تفريغ بيوفارما

اسم الموضوع: Drug Absorption

Slides [27-46]

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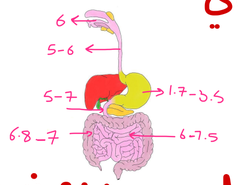
لجان الدُّفعات

إنتقال الدواء من مكان إعطاءه لحد الدم

Drug absorption

I. Characteristics of GI physiology and Drug Absorption



The environment within the lumen:

① *Gastrointestinal pH*

- As we observed from the previous tables, the pH of fluids varies along the length of the GIT.
- The gastrointestinal pH may influence the absorption of drugs in a variety of ways:

A- It may affect the chemical stability of the drug in the lumen e.g. penicillin G, erythromycin

B- affect the drug dissolution or absorption e.g. weak electrolyte drug

② *Luminal enzymes*

- The primary enzyme found in gastric juice is pepsin. Lipases, amylases and proteases are secreted from the pancreas into the small intestine.
- Pepsins and proteases are responsible for the digestion of protein and peptide drugs in the lumen.

I. Characteristics of GI physiology and Drug Absorption

إذا أعطيت المريض Emulsion
(oil / Fat) Lipid بكسر ال

- The lipases may affect the release of drugs from fat / oil – containing dosage forms.

في عنا بكتيريا موجودة بالقولون بتفرز enzymes بتقدر تستفيد من الانزيمات اللي بتفرزها هاي normal flora البكتيريا النافعة لـ large intestine

- Bacteria which are localized within the colonic region of the GIT secrete enzymes which are capable of a range of reactions. → قادرة على مجموعة ردود فعل

هو عبارة عن مركب فيه مشكلة فحنا عليه مواد تحسن هاي المشكلة

- e.g. Sulphasalazine which is a prodrug used to target the colon.

هو ProDrug بال inactive form خليت البكتيريا النافعة الانزيمات اللي بتفرز تفكك الدوا وتحوله لـ active form

Sulphasalazine ← inactive form

5-amino salicylic acid + anti biotic

Bacterial enzymes →

active drug

(5-aminosalicylic acid)

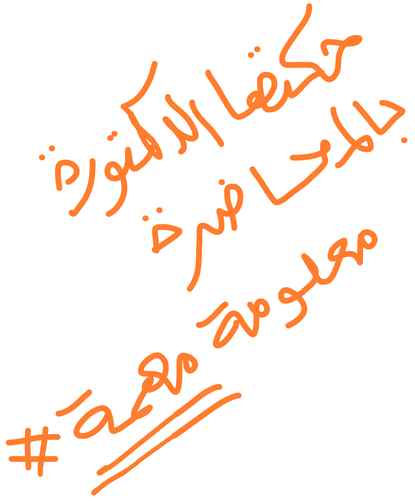
مرض مزمن ←

treat inflammatory bowel disease

+ Anti Biotic

واحد منهم بتقدر تستهدف الـ colon وبمنع التهيج تبعه

تخيل أنه حد شايل جزء من المعدة قص معدته بغض
النظر عشان يضعف او لمرض معين رح يوصل الدوا لل
small intestine اسرع وال bioavailability
احسن ..لكن هاد الشي مش لكل الادوية فيه عندي ادوية
بتحب تضل بالمعدة لوقت اطول عشان يصيرلها
dissolution مثل ال basic drug فا ال
bioavailability ⬇️ اقل وال absorpant ⬇️
ونتخيل مثلا واحد عنده heart failure رح يكون ال
blood flow ⬇️ بالتالي ال absorpant ⬇️



I. Characteristics of GI physiology and Drug Absorption

Disease state and physiological disorders

- Local diseases can cause alterations in gastric pH that can affect the stability , dissolution and absorption of the drug.

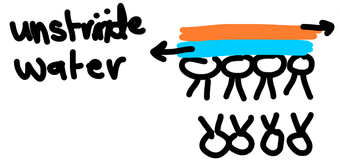
- Partial or total gastrectomy results in drugs reaching the duodenum more rapidly than in normal individuals. This may result in an increased overall rate of absorption of drugs that are absorbed in the small intestine.

- However, drugs that require a period of time in the stomach to facilitate their dissolution may show reduced bioavailability in such patients.

I. Characteristics of GI physiology and Drug Absorption

The unstirred water layer

- It is a more or less stagnant layer of water and mucous adjacent to the intestinal wall.



- This layer can provide a diffusion barrier to drugs.

- Some drugs (antibiotics e.g. tetracycline) are capable of complexing with mucous, thereby reducing their availability for absorption.

II Gastric emptying and motility

حركة الدواء من Stomach الى small intestine

يُطلق عادةً على الوقت الذي تستغرقه الجرعة لعبور المعدة:

- The time a dosage form takes to traverse the stomach is usually termed: the gastric residence time, gastric emptying time or gastric emptying rate.

تفريغ المعدة — كم يفضل بالStomach

هسا هي بتفرق بس المصطلح بشكل عام نفس الشي يعني هي بتفرق بالعلاقة انو كل ما زادت سرعة الemptying بكون اخد وقت اقل يعني انتي لما بتحكي عن emptying rate برضو بتحكي عن emptying time

الدكتورة لقرام بتحكي أنعم بخلفوا كيف؟!

↑Rate ↓time ↑blood conc

- Generally drugs are better absorbed in the small intestine (because of the larger surface area) than in the stomach, therefore quicker stomach emptying will increase drug absorption.

أحسن امتصاص للدواء وين؟! Small intestine

↑emptying rate ↑absorpant

- For example, a good correlation has been found between stomach emptying time and peak plasma concentration for acetaminophen. The quicker the stomach emptying (shorter stomach emptying time) the higher the plasma concentration.

علاقة — بنادول [Paracetamole] نفسه

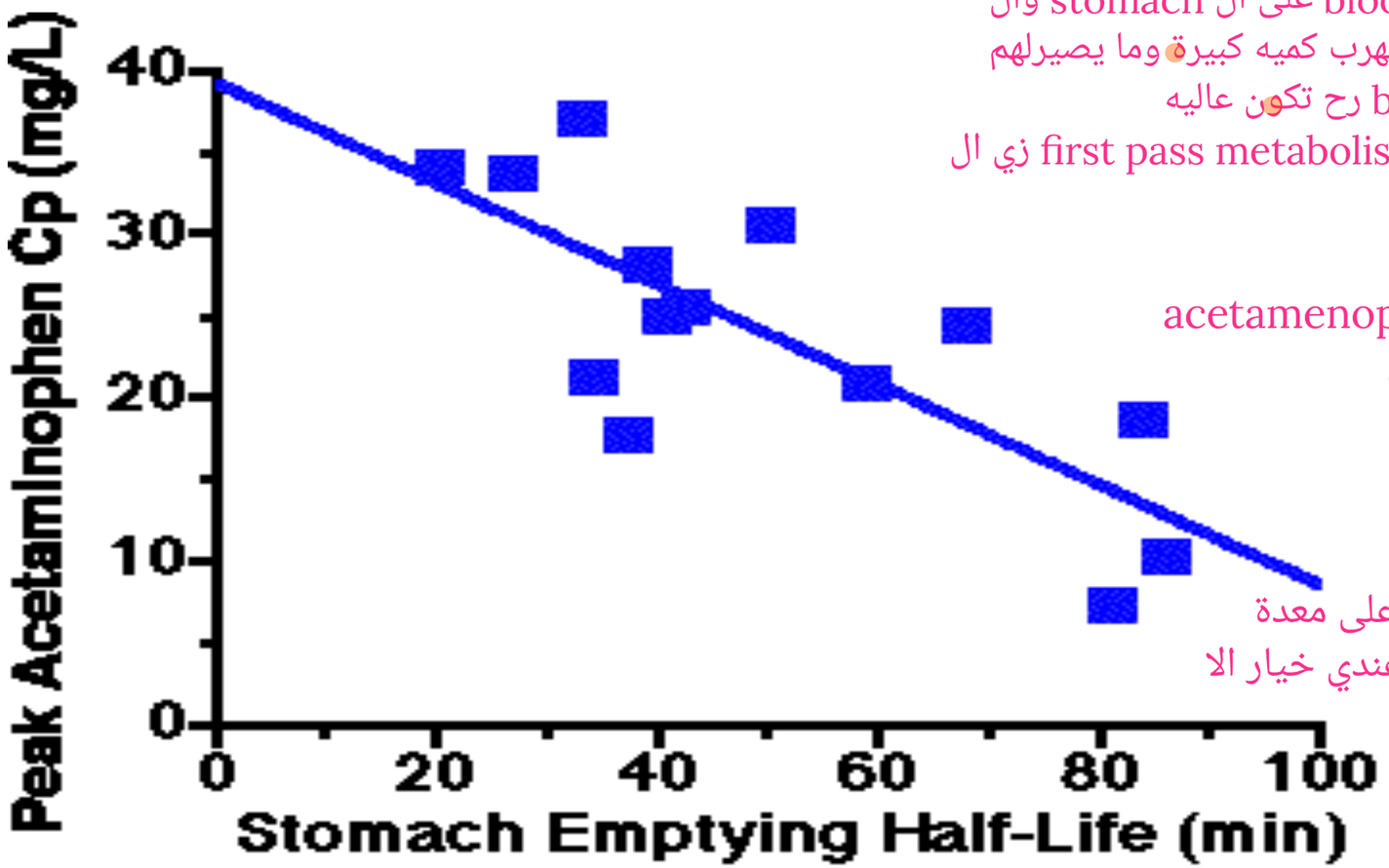
↓emp ↑cp

يحي اخد الPanadole * ← صح — على معدة فاضية بعطيني effect أحسن

- Also slower stomach emptying can cause increased degradation of drugs in the stomach's lower pH; e.g. L-dopa.

بس فيه أدوية الحكس اذا اخدته على معدة فاضية بتكسر لانه بكون low pH تقريبًا 1.7 لانه الأكل بزيد الpH تاخن المعدة

II Gastric emptying and motility



لما الواحد يكون ماكل بزيد ال blood flow على ال stomach وال liver ف الدوا بروح عال liver ورح يهرب كميه كبيرة وما يصيرلهم metabolism ف ال bioavailability رح تكون عاليه
طبعا هاد للادويه الي بتعتمد على ال first pass metabolism زي ال propranolol

بالنسبة لل paracetamol اوacetamenophene
اذا اكلته عمعده فاضية بكون اسرع ال bioavailability عاليه

والنسبة لل NAaSID هي احسن تناخد على معدة فاضيه لكن ببتعمل قرحه مشان هيك ماعندي خيار الا اخده عمعدة مليانه

Dependence of peak acetaminophen plasma concentration as a function of stomach emptying half-life

II Gastric emptying and motility

↑Rate
↓time
↑blood conc

Factors Affecting Gastric Emptying

	Rate
Volume of Ingested Material	As volume increases initially an increase then a decrease. Bulky material tends to empty more slowly than liquids
Type of Meal	
Fatty food	Decrease
Carbohydrate	Decrease
Temperature of Food	Increase in temperature, increase in empyting rate
Body Position	Lying on the left side decreases emptying rate. Standing versus lying (delayed)
Drugs	
Anticholinergics (e.g. atropine)	Decrease
Narcotic (e.g. morphine)	Decrease
Analgesic (e.g. aspirin)	Decrease

بالبداية بزيد الRate بعدين بقل

يعني انا شو اكلت رح تطول أو لا
وجبة (عادي، سوبر، دبل، تربل)

نوع الأكل

الأكل السخن بزيد

مشان هيك الرسول نهى عن الأكل السخن والنفخ على الأكل صلى الله عليه وسلم

إذا قاعدة أو قايم أو واقفة المفروض

↓Parasympethitic
↓GER

II Gastric emptying and motility

Factors Affecting Gastric Emptying

Viscosity (Fat)	Rate of emptying is greater for less viscous solutions
Emotional states	- Stressful emotional states increase stomach contraction and emptying rate - Depression reduces stomach contraction and emptying
Disease states	-Rate of emptying is reduced in: Some diabetic patients, hypothyrodism -Rate of emptying is increased in: hyperthyrodism
Excercise	Reduce emptying rate

III Effect of Food

- The presence of food in the GIT can influence the rate and extent of absorption, either directly or indirectly via a range of mechanisms.

A- Complexation of drugs with components in the diet ex: Milk + iron

e.g. Tetracycline forms non-absorable complexes with calcium and iron, and thus it is advised that patients do not take products containing calcium or iron, such as milk, iron preparations or indigestion remedies, at the same time of day as the tetracycline.

B- Alteration of pH

Food tends to increase stomach pH by acting as a buffer. This liable to decrease the rate of dissolution and absorption of a weakly basic drug and increase that of a weakly acidic one.

absorpant
weakly base
weakly acid
pH

III Effect of Food

الطعام بعادل حموضه المعدة بقللها الادوية القاعدية بتقلل ال dissolution مشان هيك بعض الادوية القاعديه يفضل اني اكلها بعد الاكل بساعتين او قبل الاكل

C- Alteration of gastric emptying

Fat بعد اكل ↓ gastric emptying delay onset time

Fats and some drugs tend to reduce gastric emptying and thus delay the onset of action of certain drugs.

D- Stimulation of gastrointestinal secretions

بعزز نتيجة الاكل

- Gastrointestinal secretions (e.g. pepsin) produced in response to food may result in the degradation of drugs that are susceptible to enzymatic metabolism, and hence a reduction in their bioavailability.

تعرض ل

- Fats stimulate the secretion of bile. Bile salts are surface active agents which increase the dissolution of poorly soluble drugs (griseofulvin).

↑surface area ↑solubility

antifungal

↑Bile Salt
↑emelsefing agent
↑Solubility
↑dessolving rate
↑Bioavalibity

Bile salts can form insoluble and non-absorbable complexes with some drugs, such as neomycin and kanamycin.

بعطيهم قبل الاكل عشان مايمسك فيه ال bile بخرب الامتصاص عليهم
همه اصلا بنعطوا local effect لناس الي عندهم ammonia &urea in the blood و renal falier عشان مانرفع الامونيا بالدم
ومايمتصه الجسم بنعطيه هاد الدوا وهو اصلا عليه charge

III Effect of Food

المنافسة بين مكونات الغذاء والأدوية على آليات الامتصاص المتخصصة

E-Competition between food components and drugs for specialized absorption mechanisms

active transport زي الادوية اللي بتليها تدخل عن طريق

There is a possibility of competitive inhibition of drug absorption in case of drugs that have a chemical structure similar to nutrients required by the body for which specialized absorption mechanisms exist.

5-fluvourcil مثل L-Dopa

F- Increased viscosity of gastrointestinal contents

The presence of food in the GIT provides a viscous environment which may result in:

- Reduction in the rate of drug dissolution
- Reduction in the rate of diffusion of drug in solution from the lumen to the absorbing membrane lining the GIT.

Hence, there is reduction in drug bioavailability.

III Effect of Food

اشي وهو مارق رح يتكسر رحت ثبطت الي بكسرة بالتالي رح يزيد ال bioavailability

د.ايمان

د.نزار

البوملي والجريب فروت بنزلوا ضغط الدم ويصل interaction

G- Food-induced changes in presystemic metabolism

- Certain foods may increase the bioavailability of drugs that are susceptible to presystemic intestinal metabolism by interacting with the metabolic process.
- E.g. Grapefruit juice is capable of inhibiting the intestinal cytochrome P450 (CYP3A) and thus taken with drugs that are susceptible to CYP3A metabolism which result in increase of their bioavailability.

الاكل بزيد ال blood flow فا كمية اكبر رح توصل فارح يزيد الامتصاص

H- Food-induced changes in blood flow

- Food serve to increase the bioavailability of some drugs (e.g. propranolol) that are susceptible to first-pass metaolism.
- Blood flow to the GIT and liver increases after a meal. The faster the rate of drug presentation to the liver; the larger the fraction of drug that escapes first-pass metabolism. This is because the enzyme systems become saturated.

بزيد olic acid الامتصاص وح الـ Fed state وبكون اسرع الـ B.F

لما الواحد يكون ماكل بزيد ال blood flow على ال stomach وال liver ف الدوا بروح عال liver ورح يهرب كميه كبيرة وما يصيرلهم metabolism ف ال bioavailability رح تكون عاليه
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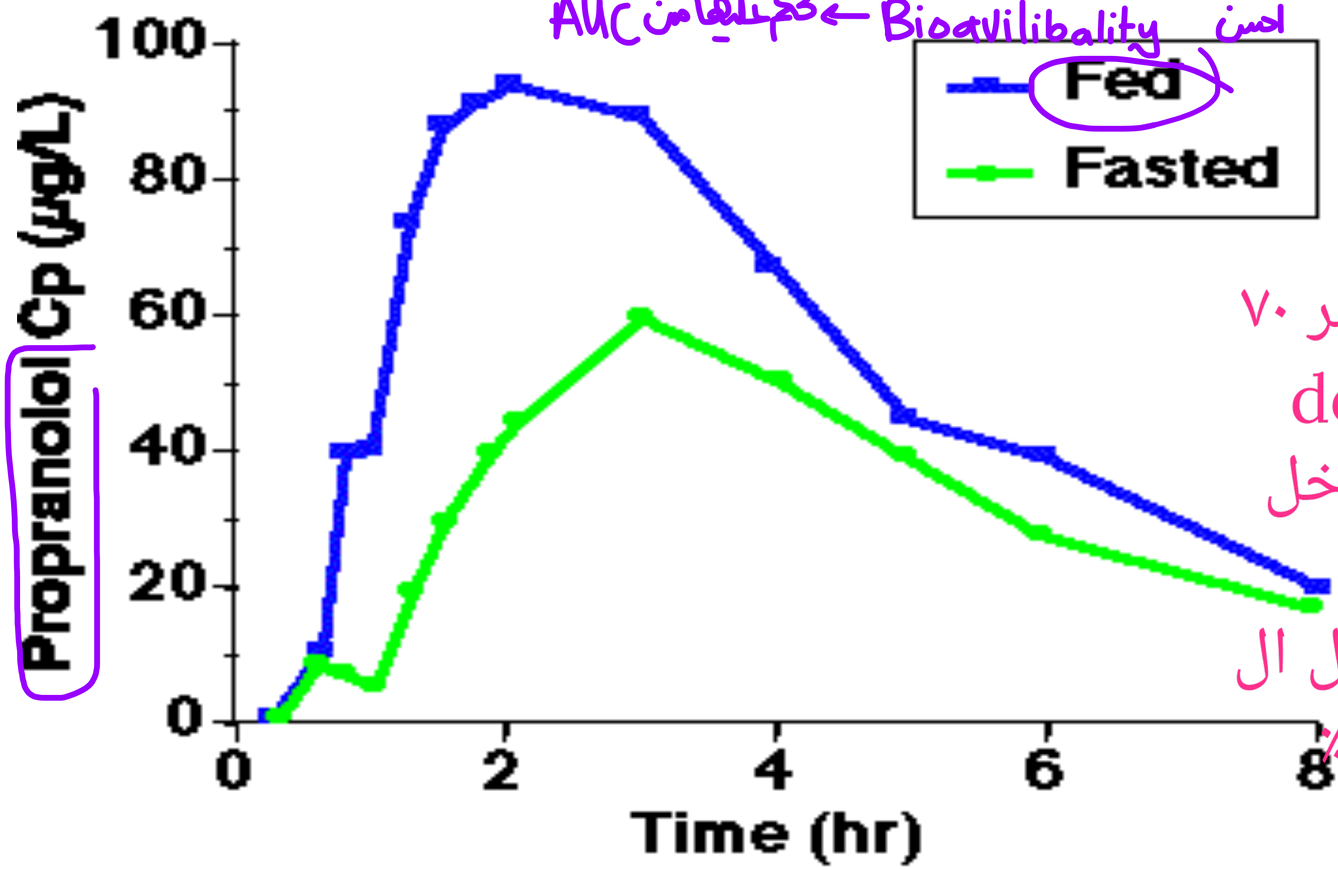
III Effect of Food



لما يدخل على الكبد بكسر ٧٠ ٪ منه فا بزيد ال dosage تبعته فالكمية الي رح تدخل على الكبد بتكون كبيرة مابتكسر الجميع فابتوصل ال bioavailability ل ٣٠٪

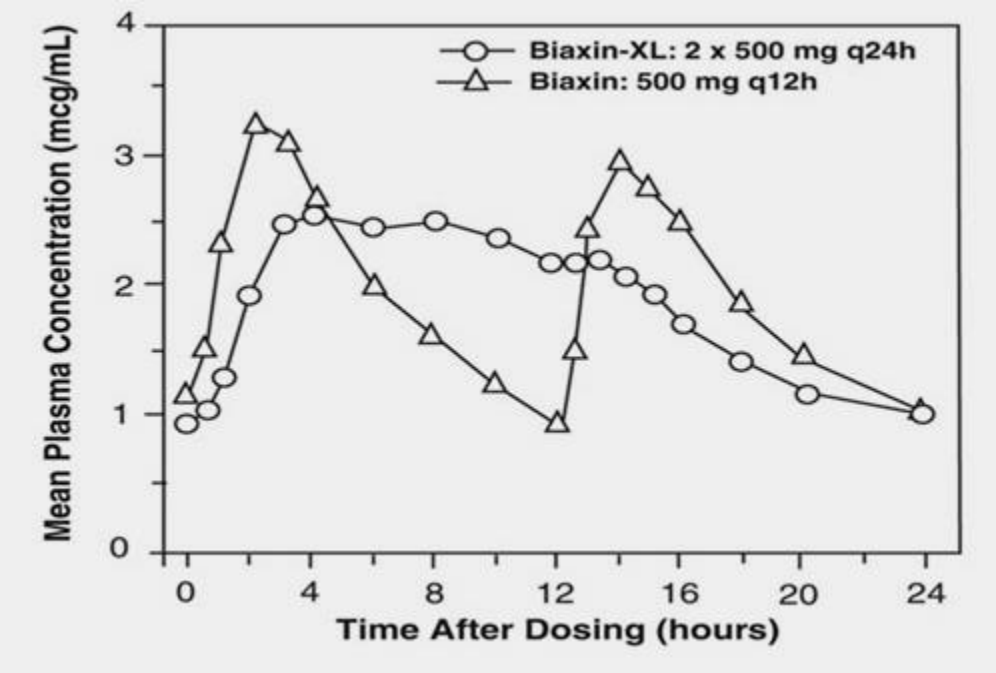
Effect of Fasting *versus* Fed on Propranolol Concentrations

" نبلش بالبارت التاني ونكمل "
Ghada

Double peak phenomena

- Some drugs such as cimetidine and ranitidine, after oral administration produce a blood concentration curve consisting of two peaks.

- The presence of double peaks has been attributed to variability in stomach emptying, variable intestinal motility, presence of food, enterohepatic cycle or failure of a tablet dosage form.



Presystemic metabolism

هو الـ metabolism اللي بصير للدوا قبل ما يوصل الـ systamic circulation

Definition:

The metabolism of orally administered drugs by gastrointestinal and hepatic enzymes, resulting in a significant reduction of the amount of unmetabolized drug reaching the systemic circulation.

ممكن بعض الأدوية تخرب نفسها بهذة الطريقة .

النوع الاول من Presystemic

Gut wall metabolism

الـ Small Intestine تحتوي على أنزيمات

- This effect is known as first-pass metabolism by the intestine.
- (Cytochrome P450 enzyme), (CYP3A), that is present in the liver and responsible for the hepatic metabolism of many drugs, is present in the intestinal mucosa and that intestinal metabolism may be important for substrates of this enzyme e.g. cyclosporin.

بنعطية orally

هاد الدواء بصير له metabolism بالانزيمات اللي ذكرناهم بالـ Small Intestine

Presystemic metabolism

Pre ومكن يكون Systemic ممكن يكون Hepatic ال

متى يكون Pre ← Portal Vein بس يصير عندي من خلال

النوع الثاني

Hepatic metabolism

- After a drug is swallowed, it is absorbed by the digestive system and enters the hepatic portal system. It is carried through the portal vein into the liver before it reaches the rest of the body.

مثال عالادوية

- The liver metabolizes many drugs (e.g. propranolol), sometimes to such an extent that only a small amount of active drug emerges from the liver to the rest of the circulatory system.

- This *first pass* through the liver thus greatly reduces the bioavailability of the drug.

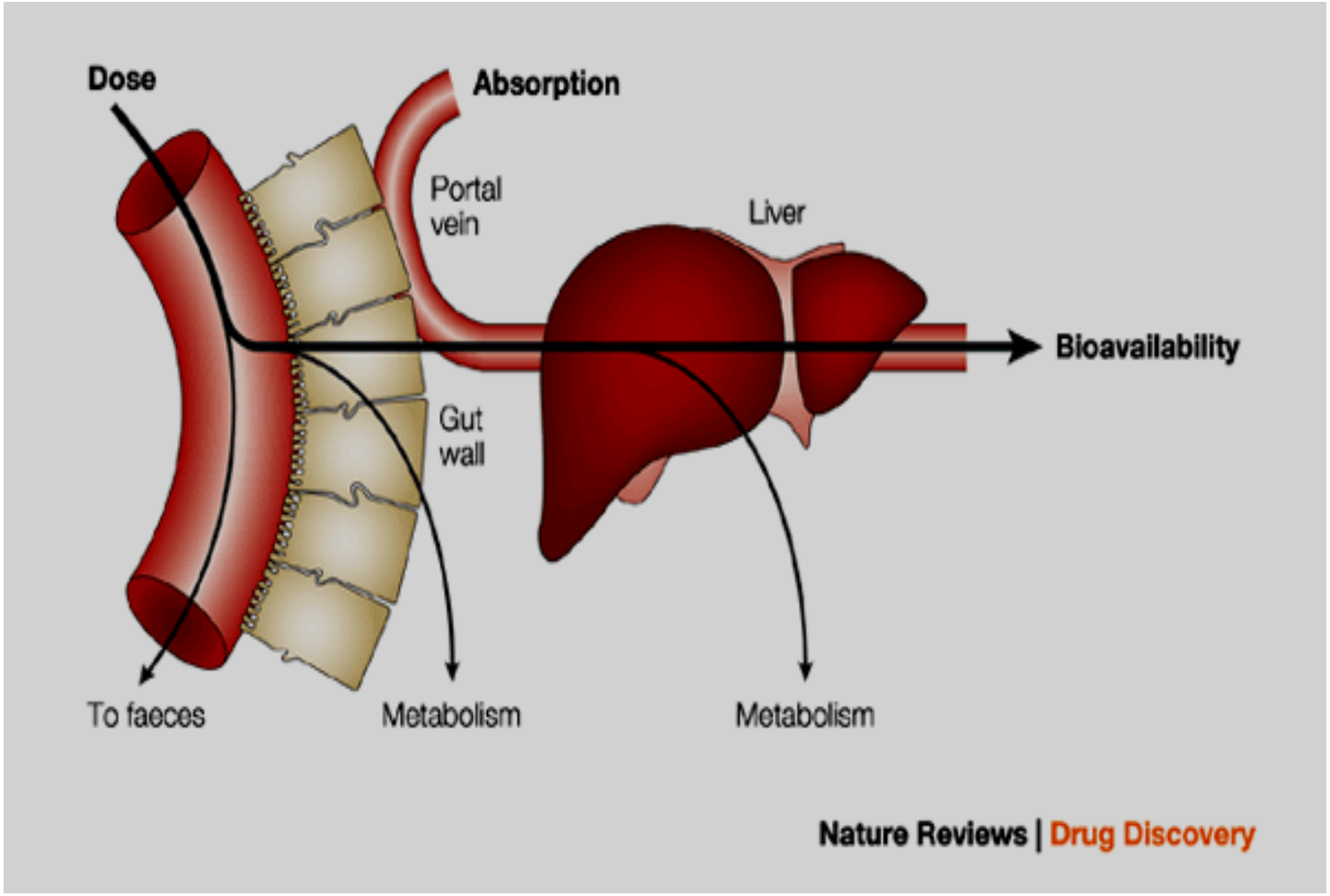
↑ ↑ ↑

- لما حكينا إنه المعدة والأمعاء Large, Small ماعدا Lower rectal vein + buccal صدول كلشي لما يمتصوا بروحوا من خلال الـ Portal Vein على Liver قبل ما يوصلوا الـ Circulation وهاد نوع خط دفاع ربنا عزّ وجل حطه بجسمنا عشان مش أي اشي Toxic أنت أخذته يروح على الـ Circulation ، لكن هالطريقة أحيانًا بتخرب بعض الأدوية مثل Propanolo وهذا لا يعني بعد ما يروح من Portal Vein مارح يروح لـ Liver مرّة ثانية -- ؟ عادي بروح لـ Liver بس عالأقل بكون توزع عالجسم .

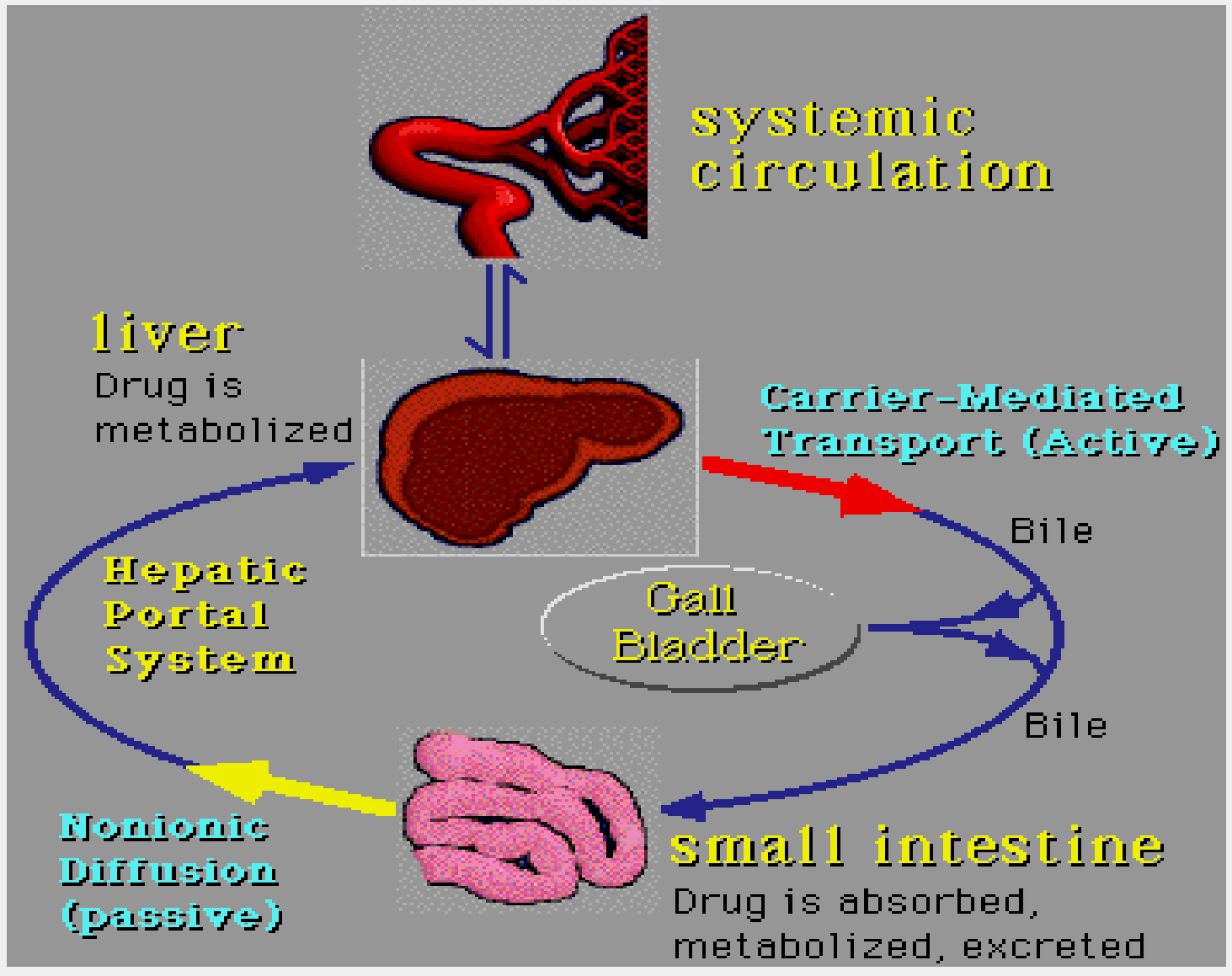
- الـ first Pass metabolism ما بجير لكل الأدوية ، في بعض أدوية بتمر بالـ Portal Vein بس ما بجير عليها هالدرجة العالية من الـ metabolism .

Presystemic metabolism

صورة بتبين كيف ال Systemic circulation على إتحال بال Liver



Hepatic metabolism



II Physical-Chemical Factors Affecting Oral Absorption

Physical-chemical factors affecting oral absorption include:

A- pH-partition theory

B- Lipid solubility of drugs

C- Dissolution and pH

D- Drug stability and hydrolysis in GIT

E- Complexation

F- Adsorption

A. pH - Partition Theory

- According to the pH-partition hypothesis, the gastrointestinal epithelia acts as a lipid barrier towards drugs which are absorbed by passive diffusion, and those that are lipid soluble will pass across the barrier.

- As most drugs are weak electrolytes, the unionized form of weakly acidic or basic drugs (the lipid-soluble form) will pass across the gastrointestinal epithelia, whereas the gastrointestinal epithelia is impermeable to the ionized (poorly-lipid soluble) form of such drugs.

- Consequently, the absorption of a weak electrolyte will be determined by the extent to which the drug exists in its unionized form at the site of absorption.

- ٪45 من الأدوية Weak Acid or Weak Bais
- ٪5 فقط هي Nutral

- كونه معظم الأدوية Weak electrolyte فالتي عنده القدره ليخترق الـ Cell membrane هو الـ Unionized ← less hydrophilic ، عندة القدرة إنه يمر by Passive diffusion

فالكم الـ A+

Ph. Ghada لولنا دعوا!

Ph. Aya