PHARMACOLOGY

lecture :

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Acid-related disorders

Lecture 1

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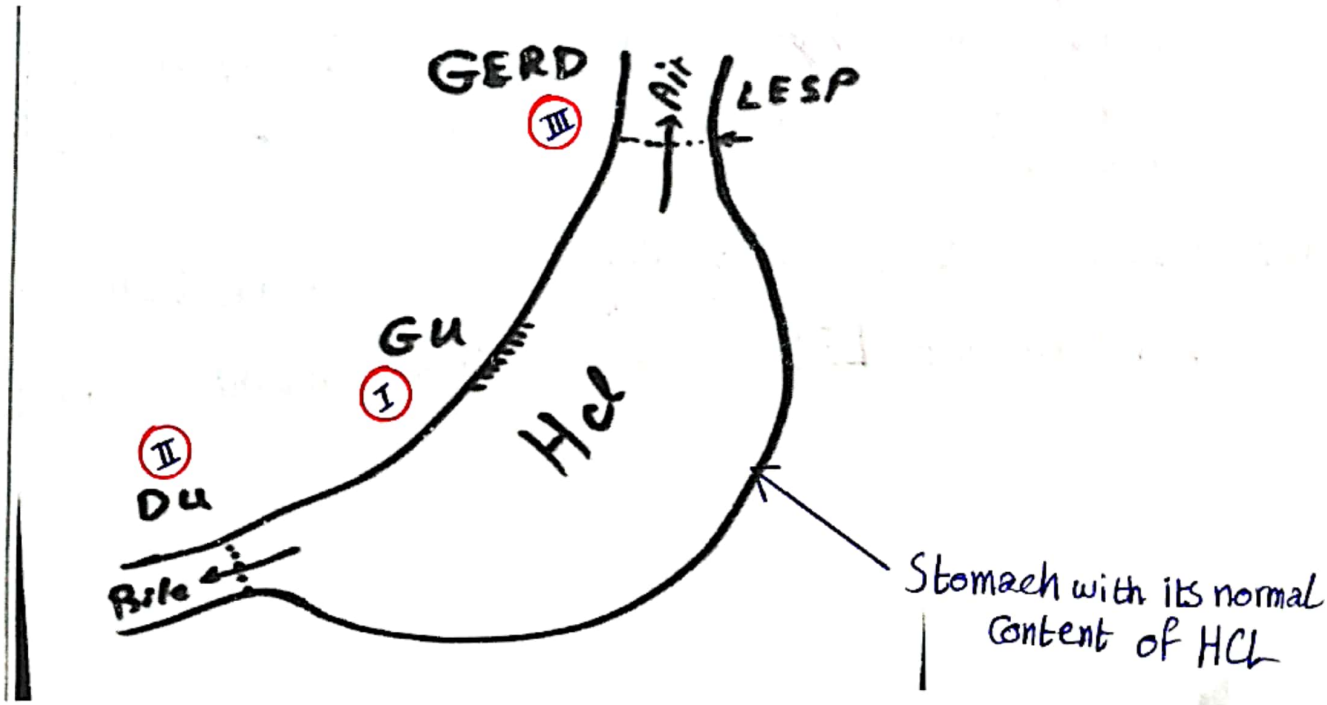


- Acid-related disorders are one of the most important disorders clinically.
- these disorders aren't always caused by excess HCL in the gut.
  e.g. suppression of HCL levels may result in improvement of such diseases. So, HCL in these disorders are related to the etiology/therapy ...etc.

(I) Normal stomach has its own Preventive/Defensive mechanisms against HCL → فلذلك في الطبيعي زيادة الـ HCL فيها دافع يسبب لها مشاكل

- وجود الـ HCL في مكان غير مكانه الاعتيادي - مثلاً في العرئ esophagus - Stomach will result in several clinical disorders ← Duodenum أو في الاثني عشر

- Gastric Ulcer, however, is the result of breakage of Stomach's defence against the acid, that is, breakage of epithelial continuity

لذلك، أسباب هذه الأمراض ليست دائمًا ناتجة عن زيادة تركيز/فعل الـ HCL، فقد تكون عندنا مثلاً في الـ (GU) السبب هو defence mechanisms loss in the gastric mucosa

- mild gastric erosion
- complete epithelial Loss (ULCER) → Acute / Chronic/Prolonged ← (وهنا نعتبر من أنواع الـ Peptic Ulcer)

(II) Duodenal Ulcer (DU): Due to duodenal lack of defence against acids, excessive HCL amounts will cause DU

- فلذلك هو نتيجة excess HCL عكس الـ Loss of defence mechanism ← التي كان سببه (GU)

- What causes this excess HCl? - it may result from [H.Pylori] bacterial infect
- Bile regurgitation into the stomach may cause (GU).
- Both, gastric and duodenal ulcers, in chronic presence are called Peptic Ulcer. (they are Chronic diseases)

III Air is normally present in esophagus. So, excess HCL coming from stomach towards esophagus will result in which is known clincally as GERD (Gastro-esophageal Reflux Diseases). GERD results usually from [Reflux Esophagitis] (يعني الـ reflux esophagitis - حدث كنتيجة ثانوية للارتجاع لـ HCL من المعدة retrograde flux of gastric HCL into esophagus)

- LESP : [Lower esophageal sphincter pressure] ↳ a junction between esophagus and Stomach. It is a Competent / Intact sphincter that prevents backward regurgitation of gastric HCL from stomach into esophagus. Weakness of this sphincter or LESP will cause → Regurgitation of HCL → causing Reflux Esophagitis → GERD

(LEB)

(الجزء)

→ Symptoms of those diseases occur much more than (35%), but here we are talking about real classified diseases.

Acid - related GIT diseases

They are very common clinically occurring in 35 % of adult people. (1/3)

A) Peptic ulcer (PU):

Life time prevalence is 15% in men &10% in women.

1. Duodenal ulcer (DU):

The most common type. ↑Hcl caused by chronic H pylori infection.

2. Gastric ulcer (GU):

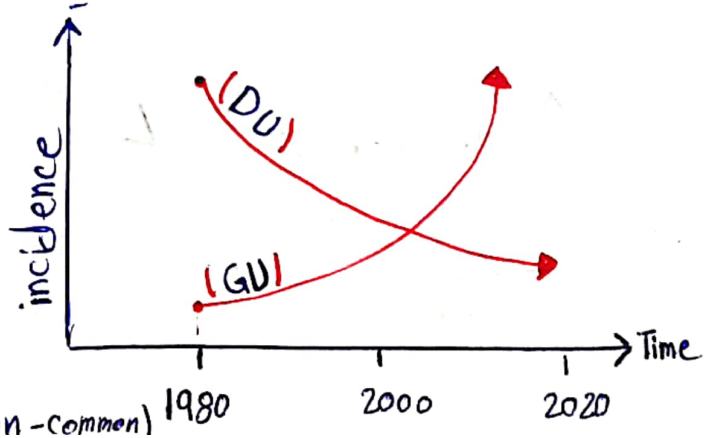
There is normal or low Hcl. Usually caused by chronic NSAIDs therapy reducing PG → diminished defensive mechanisms.

- Also **acute gastritis** and **gastric erosion**. e.g. NSAIDs gastritis.

In the past 40 years the incidence of DU has been declining due to widespread use of antimicrobials, while that of GU is increasing due to the extensive use of NSAIDs.

- Especially broad spectrum antibiotics (they unintentionally treat DU)
- NSAIDs are highly used as they're considered to be pain relievers. (causing ↑ incidence of GU)

لعبنا نحلل الحكي ↑ بدسم بياني :-



3. Stress ulcer:

By severe medical or surgical stress. (non-common)

مصطلح الـ Life time Prevalence هو (إذا الإنسان وصل للعمر الخاص بهذا المرض فكم هي احتمالية إصابته به ؟)

- Life-time-Prevalence represents the actual Prevalence of the disease.

- لسّا ما حكينا شي عن الـ MSS-Pharma انه الـ PGE_1 / الها دور بحماية الـ Mucosal PGI_2 ← gastric Cytoprotection) ← HCL المعدة من تأثير حمض الـ

وانه أحد أهم الـ adverse effects من تناول Chronic NSAIDs هو الـ GIT bleeding /ulcer

- هذه الأدوية على الخصوص بتعمل النوع الأول من الـ ulcer وهو (I) GU

- NSAIDs are very commonly prescribed and used (about 30% of Prescription)
- Chronic peptic ulcer usually begins with acute mild gastritis and results in gastric erosion: (NOT COMPLETE LOSS OF EPITHELIAL LINING)
- Acute gastritis and gastric erosion are usually caused by Short-term NSAIDs, however, Chronic NSAIDs administration can cause Chronic Peptic ulcer...

to be Pain relievers. (causing ↑ incidence of GU)

3. Stress ulcer:

By severe medical or surgical stress. → (non-common)

4. Zollinger - Ellison syndrome: Multiple extensive ulcers. (tumors that release much more gastrin → multiple peptic ulcer)

B) Gastroesophageal reflux disease (GERD):

↓LESP (lower esophageal sphincter pressure)

LESP is usually normal but reflux occurs during transient relaxation of LES by gastric distension.

Life time prevalence is 20%. In adults & children. Accordingly, it ① (is more common than PU.) + (occuring inearly age) ②

In addition, reflux symptoms occur in 50% of people. → نتكلم هنا عن أعراض وليس مرضًا ثابتًا

Acid - related GIT diseases are due to imbalance between defensive and aggressive mechanisms.

(Prostaglandins) (HCL)

- Acute gastritis and gastric erosion are usually caused by Short-term NSAIDs, however, Chronic NSAIDs administration can cause Chronic Peptic ulcer...

3. Stress ulcer :-
يعني يكون نتيجة قلق / خوف المريض من عملية / اجراء جراحي يخضع له فيحصل معه ulcer
(due to ↑ acidity of stomach) ← بالعادة تكون غير مجبية في أمثال هؤلاء المرضى ← Oral medications-

(B) أغلب حالات الـ GERD يكون بسبب الأدوية و التي بعدها بتعمل gastric dist-ension ←
↳ relaxation of LES ⟶ regurgitation of HCl into esophagus → GERD

LESP will cause ⟶ Regurgitation of HCL ⟶ causing
(الارجاع)

A) Defensive mechanisms

1) Mucus.
2) Na HCO3.
3) Integrity of gastric mucosa: tight junctions between cells prevent back diffusion of Hcl.
4) PG: decreases with age, with increased incidence of PU. (Protective factor against PU) PG: (تُعتبر أهم)

B) Aggressive mechanisms

A) Endogenous: 1. Hcl. 2. Pepsin. (responsible for digestion of proteins) 3. Bile.

B) Exogenous:

1) Smoking: by ↑ Hcl, VC → ischemia & ↓ NaHCO3 by pancreas. (Ischemia will cause ↓ mucosal vitility)
2) Stress. (PARASYMPATHETIC)
3) **Drug – induced PU: drugs increasing Hcl.**

- Aggressive mechanisms must be ↓ in patient with PU
- In life-style therapy (1–3) must be avoided in patients with PU ...

- مريض ال PU المُصر على التدخين ← صارع تخفيف الأعراض أبدًا لأنه بالـ(٣) نقاط فوق بيقل ال defensive و بيزود ال aggresive

Defensive Mechanisms :-

1. Mucus + 2. $NaHCO_3$ ⟶ Act as a buffer for HCL to Prevent (DU)

↓ by intestinal Pancreatic secretion

← هندل الاثنين مسؤولين عن حماية الـ Duodenum من الـ HCl النازل عليه من الـ Stomach ... يعني الـ (DU) بشكل رئيسي بتكون أسبابه الخلل / النقصان في افراز الـ Mucus و $NaHCO_3$ ...

كتاخيص :-

- الـ Duodenum ← وجود الـ HCl ← سبب الـ ulcer

3. Bile :

- الـ Stomach ← وجود الـ Bile secretion تسبب ulcer

[PU ← Bile Regurgitation into the Stomach] إذا حصل

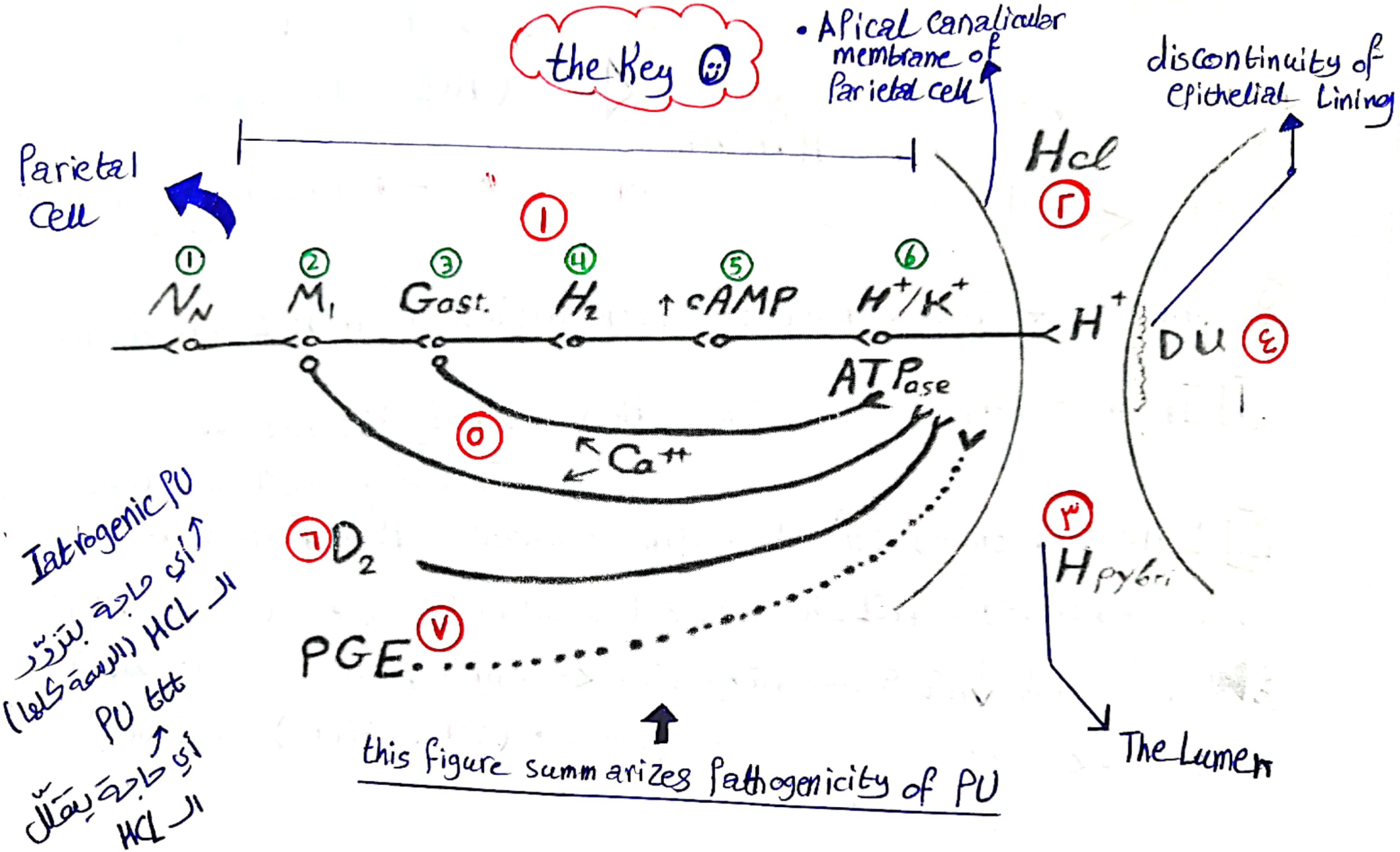
- سبق وتبيّن أنّ الناس عند الـ STRESS ، تزداد فيهم كمية من الأتنين :

OR

↑ Sympathetic activity
- HT
- arrhythmia
- tremors
- insomnia

PU ← وهذا هو سبب الـ
(All digestive system disorders are Nocturnal due to ↑ Para-sym. during night)

↑ Para Sympathetic activity
- ↑ HCL
- Colic (تشنج)
- Vomiting
- irritable bowel syndrome



• PU IS A TETRAD :-

① In Parieta cell → HCL formation
- Any drug ↑HCL → drug-induced PU
- " " ↓HCL → Acid suppressant (لوعكسنا كل الموجود بالبسعة)

- In Lumen, there are two lines for ttt
② buffering HCL → Antiacids
③ Anti-H.Pylori

④ For ttt of DU, we must provide protection to the duodenal mucosa
→ (نعالج الـ discontinuity الكاملة بالجدار) → through mucosal protectives / Cytoprotectives of PU

1- Acid suppressant
2- Anti Acid
3- Anti-H.Pylori
4- Cytoprotectives

من الكلام السابق يوجد أربعة أنواع أدوية لل PU

* How HCL is formed? BY THE FOLLOWING CASCADE

(1) N_N (1): nicotinic ganglion → WHEN SIIMULATED → ↑release of Ach → (Parasympathetic)

→ Ach will stimulate the Muscarinic - M1 receptors (2) → stimulated M1 receptor will release Gastrin → gastrin will stimulate (3) gastrin receptors → Stimulated gastrin receptors will start to release histamine (H_2) → histamine will stimulate H_2 (4) receptors → Stimulated H_2 receptors will cause stimulation of (6) Adenyl Cyclase - cAMP System → (5) ↑cAMP → Stimulation of H^+/K^+ ATPase → responsible for formation of (H^+) → Resulting in HCL formation

• the inhibition will be MORE Potents ← كلما مشينا بالدرجة من اليسار والى اليمين
(stronger suppressors)

ما معنى هذا الكلام ؟

العمق لو كان عندنا 3 أدوية لتقليل إفراز الـ HCL لثلاثة receptors مختلفة: فإنك أقوى دافع فيهم رح يكون الأقرب لليمين (المراحل الأخيرة من تكوين الـ HCL)

N_N ⊖ ← Gast. ⊖ ← H^+/K^+ ATPase ⊖ ← ⊖ inhibition of Corresponding receptor

الأضعف < بينهما < الأقوى

⊙ M_1 (Ach) + Gastrin have two Pathways involved in HCL formation:

[1] Indirect: throug stimulation of H_2 receptors by Histamine ...
(هنا نفس اللي حكينا عنه فوق)

[2] Direct: throug Ca^{++} they can stimulate H^+/K^+ ATPase ...

لذلك، Ca^{++} يعتبر عامل مساعد لزيادة تكوين الـ HCL بالرغم من وجوده في الحليب/وأدوية Antiacids كثيرة ← فقط يعتبر مفيد إذا ↓HCL واستخدم بالكميات البسيطة (for buffer). لو شرب كمية كبيرة من الحليب ← ↑HCL ← وتزداد الحالة سوءًا

⑥ Dopamine also can increase HCL secretion by D_2 receptors, espe-cially in stress.

- All these mentioned steps eventually will stimulate H^+/K^+ ATPase ↑HCL Secretion والتي تُعدّ المنشأ الأساسي لزيادة

لذلك يُعتبر الـ PU مرض مهم ومنتشر ← لأنّ جميع هذه الـ receptors تساهم بشكل أو بآخر في زيادة تركيز الـ HCL

⑦ PGE → العنصر الذي يقف أمام كل الـ receptors المذكورة ويخالف وظيفتها ← ↓HCL

* كلما كان أقرب لجوه ال apical canalicular membrane من ال basolateral membrane كان أقوى ← الرجاء

N_N < Gastrin < H^+/K^+ ATPase ← قبل ما حكينا قبل ← ↓HCl ← بخفض ال

Mechanism of Hcl secretion

H2 receptor stimulation →↑cAMP→ activation of protein kinase → stimulation of H+/K+ ATPase (proton pump) → H+ formation.

* H+ pump occurs in apical canalicular membrane of parietal cell.

All cause ↑HCl

Activation of muscarinic (M1) & gastrin receptors increases permeability to Ca ++ leading to activation of proton pump. Their action is also mediated via H2 receptors. All these receptors are present in * basolateral membrane of parietal cell.

Central dopamine receptors mediate increase Hcl secretion. (D_2)

Prostaglandins (PGE), in contrast to other receptors, ↓Hcl secretion.

the only HCL-decreasing agents → ↓HCL

• يعني المريض لازم يتجنبهم أثناء العلاج أو يأخذ معهم الـ Anti-Ulcer-Drugs

→ PU Caused by or result from medical ttt/drugs e.g. Drug-induced ulcer

Drugs increasing Hcl secretion (Iatrogenic PU)

الأدوية دي كلها تأليف عقاسبت

1. NSAIDs : by ↓PG. → by inhibiting COX (NSS)
2. Corticosteroids : by ↓PG. → by inhibiting Phospholipase A_2

(the only Protective)

3. Nicotine (smoker's ulcer): by stimulation of nicotinic receptors.
4. Cholinomimetics : by muscarinic M3 receptor stimulation. (M1+M3 both ↑ HCL secretion)
5. Alpha methyl dopa: by parasympathetic predominance → by decreasing Catecholamines → ↓ sympathetic activity → Parasym. Predominance
6. Gastrin: by stimulation of gastrin receptors.
7. Histamine: by stimulation of H2 receptors.
8. Antacids : may increase Hcl (rebound).
9. Calcium: increases gastrin. (e.g. Milk)
10. Caffeine: by increase cAMP. (tea, coffee) (by inhibiting phosphodiesterase)
11. Dopamine agonists as (L-dopa & bromocriptine) (used in ttt of Parkinsonism)
12. Alcohol. (by direct irritation to git mucosa)

(8) especially by big doses → Negative feed back mechanism → Rebound
[الـ HCL تقل في البداية ثمّ تزيد بقوّة لاحقًا]

Membrane Phospholipids → (Phospho Lipase A_2, inhibited by (2)) → Arachidonic Acid → (COX, inhibited by (1)) → Prostaglandins

- Blood group O → they've high immune function ☺ →
لذلك أكثر الناس عرضة لـ infections هم groupA وبعدهم groupO

PEPTIC ULCER (عكس كل العمليات والوسم السابقة)

Aetiology

1 - Age: DU : 30 - 55 year. Men > women. [Mainly caused by H-pylori infection]
GU : 55 - 70 years (age of use of NSAIDs & ↓PGs). Women > men.

2 - Genetic predisposition.

3 - Blood group O. (high risk for → PU, → Bleeding tendency) ☹

4 - Type A persons (people with stressful character).

5 - Absence of breakfast.

6 - Infrequent meals.

(Obese) DU: fasting or nocturnal, relieved by food. → because of para sym. Activity (↑HCL)

(Thin) GU: increased by food. → because of loss of defence-mech. (↓ الأكل يسبب مشاكل)

7 - Sleep disturbances:
↓sleep duration → ↓defense mechanism & ↑Hcl.

8 - Aggressive factors & drugs: mentioned before, very important
(الأدوية والوسمة السابقة)

[loss of defensive mechanisms] → People with age 55-70 years are exposed to many many inflammatory/immunity diseases such as osteoarthritis → thus they administer NSAIDs frequently → high risk for GU development

- Breakfast is very important in buffering HCL.
- العيّان لازم يفطر عشان لا يحرق الـ PU لأنه صعب يعادل الحموضة النائمة
- Infrequent Meals: 2 meals daily is wrong...
- لازم تكون عندهم في اليوم الواحد ٥ - ٦ وجبات متفرقة متوزعة على

→ Continuous buffe of HCL

[متأثرة بالفروق بين إنسان وآخر] - يعني فيه ناس بتكون واقعة عنهم جدًا وناس لأ

Patients individual tolerance:

a. Caffeine in coffee, tea, colas, chocolates, decaffenated coffee &tea.
b. Spicy food. (المشروبات السودا)
c. Citrus fruits. (Orange, Lemon)

A. The cause of DU is infection by H pylori, in almost all patients. H pylori infection is acquired in childhood with person to person transmission. There is high luminal Hcl. (↑HCl by aggressive mechanisms)

B. The main cause of GU is NSAIDs: 25% of patients given NSAIDs have symptoms and 50% have endoscopic evidence of gastritis. 15% present with complications. → مضاعفات → e.g. perforating ulcer / bleeding ulcer

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- The ulcer is caused by defensive mechanism due to ↓PG. There is normal or low luminal Hcl, but this can cause ulcer in the gastric mucosa with diminished defensive mechanism. Accordingly, acid - suppressives are used, but are less effective than in DU. Also recurrence rates are higher.

- Acid suppressives are much more effective in ttt of (DU) than (GU)
← أهم عامل فيه هو زيادة الـ HCl لذلك هذه الأدوية فعّالة جدًا

- لكن في الـ (GU) السبب الأساسي للقرحة هو فقدان الـ defence لذلك هذه الأدوية رح تساعد بشكل أقل في تخفيف الـ ulcer ...

- عن طريق الضغط على منطقة Epigastric ← لو موجود الألم
فقط في منطقة وحدة ← PU (الحالة أسوأ)

- بيخالو كان الألم في أكثر من منطقة ← على الأغلب يكون irritable bowel syndrom (أخف خطرًا من الـ PU)

Diagnosis

1. Epigastric pain and point tenderness, rhythmicity (relation to meals, nocturnal) & periodicity (symptoms for weeks or months).
   - DU: fasting or nocturnal, relieved by food.
   - GU: increased by food.

   ← تكون مثلًا أكثر في الخريف والربيع لأنه فيه كتير antigens + immune responses

2. For H pylori: urea breath test or fecal antigen test. Stop antimicrobials 4 weeks, PPIs 2 weeks and H2 antagonists 24 hours before. ⇒ to avoid false-Negative result

   لازم المريض يوقف عن هاي الأدوية حسب المدد الزمنية المحددة بسبب نوع بعمل الفحص

3. Endoscopy with biopsy (for H pylori) and (to exclude malignancy.) (especially in chronic cases)

* Cancer in GU is > DU.

* Cancer in GU is > DU.

A+B Are related to Life-style ↔ related to drug therapy.

Treatment of peptic ulcer

كل الأمور المسؤولة عن زيادة الـ HCl والضغوطات السابقة يجب تجنّبها!

A) Avoid aggressive factors and aetiology: mention them.

B) Diet:

Decrease manifestations ① and avoid flare ② by:

1. Small frequent meals & milk.
2. High fibers (mainly soluble) in fresh organic fruits & vegetables, legumes, Mechanism: 1) antioxidant, 2) antiinflammatory, 3) cytoprotective and 4) antimicrobial. ➡ in Chronic states, very beneficial ...
3. Bland diet only in severe acute cases. (Bland= food that are low in fibers)
4. ↑flavonoids in colored fresh organic fruits & vegetables, ...
5. ↑vitamin A (good for mucosa) → - Vitamins
   - Minerals
   - Colored fruits (Phytochemical)
   - سلفة من فيتامينات بألوان مختلفة ← مهمة جدًا في healing of PU
6. Probiotics: anti-H pylori.
   ↳ More healthy bacteria than harmful bacteria → Very effective in tt of [redacted] intestinal dysbiosis.

- Small frequent meals ⟶ for continuous HCL buffer
- " " milk ([redacted] remeber that drinking large amount of milk will ↑ Ca^{++} and result in ↑HCL
  highly
  بتحفز البداية وبعمل بتعب لفترة ...
- High fibers must be soluble ⟶ If were insoluble ⟶ will cause more irritation ⟶ worsening of PU

C. Drug therapy: 4 Major Lines [TETRAD]

a. Acid - suppressive therapy

1. Proton pump inhibitors (PPIs).
2. H2 antagonists.
3. Anticholinergic drugs.
4. Sulpride.

→ discussed later in lecture 2

b. Mucosal protectives (cytoprotectives) (in duodenum)

1. Sucralfate.
2. PG analogues (e.g. misoprostol).

c. H pylori therapy (in Lumen)

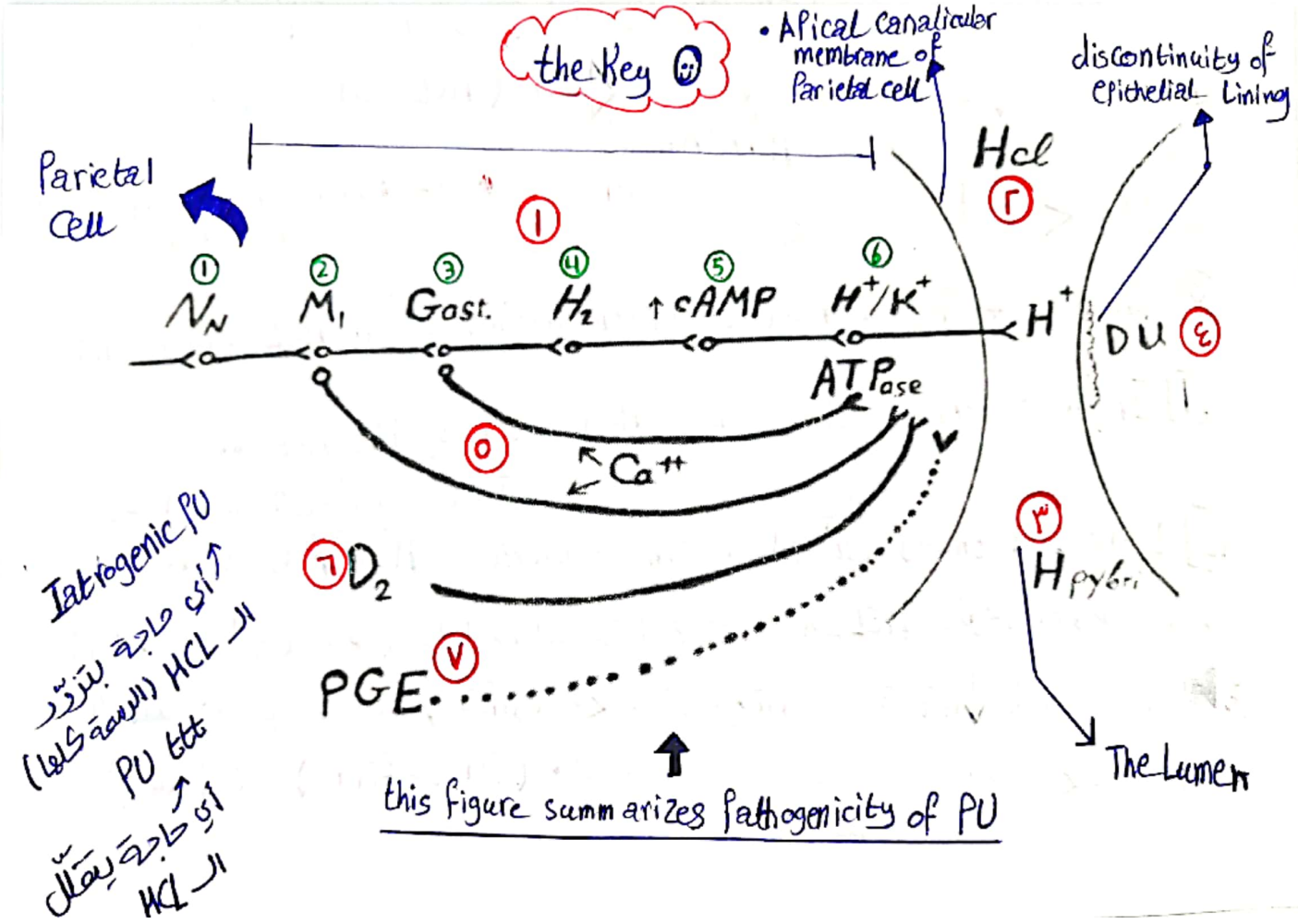
d. Antacids

Curative therapy : acid – suppressives & cytoprotectives. A+B → Alone there is a chance for recurrence

Radical therapy : H pylori therapy. C → Killing Causative MO

Symptomatic therapy: antacids. D → (وظيفتها إطفاء النار فقط وكأنها)

- Commonly, in ttt of PU, [Combination therapy] is always applied



this figure summarizes pathogenicity of PU