (VIP, SP, CGRP)**
- **Vasodilators: Kinins (Kallidin, Bradykinin)**
- **Decreased O2 concentration**
- **ANS (Sympathetic and parasympathetic)**

The blood flow to the gut is closely related to local activities. After a meal, the increase in absorption, secretion, and motor activities is accompanied by an increase in blood flow. This increase continues during the next few hours after a meal and returns over the next 2-4 hours.

Regulation of gastro-intestinal blood flow:

Possible factors that cause an increase in blood flow:

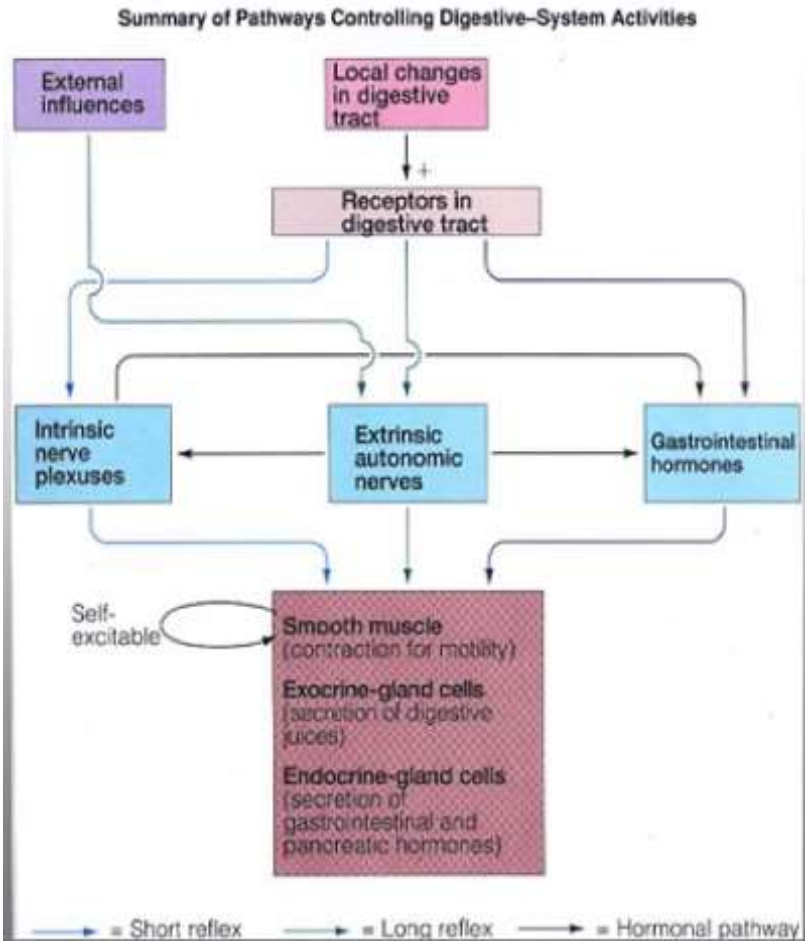
- The release of vasodilator substances after mucosal stimulation caused by meals, Such as CCK, VIP, Gastrin and Secretin. These factors are also important in controlling smooth muscle cells activities.

- Some glands release kinins (kallidin and bradykinin) into the lumen and the gut wall.

- Decreased oxygen concentration increase blood flow possibly by the release of adenosine.

Like muscle activity, vascular flow is also under the control of enteric nervous system. Many transmitters are known to affect the vascular flow of the gastrointestinal tract, such as SP, VIP, CGRP, and others. These transmitters are released by neurons of the ENS.

The autonomic nervous system has also effects on the blood flow to the gut. Sympathetic stimulation causes vasoconstriction, which results in decreased blood flow, while the parasympathetic system causes an increase in blood flow. Although the parasympathetic system has no direct effect on vessels, the effect of this system appears to be indirect by increasing glandular activity, which results in the secretion of vasodilator mediators (such as kinins).



-how are we activating the control system??

- By local changes (like when we eat)
- External influences (like hormones when smelling, or seeing food which may increase GIT activity)
- Through extrinsic nervous system

Past Papers

One of the followings is NOT true with regard to the ICCs:

A. Are generating action potentials

B. Are considered as pace maker cells in the gastrointestinal tract

C. Are under the control of autonomic nervous system

D. Are connected by gap junctions

E. Are responsible for generation of basic electrical rhythm (BER) at smooth muscle cells

Answer: C

Choose the correct statement regarding the interstitial cells of Cajal (ICCs):

A. ICCs are responsible for tonic contraction of GI smooth muscle cells

B. ICCs are responsible for the slow action potentials (slow waves) in smooth muscle

C. ICCs are neurons that communicate with smooth muscle cells through gap junctions

D. ICCs control ENS activity

E. None of the above

Answer: B (about (D) ICCs controled by ENS but not the opposite)

One of the followings regarding control systems of the gastro-intestinal functions is NOT TRUE:

A. Tonic contraction is set by released neurotransmitters.

B. Sympathetic generally is decreasing blood flow by direct effect over vessels.

C. Parasympathetic system generally causes increase in secretions.

D. Salivary secretion is increased by intrinsic reflexes.

E. Basic electrical rhythm (BER) is controlling phasic contraction

Answer: D

إن تَوَقفتَ اليَوم، وَفقدت طاقتك.. ورأيتَ أنَّ الوصولَ إلى نهاية الطَريق مازال بَعيداً، توقف عن النظر إلى الأعلى وانظر قَليلاً إلى الأسفل، إلى ما قَطعته.. وَ إلى من ينظر إليك..
تَذكر كم من الأشخاص في الأسفل.. يَحلمون في أن يصلوا إلى ما أنتَ عَليه اليوم !!

يَخلقُ الله القِمة.. لكيلا يتوقف الشغف بداخلنا..
ويخلق الأسفل.. لكي نعرف قيمة مانمتلكهُ

♥♥♥