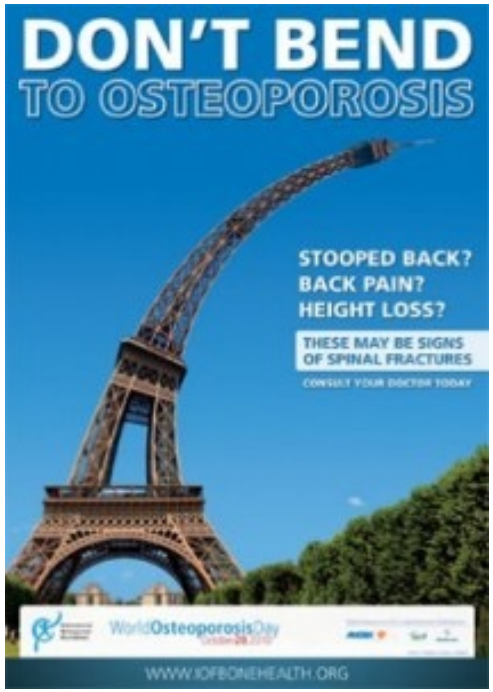
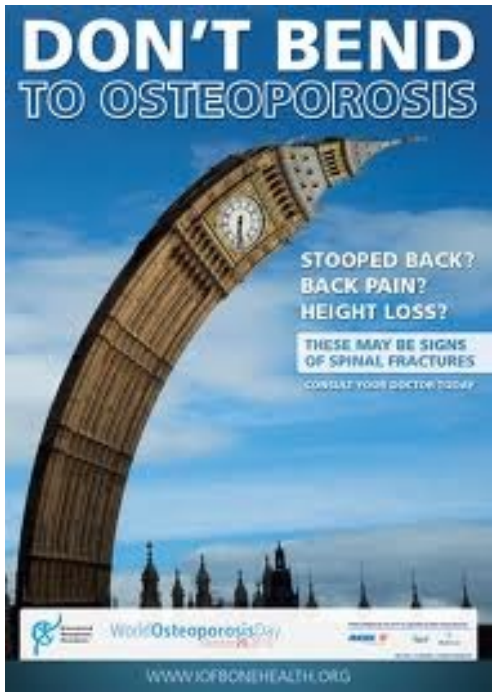
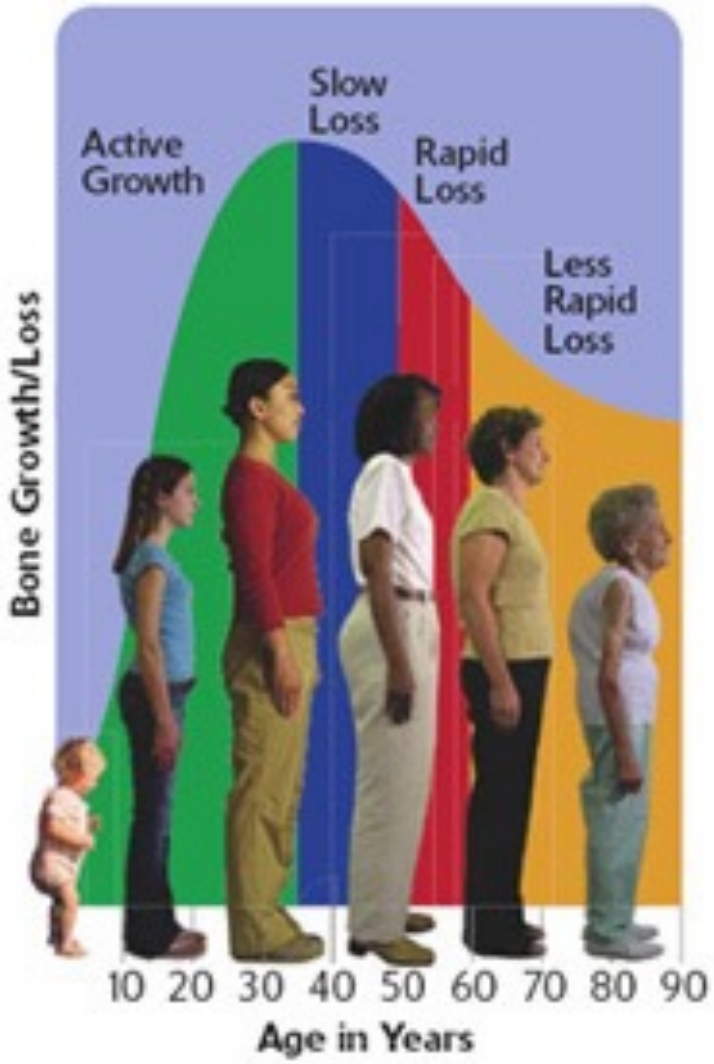
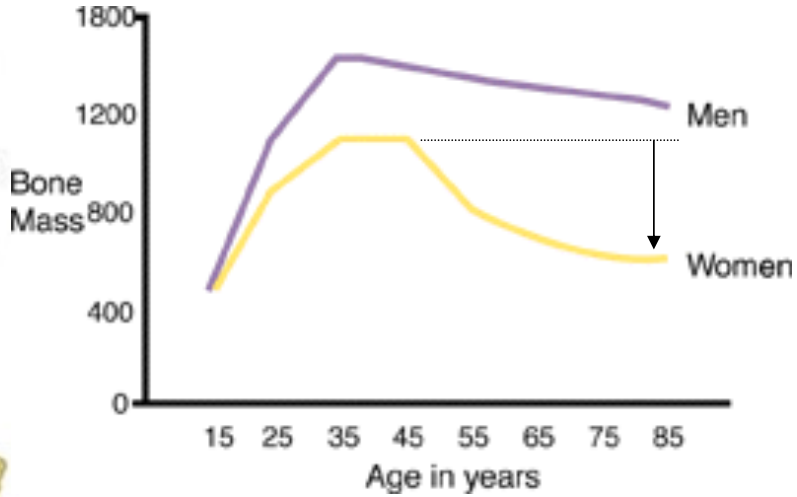




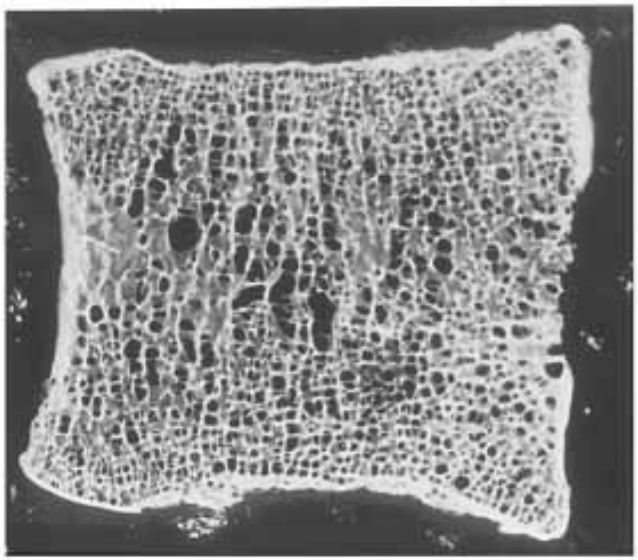
October 20 = osteoporosis day


Active Growth
Slow Loss
Rapid Loss
Less Rapid Loss
Bone Growth/Loss
10 20 30 40 50 60 70 80 90
Age in Years

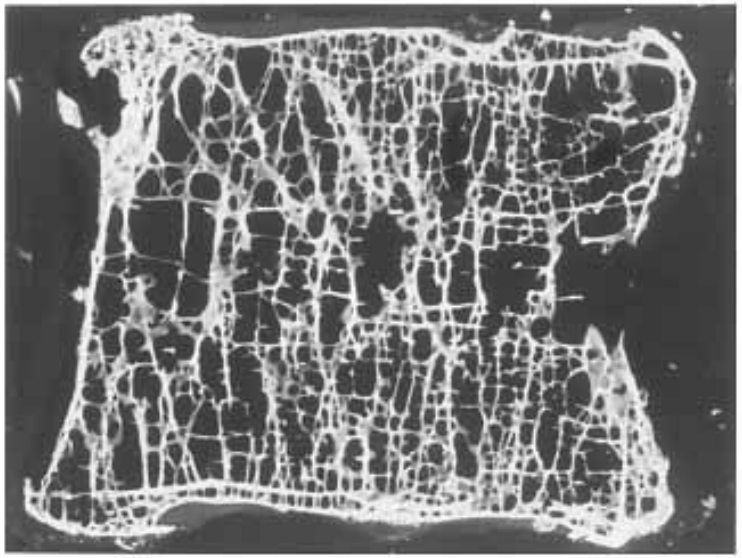
Osteoporosis



L2, 37y.o. male



L2, 75y.o. female



osteoporosis

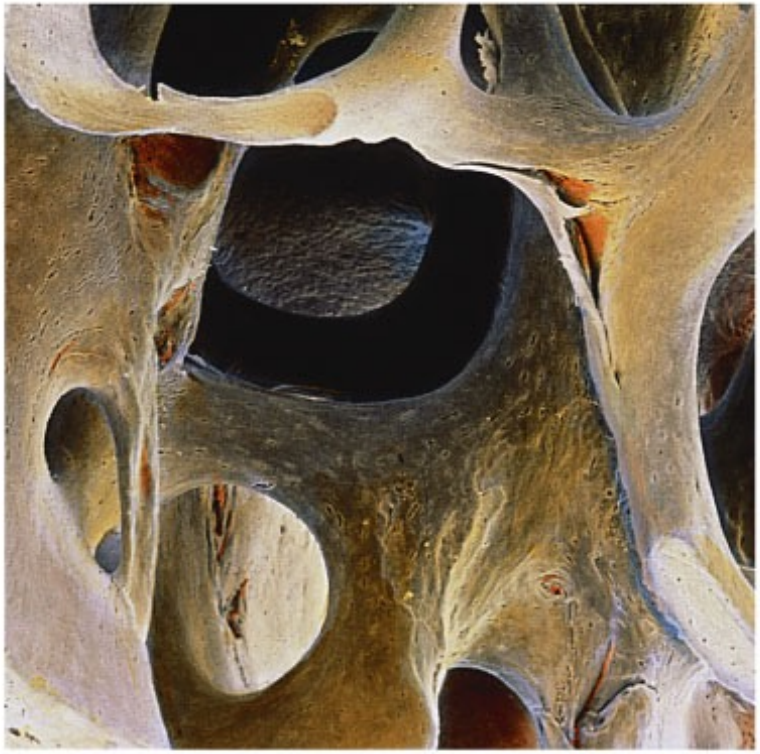
L2 : 2nd lumbar vertebra

Osteoporosis

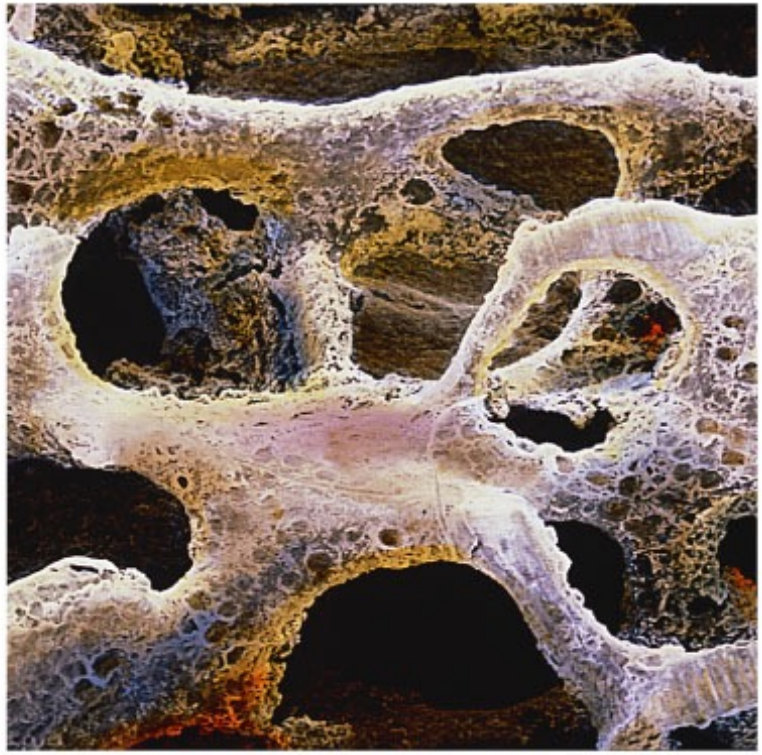
decreased bone density

Lumbar vertebrae : the last 5

Hoefnagel

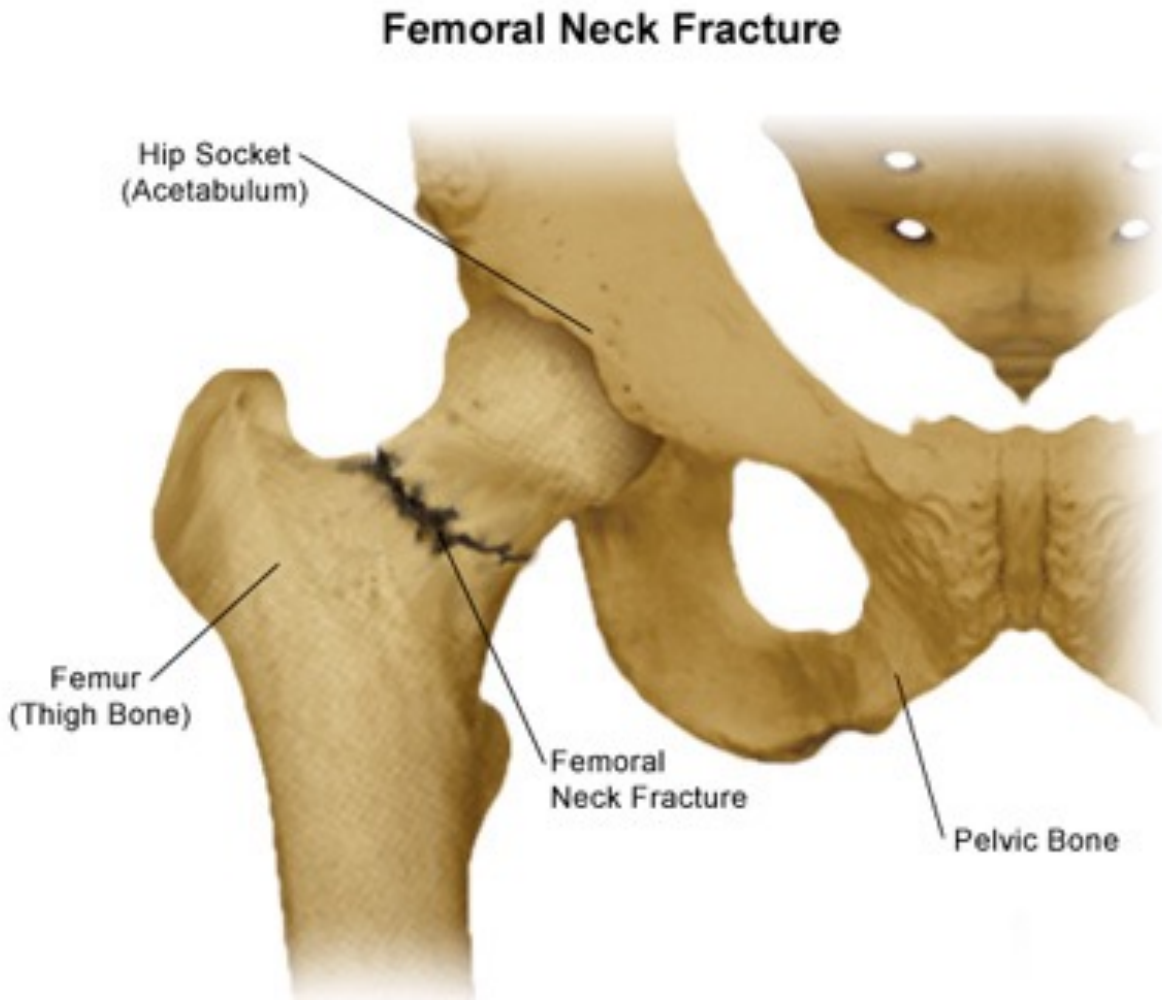


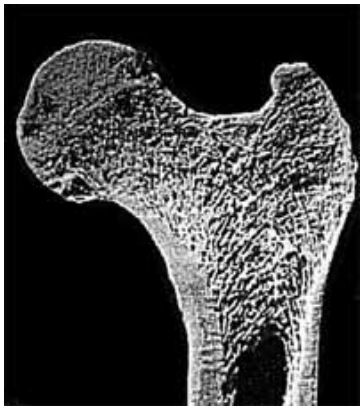
(a) Normal spongy bone (SEM × 25)

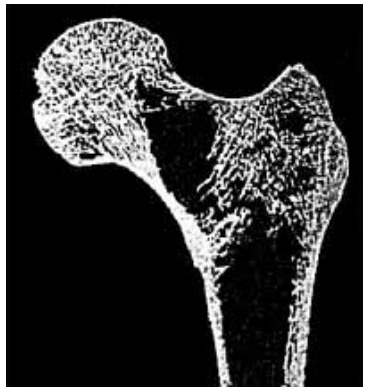


(b) Spongy bone in osteoporosis (SEM × 21)

Fracture du col du fémur



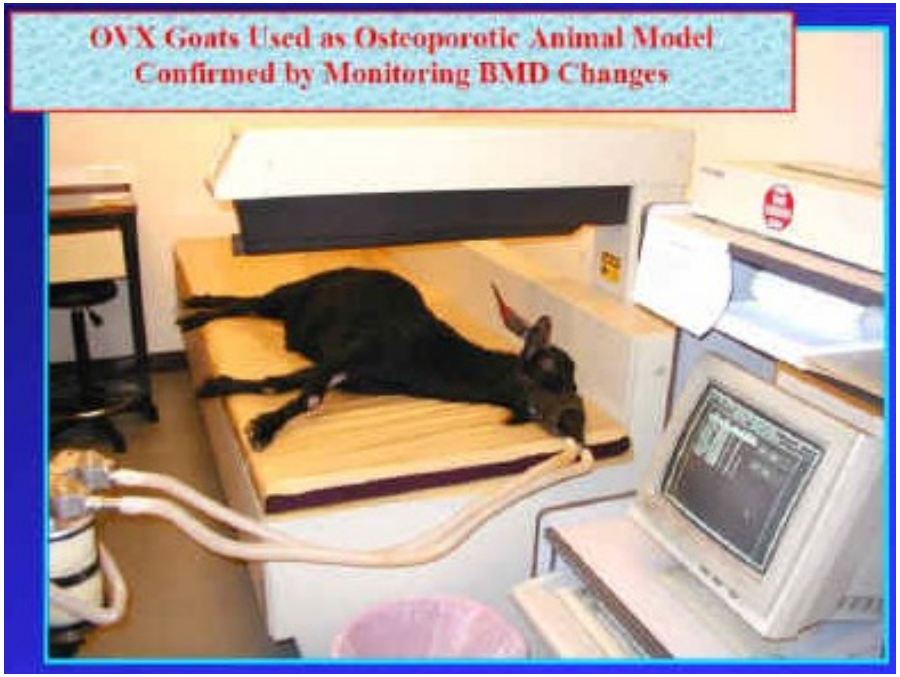




Densitometry

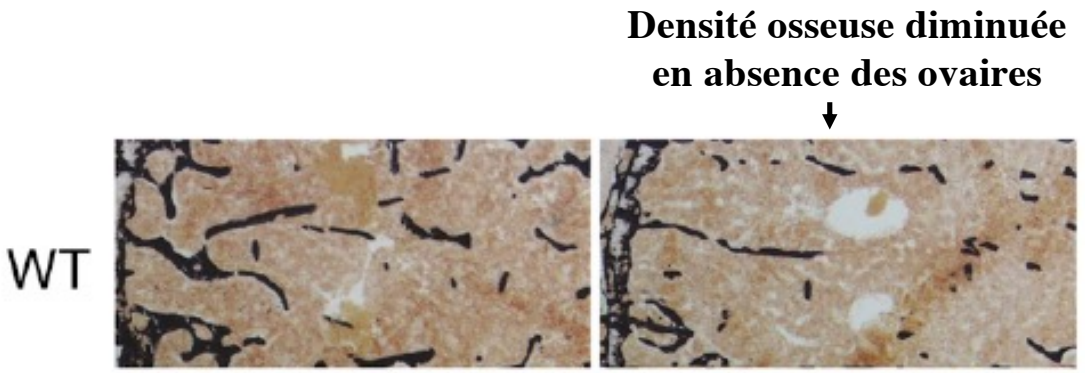
non invasive measurement of bone density

Bilateral ovariectomy in goats → osteoporosis



BMD : Bone Mass Density

Ovariectomie (OVX) bilatérale pour simuler la ménopause

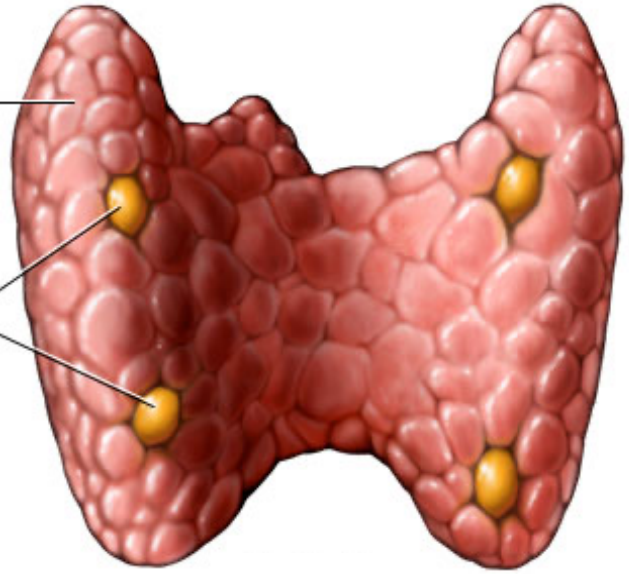


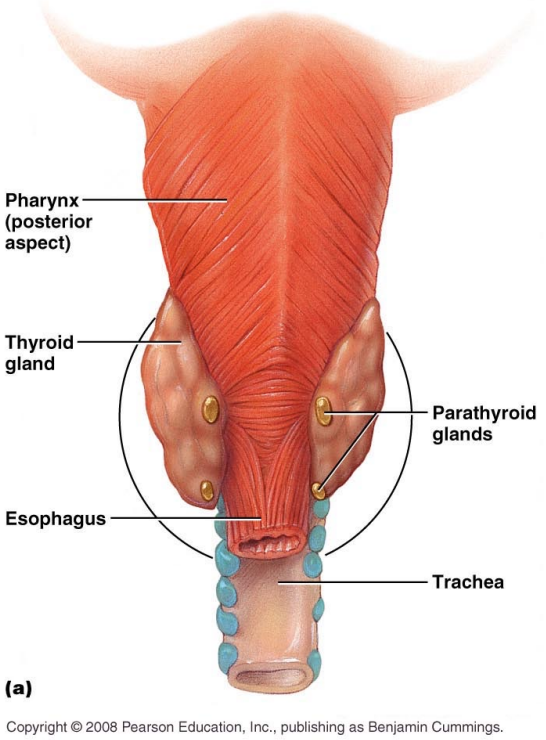
Bone mass depends on ***estrogens*** production by the ovaries.

Taille : environ la taille d’un grain de riz

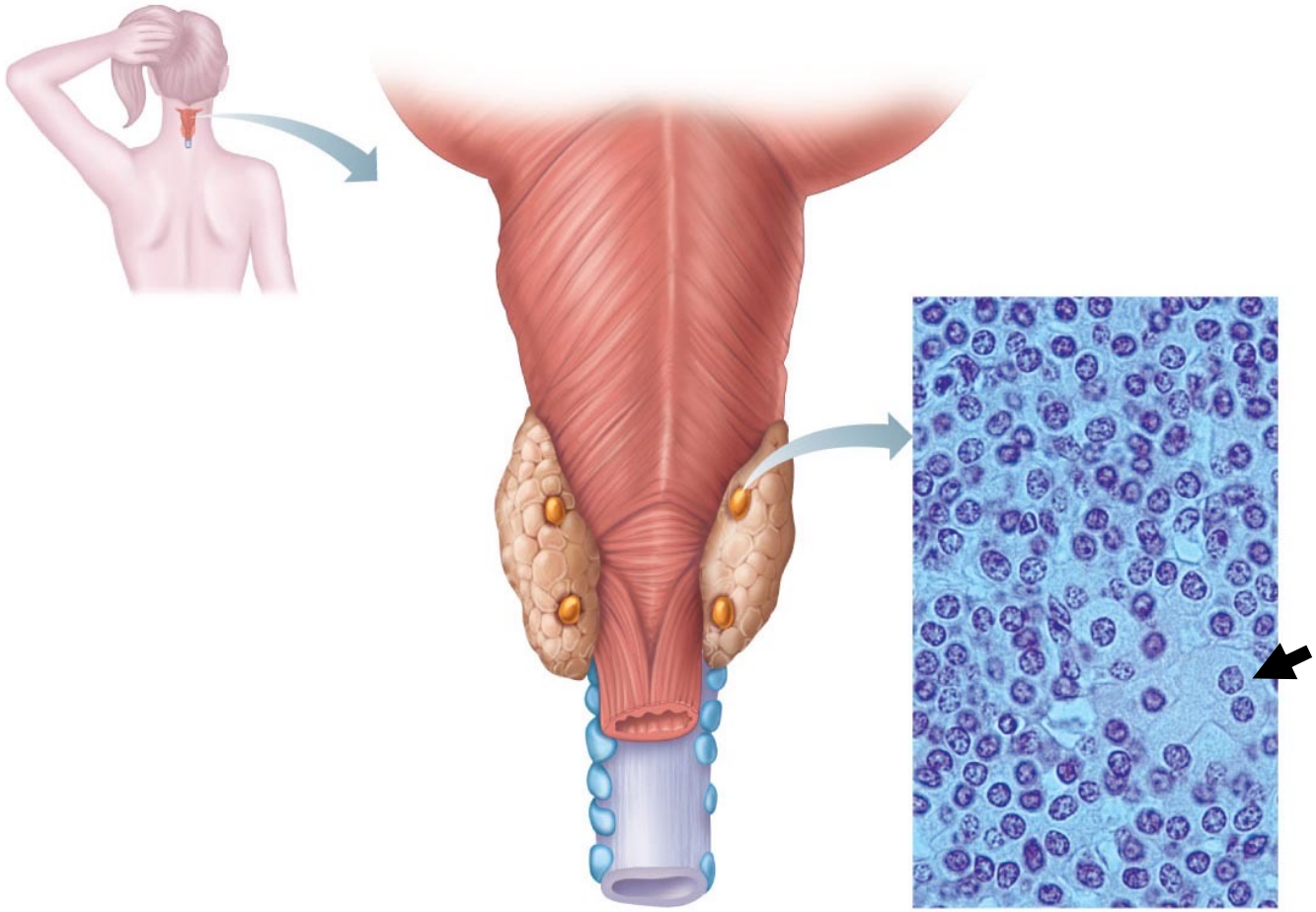
Thyroïde
(lobe gauche)

Parathyroïdes

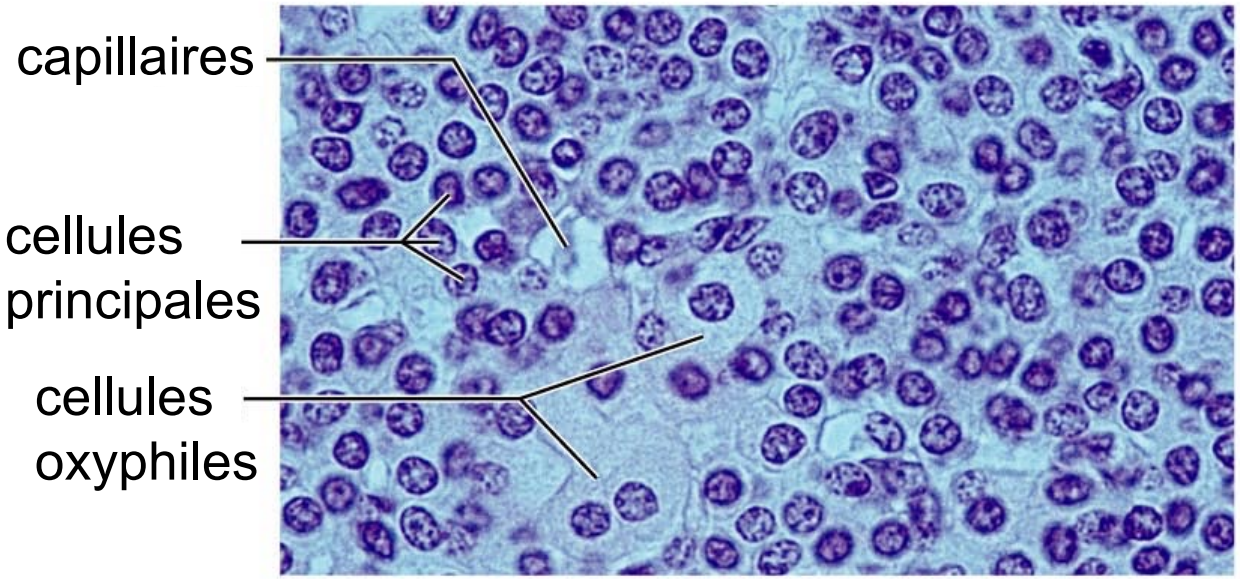




vue postérieure



Deux types de cellules dans les glandes parathyroïdes :



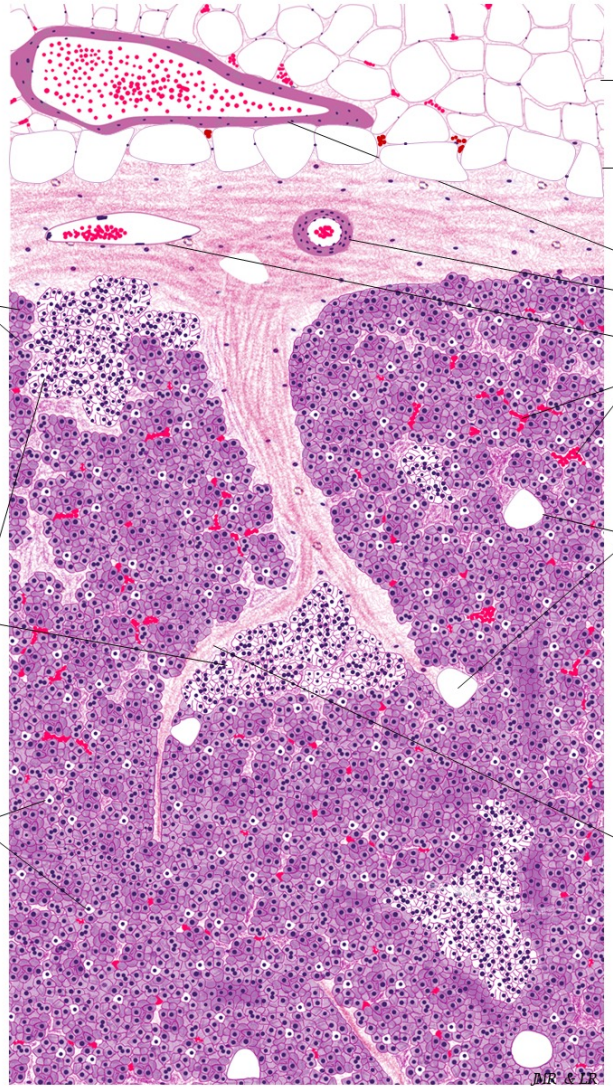
Cellules principales : produisent l'hormone PTH.

Cellules oxyphiles : fonction inconnue.

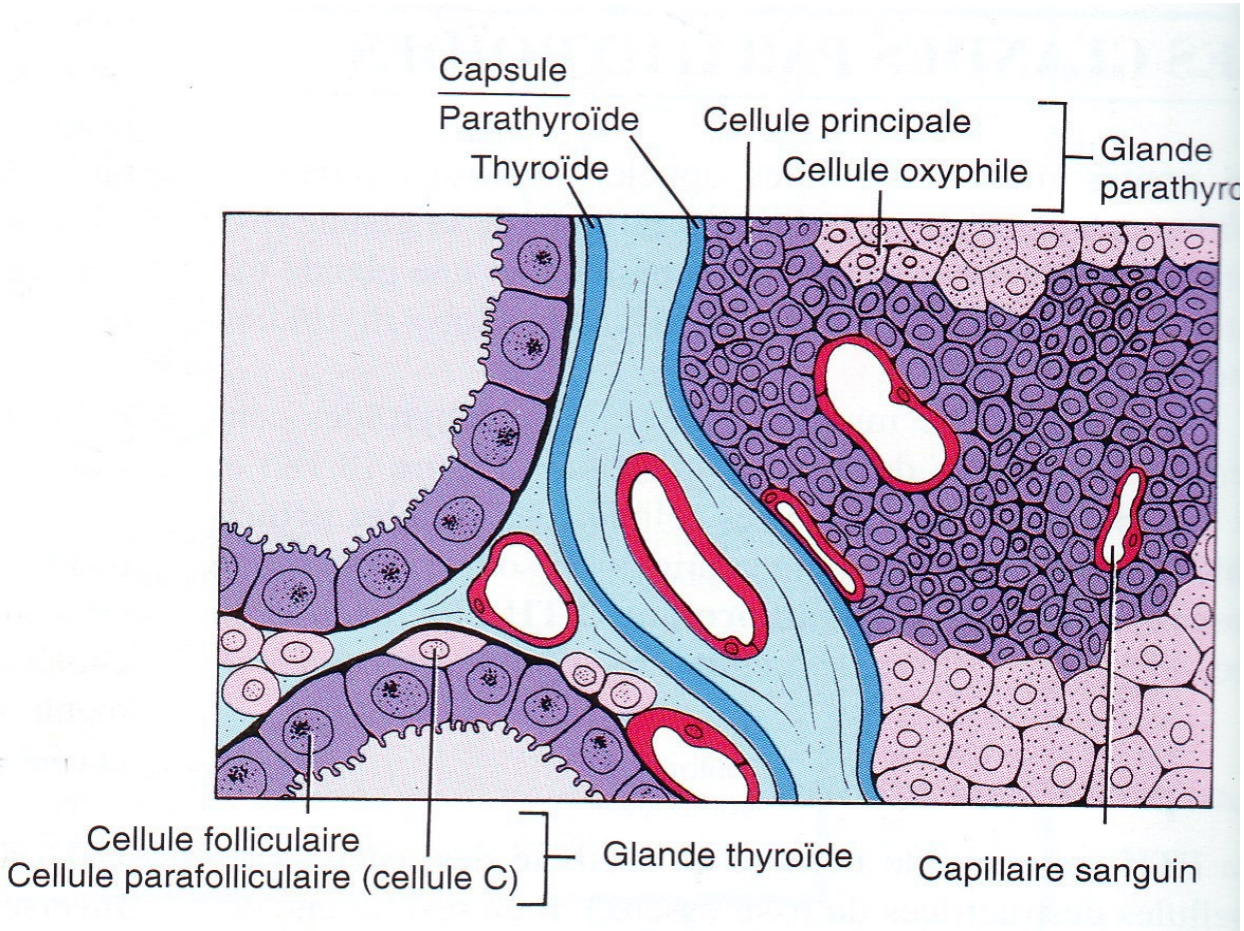
Deux types de cellules dans les glandes parathyroïdes :

Absentes avant la puberté

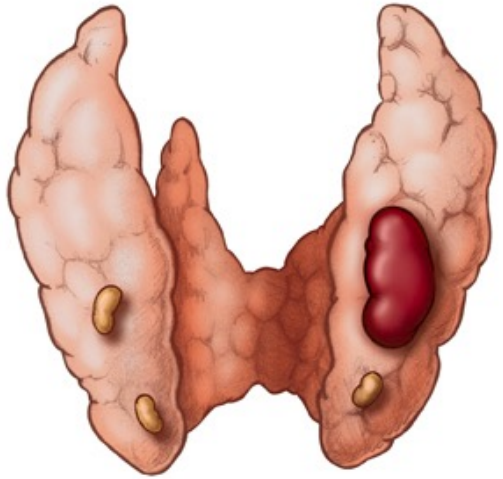
Parathyroïde Humaine



150 X Coloration HE


Capsule
Parathyroïde
Thyroïde
Cellule principale
Cellule oxyphile
Glande parathyro
Cellule folliculaire
Cellule parafolliculaire (cellule C)
Glande thyroïde
Capillaire sanguin

4 glandes parathyroïdiennes normales

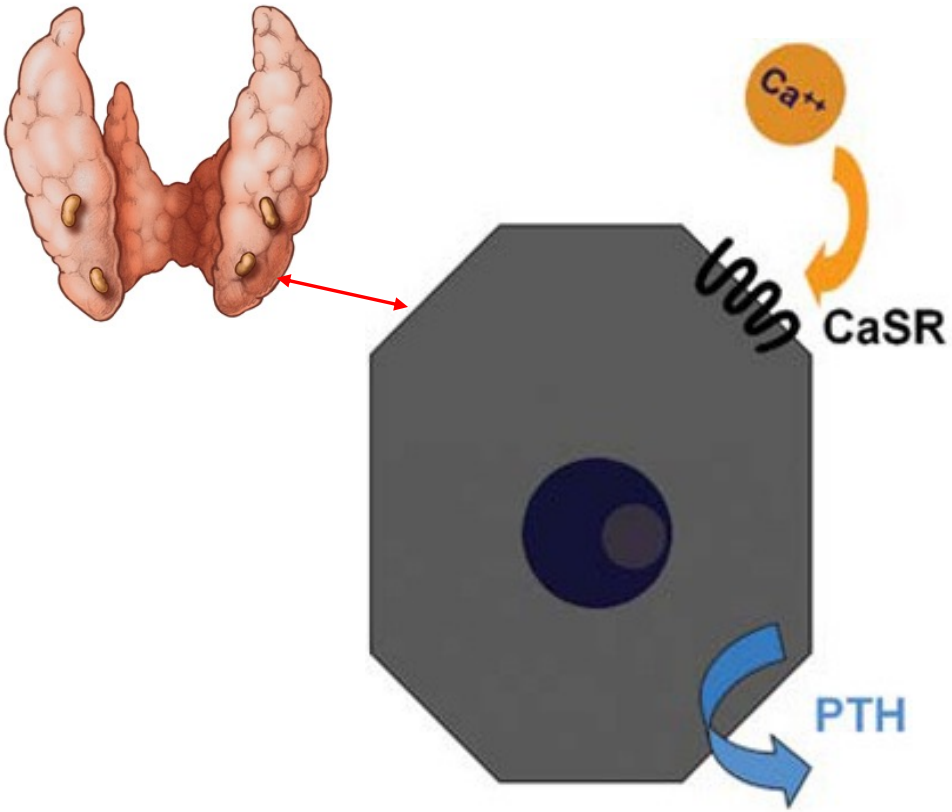


adénome

- Taille augmentéee
- Production de PTH augmentée
  → hypercalcémie

Vue postérieure

La situation normale :



Les cellules de la **glande parathyroïde** mesurent la calcémie :

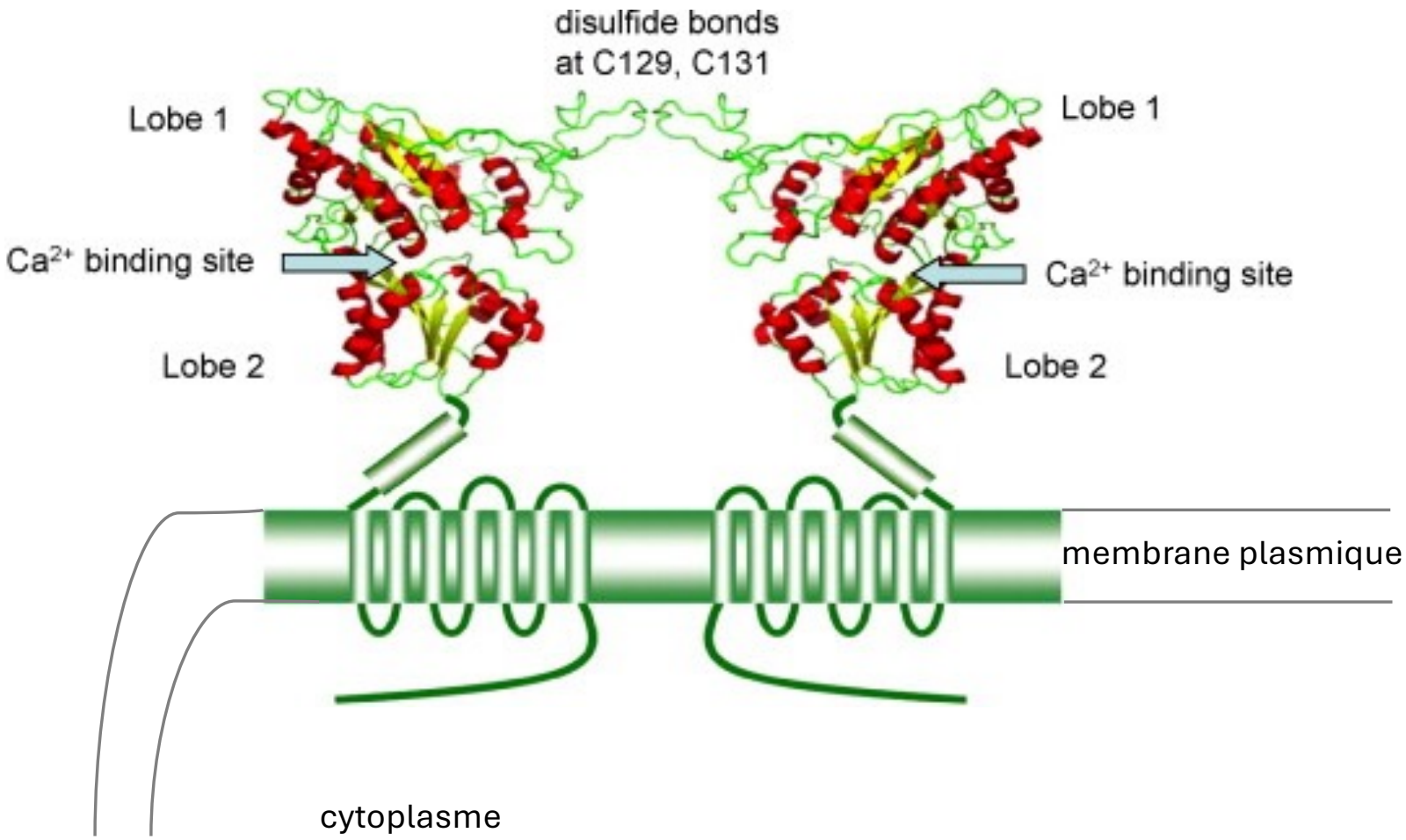
Ca^{++} Sensitive Receptor

si la **calcémie** est inférieure à la norme elles sécrètent de la PTH.

La PTH augmente la calcémie.

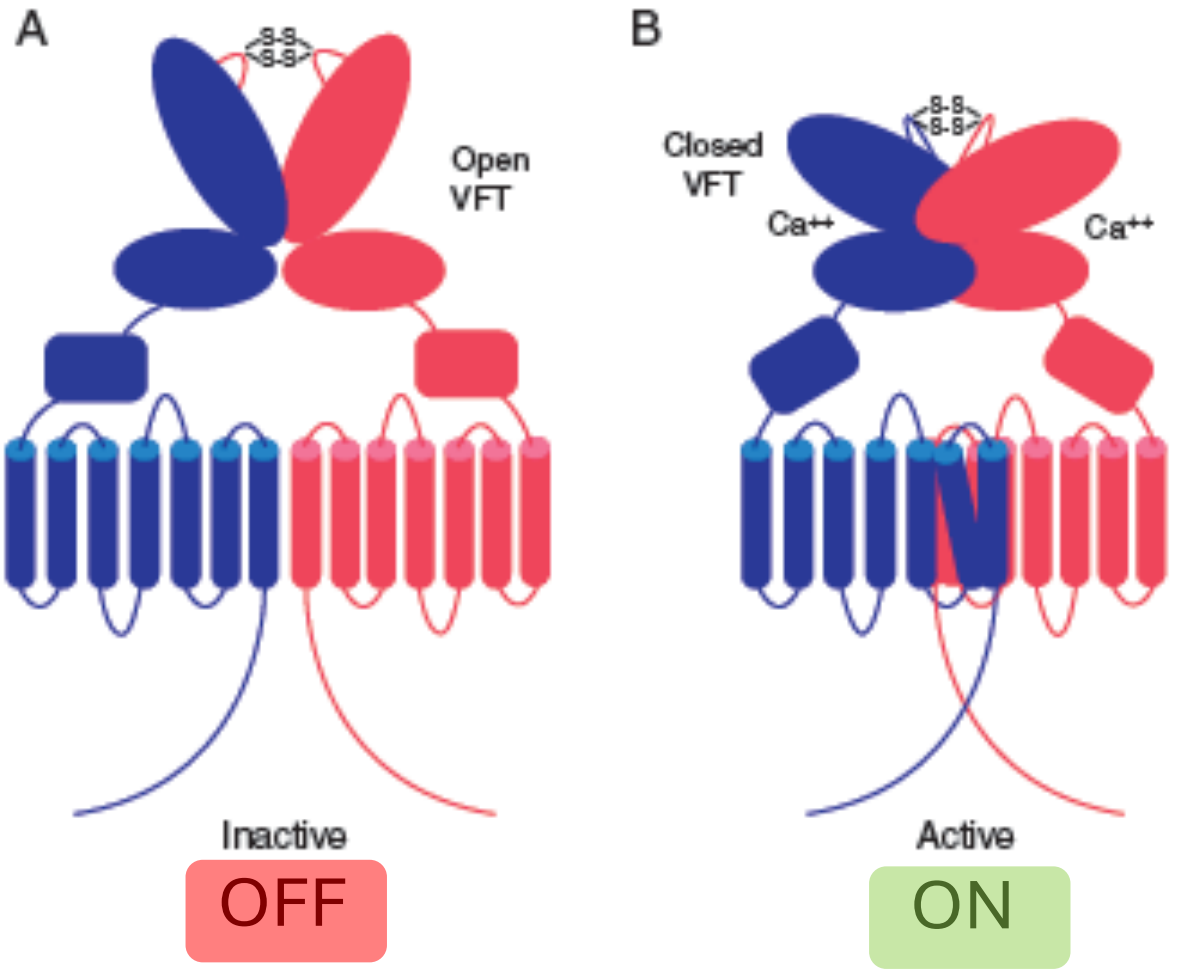
Comparez avec la mesure de la kaliémie par les cellules de la zona glomerula du cortex surrénalien.

L’appareil de mesure de la calcémie : CaSR

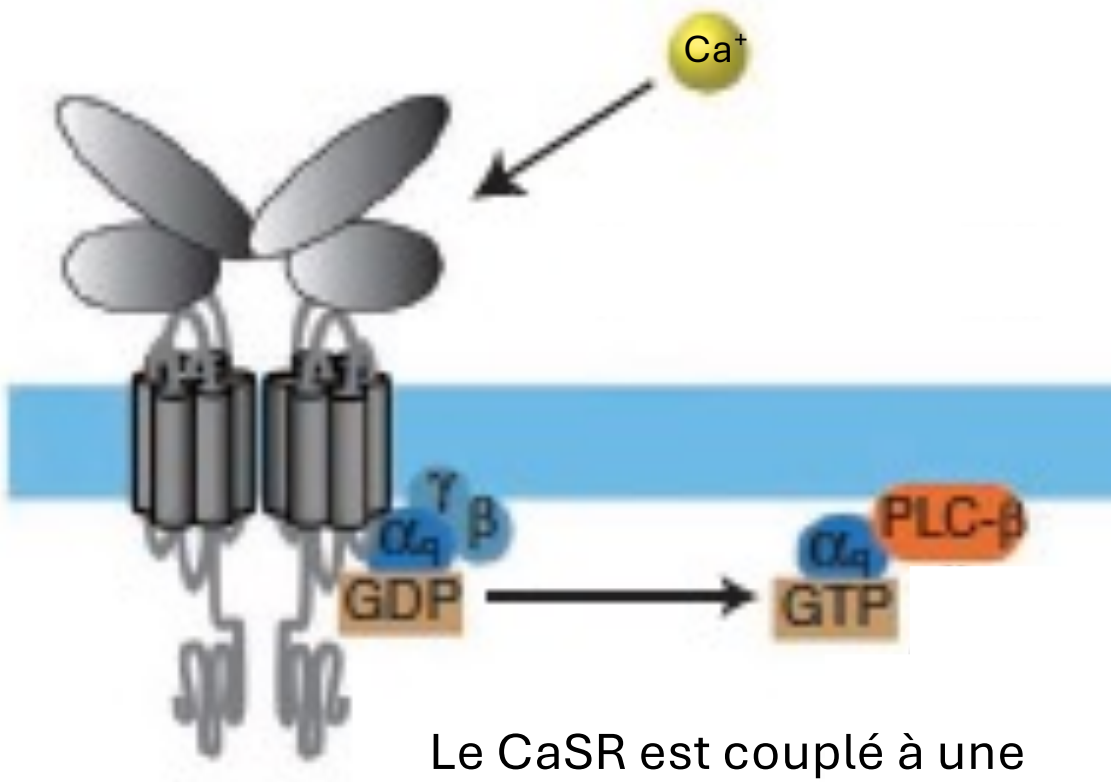


L’appareil de mesure de la calcémie : CaSR

Venus Fly Trap

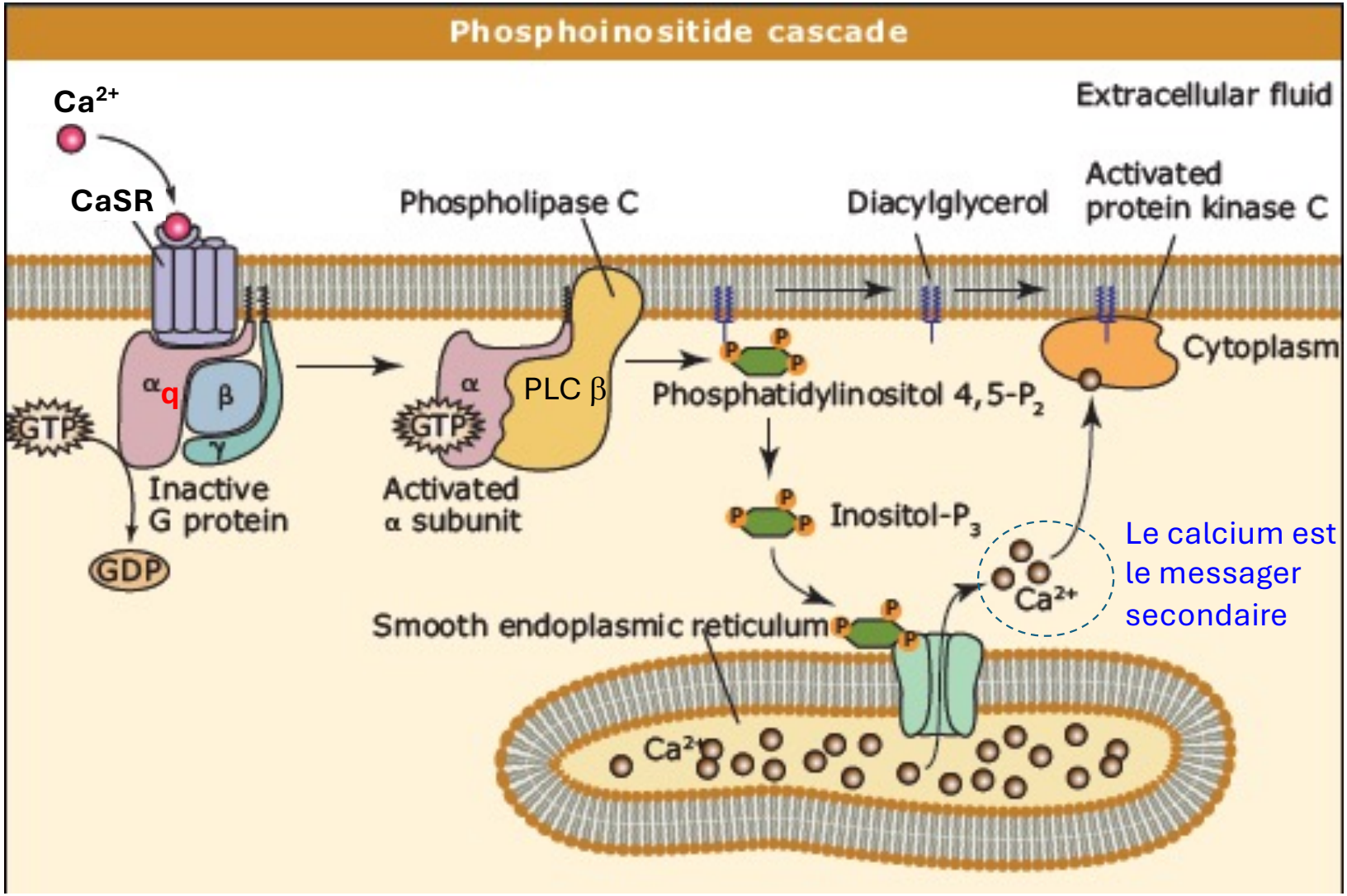


Comment une cellule mesure-t-elle la concentration **extracellulaire** de calcium ?



Le CaSR est couplé à une protéine G trimérique.

Mesure de$[Ca^{2+}]_e$



Réticulum endoplasmique lisse (REL)

Perte de fonction / Gain de fonction

CaSR :

Des **mutations** différentes touchant ***un même gène*** peuvent causer

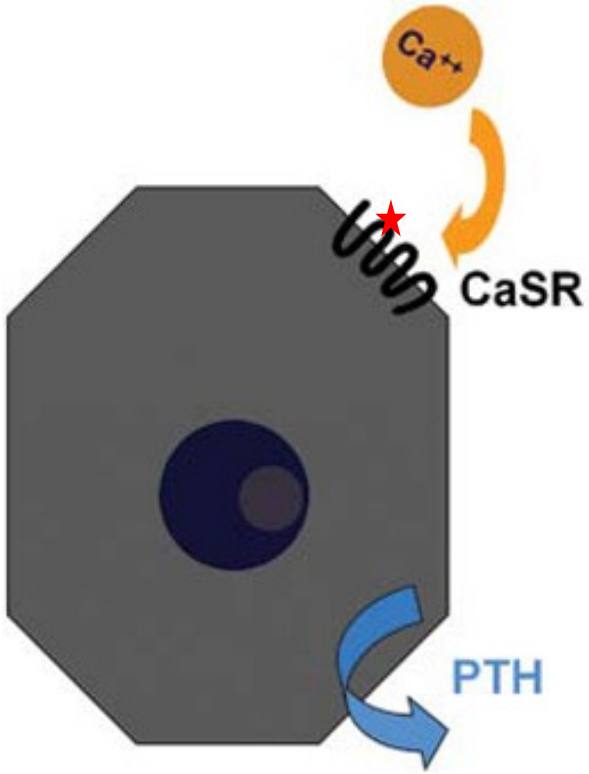
- une perte de fonction
- un gain de fonction

pour la protéine codée par le gène.

Le **phénotype** induit par la perte de fonction peut être ***l'opposé*** du phénotype induit par le gain de fonction.

★ → hypercalcémie

★ → hypocalcémie



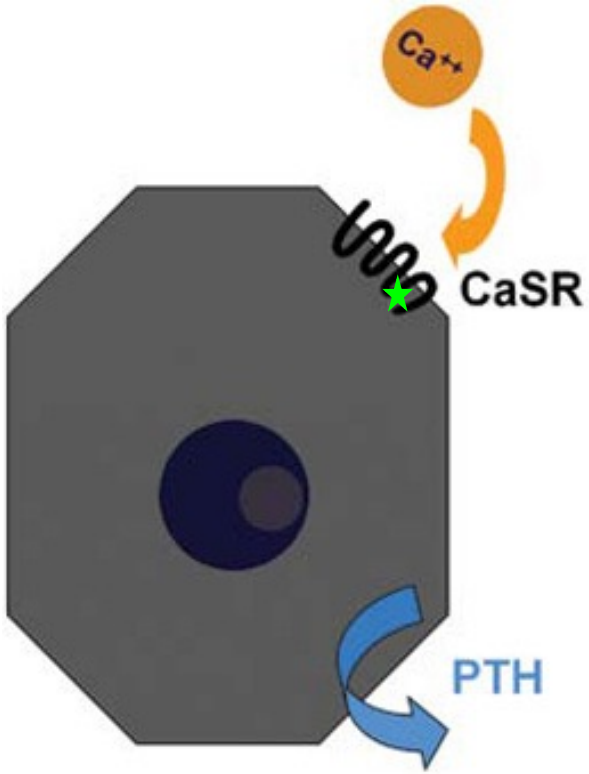
Les cellules de la glande parathyroïde mesurent la calcémie :

★ **mutation inactivante**

La cellule sous-estime la calcémie: une calcémie normale est perçue comme anormalement basse.

La PTH est sécrétée en excès :

→ hypercalcémie



Les cellules de la glande parathyroïde mesurent la calcémie :

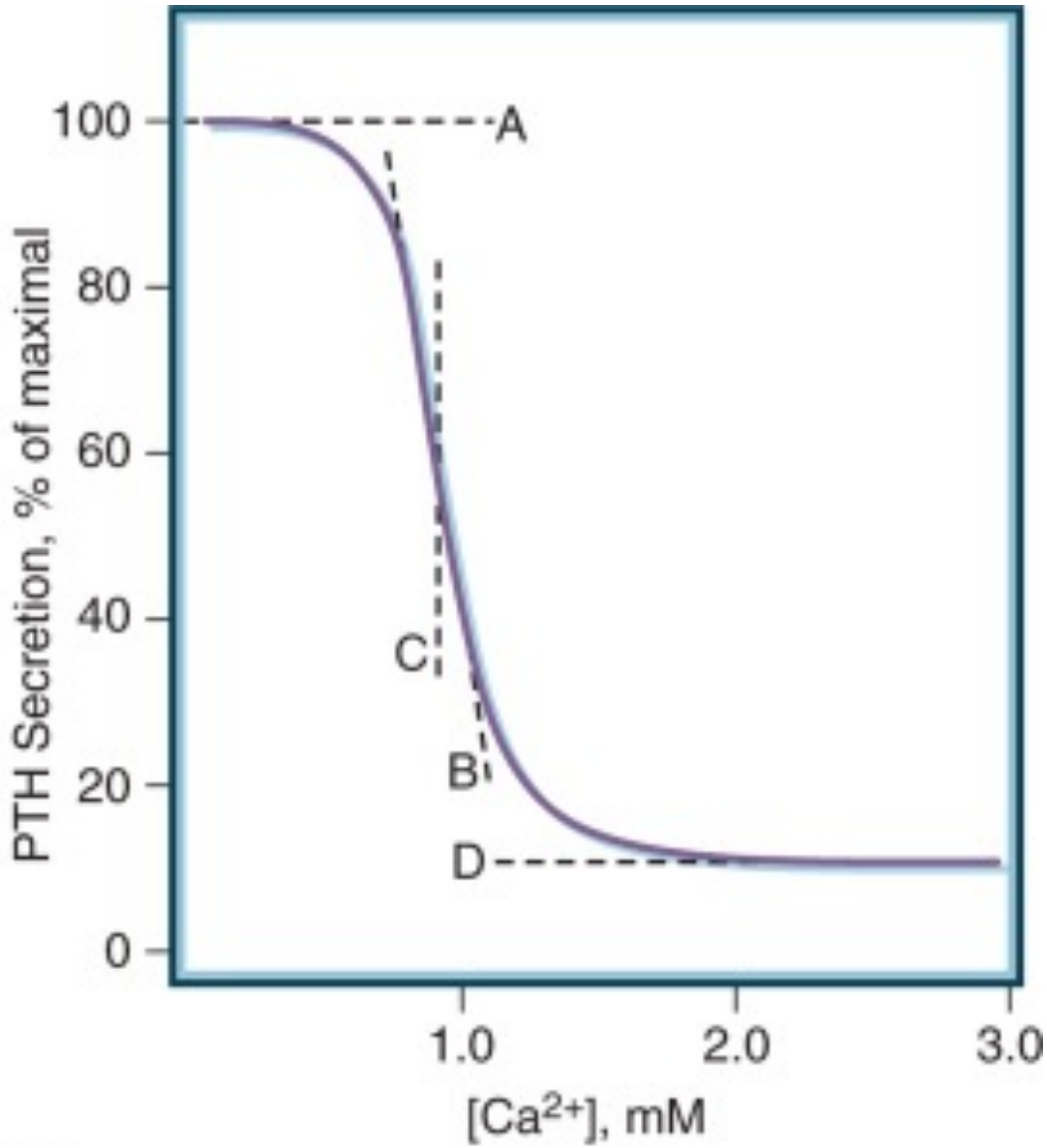
★ **mutation activante**

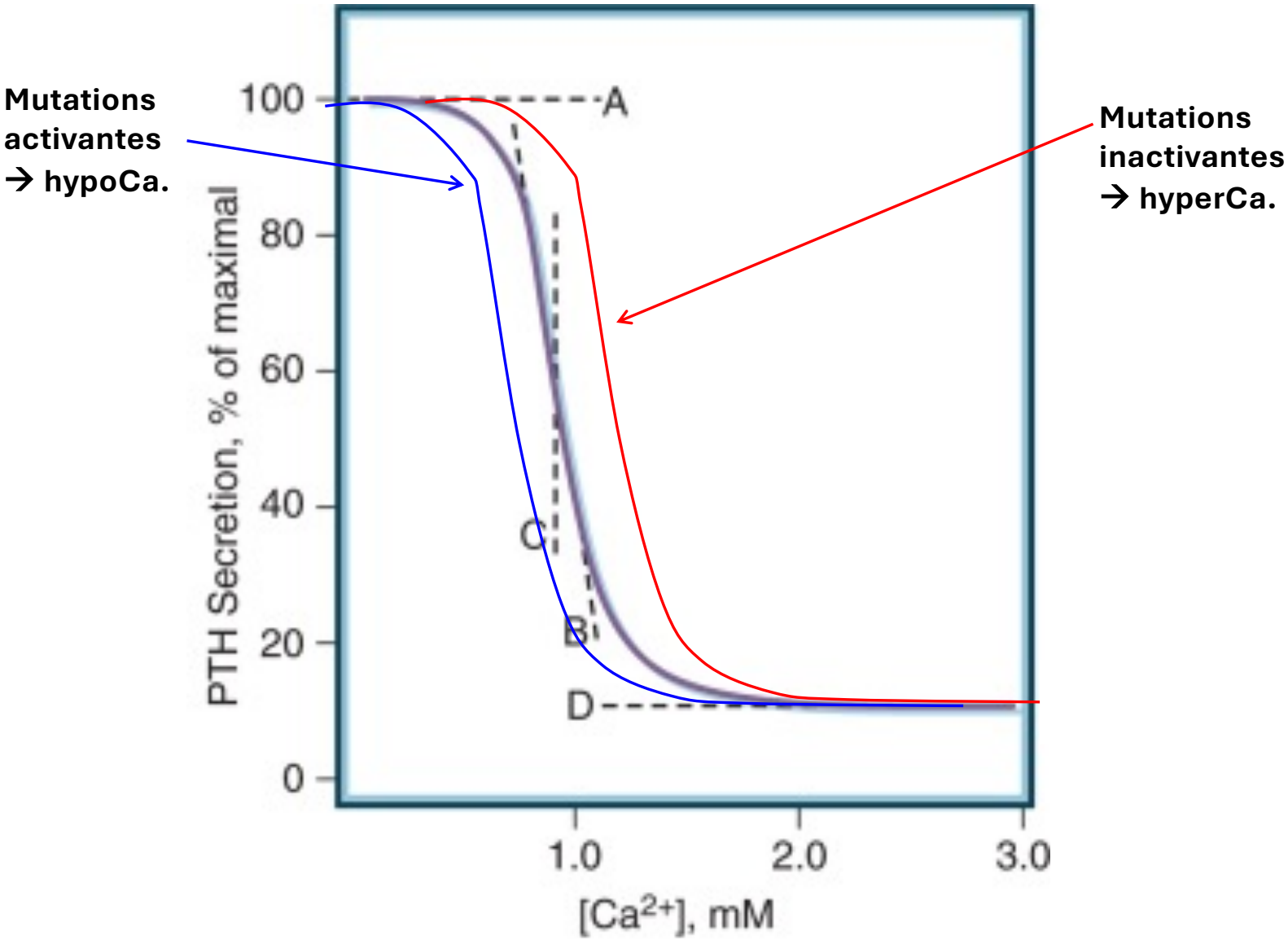
La cellule surestime la calcémie: une calcémie basse est perçue comme normale.

La PTH n'est pas sécrétée pour corriger la calcémie trop basse :

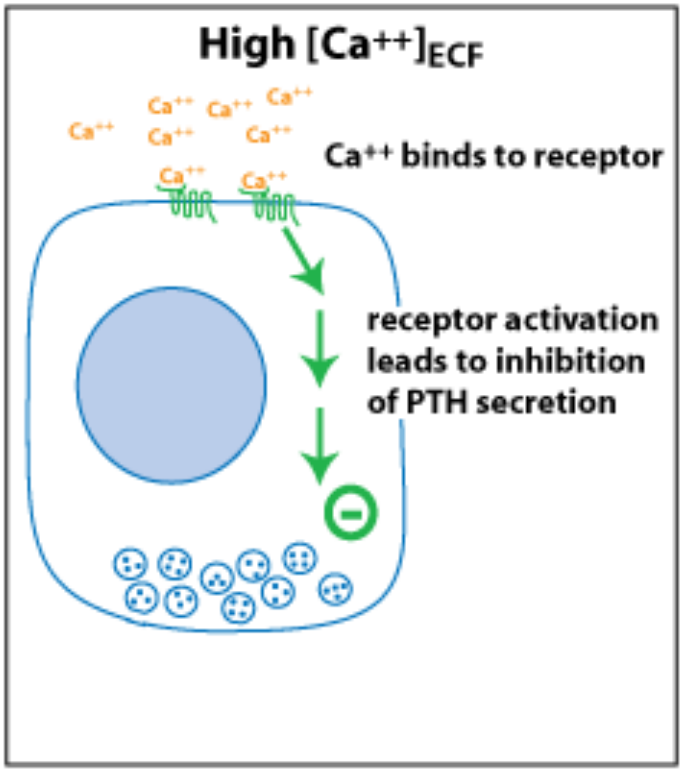
→ hypocalcémie

La calcémie régule
la sécrétion de PTH

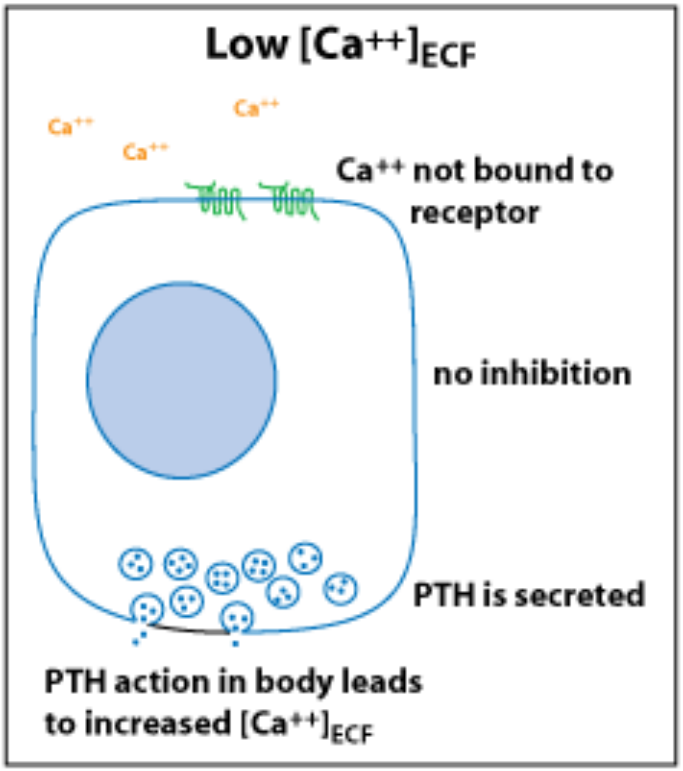



Mutations activantes → hypoCa.
Mutations inactivantes → hyperCa.
PTH Secretion, % of maximal
100
80
60
40
20
0
A
C
B
D
1.0
2.0
3.0
[Ca2+], mM

Impact de la **calcémie** sur la fonction des cellules de la parathyroïde.

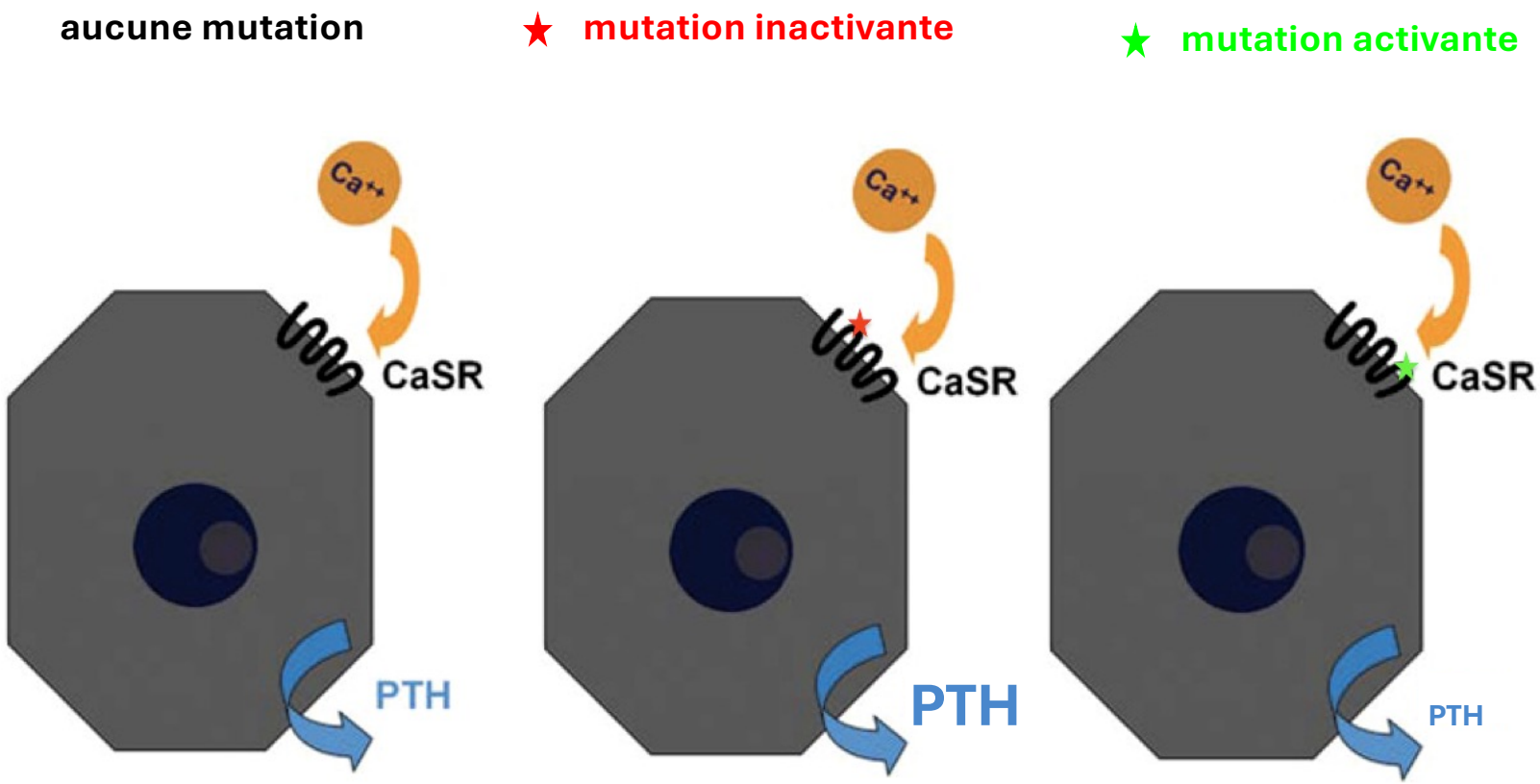


Quand la calcémie est normale les cellules fabriquent la PTH mais ***ne la libérent pas***.



Quand la calcémie est trop basse les cellules fabriquent la PTH et ***la libérent***.

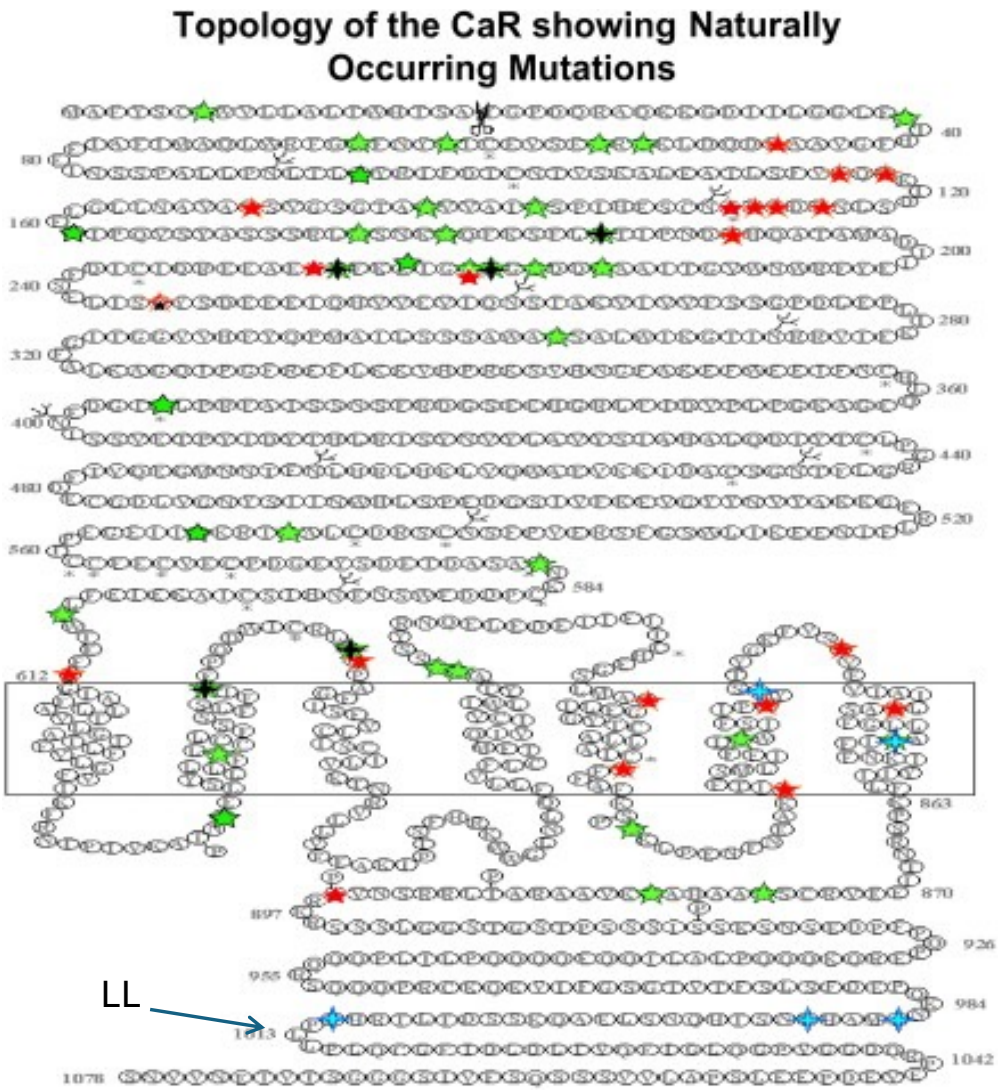
Deux types de mutations dans la même protéine :



calcémie normale

hypercalcémie

hypocalcémie



★

Q127A → ADH

C129S → ADH

Autosomique Dominante Hpercalcémie

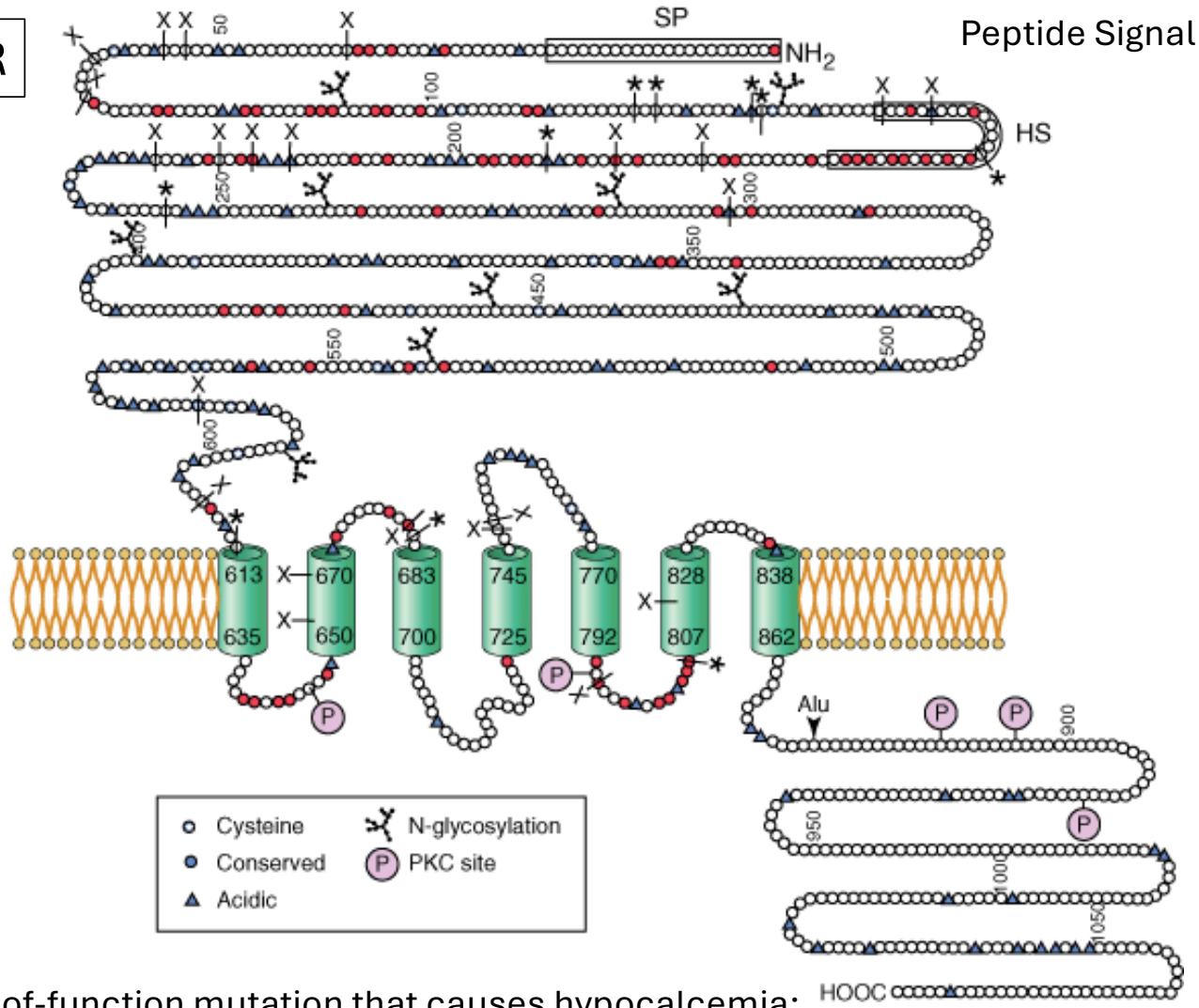
7 domaines TM

Endocytose !

LL

CaSR

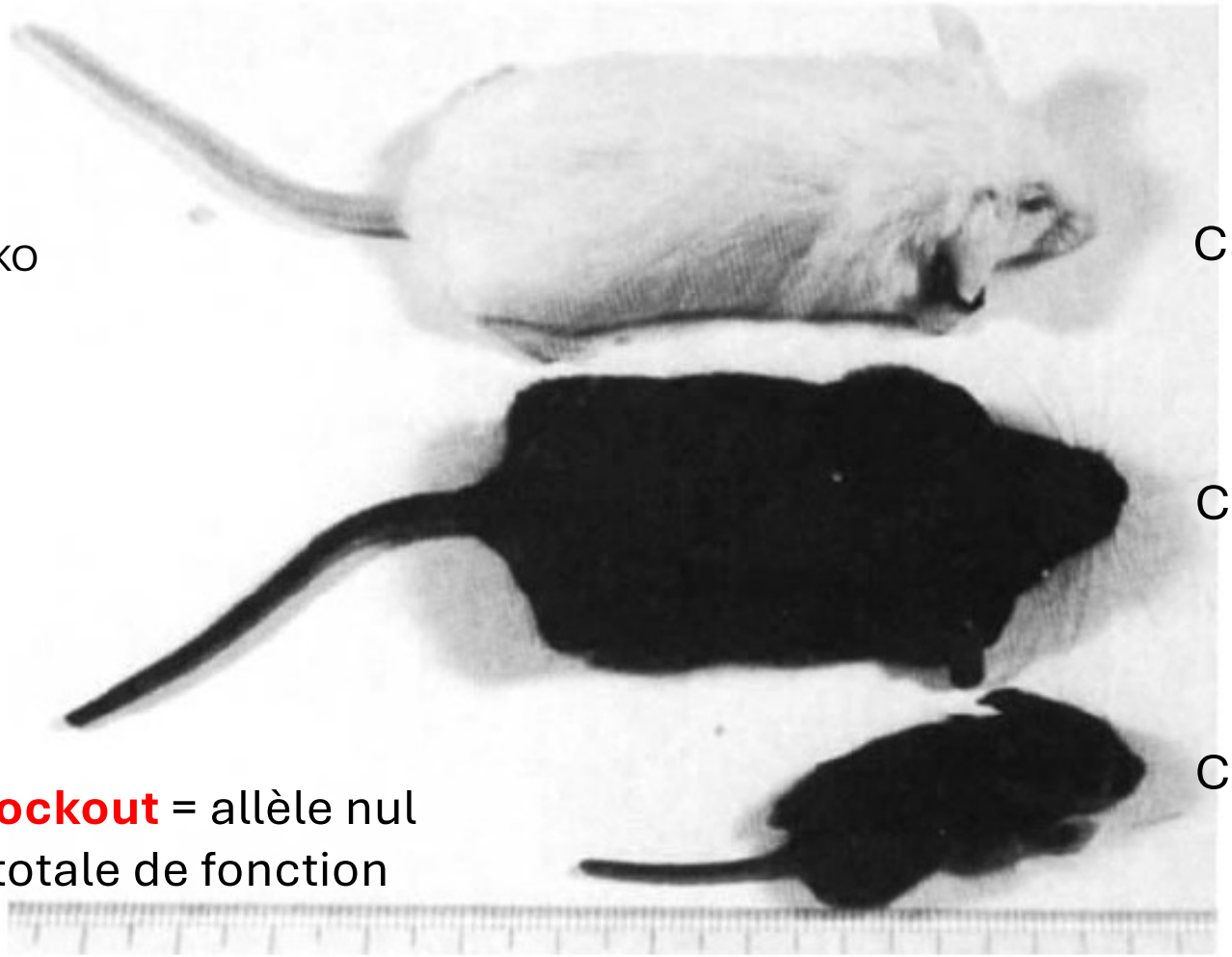
Peptide Signal



* a gain-of-function mutation that causes hypocalcemia;

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Importance de CaSR
illustréee par les souris KO



CaSR +/+

CaSR +/-

CaSR -/-

Un **knockout** = allèle nul
perte totale de fonction

Fig. 3 Gross appearance of 23 day old *Casr*$^{+/+}$ (top), *Casr*$^{+/-}$ (middle) and *Casr*$^{-/-}$ (bottom) mice.

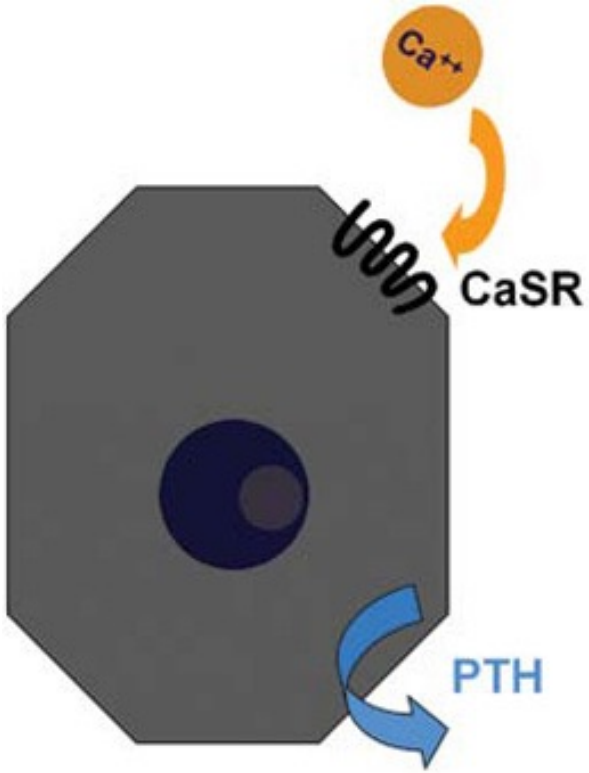
Table 1 Blood and urine profiles of *Casr*$^{+/+}$, *Casr*$^{+/-}$ and *Casr*$^{-/-}$ mice

	Casr$^{+/+}$ (*n*)	Casr$^{+/-}$ (*n*)	Casr$^{-/-}$ (*n*)
Serum total Ca^{++} (mg dl^{-1})	9.6 ± 0.3 (31)	10.4 ± 0.55 (29)**	14.8 ± 1.0 (7)**
Serum ionized Ca^{++} (mM)	1.2 ± 0.1 (4)	1.4 ± 0.0 (4)**	NA
Serum PTH[a] (pg ml^{-1})	25 ± 6.4 (8)	39.1 ± 14.7 (8)*	NA
Serum PTH[b] (pg ml^{-1})	12.2 ± 7.0 (5)	NA	129.1± 90 (6)*
Serum total Mg^{++} (mEq L^{-1})	2.43 ± 0.24 (16)	2.74 ± 0.53 (16)*	2.85 ± 0.59 (8)*
Urine[c] total Ca^{++} (mg dl^{-1})	20.18 ± 9.6 (10)	11.73 ± 9.3 (15)*	10.45 ± 7.7 (18)*
Haematocrit (%)	33.1 ± 3.5 (5)	34.35 ± 3.4 (8)	39.4 ± 3.7 (12)**
Body weight[d]	13.0 ± 1.5 (3)	12.4 ± 1.1	3.51 ± 1.8 (5)**

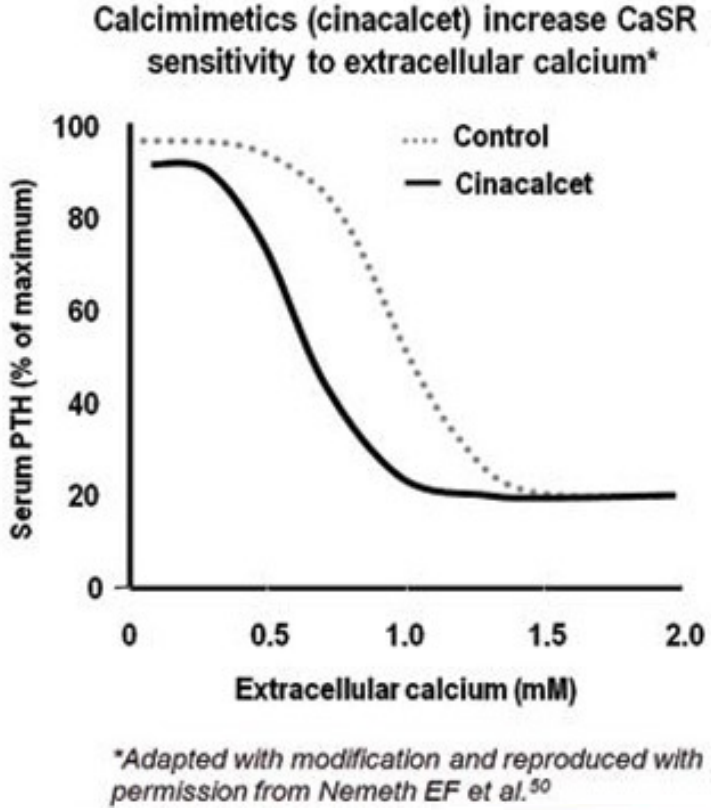
Results are means ± standard deviation (*n*, number of mice analysed).
* *P* values = 0.05 to 0.005 for t-test comparing mutant mice to *Casr*$^{+/+}$ mice.
** *P* values < 0.005 for t-test comparing the mutant mice to *Casr*$^{+/+}$ mice.
[a]PTH assays were done on 61 to 73 day old mice, fasted over night.
[b]PTH assays were done on 15 to 26 day old mice.
[c]Calcium concentrations were measured from urine aspirated from the bladders of mice (age two to three days).
[d]Body weight are measurements from 13 day old male mice.
NA test was not performed.

Un médicament augmente la sensibilité de CaSR au calcium.

Pharmacologie

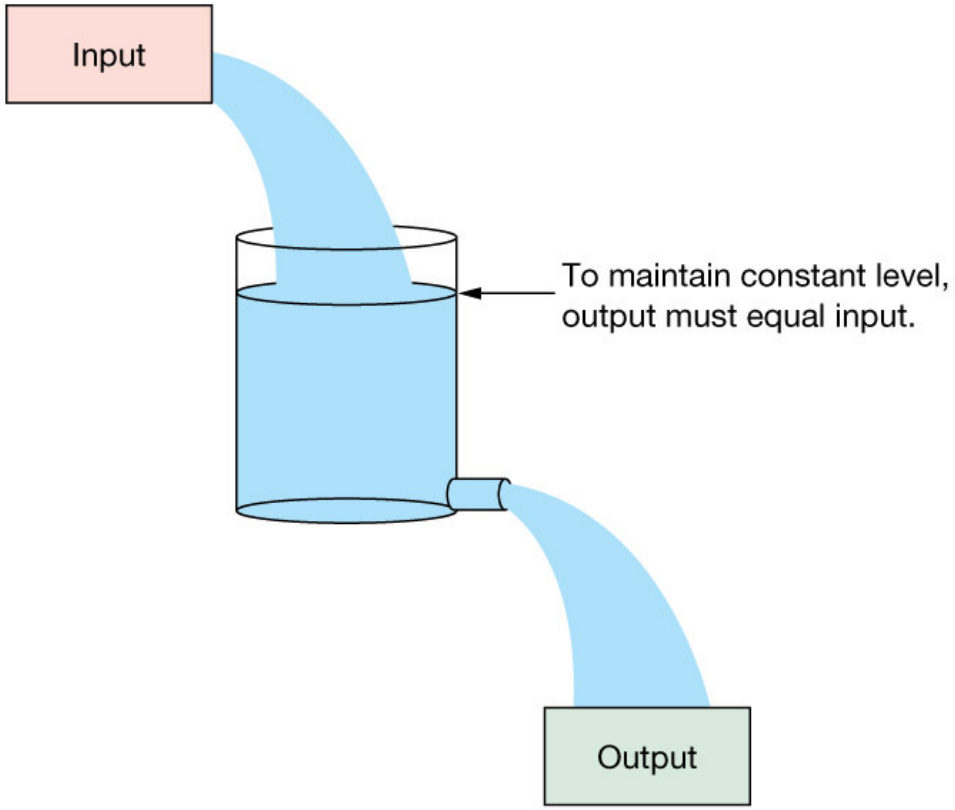


Action allostérique



https://de.wikipedia.org/wiki/Cinacalcet

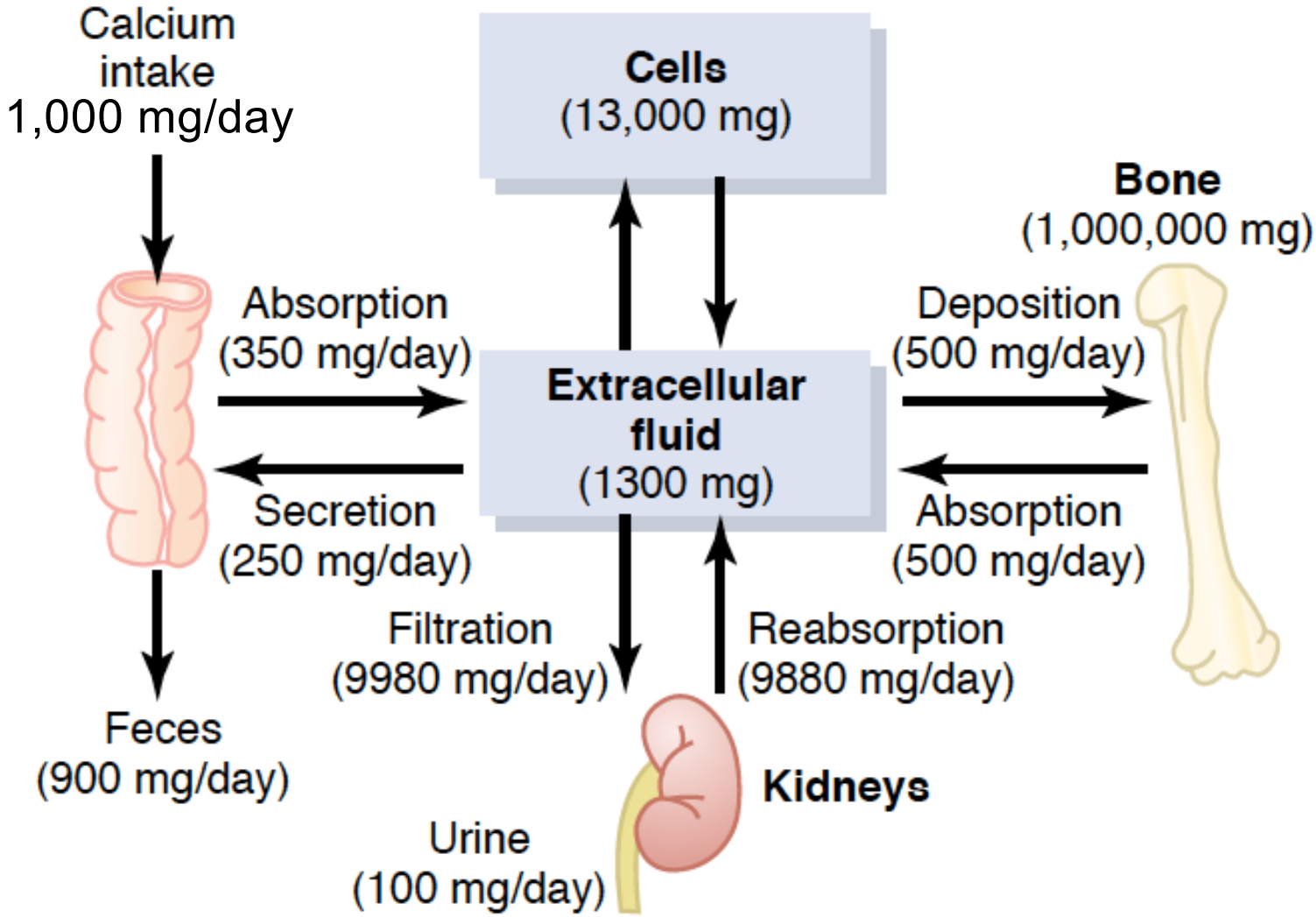
Mass balance



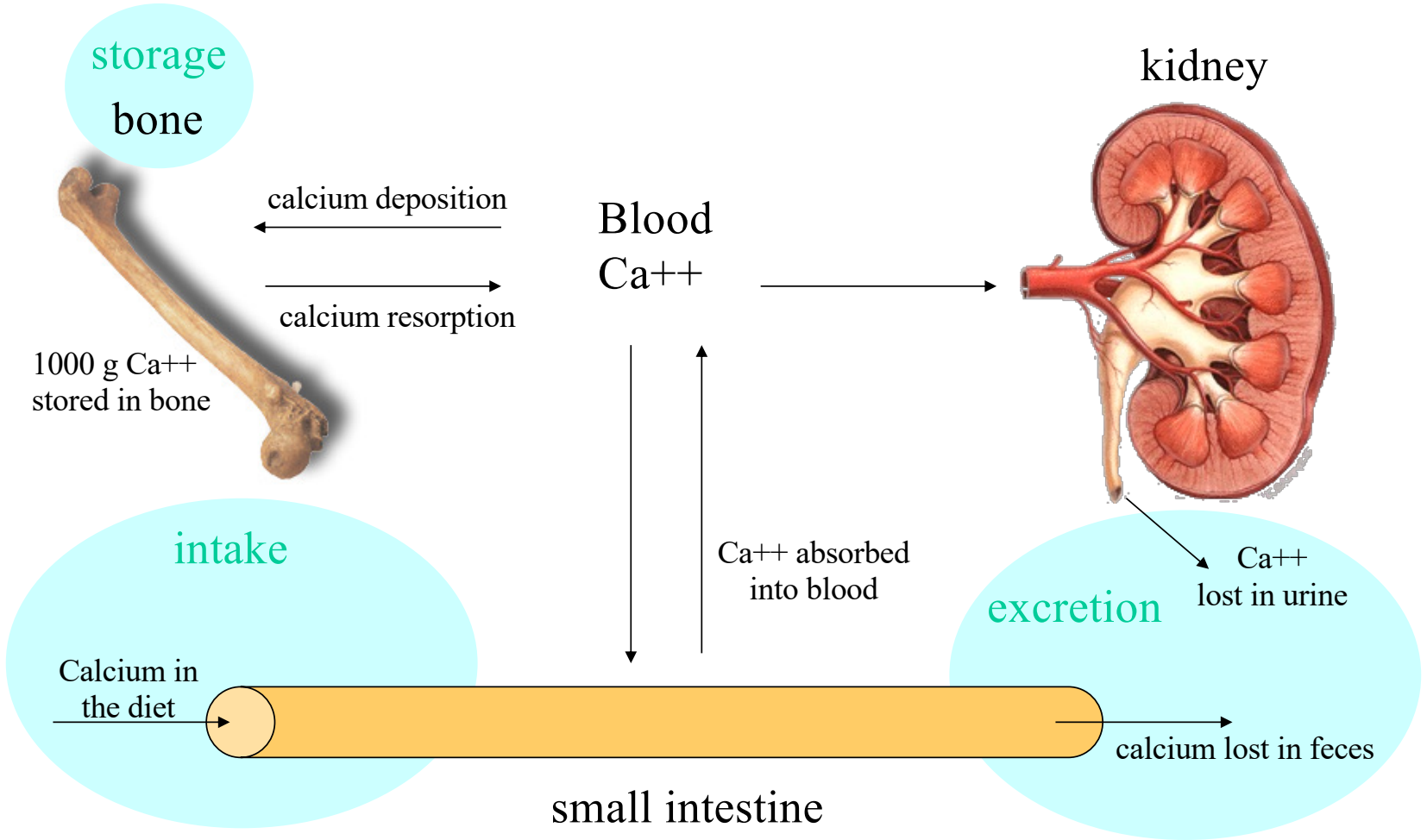
Application au Calcium

Bilan calcique :

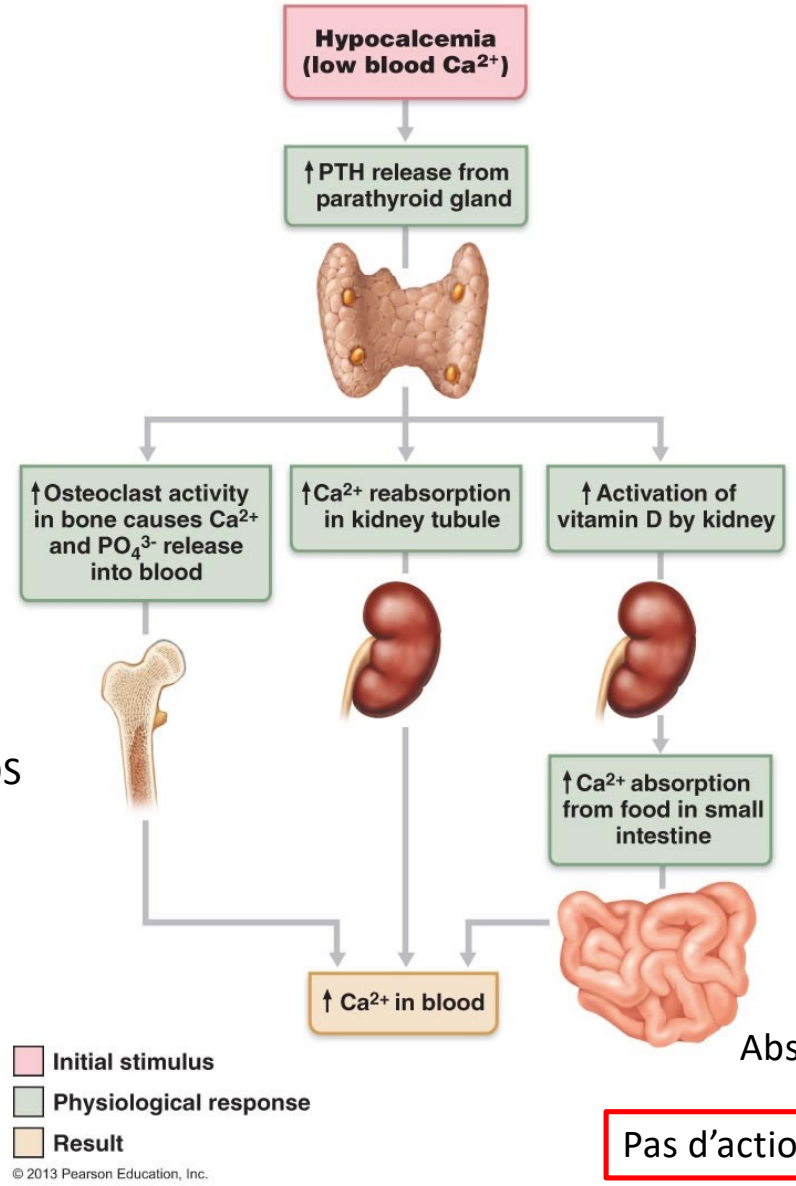
1 g/j est recommandé



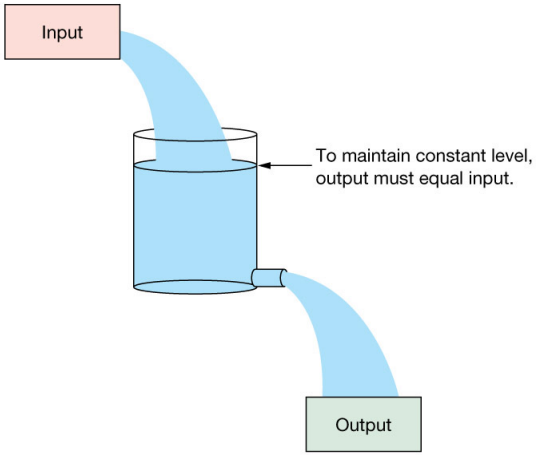
Calcium homeostasis



Sites d'action de la PTH :



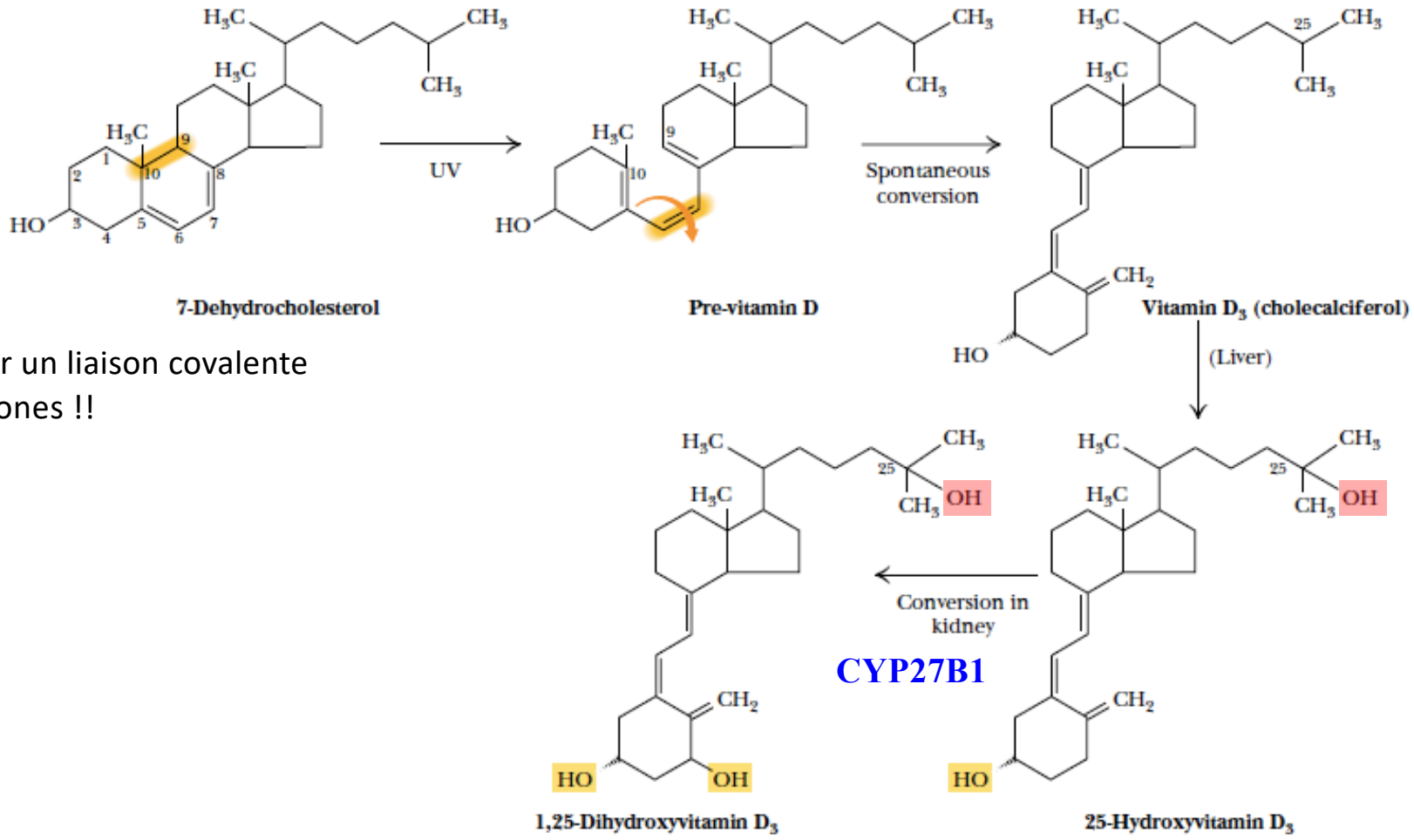
OS



Vitamine D

Absorbtion intestinale

Pas d'action *directe* de la PTH sur l'intestin

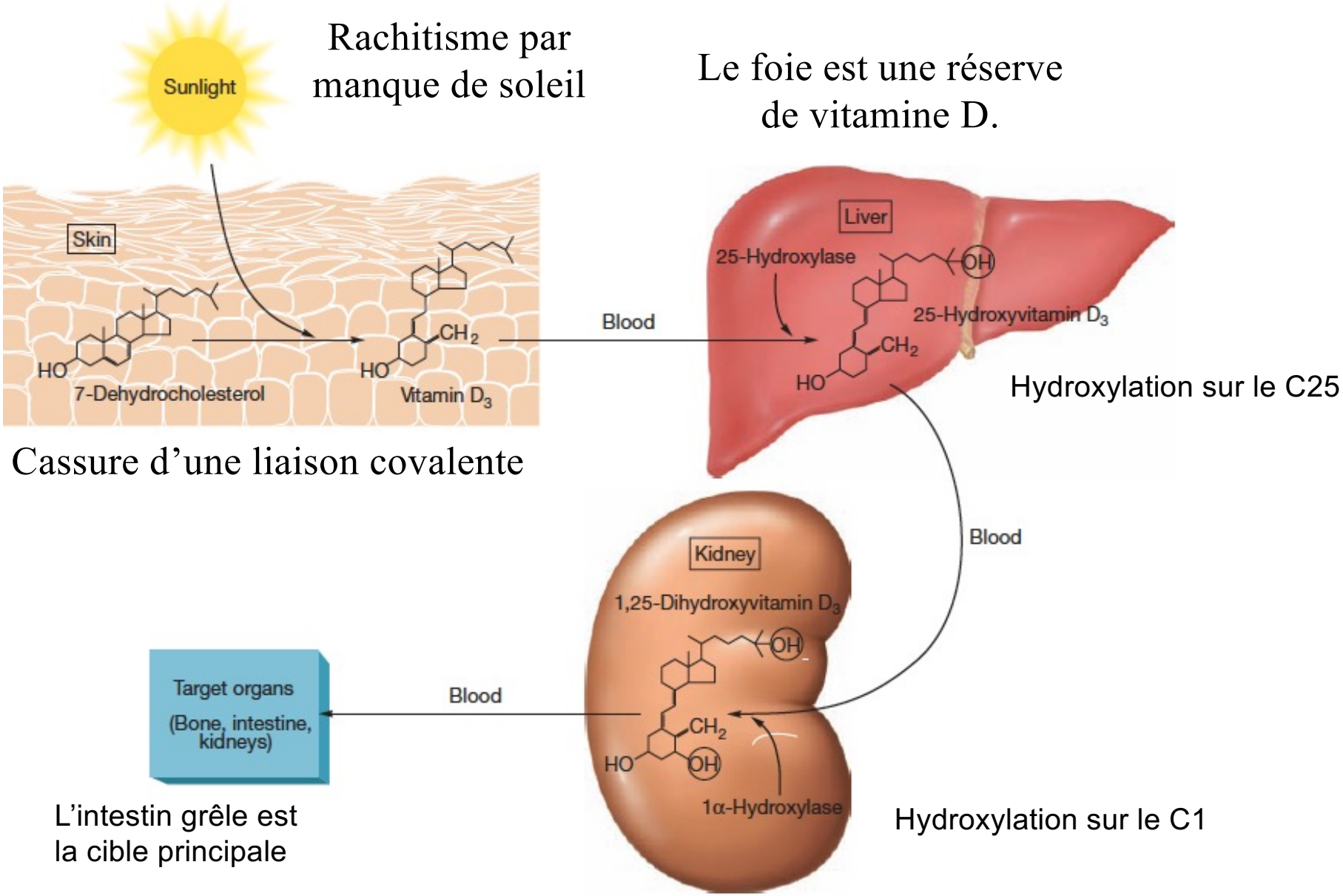


Il faut casser un liaison covalente ente 2 carbones !!

calcitriol

Rachitisme par manque de soleil

Le foie est une réserve de vitamine D.



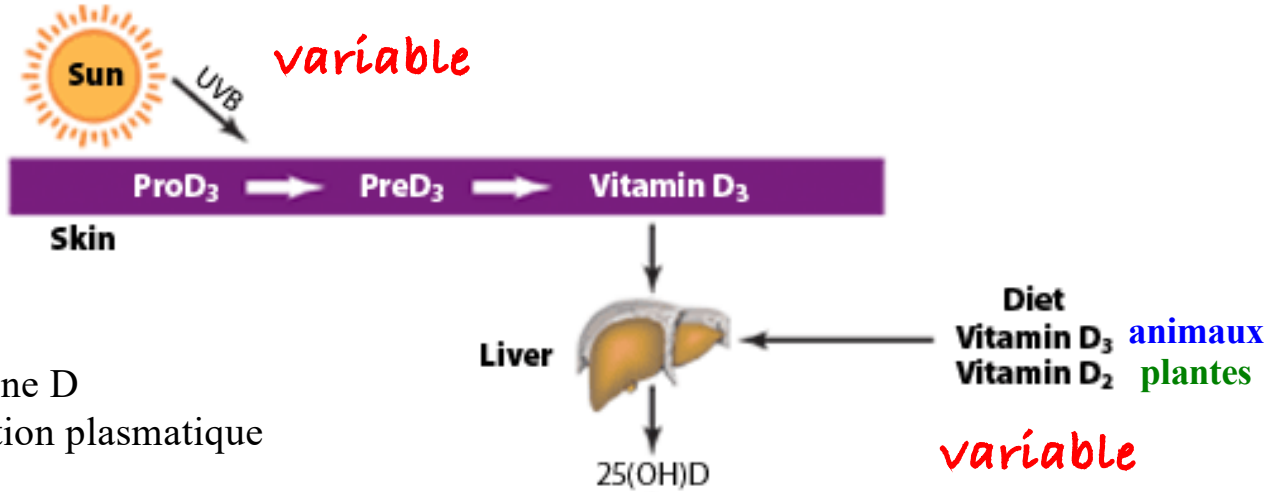
Cassure d'une liaison covalente

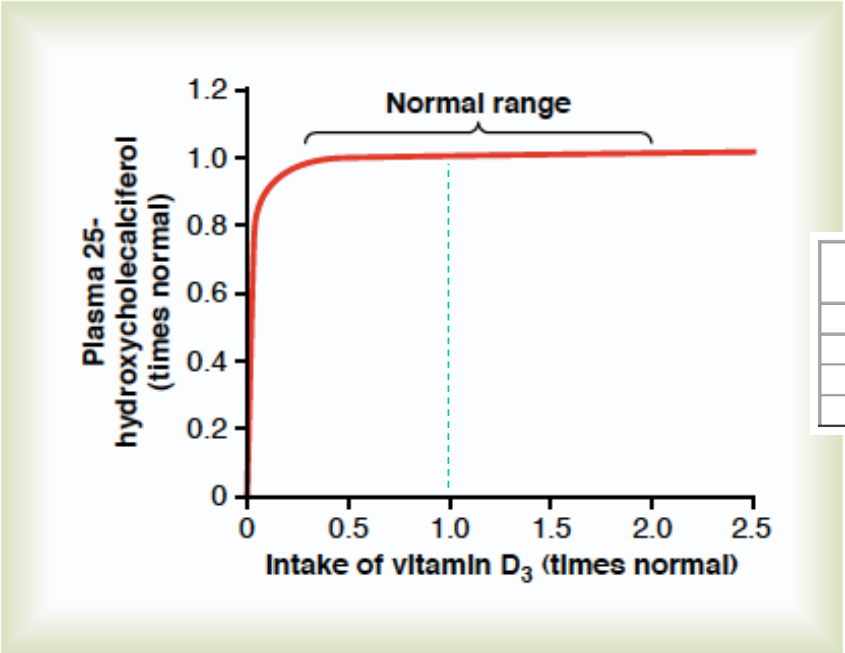
Hydroxylation sur le C25

L'intestin grêle est la cible principale

Hydroxylation sur le C1

Évaluation du statut Vitamine D
par mesure de la concentration plasmatique



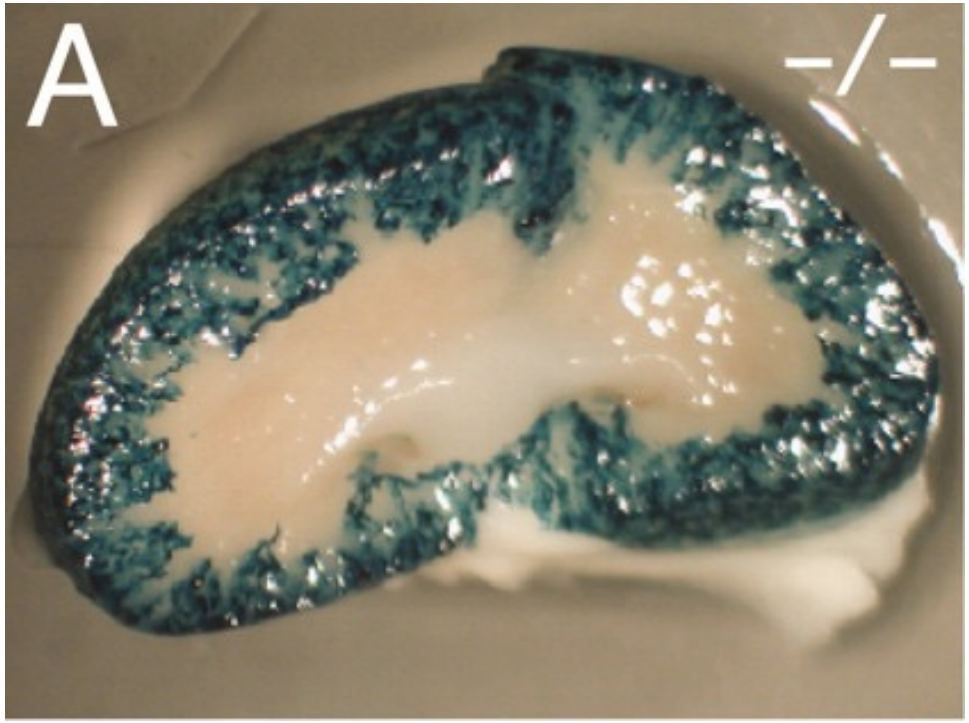


constante

Classification of Vitamin D Status by 25(OH)D Concentration[a,b]	
25(OH)D concentration	Classification
≤10 ng/mL	Deficient
11-20 ng/mL	Insufficient
>20 ng/mL	Optimal

Hydroxylation de la vitamine D sur le carbone 1.

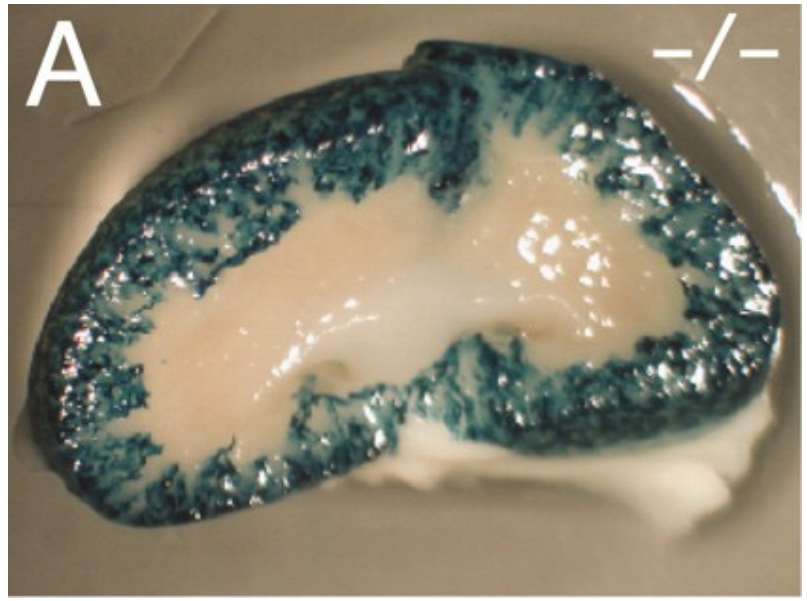
Rein trempé dans une solution de X-Gal

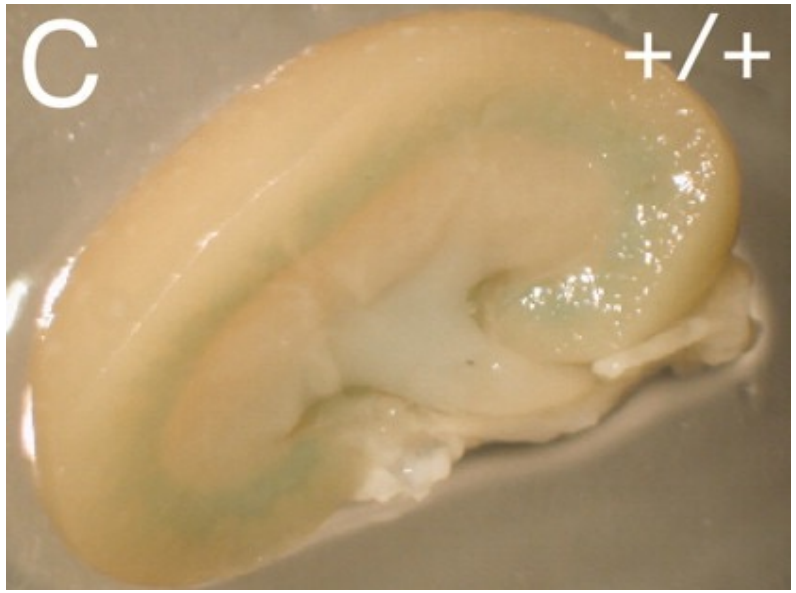


Les cellules bleues sont les cellules qui expriment **lα hydroxylase** (tubule proximal)

Vitamine D :

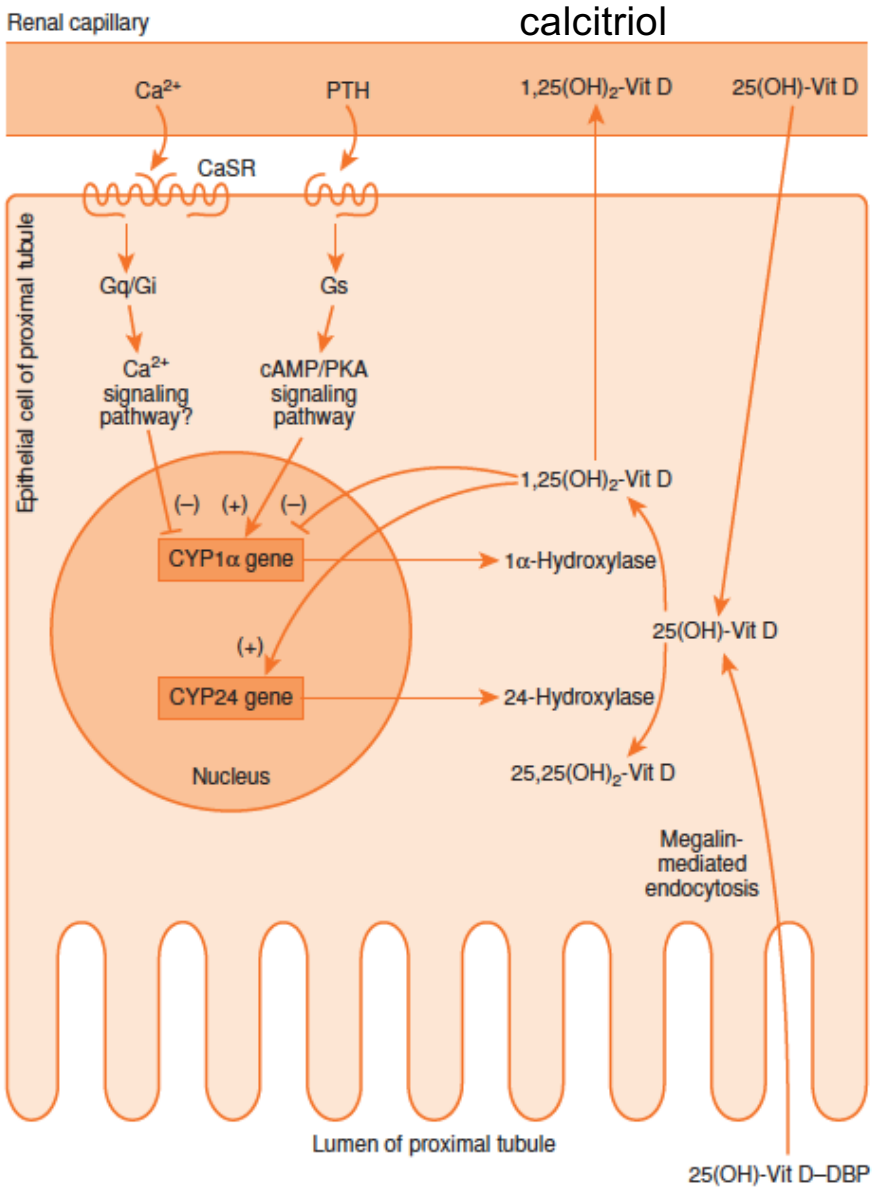
La 2ème hydroxylation se fait dans le tube proximal





Activation rénale de la vitamine D.

Tube proximal

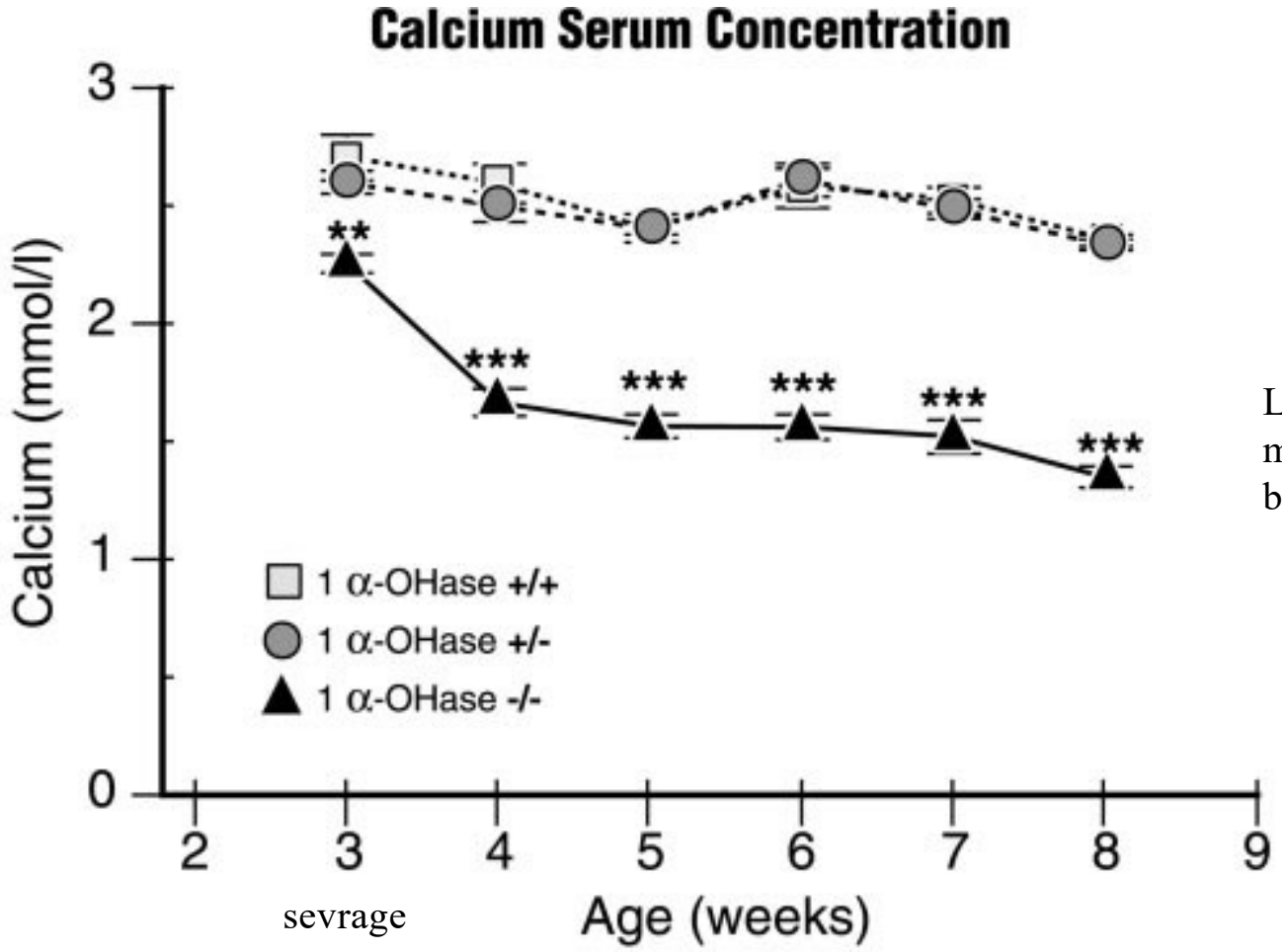


La PTH régule l'hydroxylation sur le Carbone 1.
Le rein ne fait qu'obéir à la PTH.

Passage à travers la membrane apicale

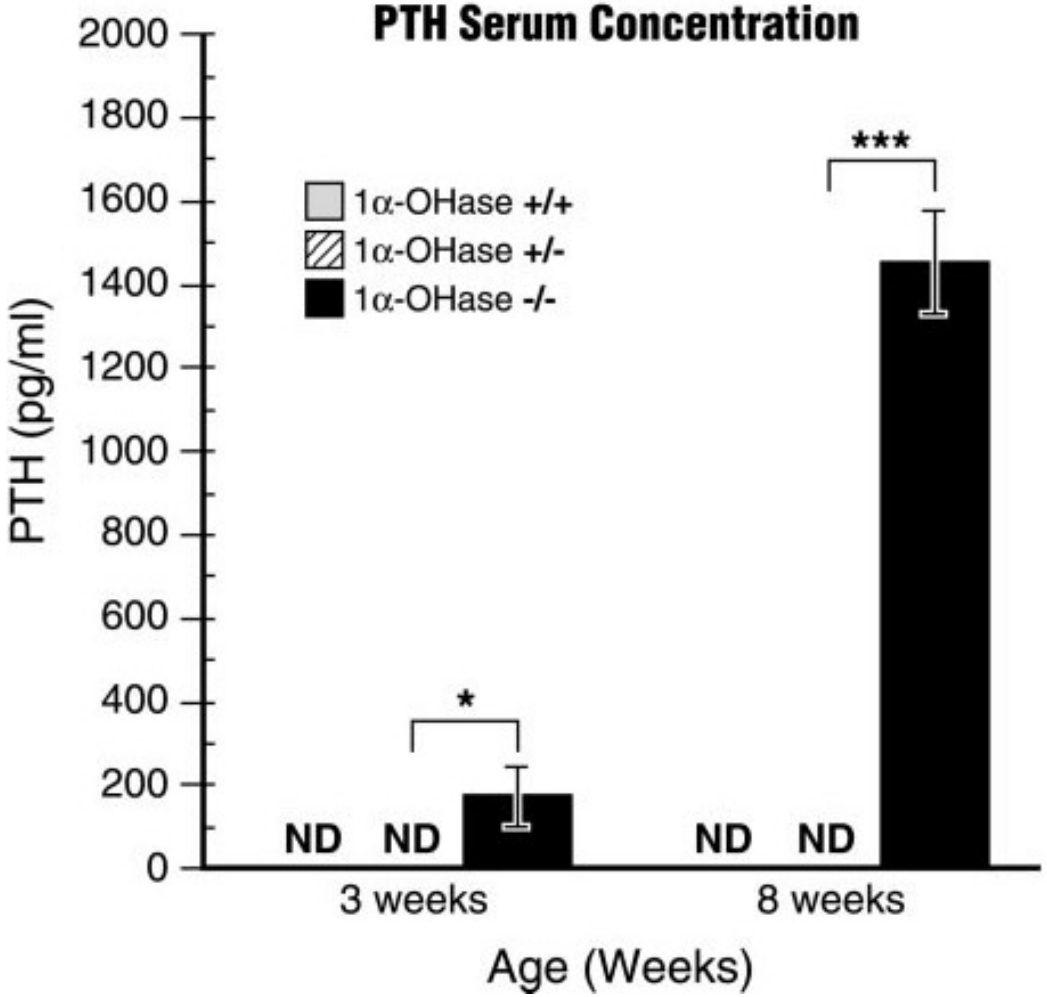
La vitamine D arrive par le côté urinaire.

Ablation du gène codant la **1 α-hydroxylase** :

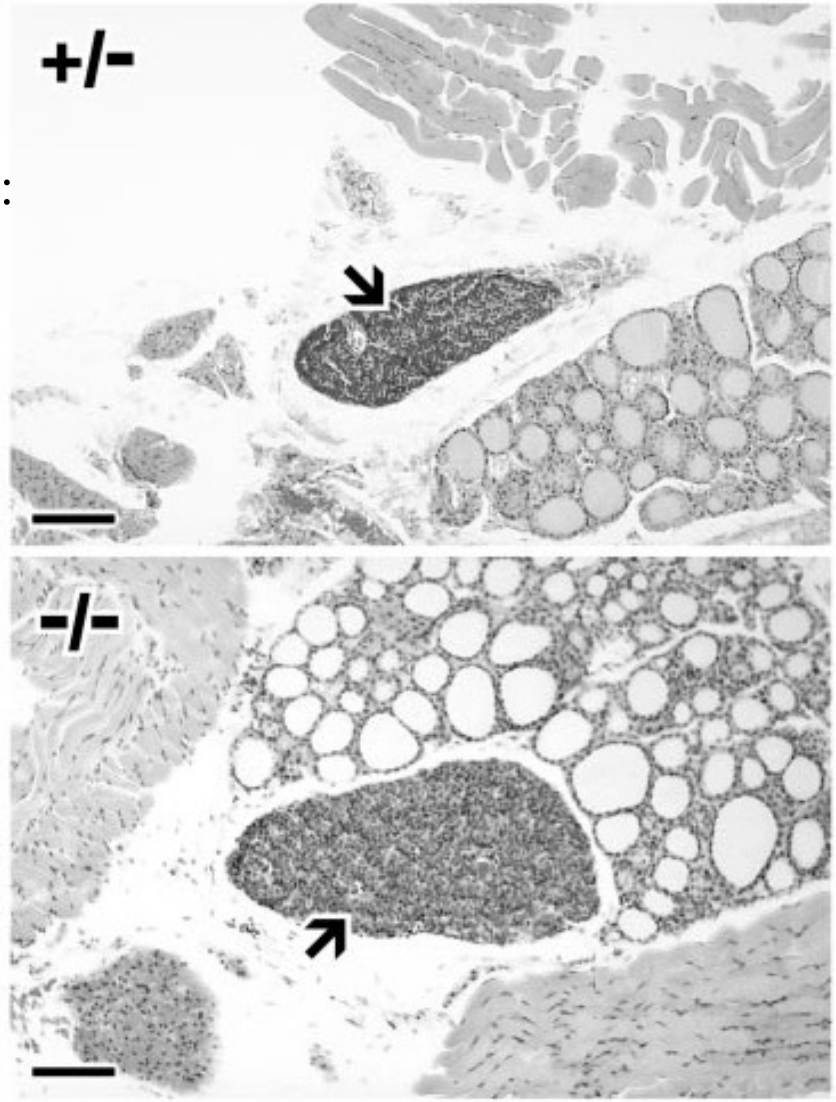


La calcémie est basse mais pas dangereusement basse!!

Ablation du gène codant la **1 α-hydroxylase** :

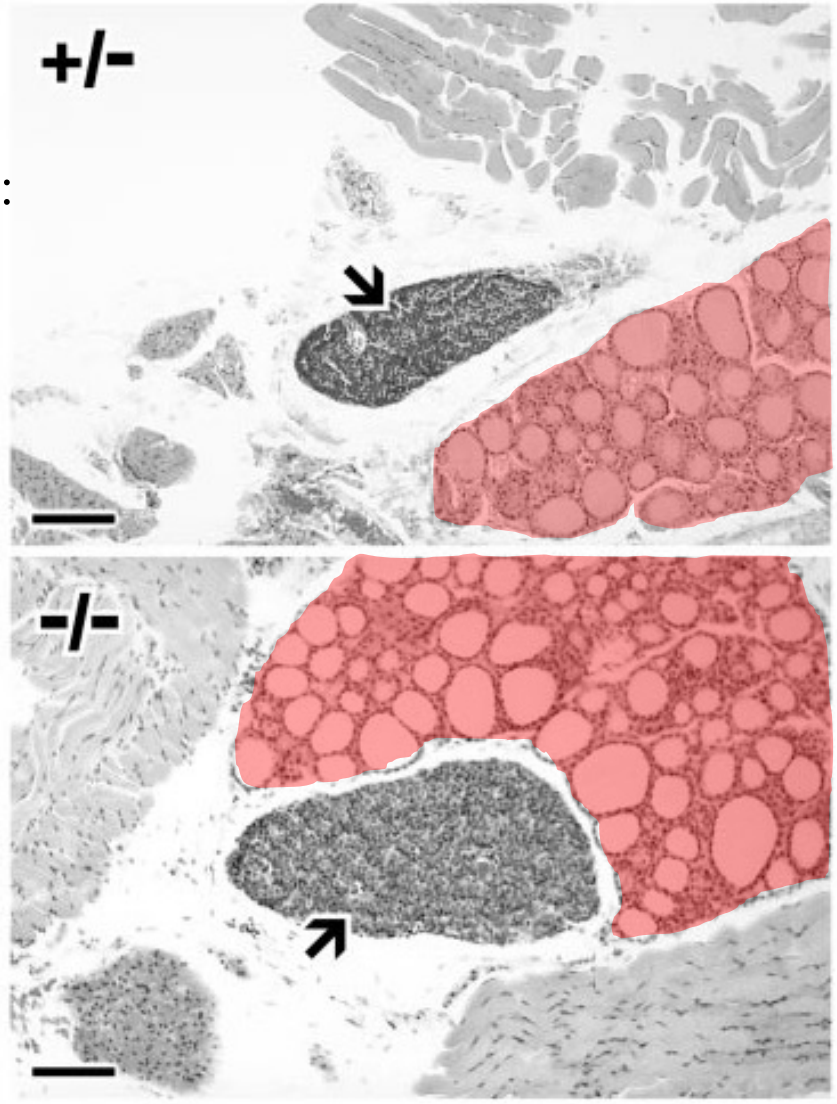


Ablation du gène codant la 1 α-hydroxylase :



Taille de la glande parathyroïdienne augmentée (hyperplasie)

Ablation du gène codant la 1 α-hydroxylase :



Taille de la glande parathyroïdienne augmentée (hyperplasie)

Hyperplasie des 4 glandes