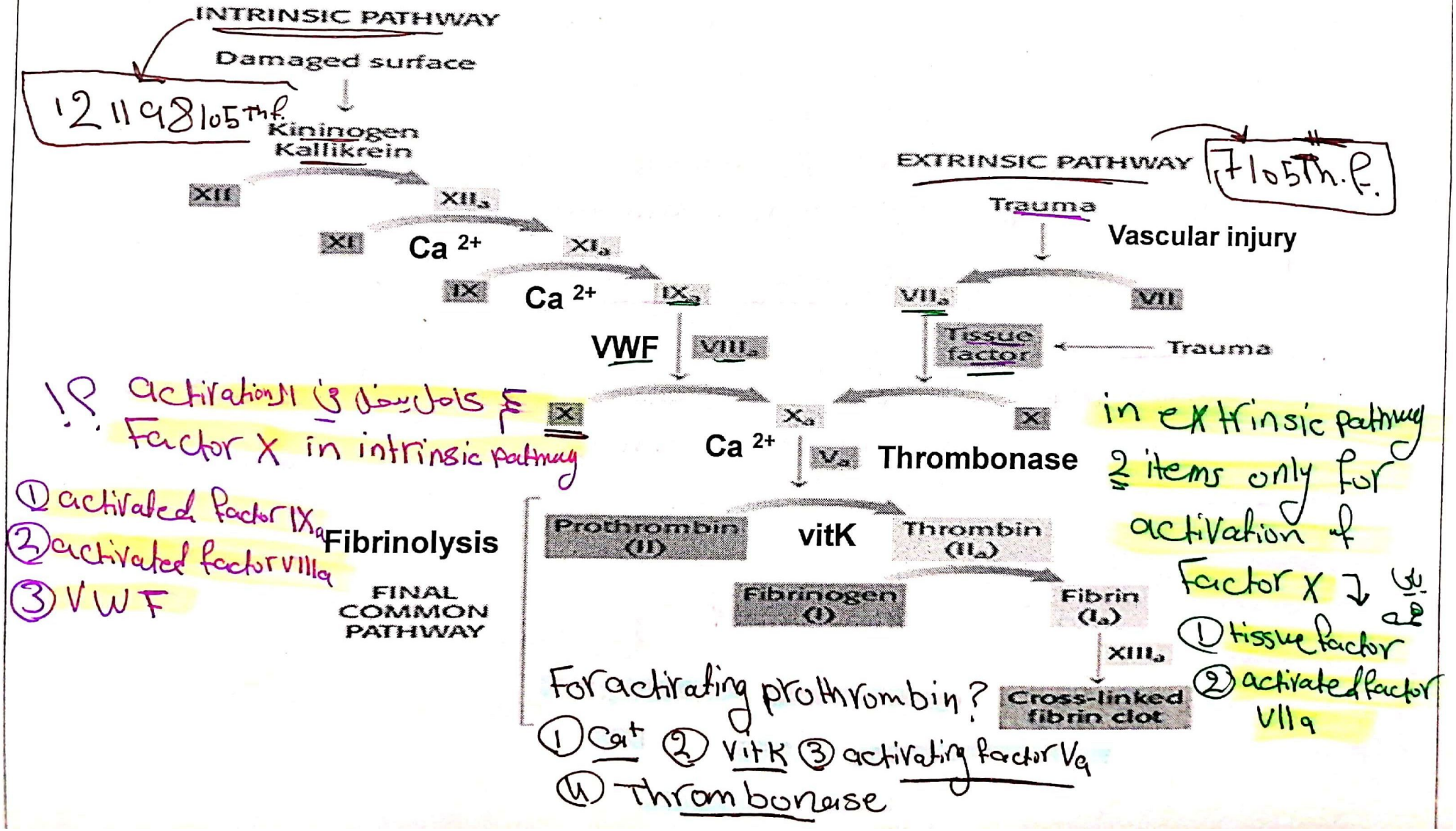
Blood coagulation cascade



!? activation الي بتحول X
Factor X in intrinsic pathway

① activated factor IXa
② activated factor VIIIa
③ VWF

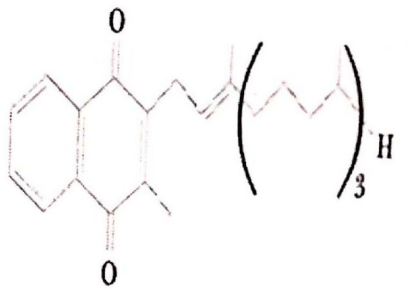
in extrinsic pathway 2 items only for activation of Factor X ↓ بدل
① tissue factor
② activated factor VIIa

For activating prothrombin?
① Ca+ ② VitK ③ activating factor Va
④ Thrombonase

Vitamin K → K_3 (synthesized) injection

Vitamin K_1 is abundant in vegetable oils and green leafy vegetables e.g. Spinach, peas and cabbage.

Vitamin K_2 is synthesized by intestinal flora and is found in animal tissues. Putrefied fish meal is a rich source. we are belonging to kingdom animalia

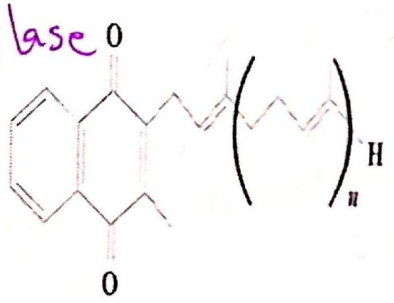


Vitamin K_1
(phylloquinone)

Sources of vitamin K include tomatoes, cheese, egg yolk, and liver.

Breast milk is NOT a good source of vitamin K.

Vitamin K is required for post translational → by Gamma-glutamyl carboxylase modifications of several proteins required in the coagulation cascade.



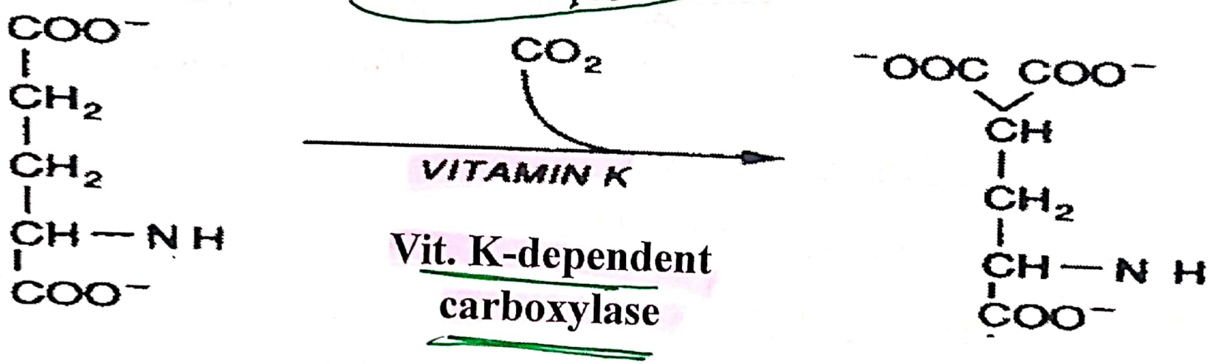
Vitamin K_2
(menaquinone series)

It converts blood clotting factors (II, VII, IX and X) to the active state. They are synthesized in liver in an inactive precursor form.

...itamin K-dependent activation for prothrombin

1. Prothrombin is synthesized in liver in an inactive precursor form called [pre-prothrombin.]
2. Pre-prothrombin (prothrombin precursor) conversion to prothrombin requires vitamin K-dependent carboxylation (of specific glutamic acid residues to γ-carboxyglutamic)

Pre-prothrombin (Glutamate) ➡ Prothrombin (γ caboxyglutamate)



Vit.K dependent carboxylase.

partially active molecule

preproThrombin → active form تتحول إلى
by more than one step?! why? to regulation

3. The γ- carboxygulatmic acid residues are good chelators which allow prothrombin (active) to bind (chelate) calcium

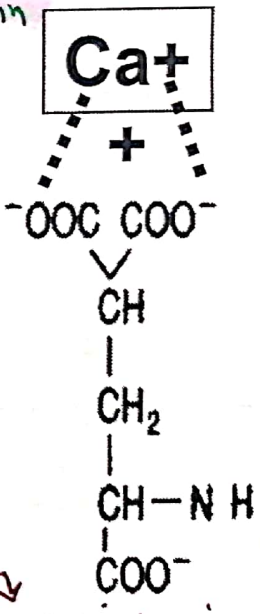
4. Prothrombin ...

by more than one step ?! why? it means where? to regulation

active → coagulation

3. The γ- carboxygulatmic acid residues are good chelators which allow prothrombin (active) to bind (chelate) calcium.
4. Prothrombin-Ca++-complex binds to phospholipids of cell membrane where proteolytic conversion to thrombin can occur.

So prothrombin converted to thrombin by proteolytic cleavage



Function:

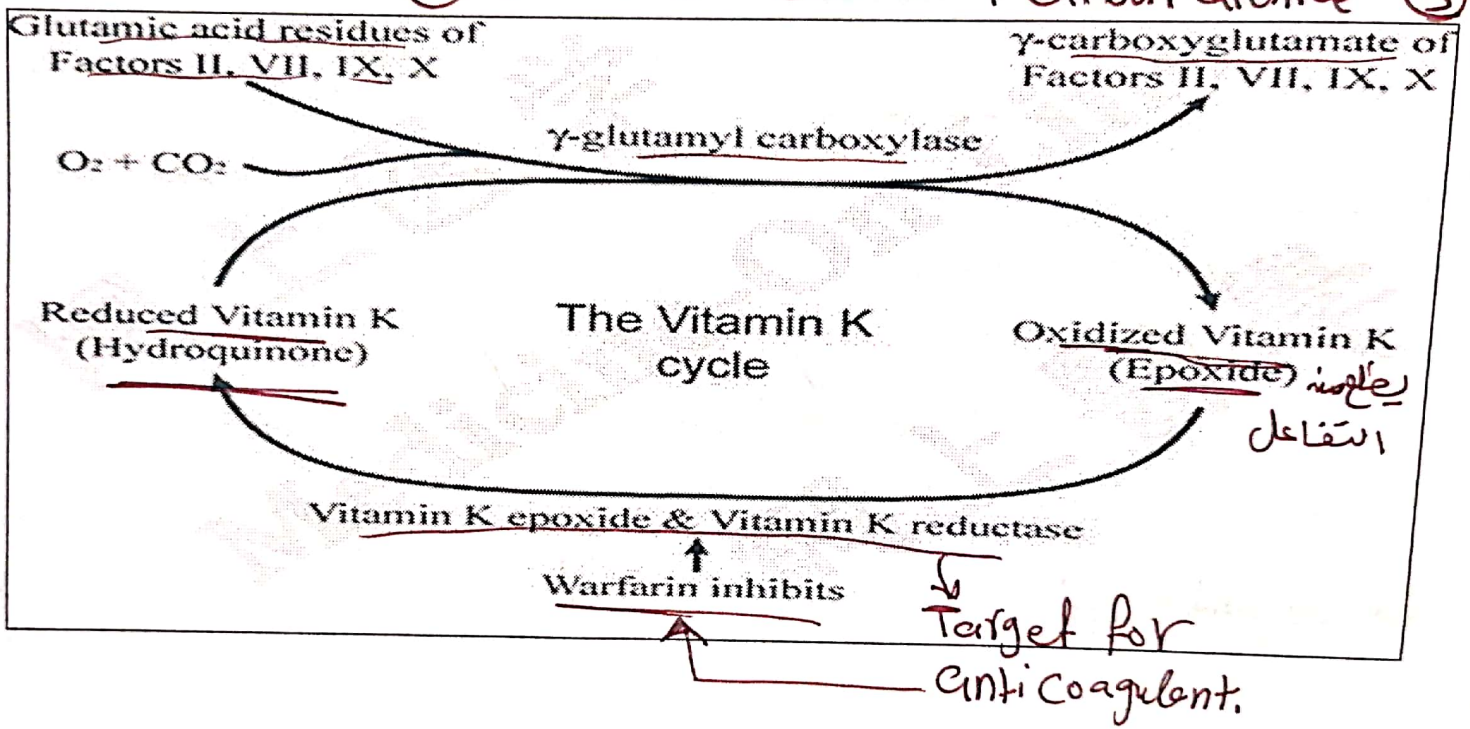
- Vitamin K is an essential cofactor for the carboxylase enzyme in specific protein molecules such as:

1- Blood clotting factors (II, VII, IX, X).
2- Bone calcium-binding proteins as osteocalcin. → Play role in regulating blood glucose level in diabetic patients
3- The product of Growth arrest specific gene Gas6 which is involved in differentiation & development of nervous system.

ايش الحاجة المفروض تكون موجودة عشان تكمل ال Carboxylation reaction !؟

Vitamin K cycle

① source of carbon dioxide (bicarbonate)
② Biotin as a carrier of carbon dioxide ③ manganese ④ ATP



يدخل التفاعل

يطلعون التفاعل

Role of liver in blood clotting:

1. Site of clotting factors synthesis.
2. Site of bile salts synthesis (to help vit. K absorption).

Liver failure: results in severe bleeding problems.

Anti-coagulants

- Dicumarol & warfarin are antagonists of vitamin K (anti-coagulants).
- Are used to reduce blood coagulation in patients at risk of thrombosis. Thus, vitamin K is the antidote to an overdose of warfarin.

Deficiency

Causes:

Primary deficiency: rare

Secondary deficiency:

- Fat malabsorption. → bile salts الأملاح اللي بتنتج
- In newborn who lack bacterial colonization. → so during the first period before the bacteria flora existing in large intestine of newly born infant we have to supply mother with Vit.K to increase the amount of vit.K in breast milk
- long-term or high-dose administration of antibiotics (they kill the bacteria in large intestine).
- Anticoagulant Therapy.
- In patients suffering from Liver diseases (obstructive jaundice). unable to بتنتج bile الأملاح اللي بتنتج be in small intstine. salt

الحاجات اللي ممكن موجوده كمان بال breast milk ؟
① iron ② Vit.K عشان طفل حديث بالنهار لازم يتعرض الطفل للشمس لمدة ١٥ دقيقة عشان عنده

Vitamin K deficiency

Manifested by:

-Bleeding tendency (GIT, ecchymoses) from minor wounds.
- Nose & gum bleeding.
- Heavy menstrual bleeding.
- Increased risk for osteoporosis. at long period of time with vit. K deficency

Diagnosed by:

- Prolonged blood coagulation time: prolonged prothrombin time (↑↑ PT). [blood takes 10-13.5 sec to clot].

Prevention: single shot of vit. K at birth in newborn.

Thrombin → switching off to blood coagulation and in the same time switching on of the deactivation by activating protien C

The clotting process must be precisely regulated

- Hemorrhage and thrombosis must be regulated by mechanisms that normally limit clot formation to the site of injury.
- Activated factors are short-lived because they are diluted by blood flow, removed by the liver, and degraded by proteases → because the coagulation factors are dynamic globular protiens

Regulation-Two Mechanisms

1- Va and VIIIa factors are digested by protein C, a protease that is switched on by the action of thrombin which has dual function:
   a- It catalyzes the formation of fibrin
   b- it initiates the deactivation of the clotting cascade. by starting activation protien c

2- Specific Inhibitors of clotting factors are crucial in terminating blood clotting as:
   a- Tissue factor pathway inhibitor (TFPI), inhibits the complex of TF- VIIa - Xa.
   b- Anti-thrombin-III, another inhibitor which is inactivates thrombin, its inhibitory action is enhanced by negatively charged heparin.

Diagnostic Tests

A- Activated partial thromboplastin time (aPTT): measures effectiveness of clotting factors (in seconds) (intrinsic pathway)
It is only elevated in:
1- Factor XI, IX, or VIII deficiency
2- Factor XI, IX, or VIII specific factor inhibitor
3- Heparin contamination
4- Antiphospholipid antibodies

هدول ستة كمان
في بنعل
Spectrophotometeric determination of Concentration of different types of coagulation factors

B- Prothrombin time (PT) (extrinsic pathway)
It is only elevated in:
1- Factor VII deficiency
2- Congenital (very rare)
3- Acquired (Vit K deficiency, liver disease)
4- Factor VII inhibitor
5- Rarely in patients with modest decreases of factor V or X

C- Measurement of the amount of each factor in the plasma and aPTT test performed as routine diagnostic tests for bleeding disorders

D- ELISA detects the presence of antibodies to clotting factor proteins.

Molecular basis of some blood clotting disorders

1- Von Willebrand disease: most common inherited bleeding disorder

- The genetic mutations result in inherited deficiency of Von Willebrand
- It is associated with an increase in aPTT, thus prolonged bleeding time despite normal platelet count
- Because vWF binds factor VIII and stabilizes it, a deficiency of vWF gives rise to a secondary decrease in factor VIII levels. so intrinsic pathway will be affected

Von Willebrand disease types

- Gene is located on chromosome 12
- Type-1 and type-3, both have reduced quantity of circulating vWF
- Type-1, an autosomal dominant disorder, accounts for 70% of all cases and the level of vWF in the blood range from 20%-50% of normal.
- Type-3 is autosomal recessive due to deletions or frameshift mutations with total deficiency, accounts for 5-10% of the cases.

- Type-2 is associated with qualitative defects in vWF, autosomal dominant due to missense mutations resulting in nonfunctional vWF levels. amount of vWF is not affected but it's ↑
- Accounts for 20% of all cases.
- Type 2 is broken down into four subtypes: type 2A, type 2B, type 2M and type 2N, depending on the presence and behavior of multimers of vWF.
- Acquired vWD: This type of vWD in adults results after a diagnosis of an autoimmune disease, such as SLE, or from heart disease or some types of cancer.
- Also, it can also occur after taking certain medications.

] by supression to gene incoding For vWf or activating the enzyme that degradate vwf.

hemophilia ↓ factor V

2- Classic Hemophilia

- Hemophilia A: most common blood clotting defect-permanent tendency for hemorrhage due to missing factor VIII of the intrinsic pathway or marked reduction of its activity. It is X-linked recessive disorder due to an inversion mutation in intron 1 (5%) or 22 (45%). Nonsense/stop mutations prevent factor production. Missense mutations may affect factor production, activity or half-life. Over 600 missense mutations identified
- Hemophilia B: factor IX deficiency (X-linked recessive disorder). Most cases associated with point mutations. Deletions in about 3% of cases. Promoter mutations in about 2%
- Hemophilia C: factor XI deficiency (autosomal recessive disorder).
- Parahemophilia: autosomal recessive disorder due to deficiency of factor V.
- Their clinical features are similar to that of hemophilia A
- The blood level of factor VIII in severe hemophilia A patient is less than 5% of normal.

- Drug-induced thrombocytopenia as quinine, sulfonamide and other antibiotics. → Suppressing the process of production of thrombocyte/or degradation of thrombocyte
- Heparin therapy, misdiagnosis can have severe consequences.

5- Disseminated intravascular coagulation (DIC)

- Disorders ranging from obstetric complications to advanced malignancy and bacterial sepsis
  → Common → Female after cesarean section and after Hysterectomy
- Organ involved release thromboblastic substances, factor X, endotoxins and cytokines

1. All increase tissue factor expression.
2. Inhibit protein C activity by suppressing thrombomodulin expression on endothelium

- Sudden widespread of fibrin thrombi in the microcirculation
- Cause diffuse circulatory insufficiency, in the brain, lungs, heart and kidneys
  end stage organ