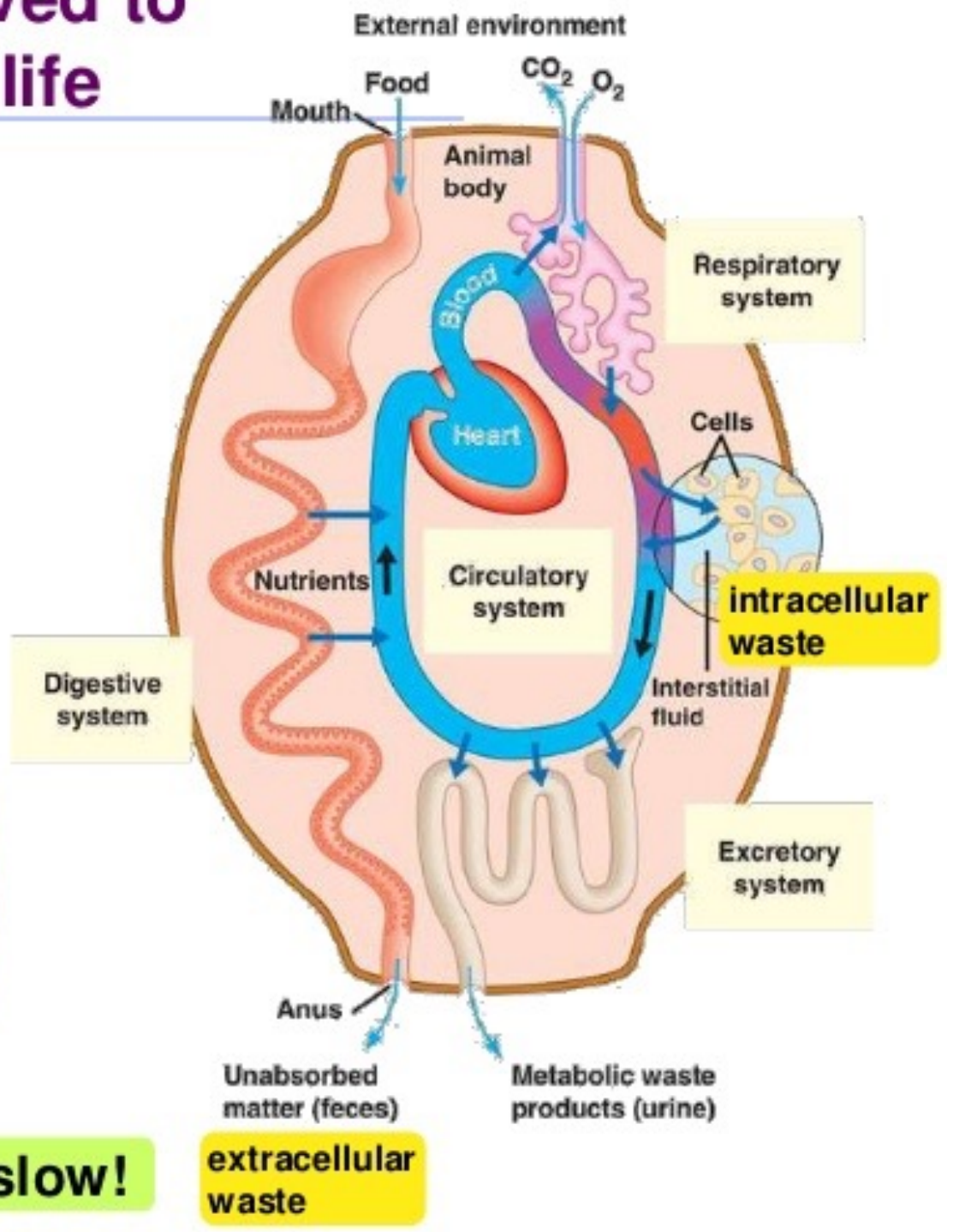
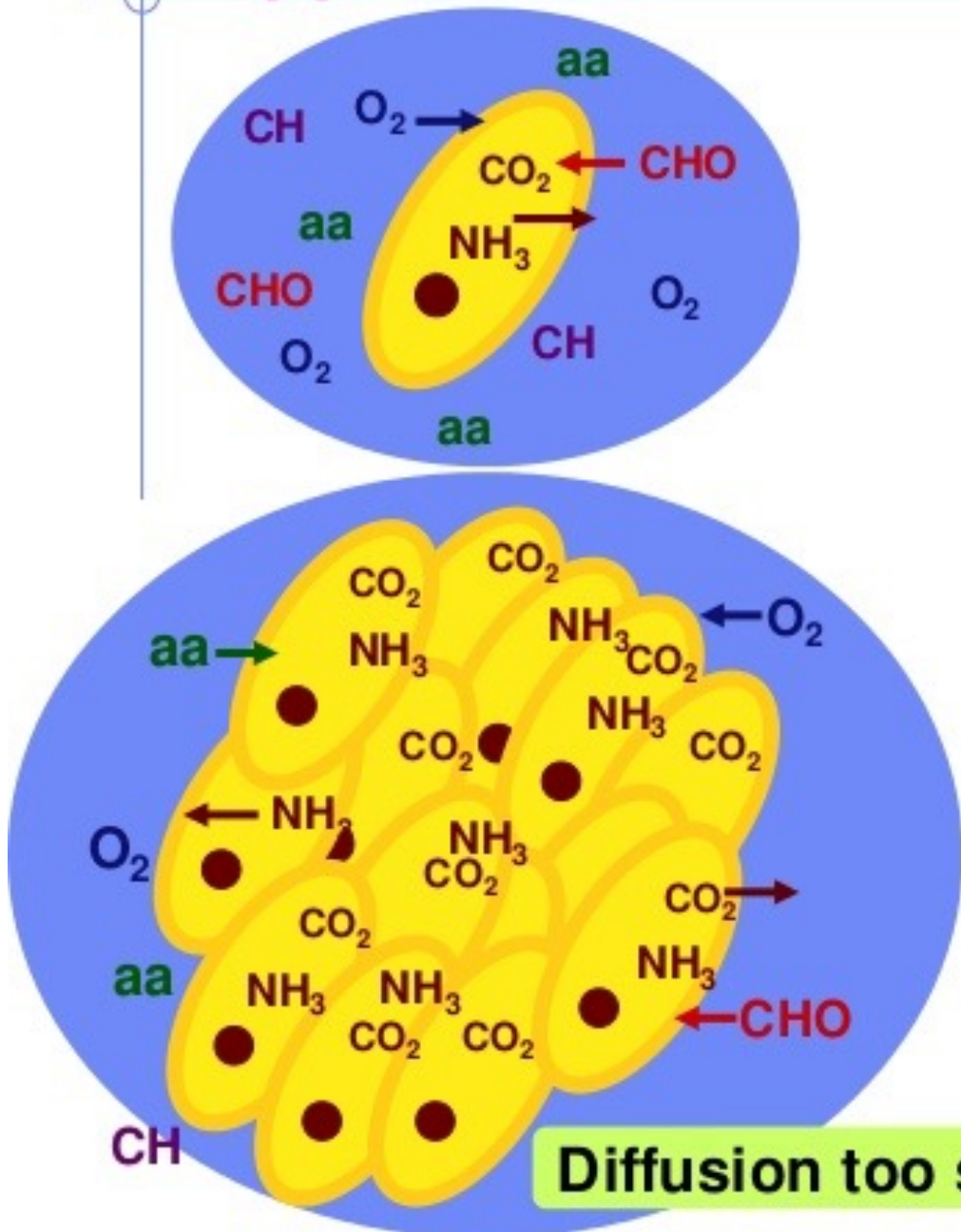
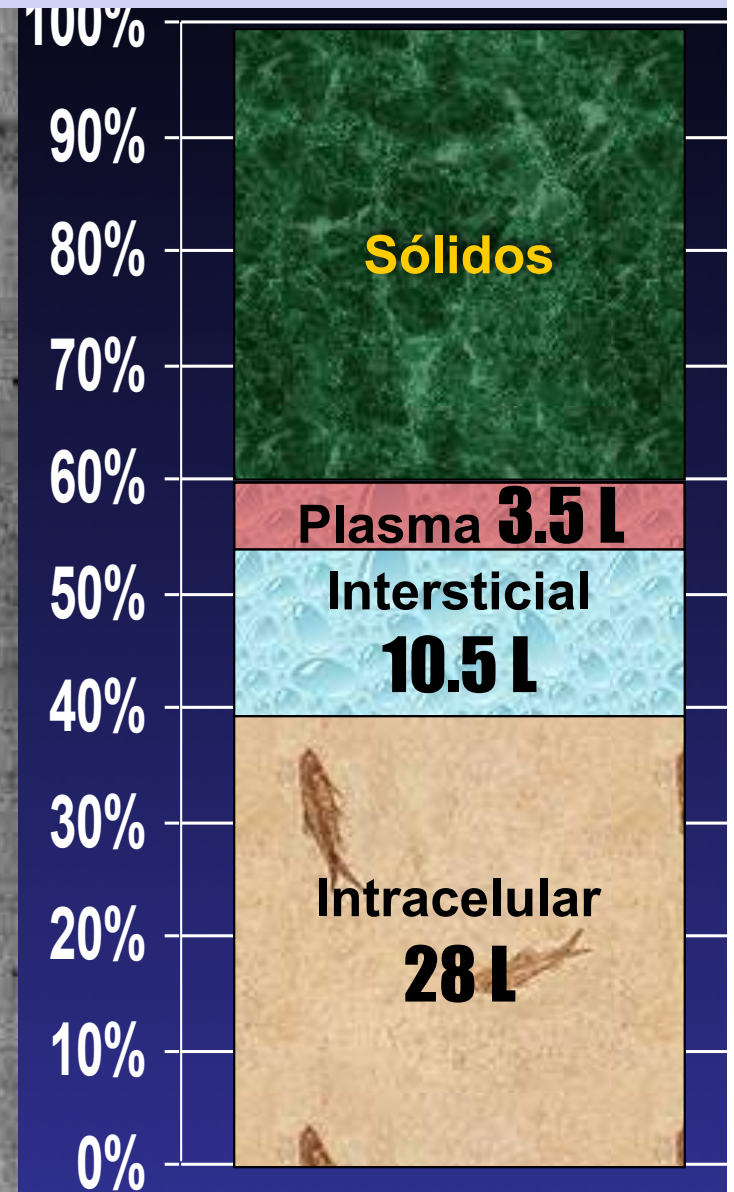
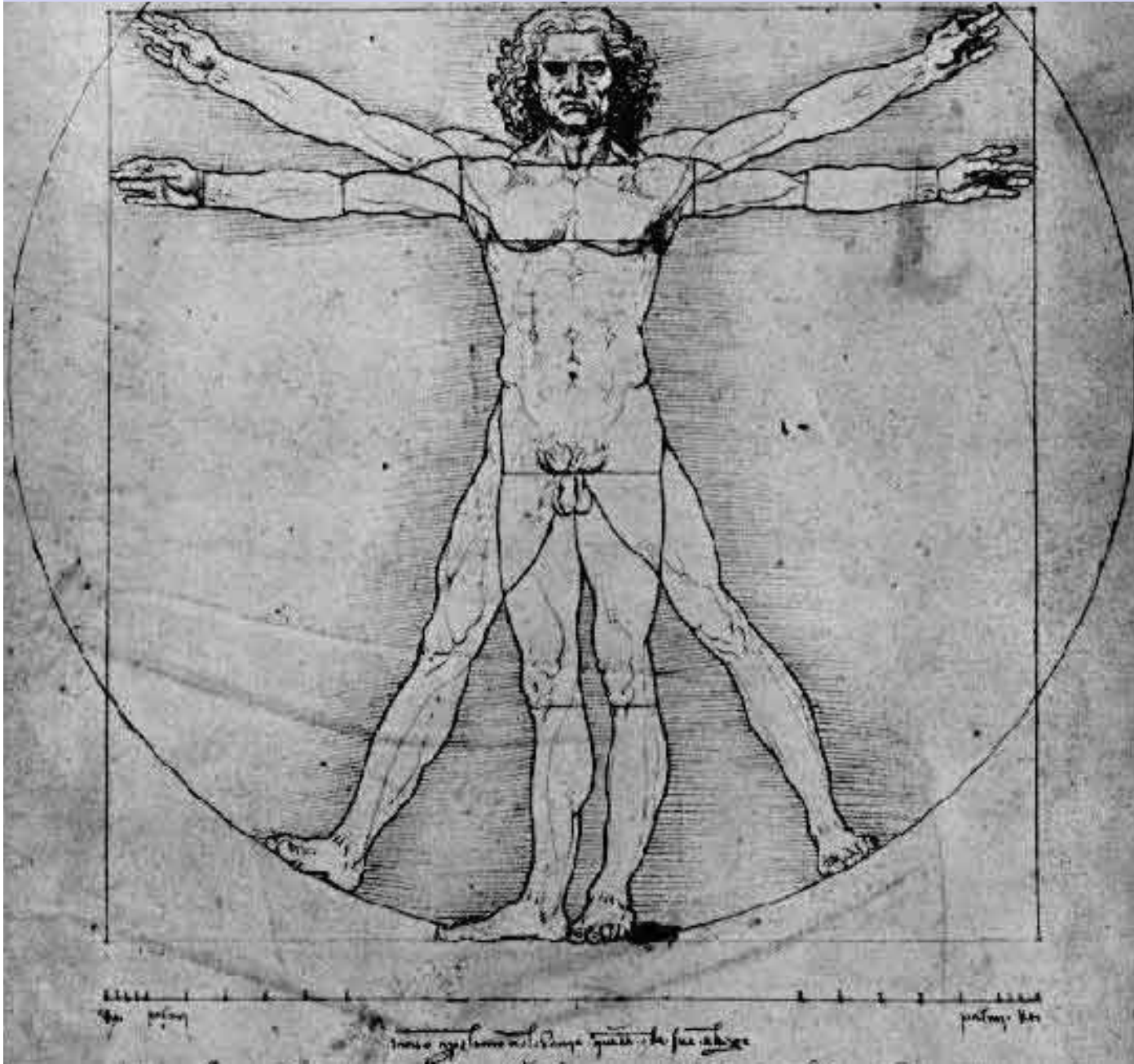


Hidratación y Osmolaridad

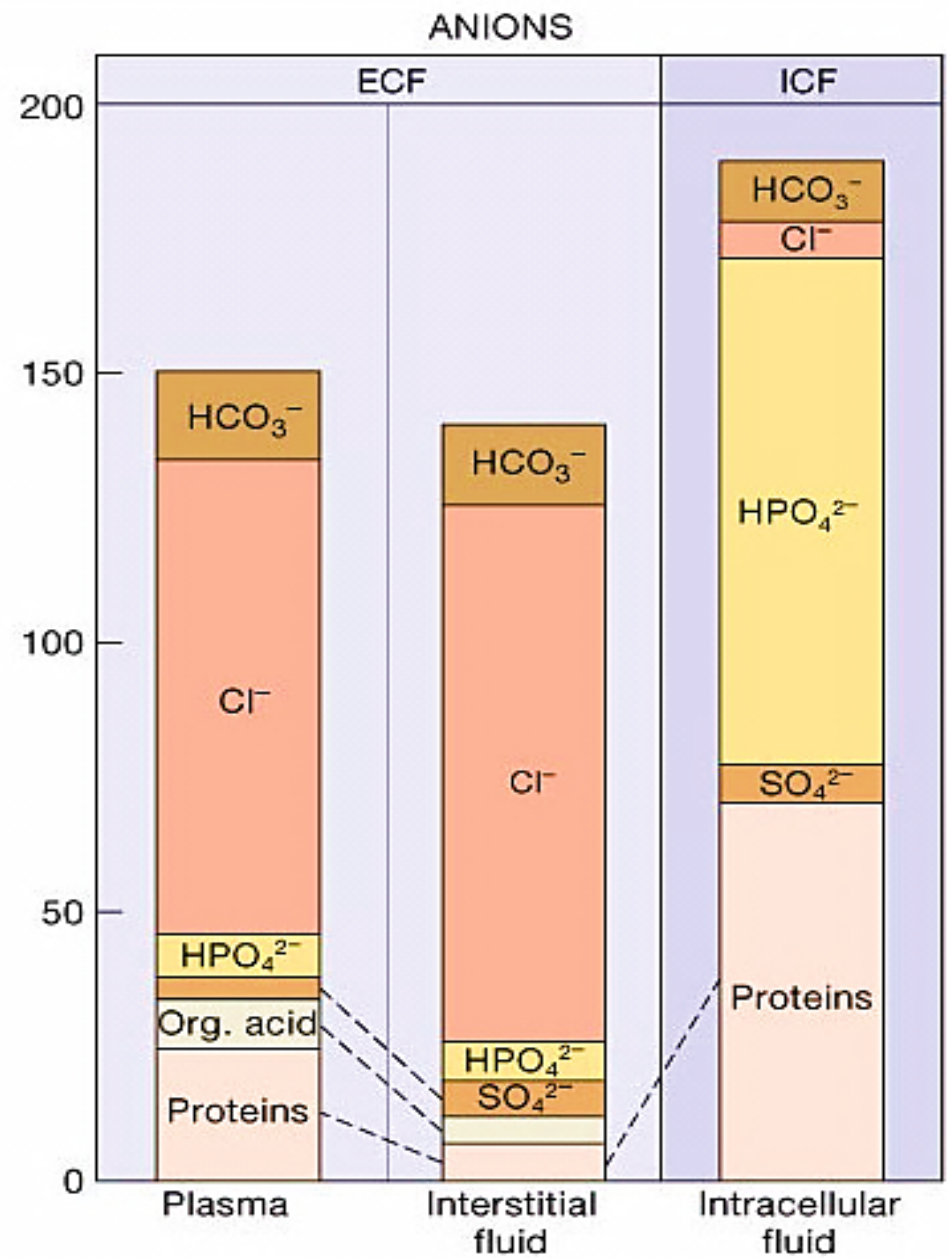
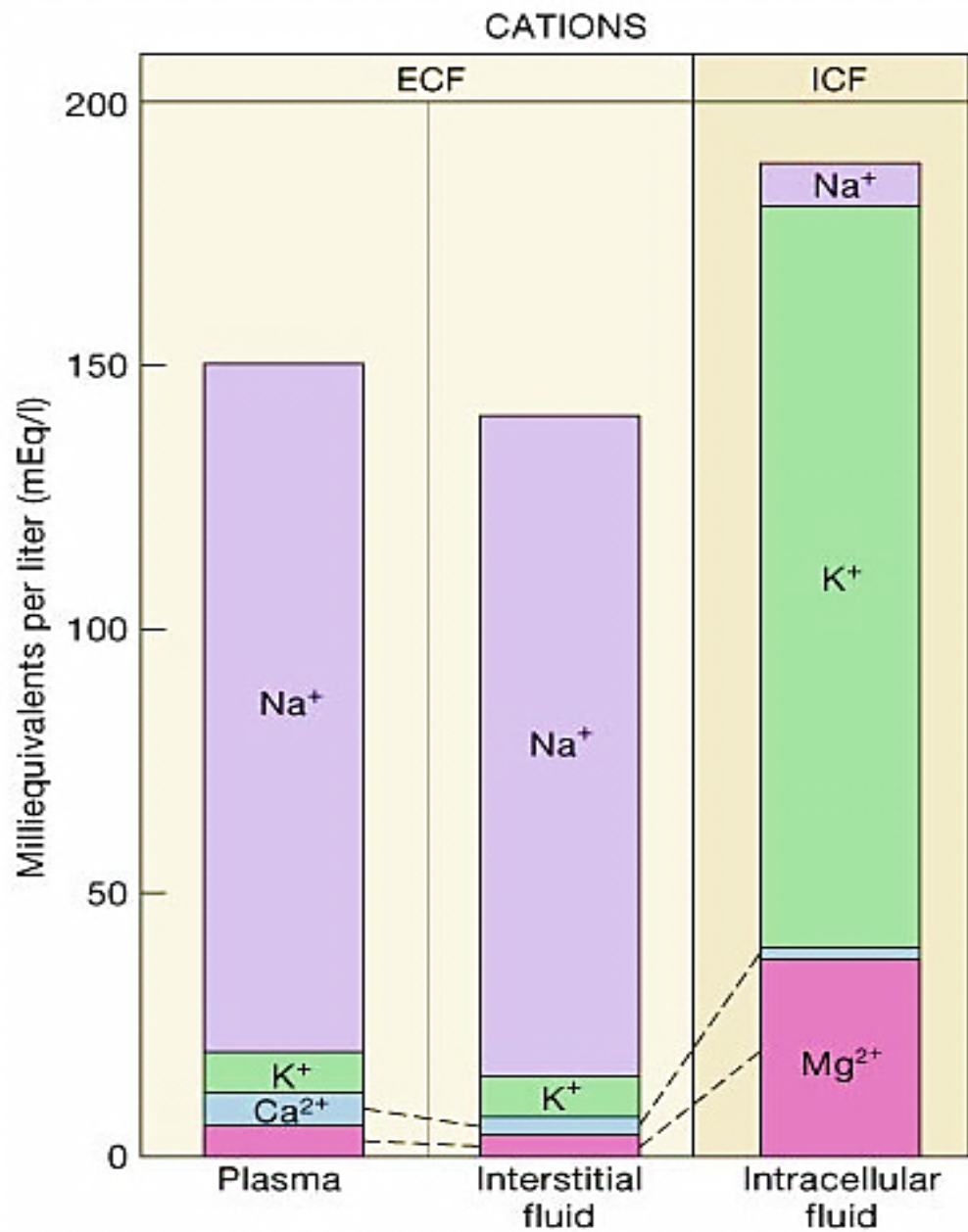
Animal systems evolved to support multicellular life



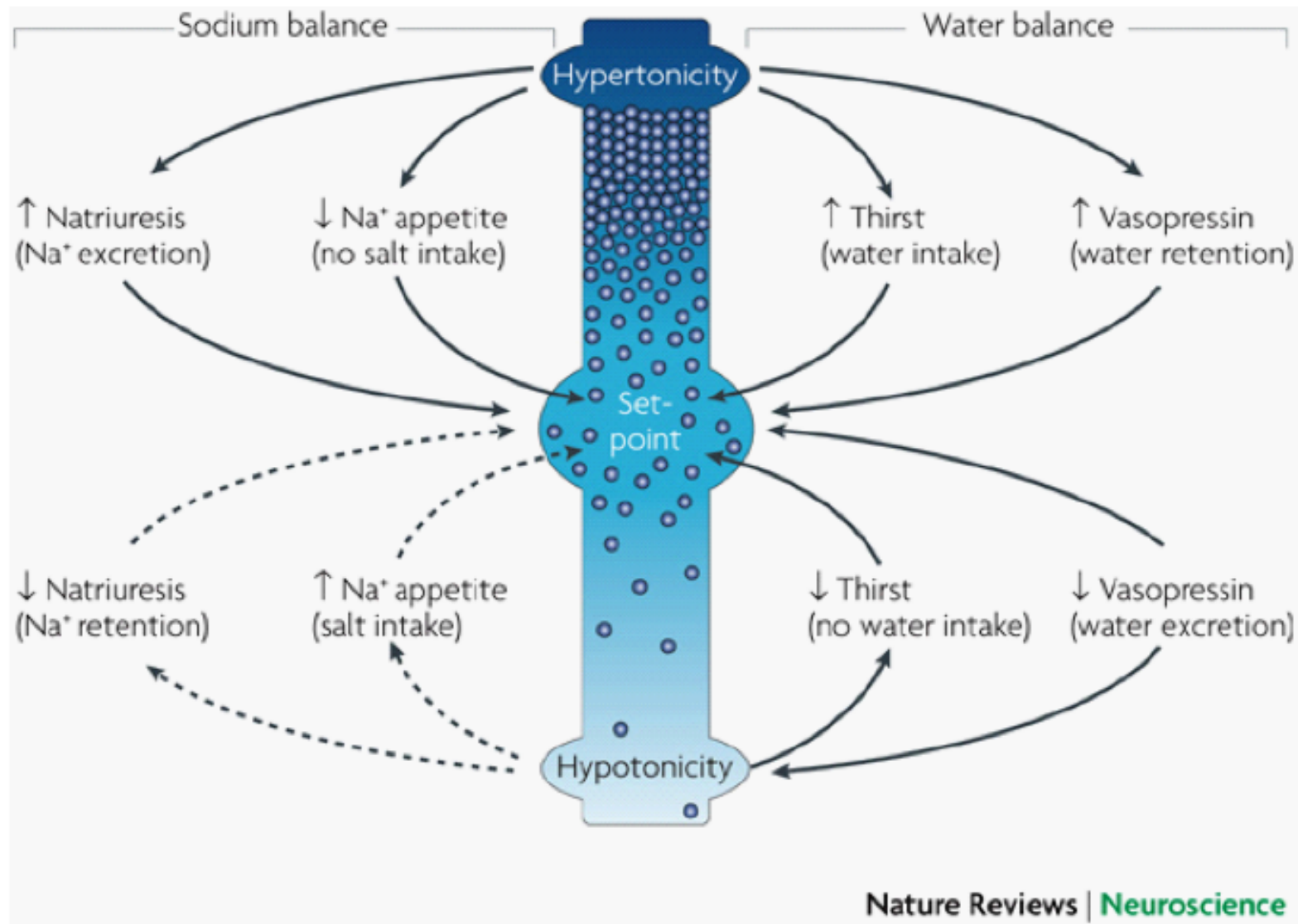
Compartimentos líquidos corporales



Equilibrio iónico de los líquidos corporales



Control del Volumen y la Osmolaridad



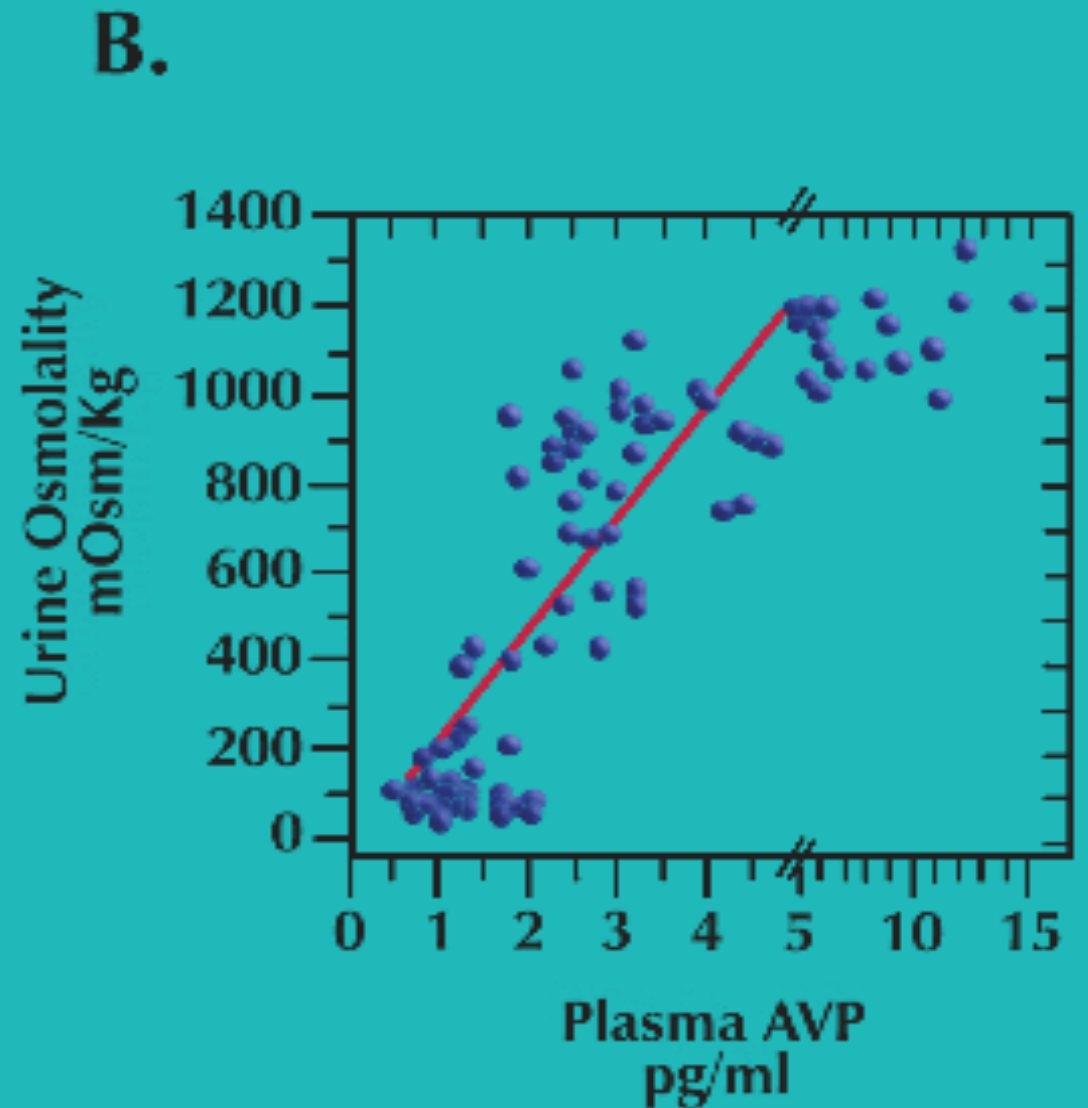
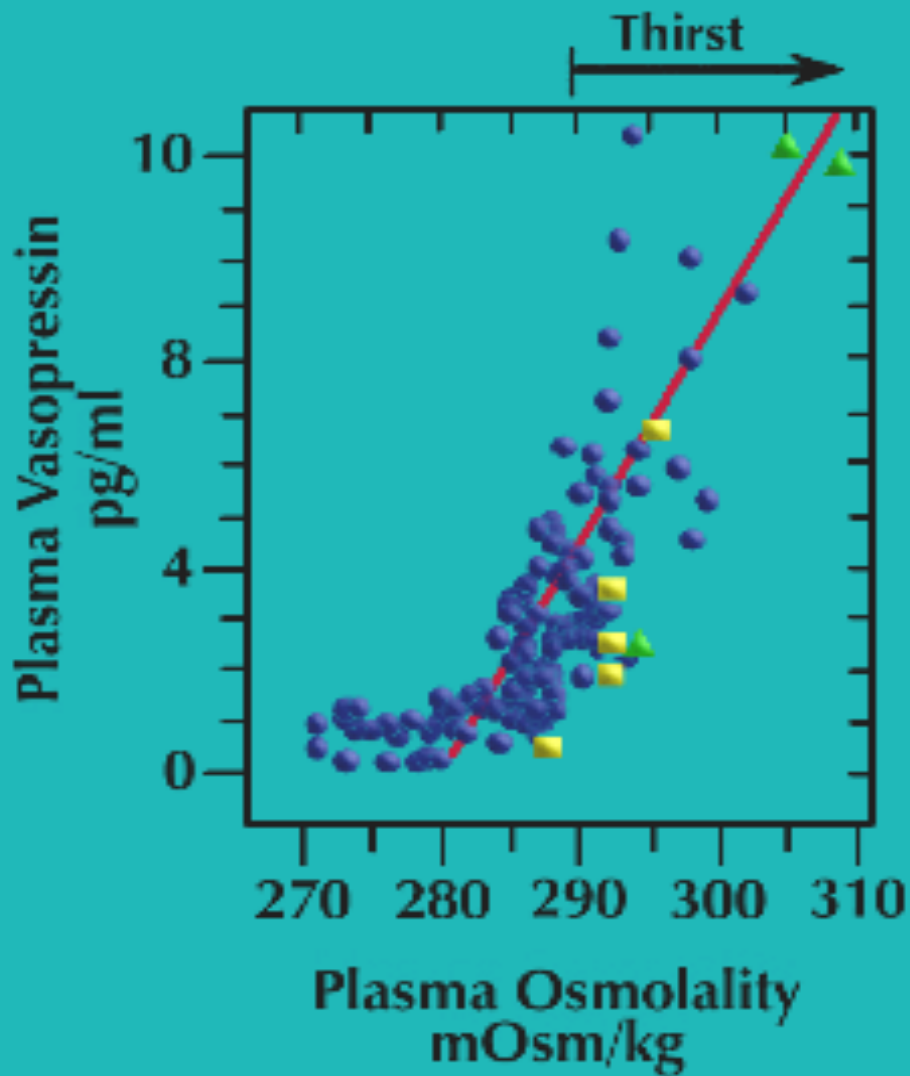
Diferencias entre el control de volumen y la osmolaridad

	OSMOLARIDAD	VOLUMEN
Parámetro medido	P_{osm}	Volumen circulante efectivo
Sensores	Osmorreceptores hipotalámicos (NSO/PV)	Barorreceptores (CC, AYG, AD, aorta, etc.)
Efectores	HAD	SSA, SRAA, natriuresis por presión, PNA, HAD
Qué se afecta	BALANCE DE AGUA Ingesta (SED) vs. Excreción (HAD)	BALANCE DE SODIO Excreción de Na
Qué defiende	VIC	VEC
[Na] sérico	Se modifica	No se modifica
Na urinario	Independiente	“siempre”= ingreso

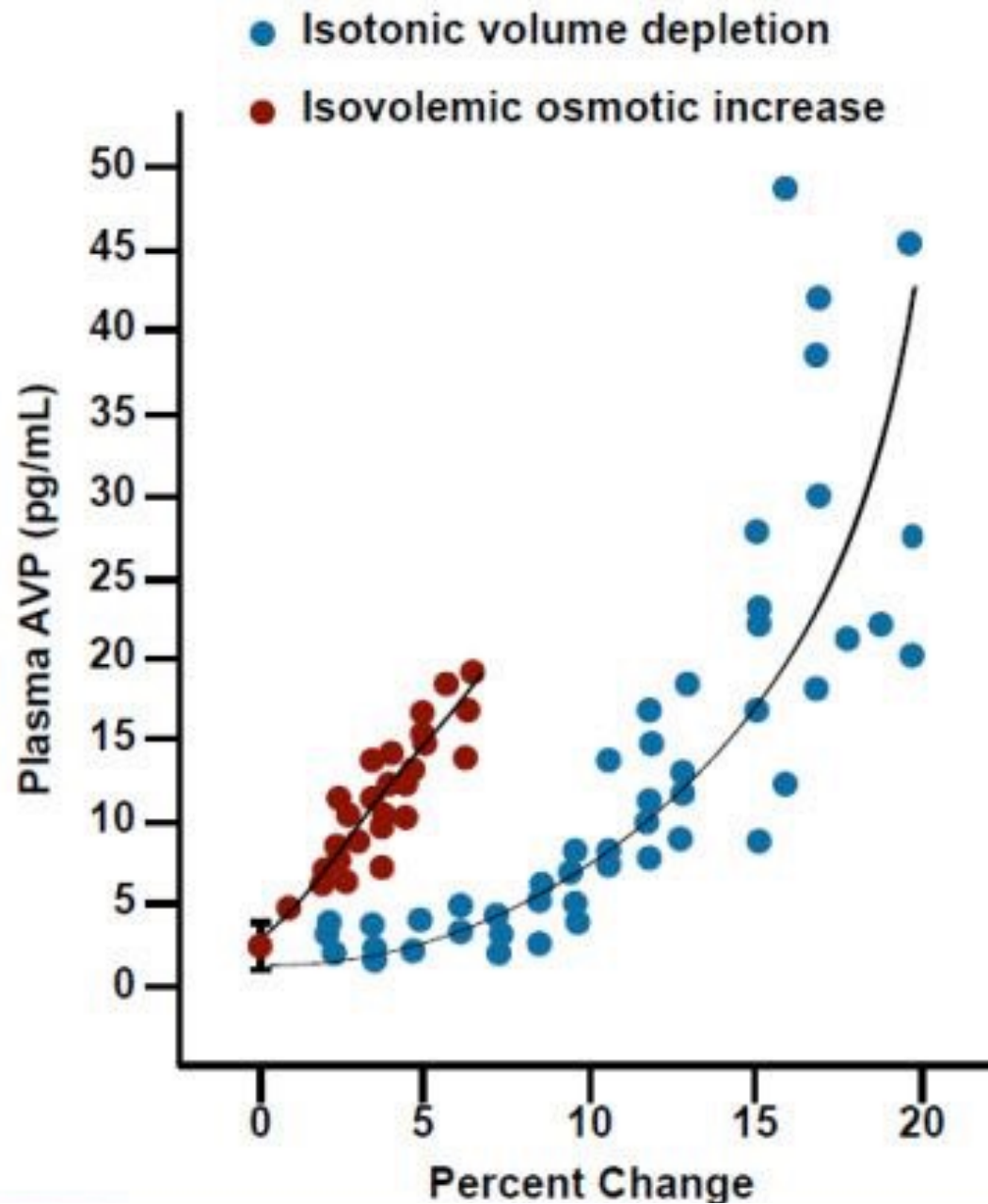


**Secreción de
HAD y
Concentración
urinaria**

Secreción de HAD



Secreción de Hormona Antidiurética

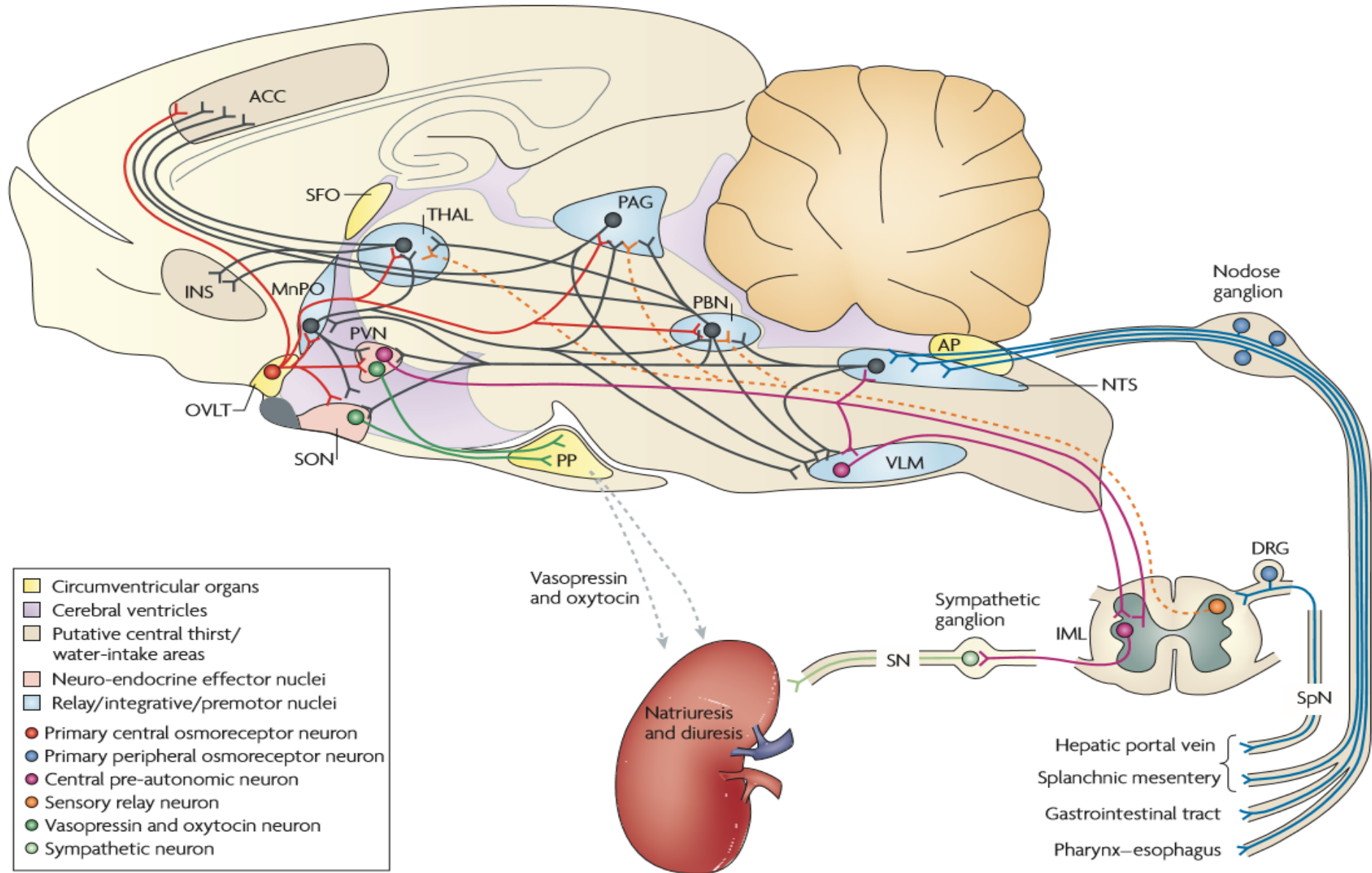


Central mechanisms of osmosensation and systemic osmoregulation

Charles W. Bourque

NATURE REVIEWS | NEUROSCIENCE

VOLUME 9 | JULY 2008 | 519

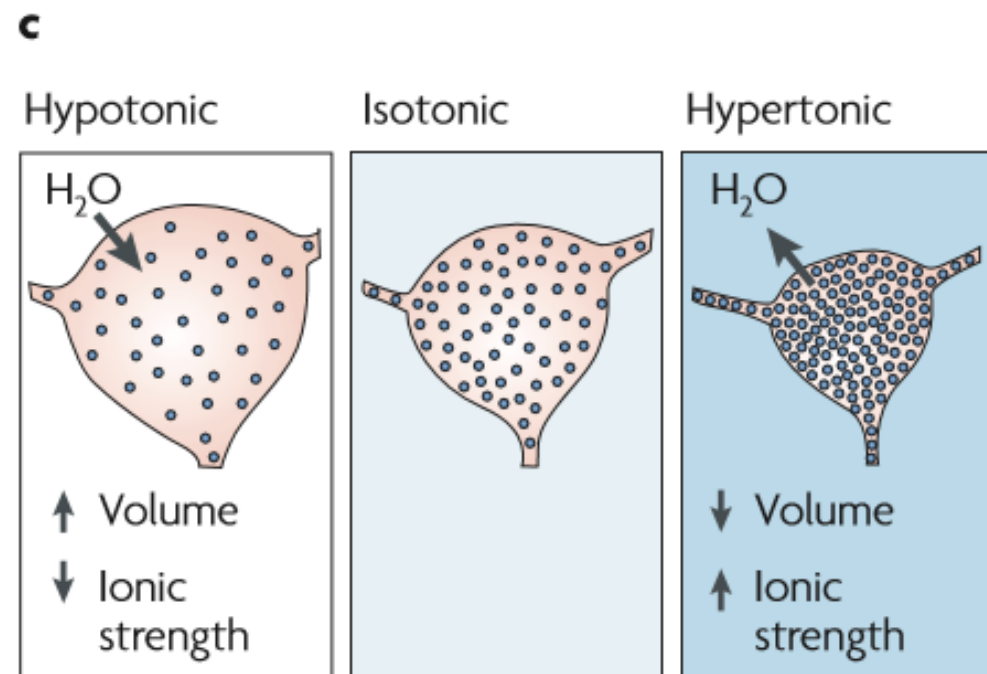
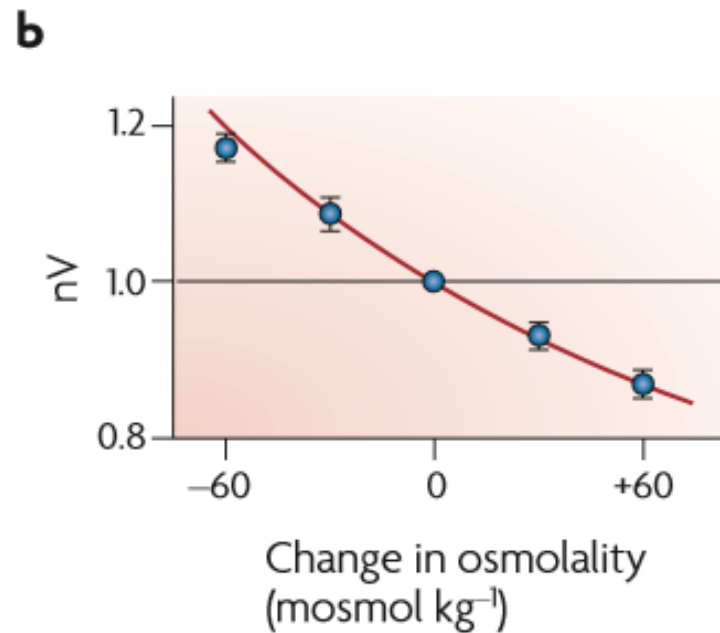


Central mechanisms of osmosensation and systemic osmoregulation

Charles W. Bourque

NATURE REVIEWS | NEUROSCIENCE

VOLUME 9 | JULY 2008 | 519

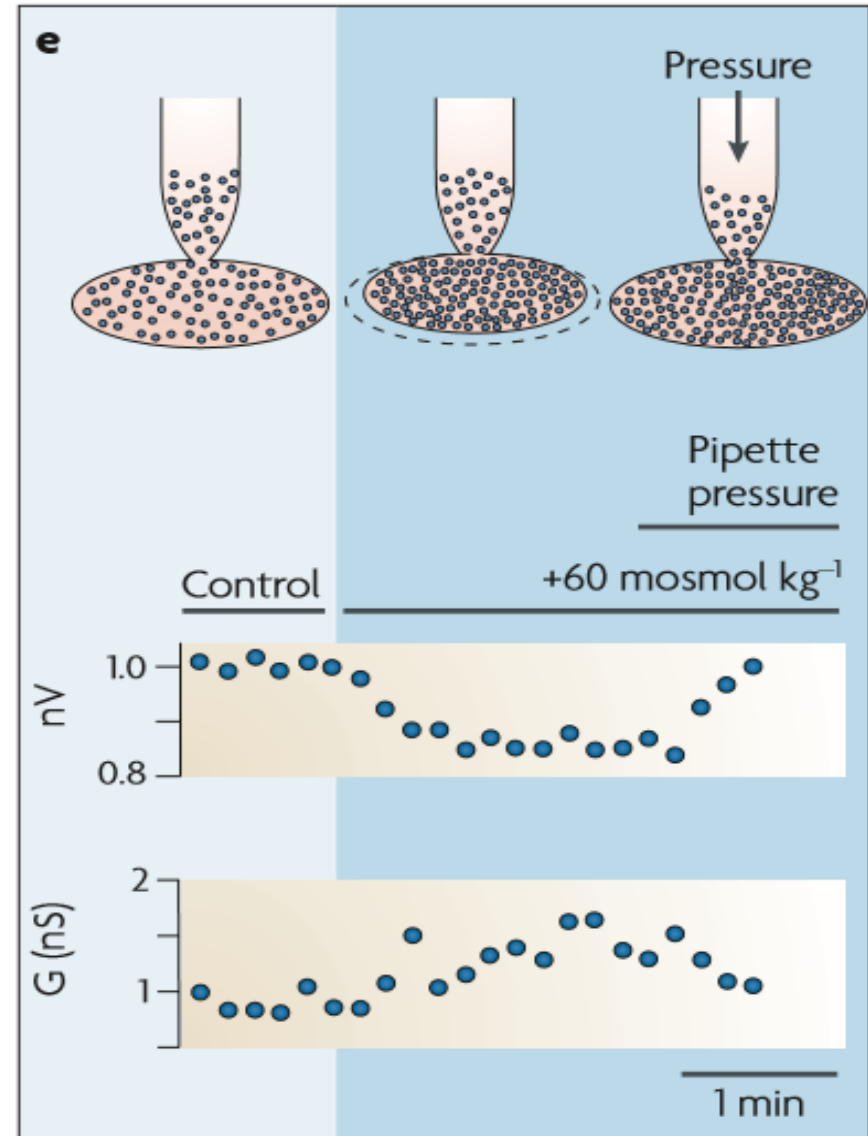
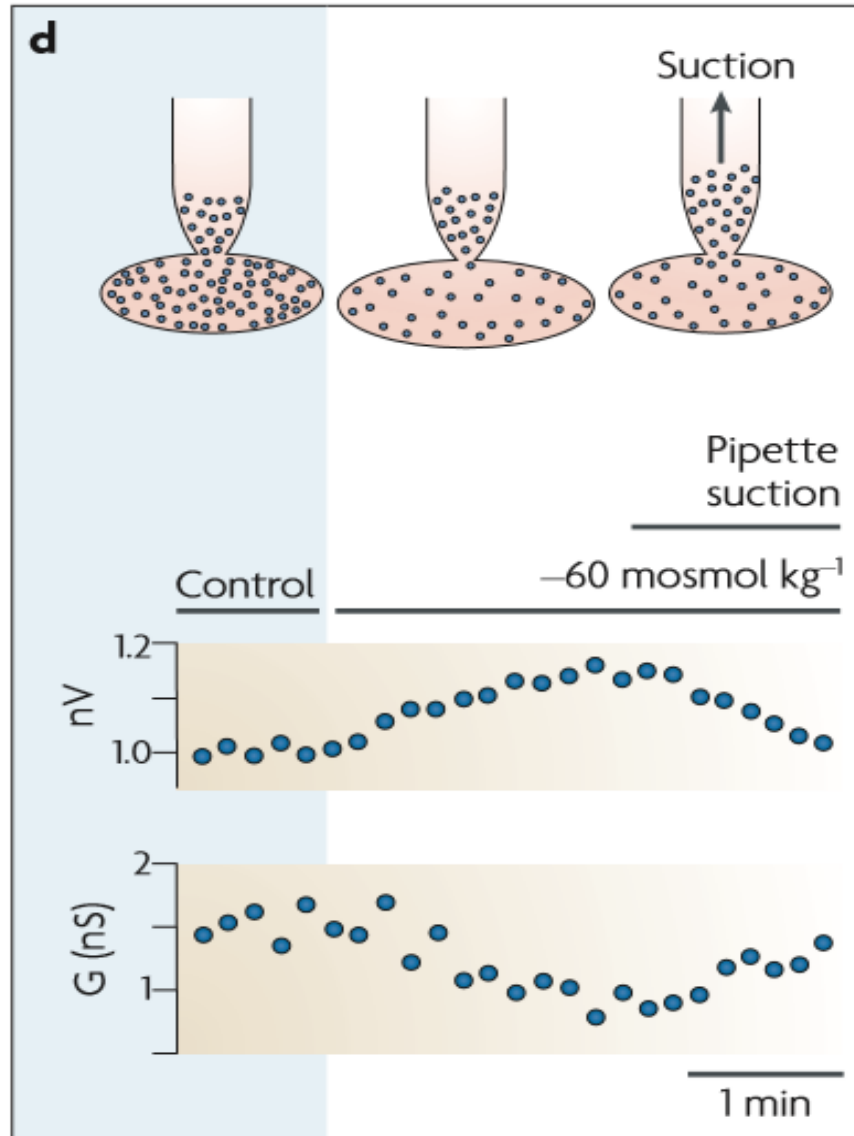


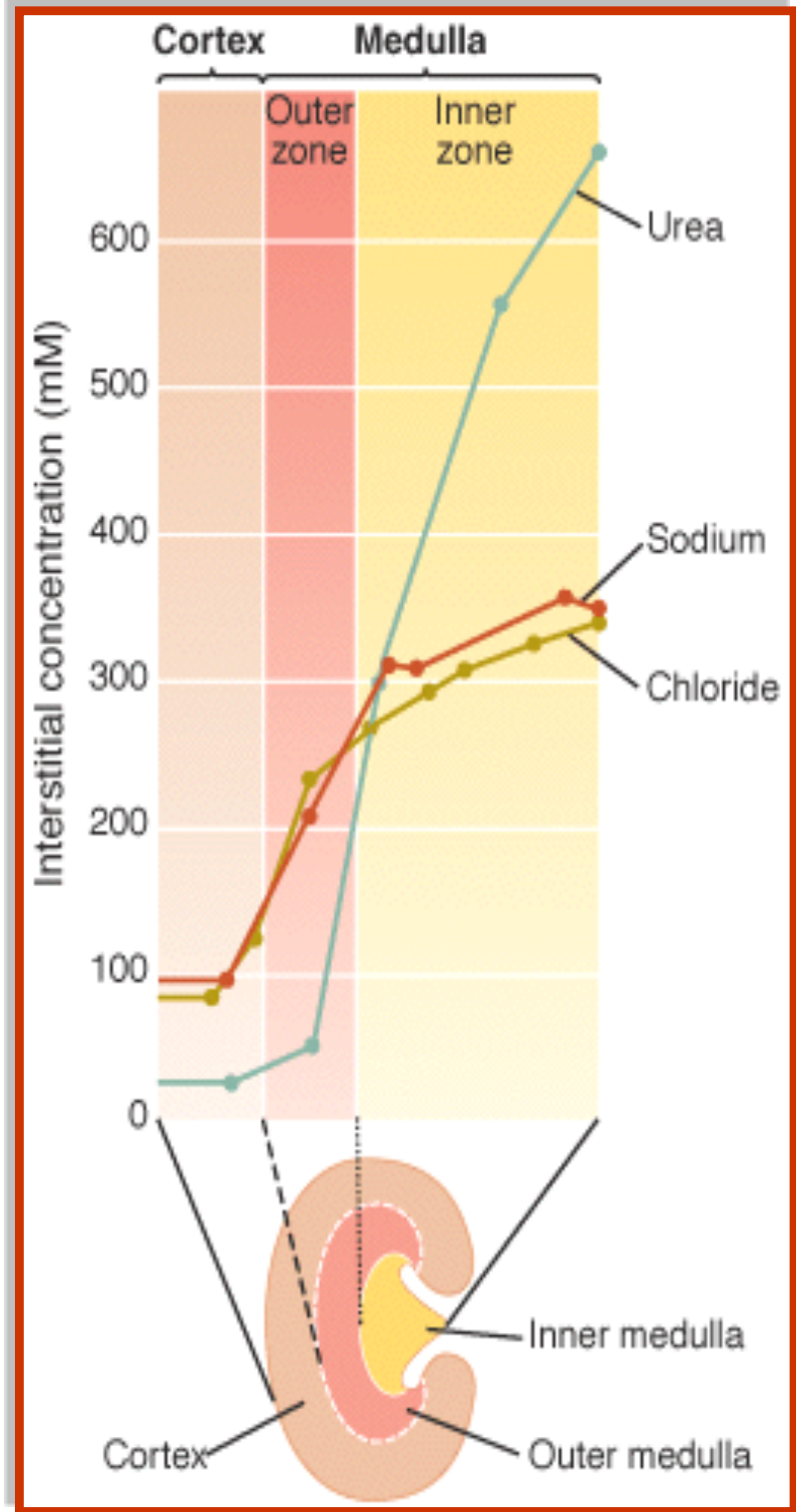
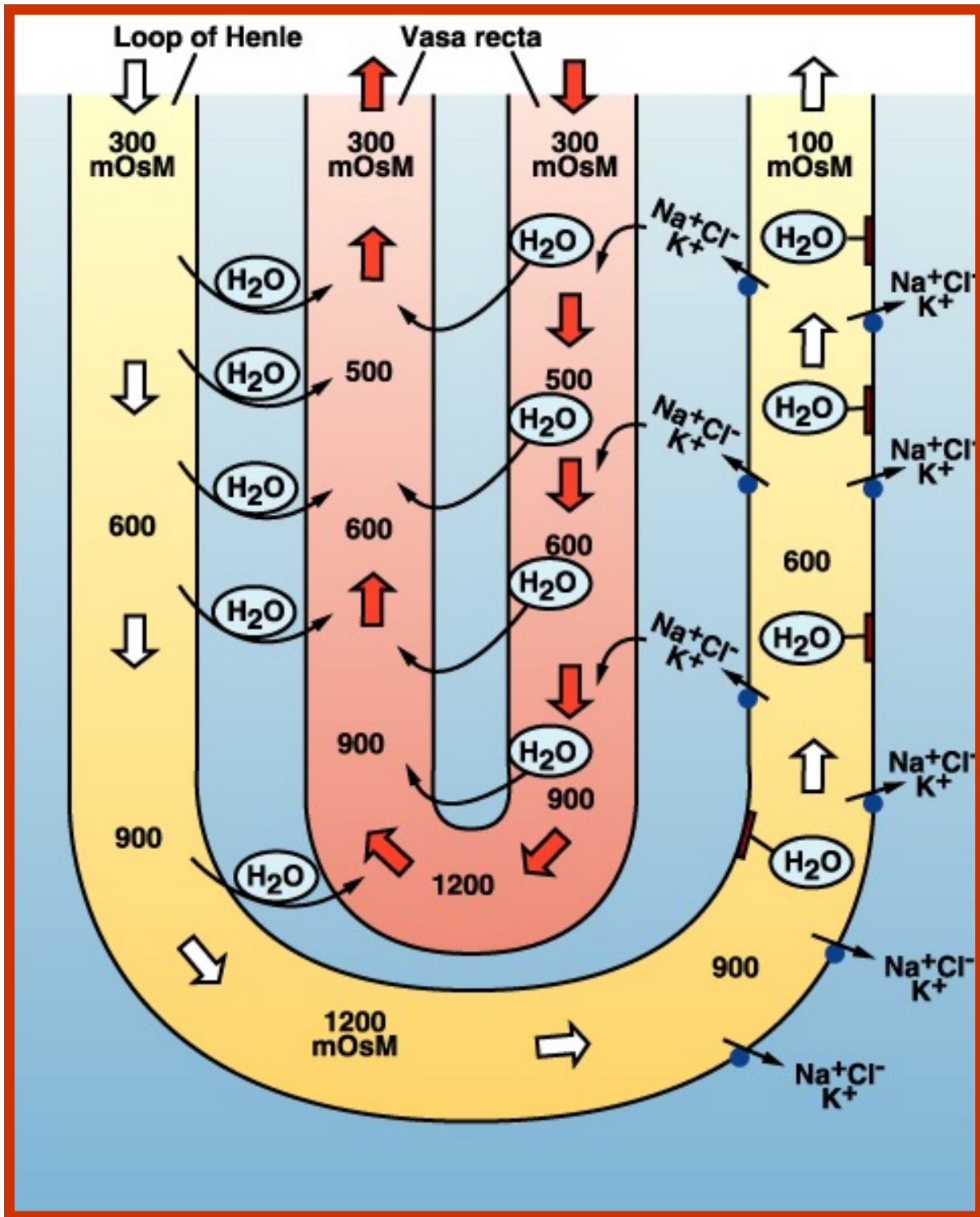
Central mechanisms of osmosensation and systemic osmoregulation

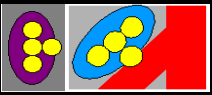
Charles W. Bourque

NATURE REVIEWS | NEUROSCIENCE

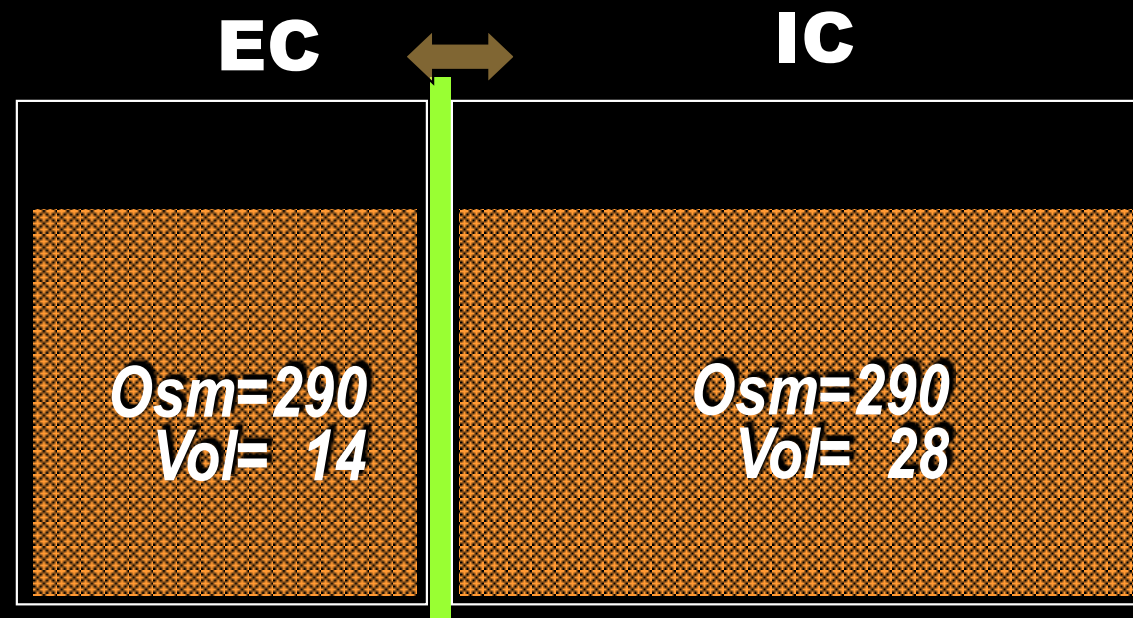
VOLUME 9 | JULY 2008 | 519

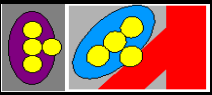






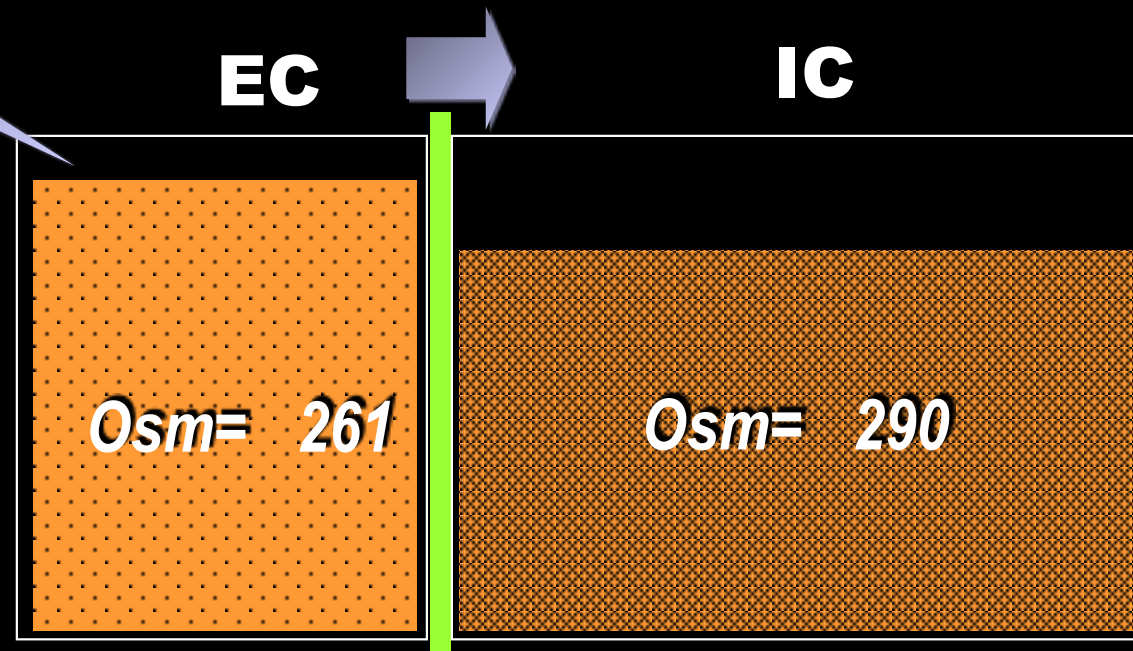
Cambios en volúmen y osmolaridad de los líquidos corporales

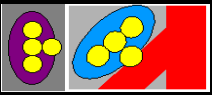




Cambios en volúmen y osmolaridad de los líquidos corporales

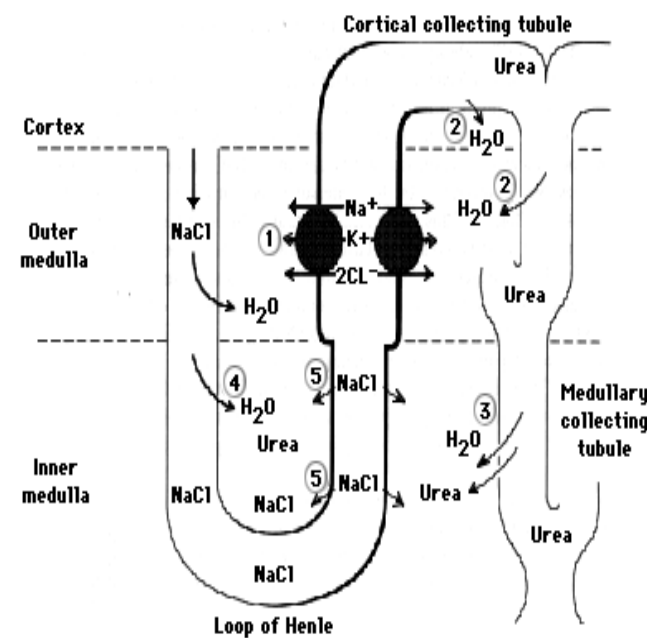
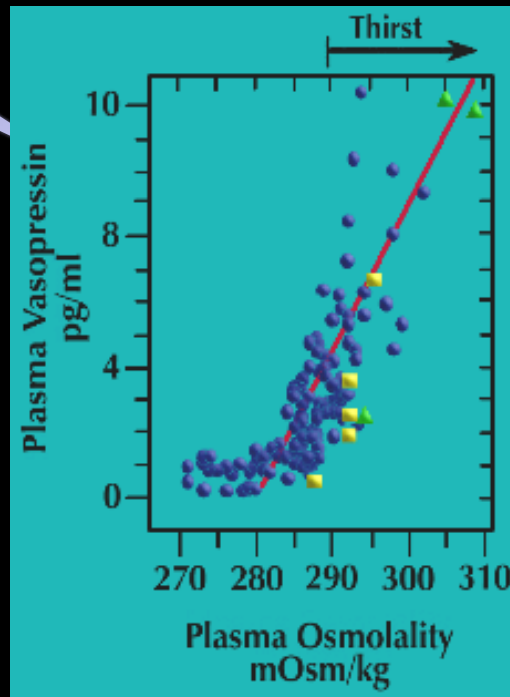
+ 4.2 L
de H_2O





Cambios en volúmen y osmolaridad de los líquidos corporales

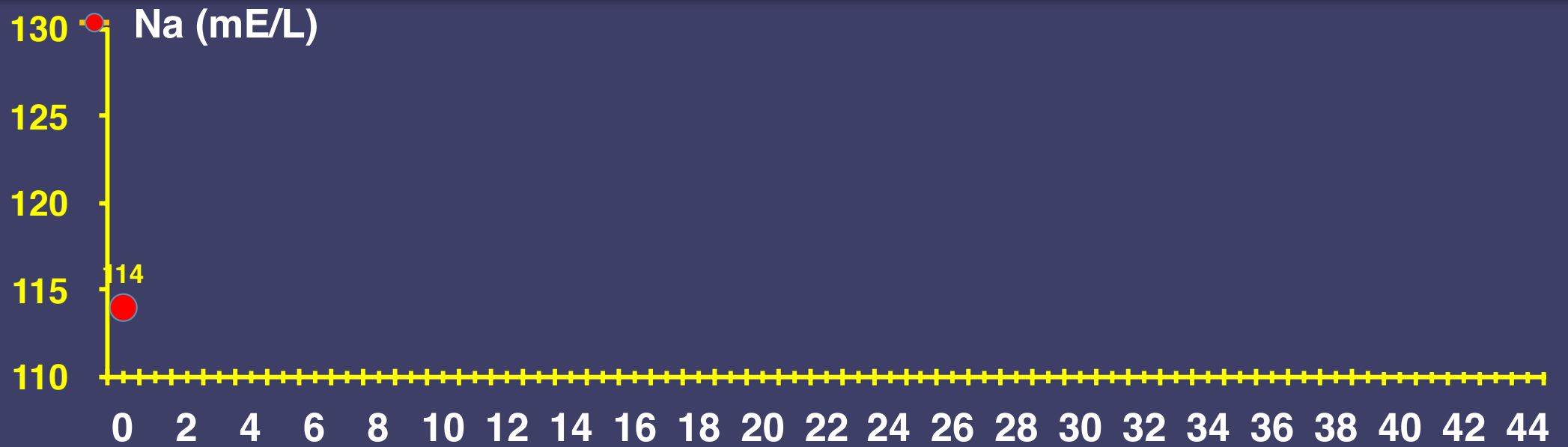
+ 4.2 L
de H_2O



Caso Clínico: Patricia O.

- Femenina de 40 años de edad con antecedentes epilepsia desde los 21 años (CCTCG), no ha convulsionado en 4 años y toma carbamazepina 200 mg: 2-1-2. Sin seguimiento neurológico.
- Litiasis recurrente (3 episodios) con hipercalciuria por lo que toma clortalidona 25 mg x1 y citrato de K 1g 1-1-1, desde hace un mes.
- Tiene varias semanas con astenia, adinamia, dificultad para concentrarse y falta de fuerza muscular.
- TA 110/70 mmHg, FC 90/min, bien orientada, apática, mucosas discretamente deshidratadas y sin edema. Exploración neurológica normal salvo hiporreflexia simétrica.
- Refiere tomar muchos líquidos y tiene buenos volúmenes urinarios.

Caso Clínico: Patricia O.

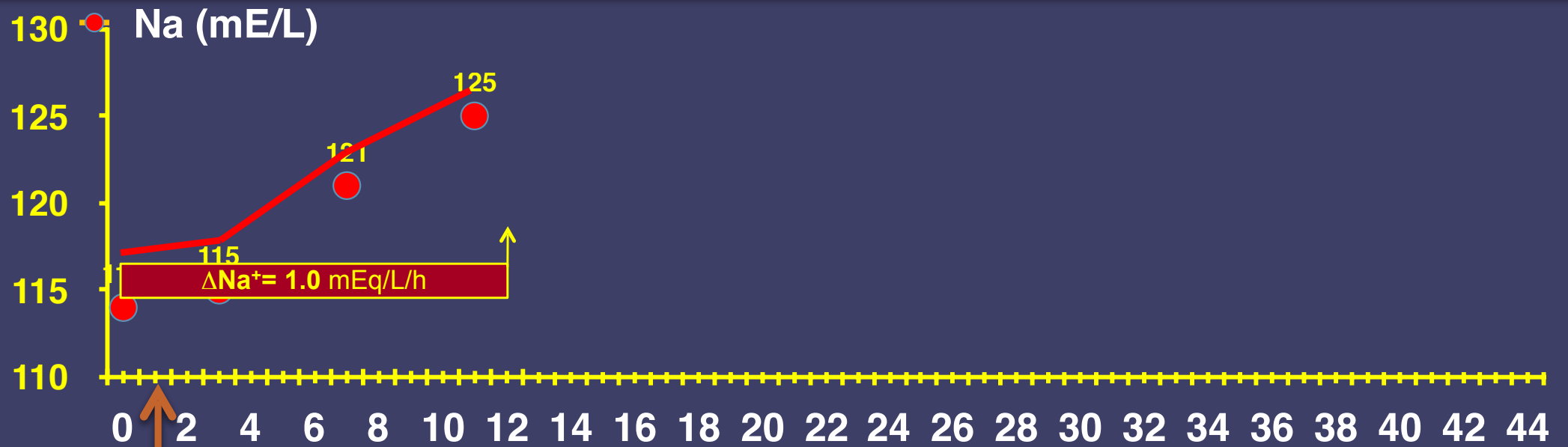


$P_{Na} = 114$
 $P_K = 2.8$
 $P_{Cl} = 80$
 $P_{OSM} = 242$

$U_{Na} = 17$
 $U_K = 32$
 $U_{OSM} = 271$
 $U_{dens} = 1015$

$P_{creat} = 1.4$
 $BUN = 44$
 $P_{gluc} = 90$
 $AcUr = 8.0$

Caso Clínico: Patricia O.



DFH 1g en
250 mL SF

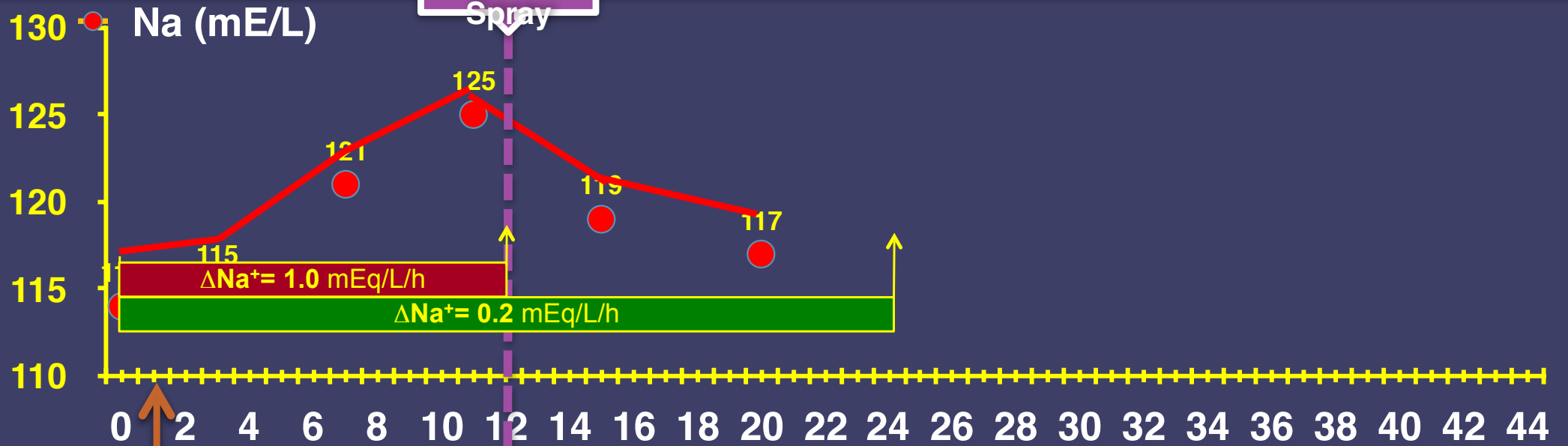
KCl 40
mEq/L

$U_{\text{dens}} = 1015$



Caso Clínico: Patricia O.

DDAVP
Spray

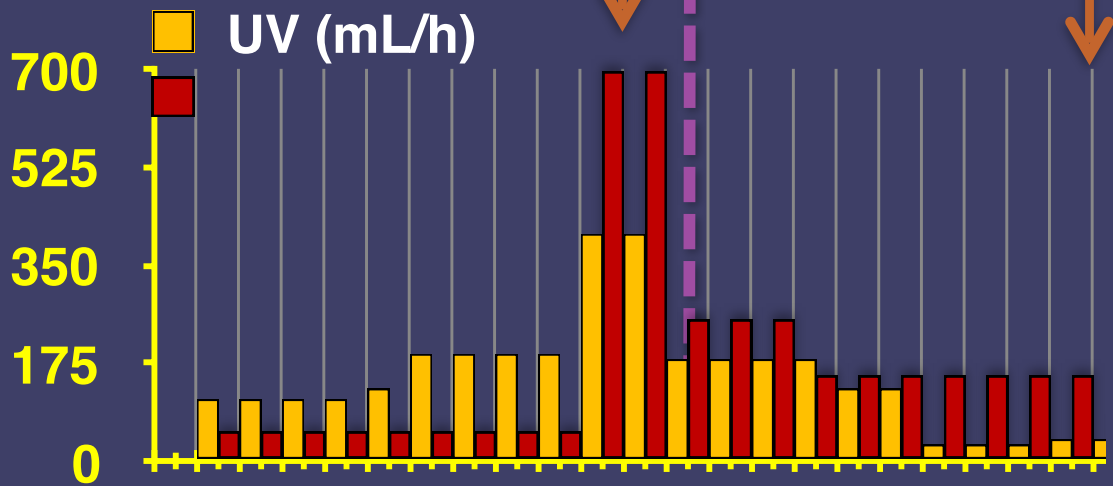


DFH 1g en
250 mL SF

KCl 40
mEq/L

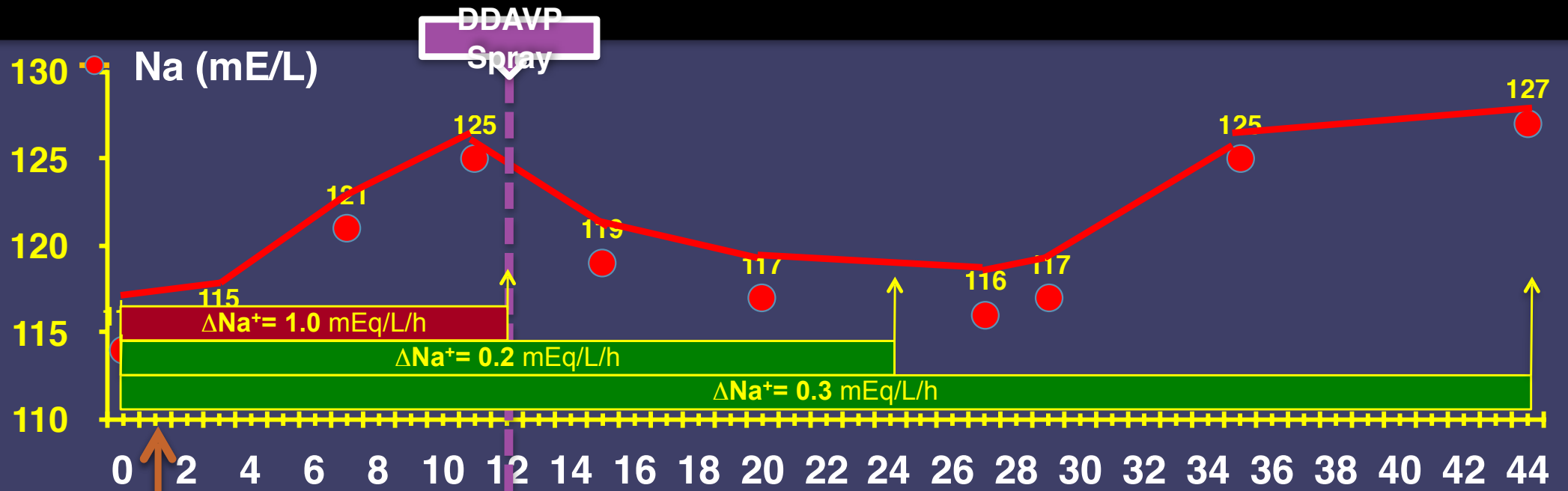
$U_{dens} = 1015$

$U_{dens} = 1025$



0.9%NaCl SG5%

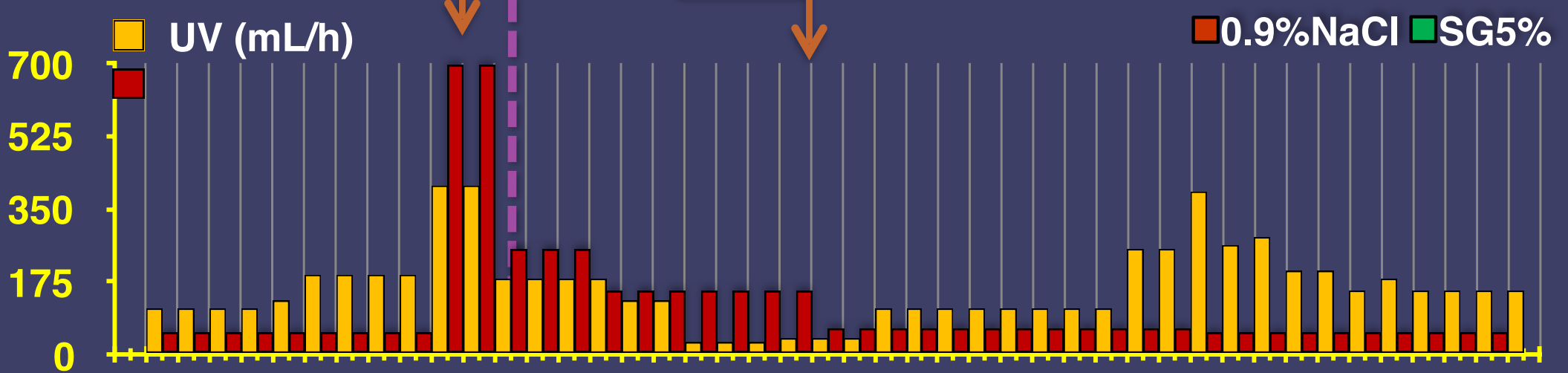
Caso Clínico: Patricia O.

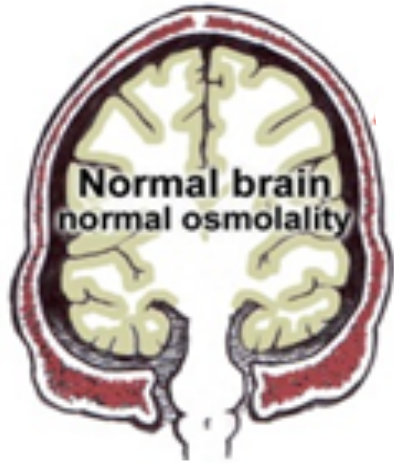


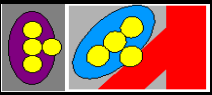
DFH 1g en 250 mL SF
KCl 40 mEq/L

$U_{dens} = 1015$

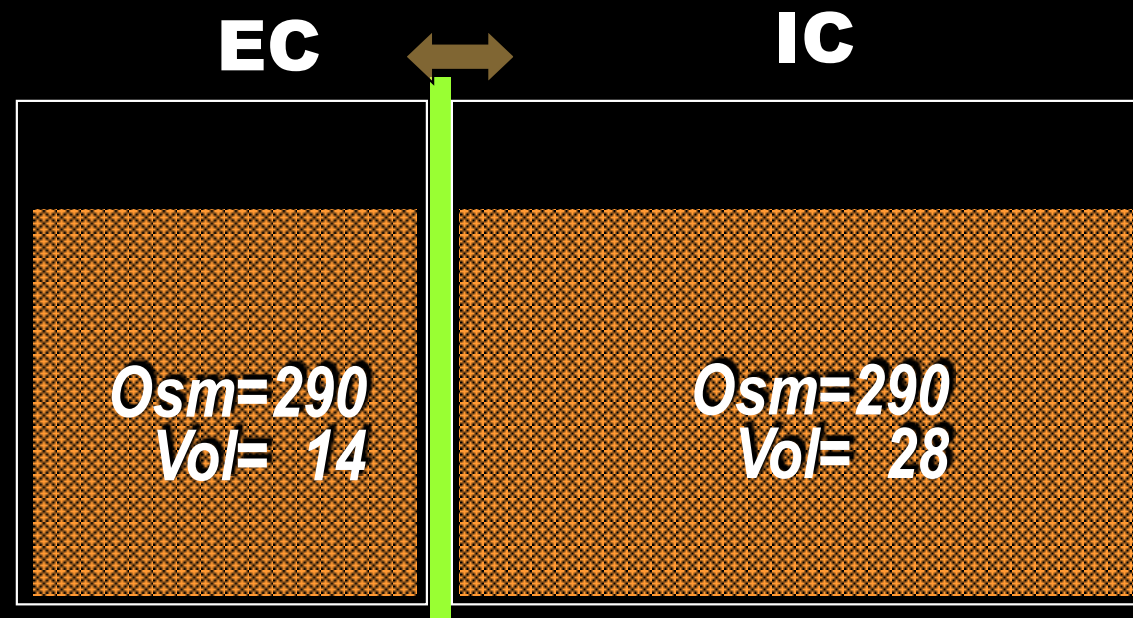
$U_{dens} = 1025$

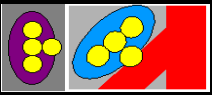




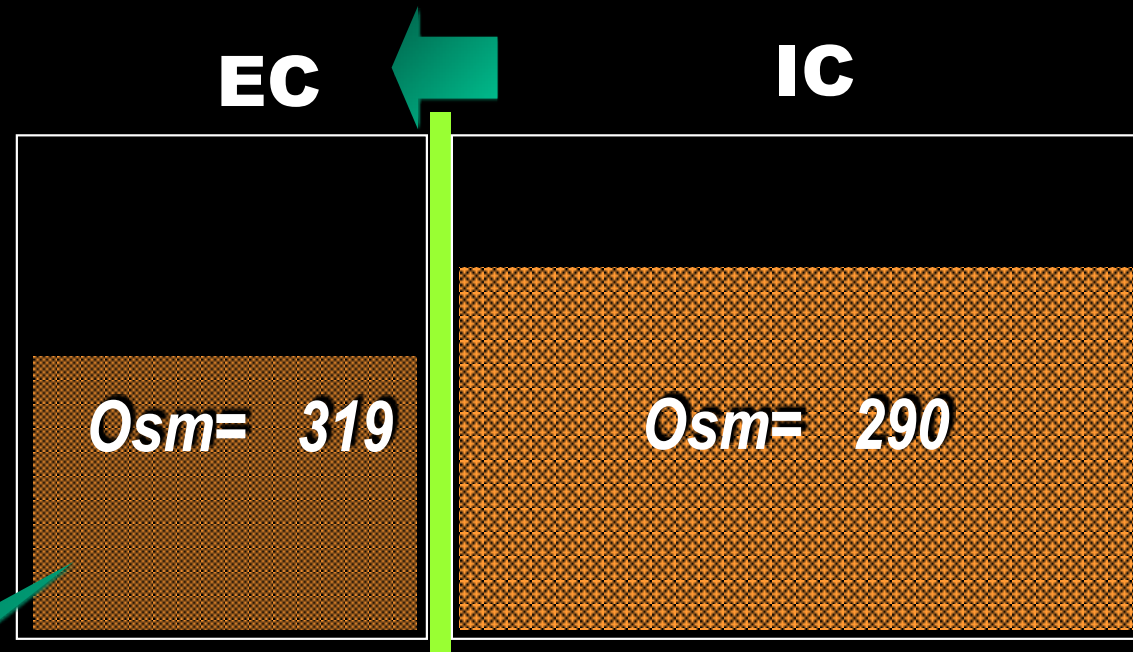


Cambios en volúmen y osmolaridad de los líquidos corporales

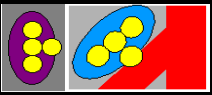




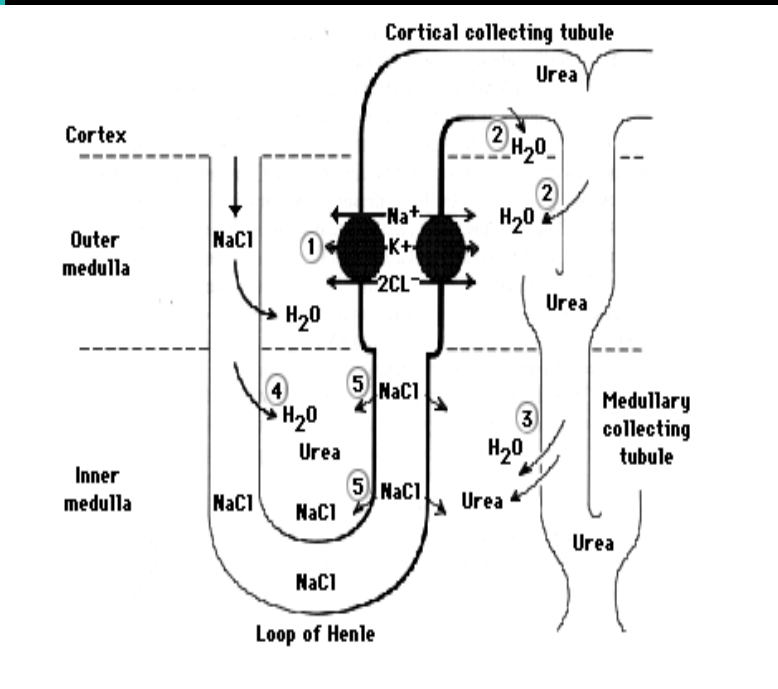
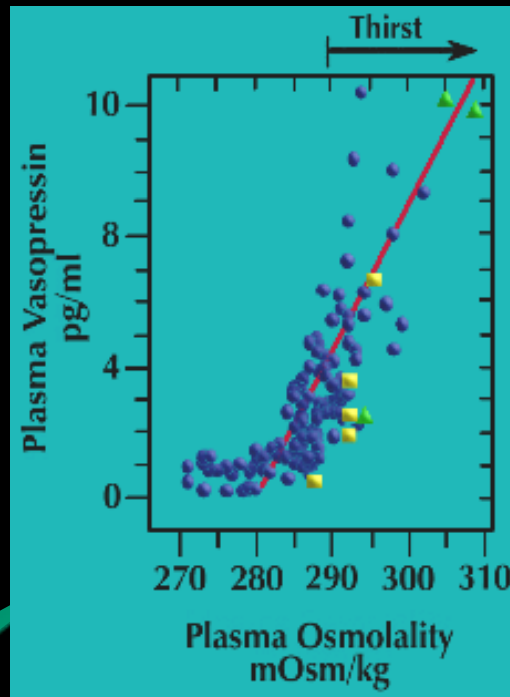
Cambios en volúmen y osmolaridad de los líquidos corporales



- 4.2 L
de H_2O



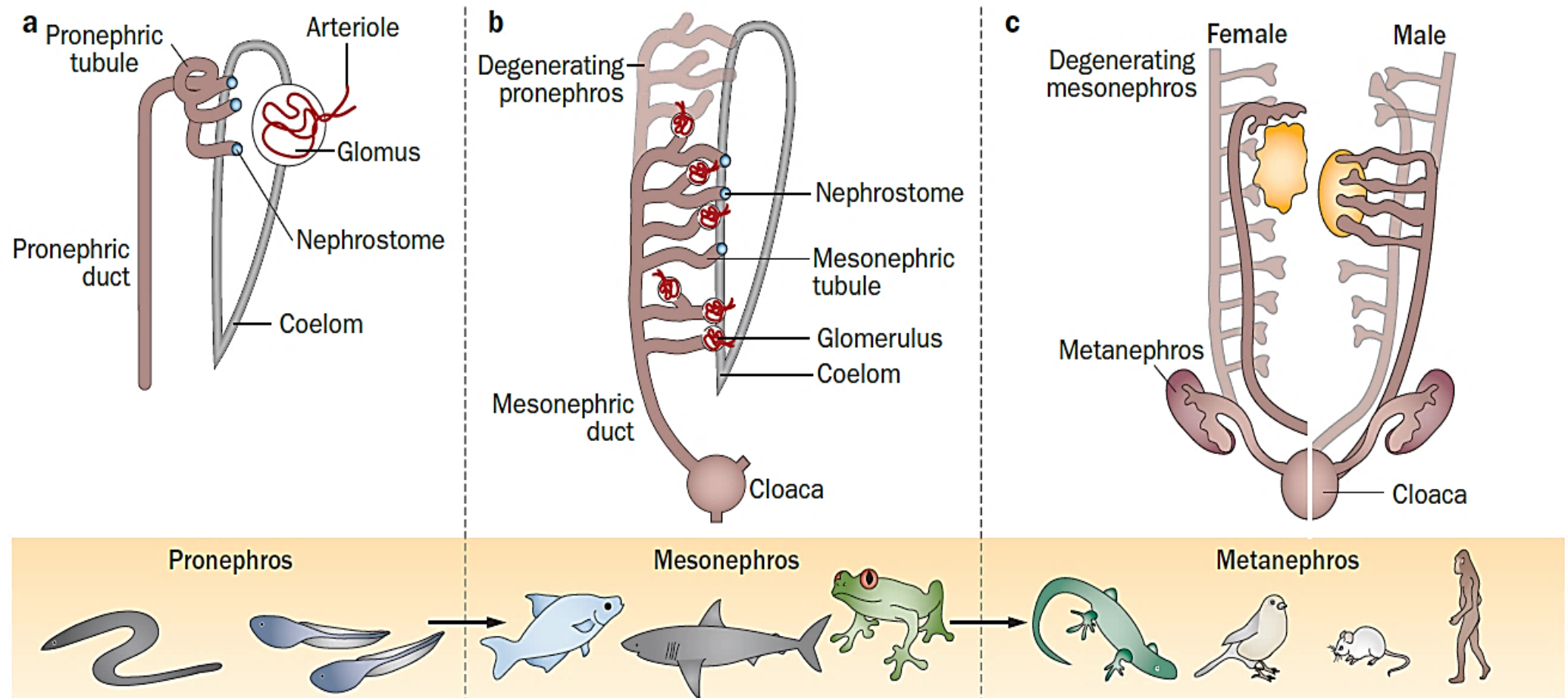
Cambios en volúmen y osmolaridad de los líquidos corporales



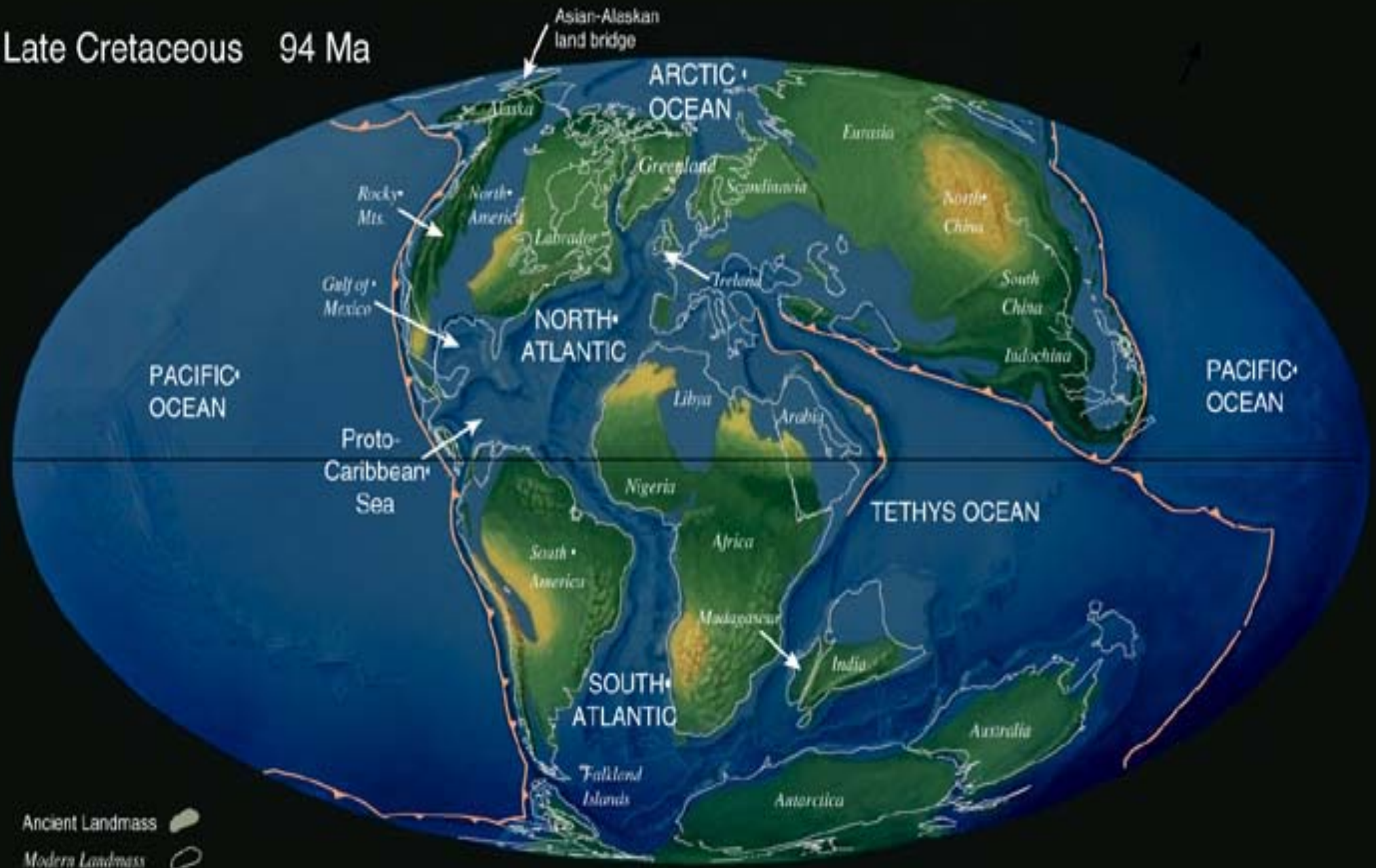
- 4.2 L
de H₂O




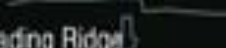
Renal progenitors: an evolutionary conserved strategy for kidney regeneration

Paola Romagnani, Laura Lasagni and Giuseppe Remuzzi

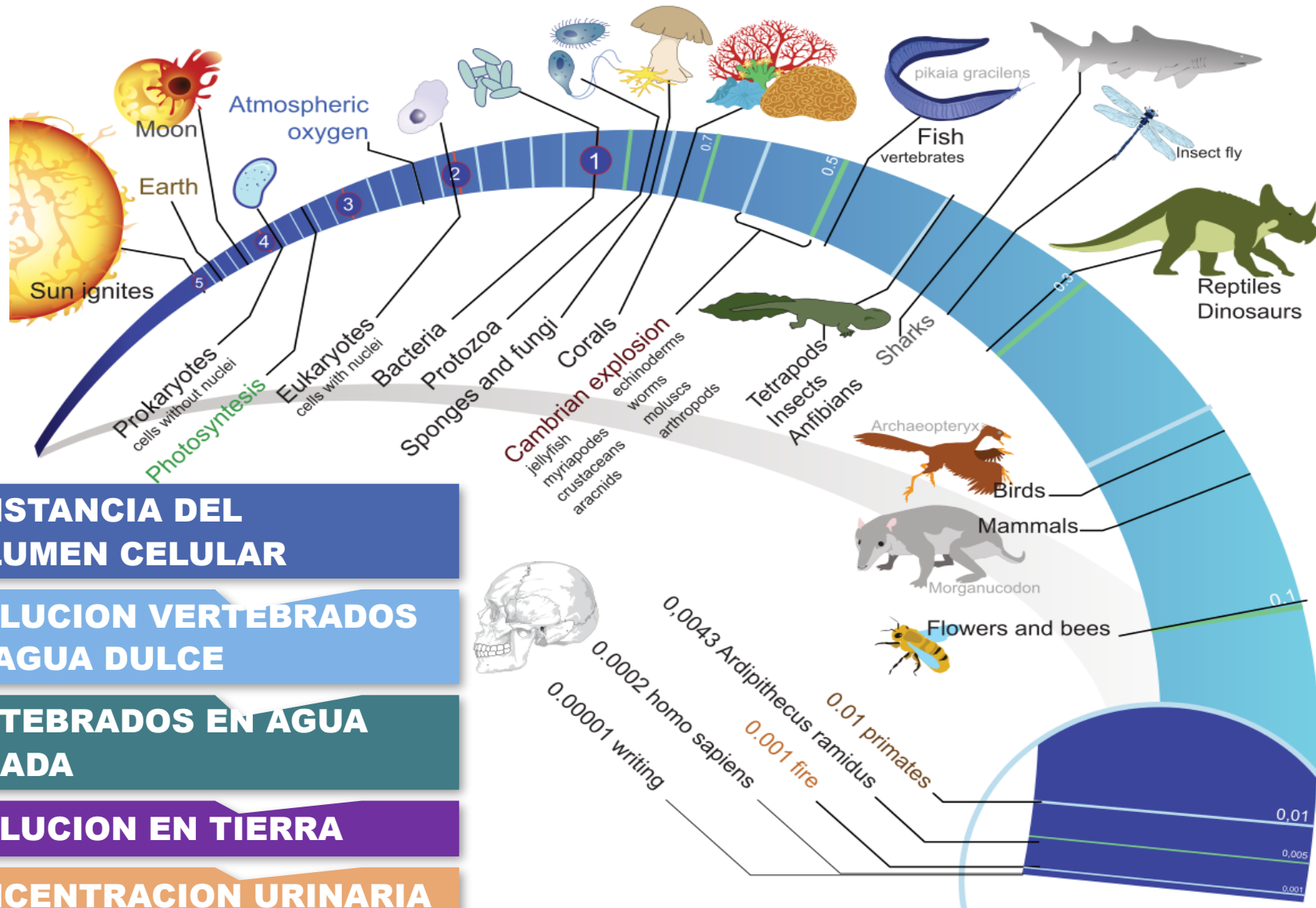


Late Cretaceous 94 Ma



- Ancient Landmass 
- Modern Landmass 
- Subduction Zone (triangles point in the direction of subduction) 
- Sea Floor Spreading Ridge 

RETOS OSMOREGULATORIOS



1. CONSTANCIA DEL VOLUMEN CELULAR

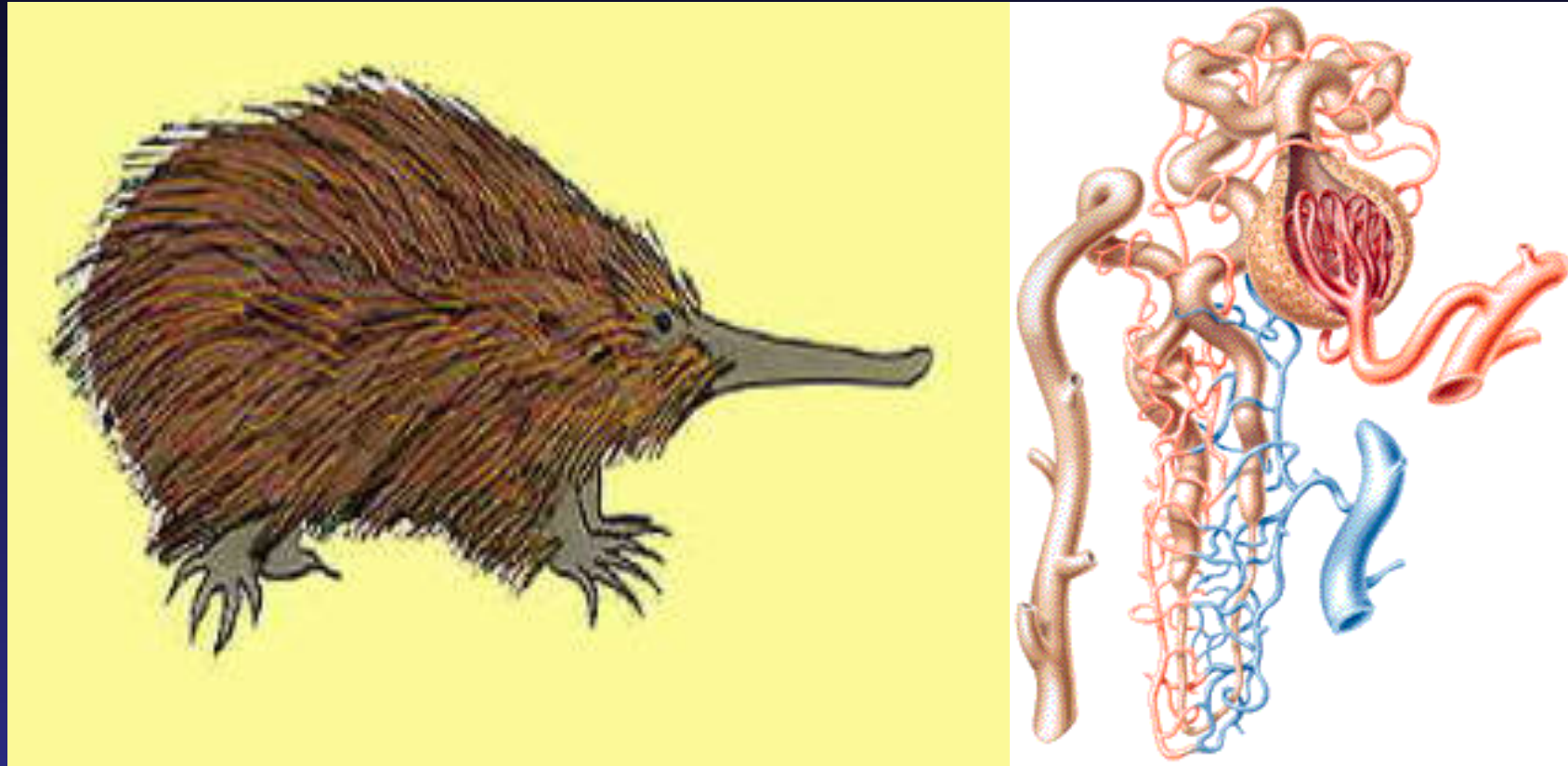
2. EVOLUCION VERTEBRADOS EN AGUA DULCE

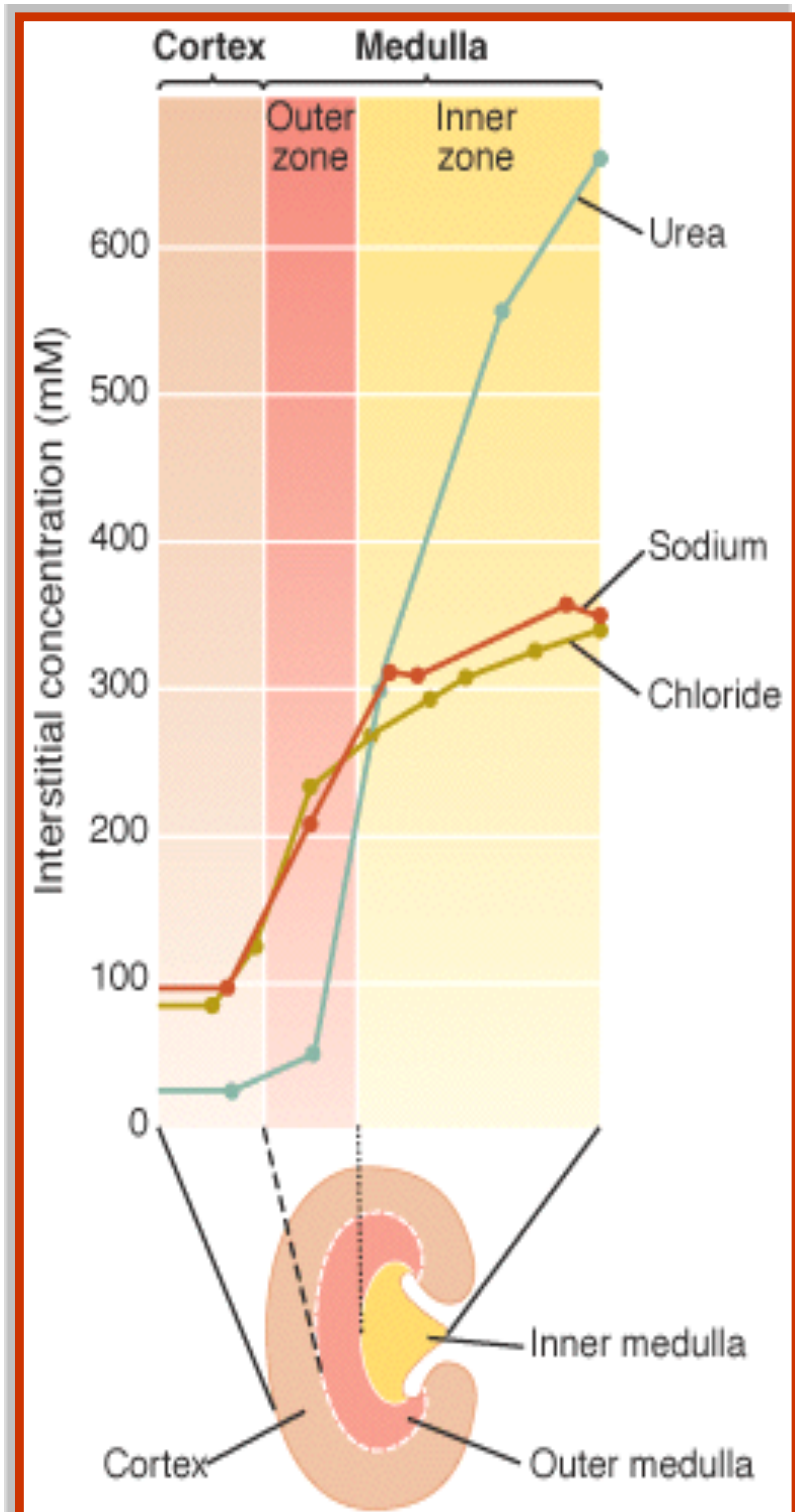
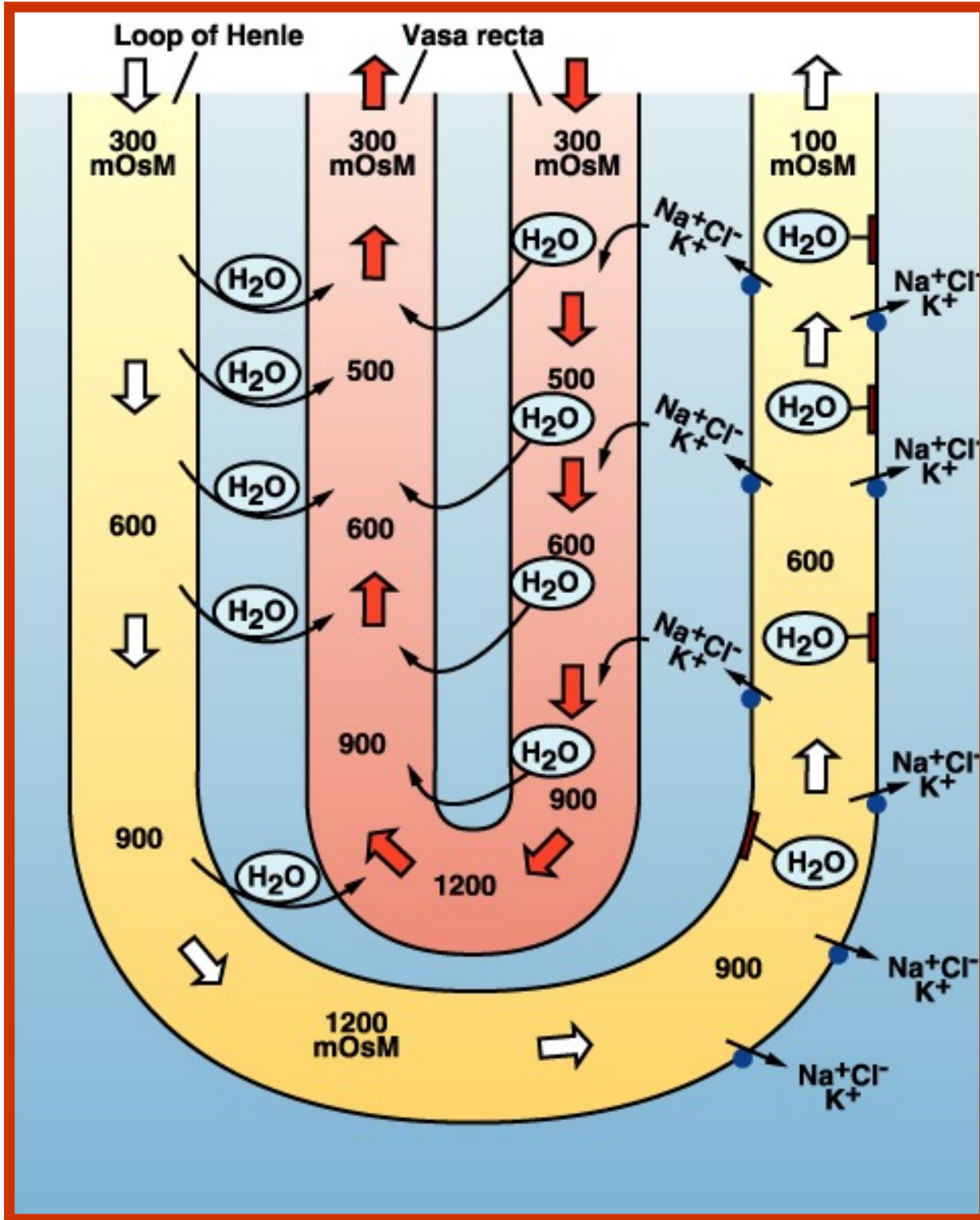
3. VERTEBRADOS EN AGUA SALADA

4. EVOLUCION EN TIERRA

4. CONCENTRACION URINARIA

Nefrona “superconcentradora” de los mamíferos





Capacidad variable de concentración urinaria en mamíferos superiores

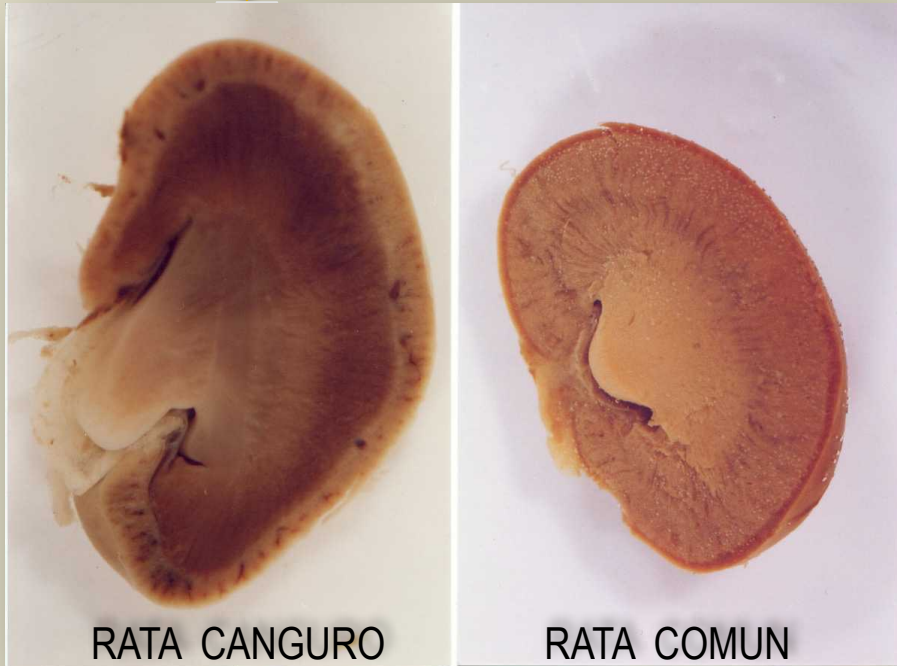
Tipo de nefronas	Concentración urinaria	Ejemplo
100% “asa corta” (corticales)	2 x Osm VEC	Castor
20% “asa larga” (yuxtamedulares)	4 x Osm VEC	Hombre
100% “asa larga” (yuxtamedulares)	25 x Osm VEC	?





Dipodomys desertii

SUPER-CONCENTRADORES



RATA CANGURO

RATA COMUN

Dipodomys desertii

Dipodomys desertii

Water balance in a kangaroo rat (2 mL/day)



Ingested in food (0.2)

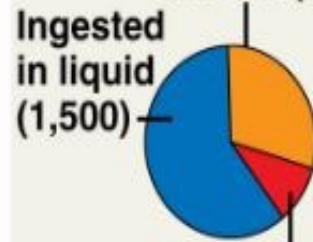


Derived from metabolism (1.8)

Water balance in a human (2,500 mL/day)



Ingested in food (750)

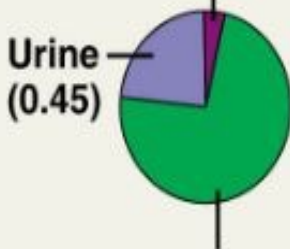


Derived from metabolism (250)

Water gain (mL)

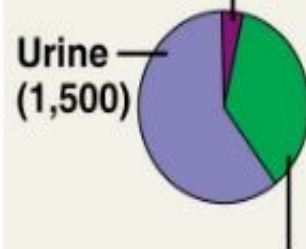
Water loss (mL)

Feces (0.09)



Evaporation (1.46)

Feces (100)



Evaporation (900)



Concentración urinaria: Diferencias entre especies y adaptación al medio



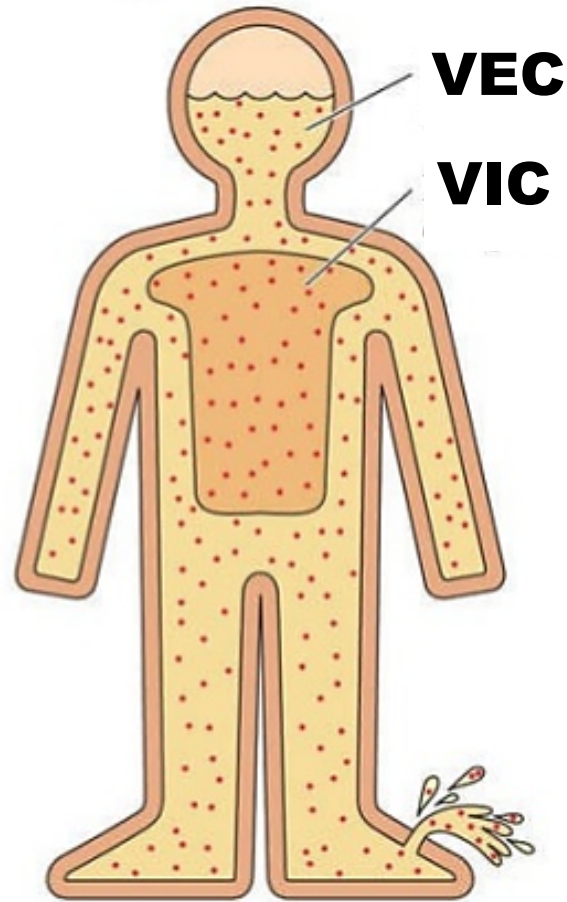
Especie	Castor
Peso (Kg) / Estatura (m)	70 / 1.7
Carga osmolar diaria (mOsm)	600
Nefronas de “asa larga”	0
Conc. urinaria max. (mOsm/L)	600
Vol. urinario mínimo diario (mL)	1000



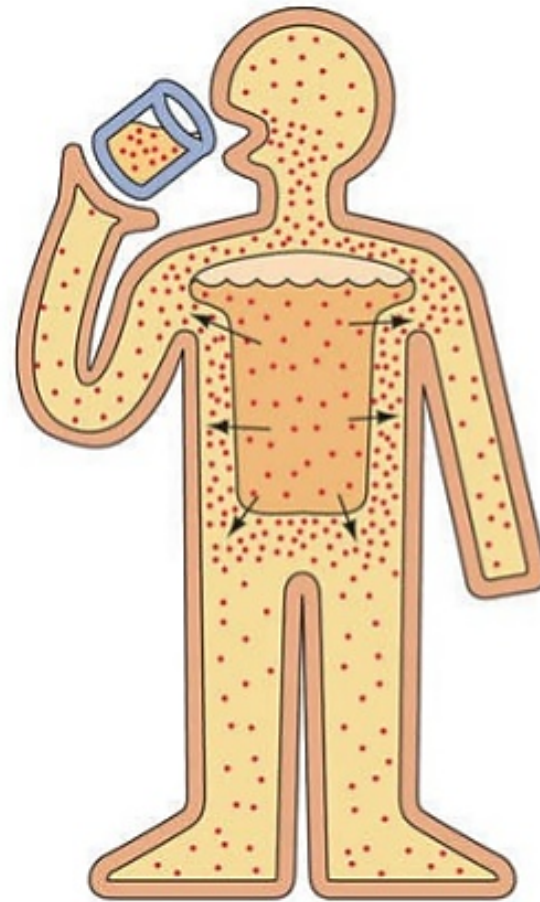
El mecanismo de la sed

Estimulación del Reflejo de la Sed

Sed “hipovolémica”




Sed “osmótica”



Maximum thirst

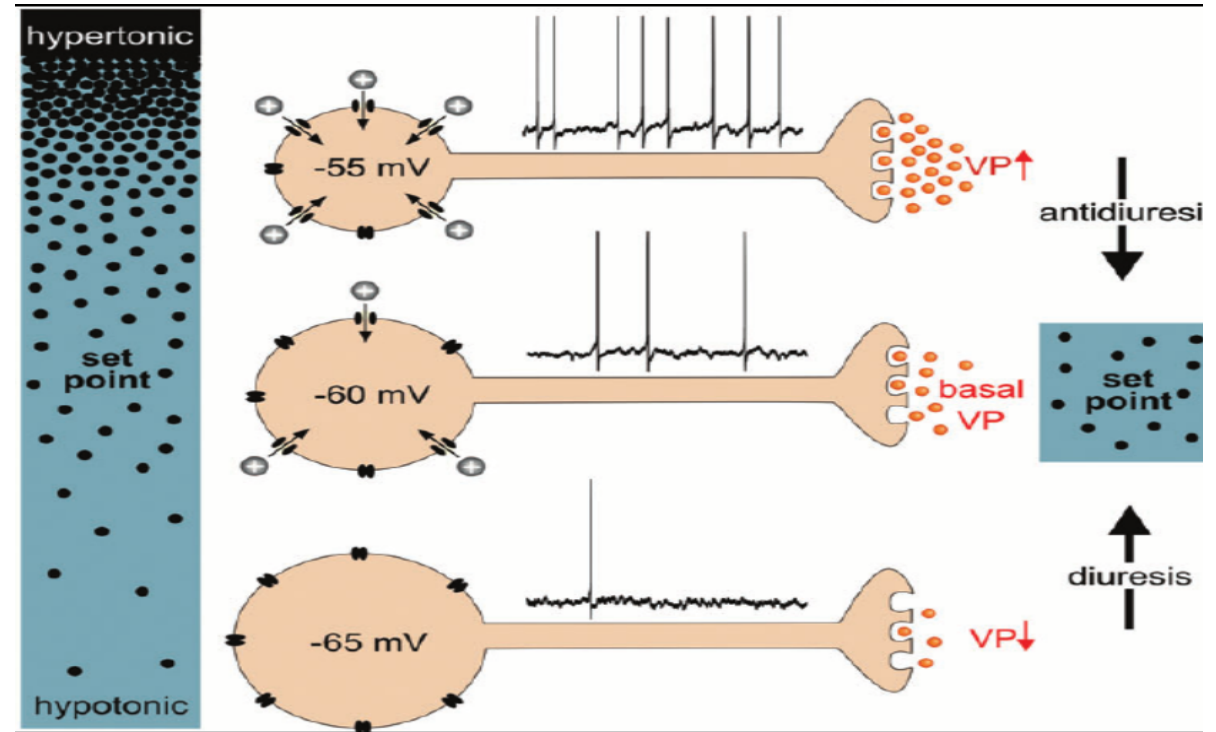
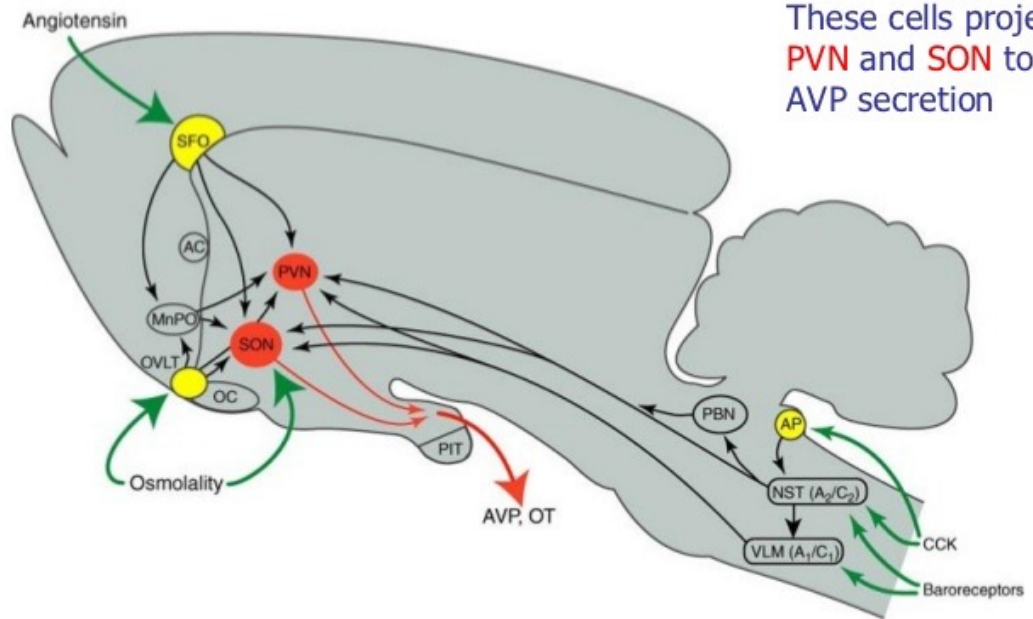
3 min after drinking

z scores
1.96  4
-1.96  -4

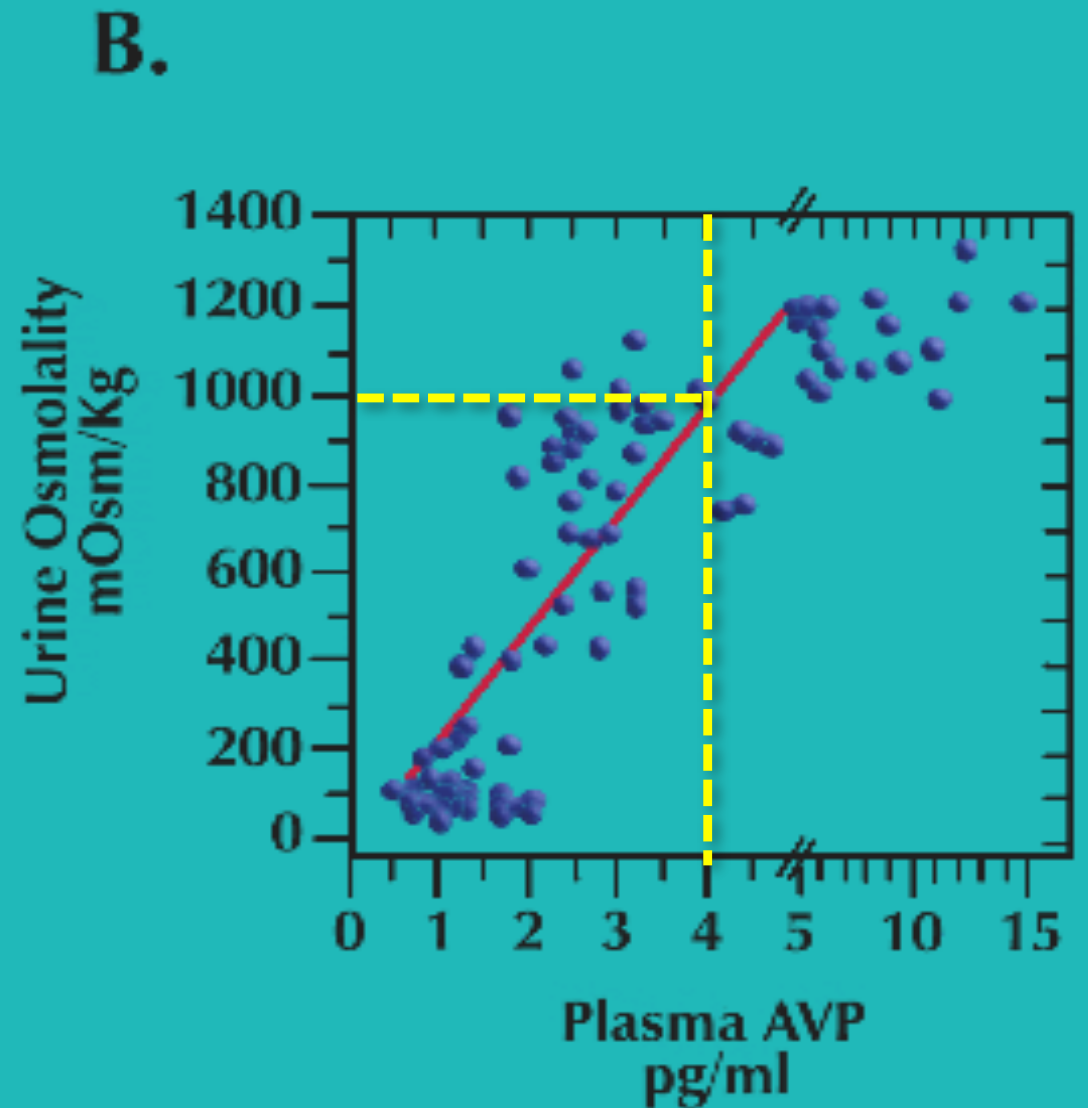
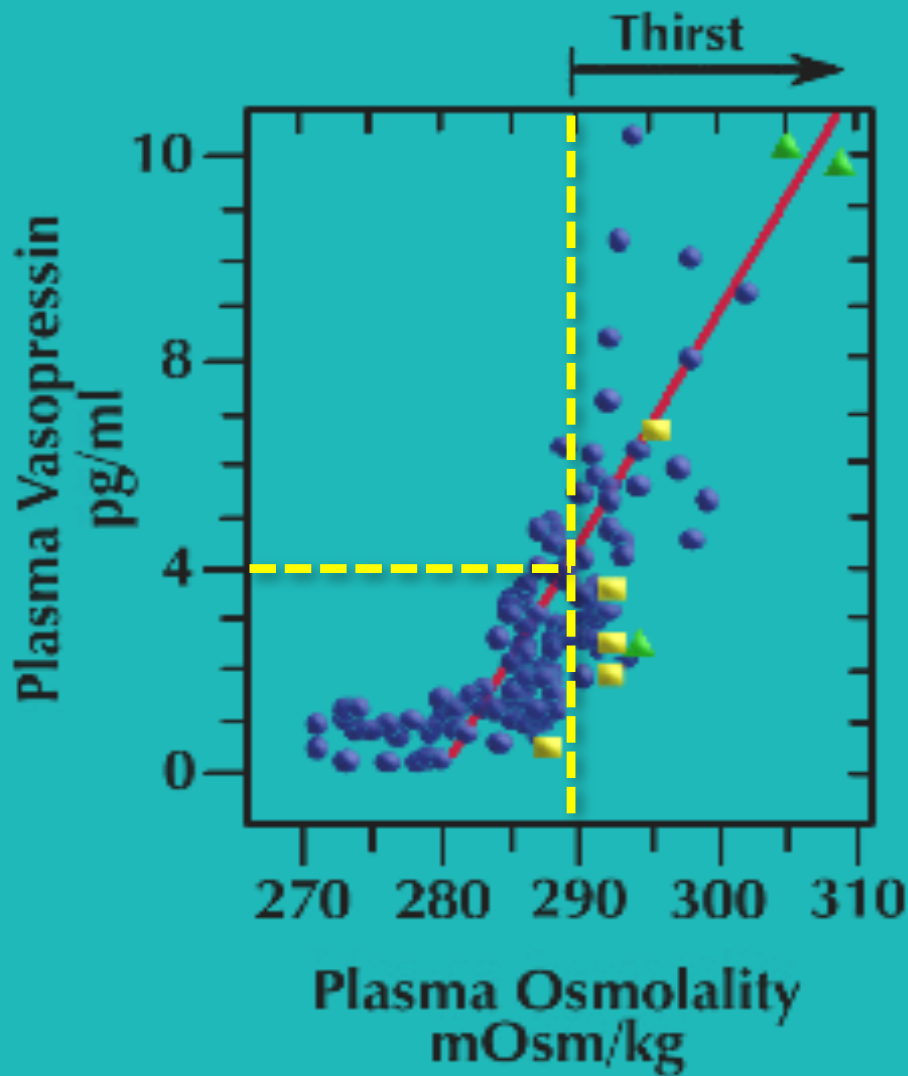
Reprinted, with permission, from Proc Natl Acad Sci USA. 1999;96:5304–5309. Neuroimaging of genesis of thirst, and satiation of thirst. Denton DA, Shade R, Zammarippa F, Egan G, Blair-West JR,

Osmoreceptors stimulate AVP secretion and thirst

The **vascular organ of the lamina terminalis (OVLT)** contains osmoreceptive neurons – also the **subfornical organ (SFO)** and the **median preoptic n. (MnPO)**



Secreción de HAD



OPTOGENETICS

Biological
Psychiatry | 2012
Optogenetics
& Psychiatry →



2012
nature
Channelrhodopsin
Crystal Structure →



The Development &
Application of Optogenetics →
Annual Review of Neuroscience
2011

2012 Analysis
nature methods
Quantitative Opsin
Properties →

2011 Primer
Cell
Opsin Genomics and
Structure-Function →

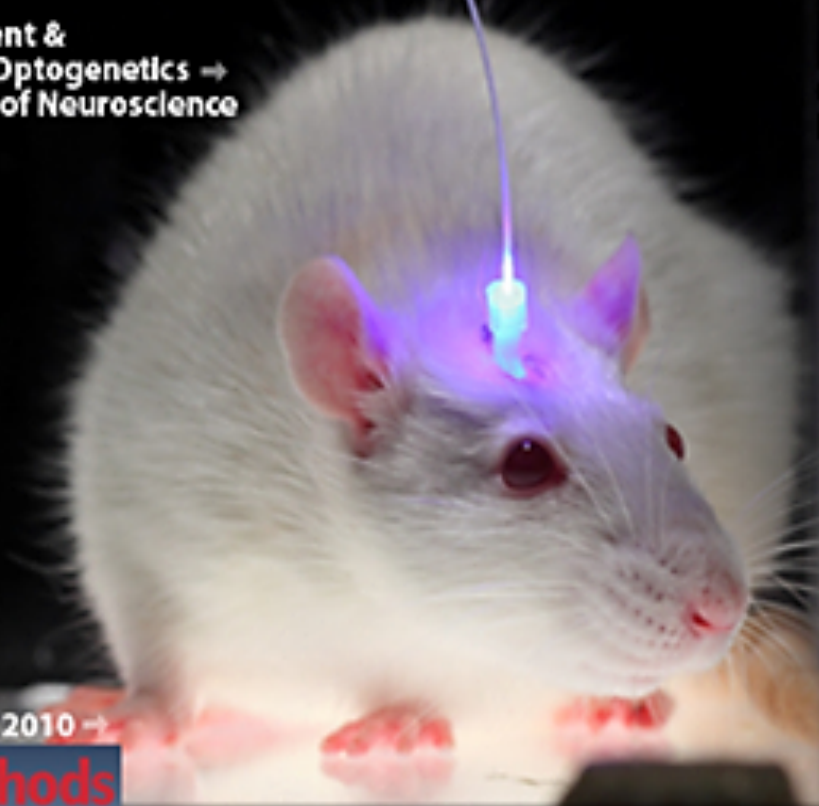
2012
nature
REVIEWS
Optogenetics & Neural
Circuits in Brain Disease →

Method of the Year: 2010 →
nature methods
Optogenetics

2011 Primer
Neuron
Optogenetics in
Neural Systems →

2010 **nature**
protocols
optogenetics
protocols →

2010
SCIENTIFIC
AMERICAN
Optogenetics Article →

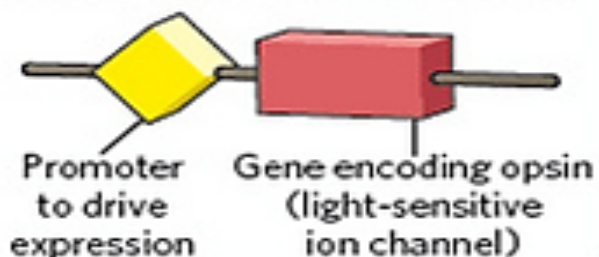


SIX STEPS TO OPTOGENETICS

With optogenetic techniques, researchers can modulate the activity of targeted neurons using light.

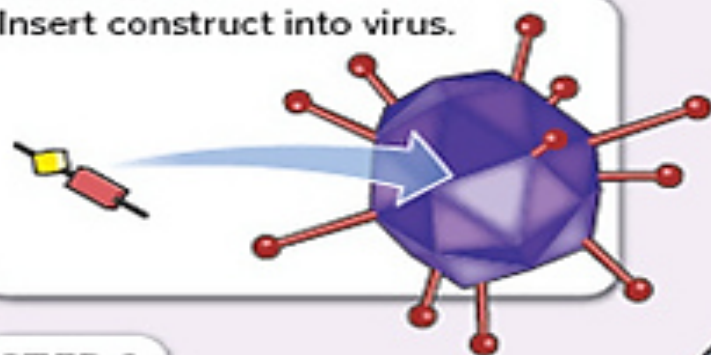
STEP 1

Piece together genetic construct.



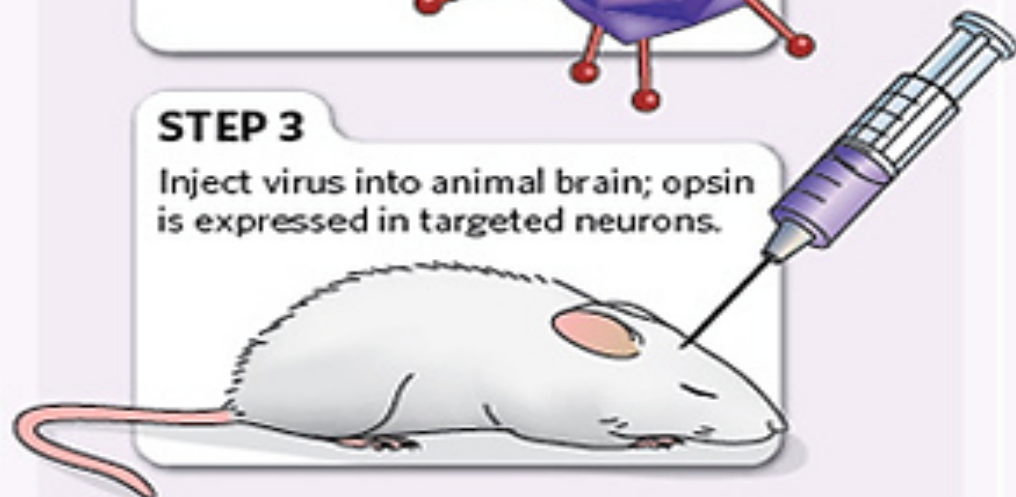
STEP 2

Insert construct into virus.



STEP 3

Inject virus into animal brain; opsin is expressed in targeted neurons.



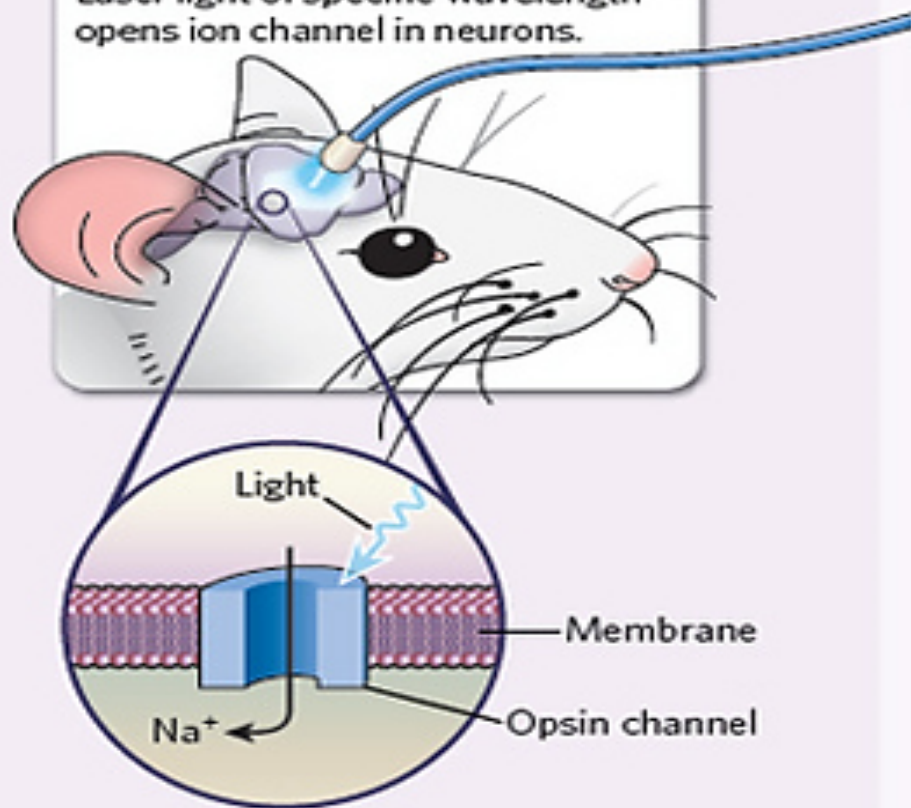
STEP 4

Insert 'optrode', fibre-optic cable plus electrode.



STEP 5

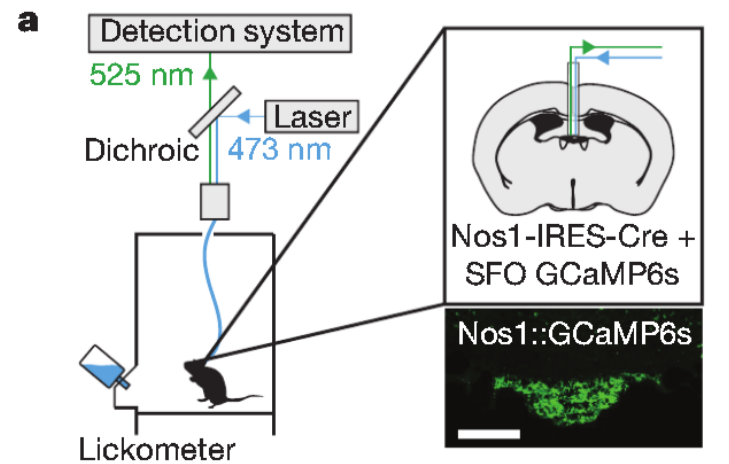
Laser light of specific wavelength opens ion channel in neurons.



Thirst neurons anticipate the homeostatic consequences of eating and drinking

Christopher A. Zimmerman^{1,2,3}, Yen-Chu Lin^{1,2}, David E. Leib^{1,2,3}, Ling Guo^{1,2,3}, Erica L. Huey^{1,2}, Gwendolyn E. Daly^{1,2}, Yiming Chen^{1,2,3} & Zachary A. Knight^{1,2,3}

**Medición
optogenética de
la actividad del
Organo
Subfornical
(SFO) para
determinar el
patrón de la sed
en distintas
condiciones
fisiológicas**



Thirst neurons anticipate the homeostatic consequences of eating and drinking

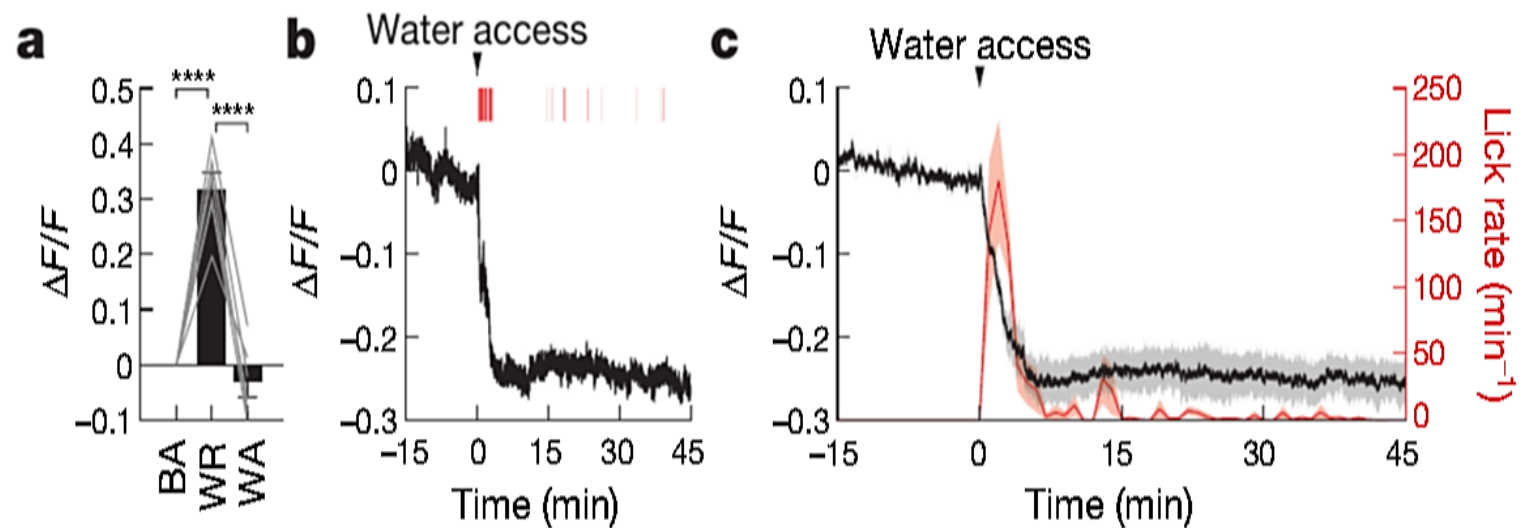
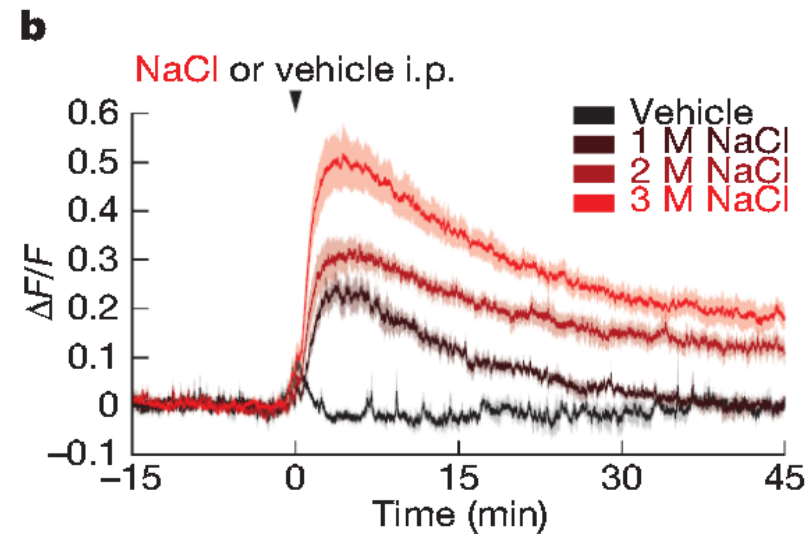
Christopher A. Zimmerman^{1,2,3}, Yen-Chu Lin^{1,2}, David E. Leib^{1,2,3}, Ling Guo^{1,2,3}, Erica L. Huey^{1,2}, Gwendolyn E. Daly^{1,2}, Yiming Chen^{1,2,3} & Zachary A. Knight^{1,2,3}

“...he comido muy salado y ¡tengo sed!”

Activación osmótica de sed vía OR

“...al despertar un trago de agua”

Activación SFO que cesa con aferencias orales en corto



Thirst neurons anticipate the homeostatic consequences of eating and drinking

Christopher A. Zimmerman^{1,2,3}, Yen-Chu Lin^{1,2}, David E. Leib^{1,2,3}, Ling Guo^{1,2,3}, Erica L. Huey^{1,2}, Gwendolyn E. Daly^{1,2}, Yiming Chen^{1,2,3} & Zachary A. Knight^{1,2,3}

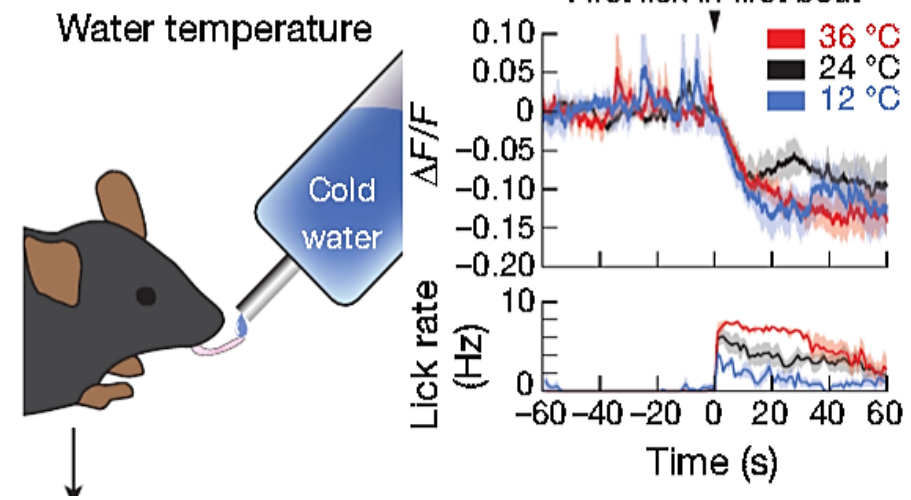
**“...¡mesero!,
esta cerveza
está caliente...”**

**La supresión del
SFO es
temperatura
dependiente**

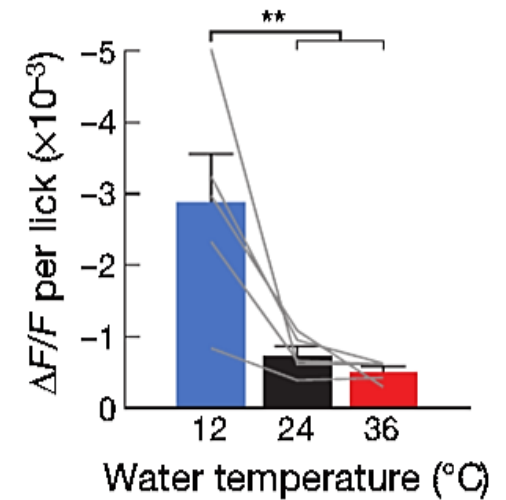
**“¡Dr. me muero
de sed!”**

**Mastique hielos
pero ¡no los
trague!**

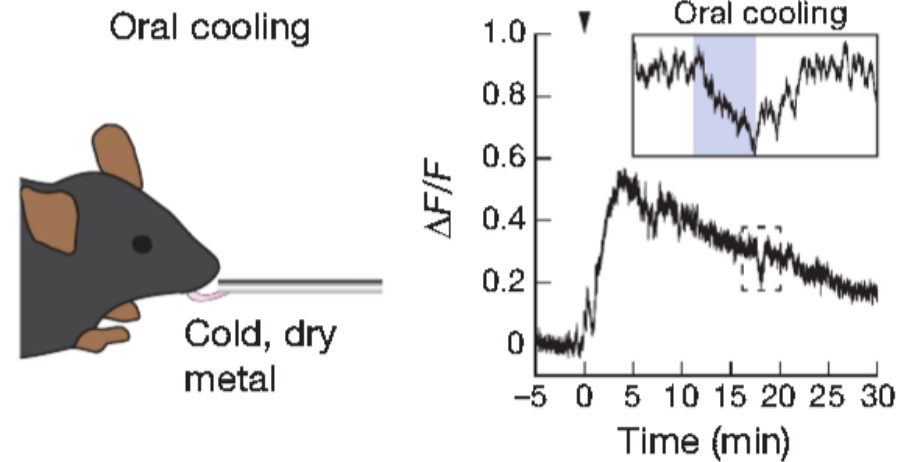
k



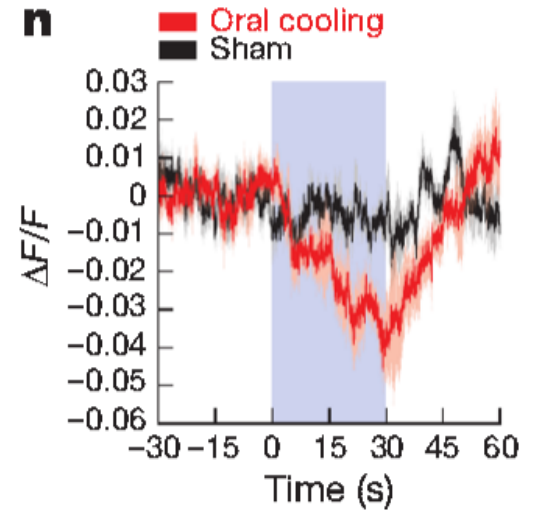
l



m



n

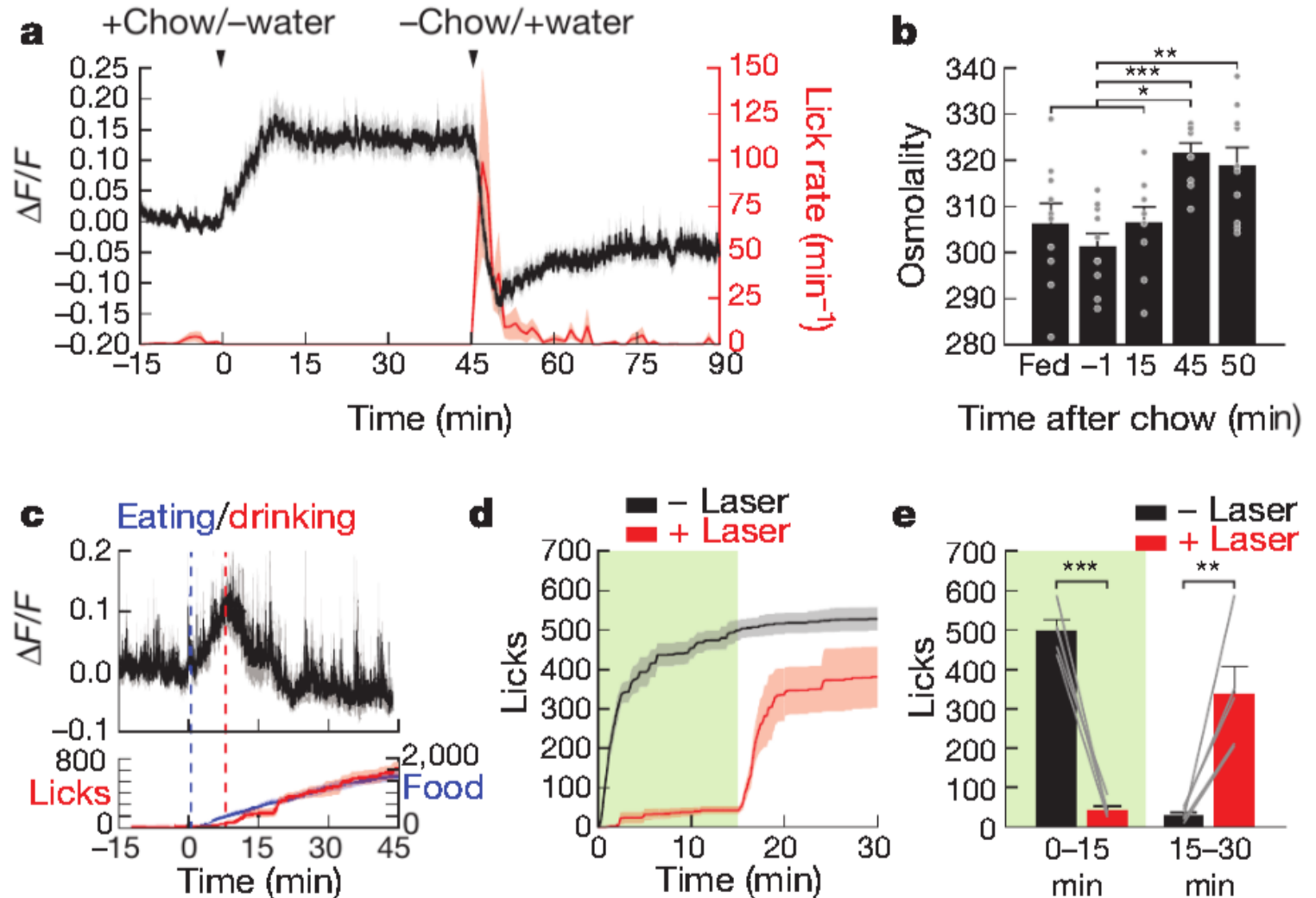


Thirst neurons anticipate the homeostatic consequences of eating and drinking

Christopher A. Zimmerman^{1,2,3}, Yen-Chu Lin^{1,2}, David E. Leib^{1,2,3}, Ling Guo^{1,2,3}, Erica L. Huey^{1,2}, Gwendolyn E. Daly^{1,2}, Yiming Chen^{1,2,3} & Zachary A. Knight^{1,2,3}

Mesero:
 “...que tal un
 aperitivo para
 empezar !?”

**La comida
 estimula el SFO
 mucho antes de
 que se generen
 cambios
 osmolares post-
 absortivos**



Thirst neurons anticipate the homeostatic consequences of eating and drinking

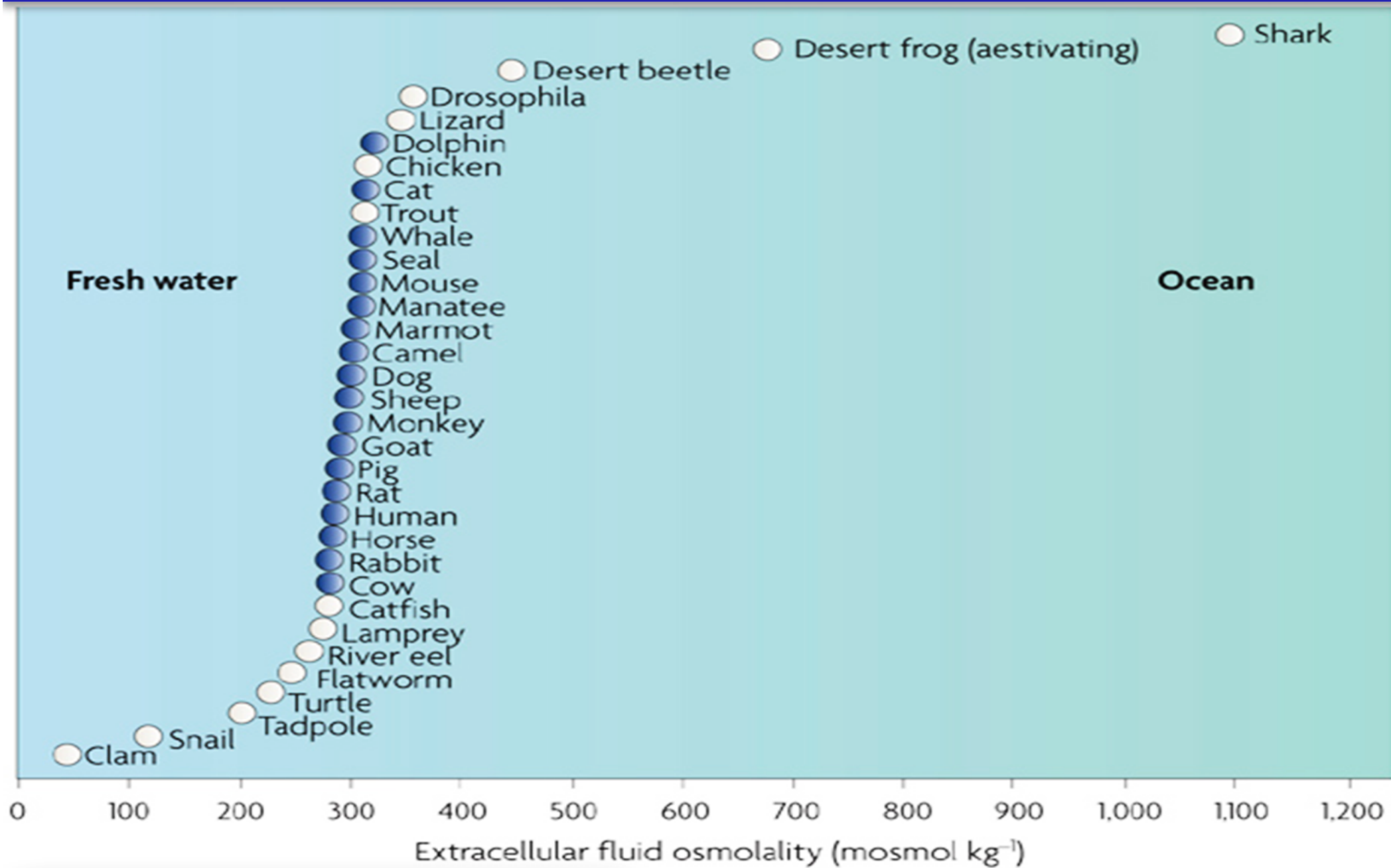
Christopher A. Zimmerman^{1,2,3}, Yen-Chu Lin^{1,2}, David E. Leib^{1,2,3}, Ling Guo^{1,2,3}, Erica L. Huey^{1,2}, Gwendolyn E. Daly^{1,2}, Yiming Chen^{1,2,3} & Zachary A. Knight^{1,2,3}

- **El comportamiento en la ingesta de líquidos está regulado por una combinación de eventos “anticipados”**
- **La base neural de la “sed anticipada” converge en las mismas neuronas homeostáticas que monitorizan la composición de los líquidos corporales.**
- **Esta convergencia resulta en patrones de conducta complejos como la velocidad en saciar la sed, la temperatura y la coordinación de la ingesta de líquidos y sólidos.**
- **El efecto de los órganos circunventriculares es complejo y dinámico y determina comportamientos en mamíferos.**

PREGUNTA

Porqué el set-point de la secreción de la hormona antidiurética se encuentra ~ 290 mOsm/L ?

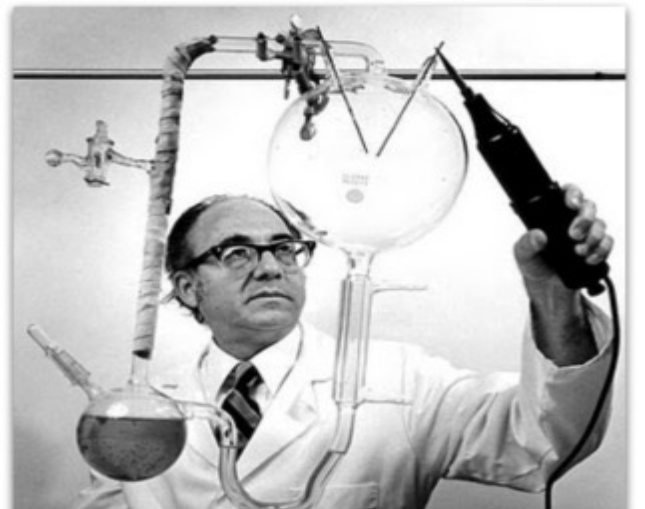
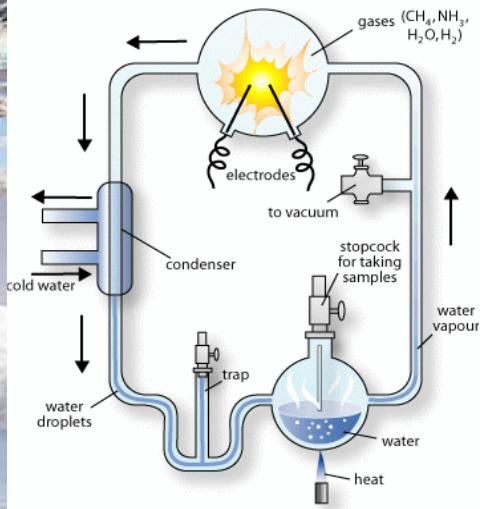
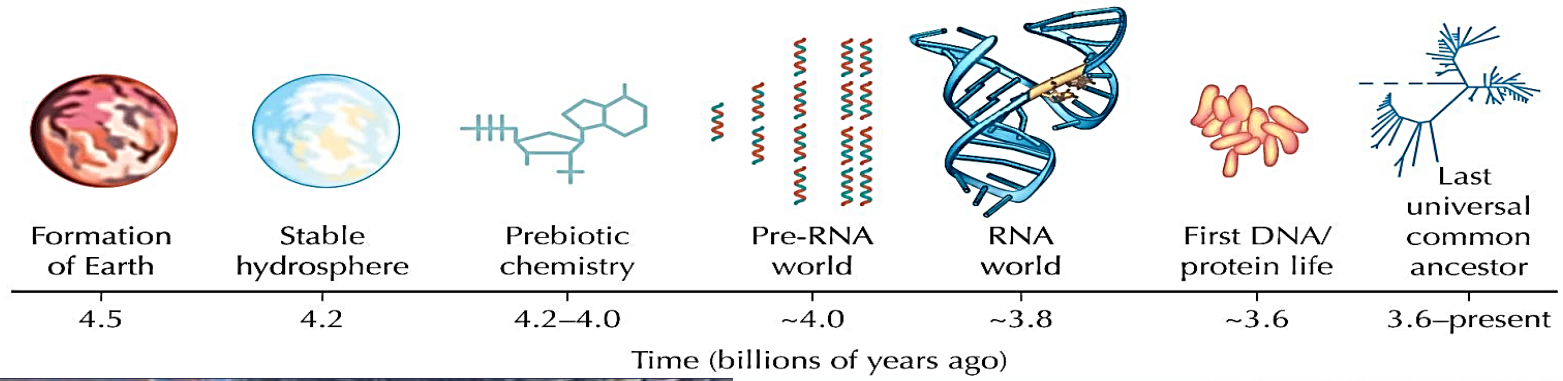
Osmolaridad de líquidos corporales en diversas especies



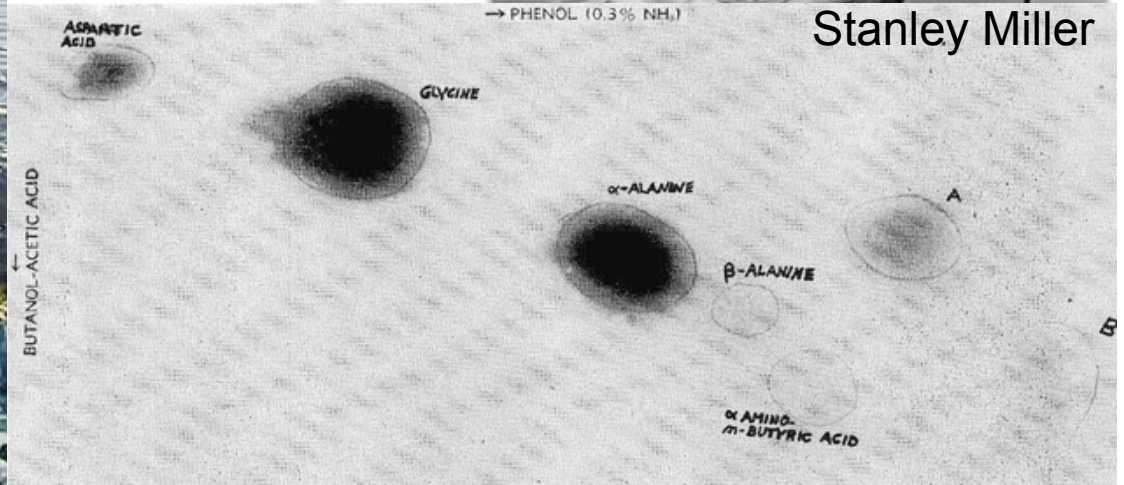


Benjamin
Gunn

ORIGEN DE LA VIDA

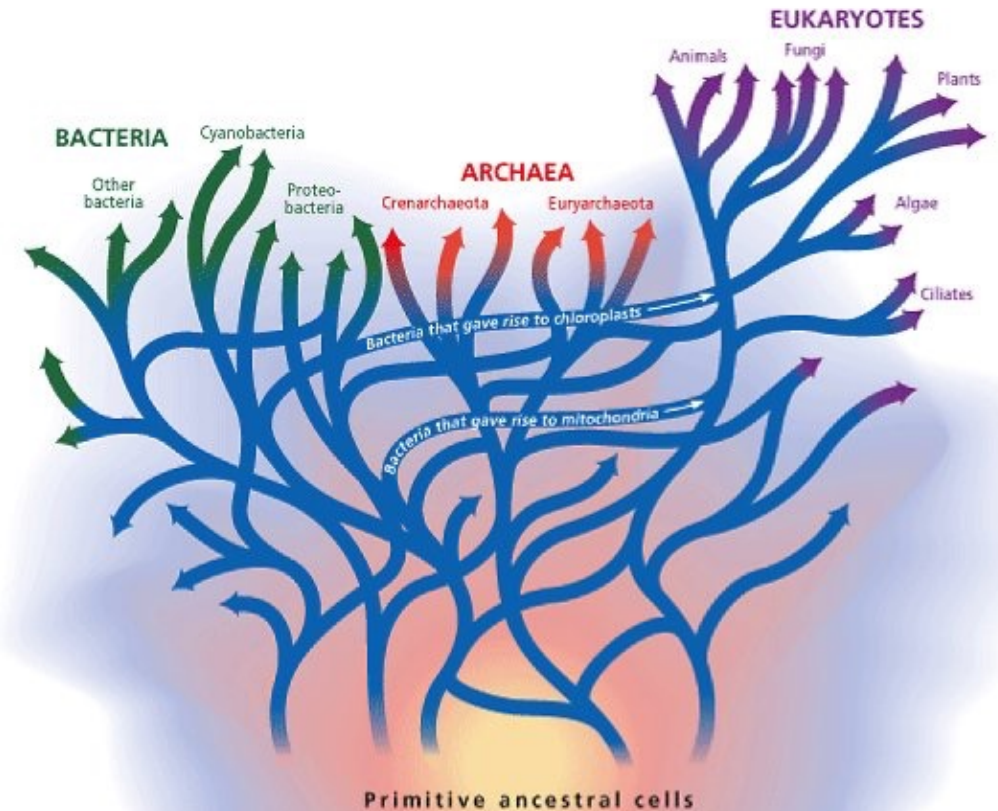
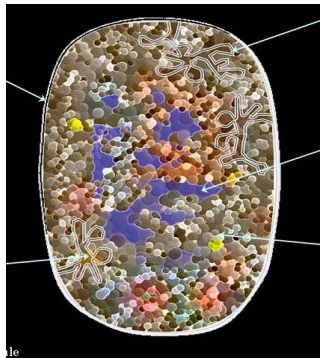
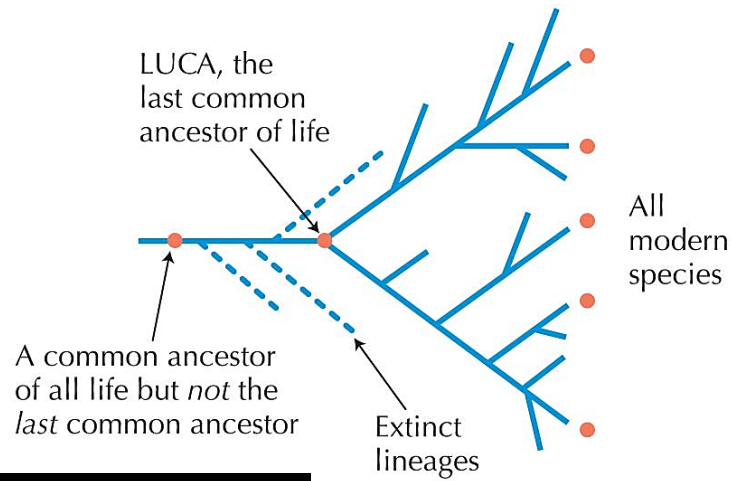
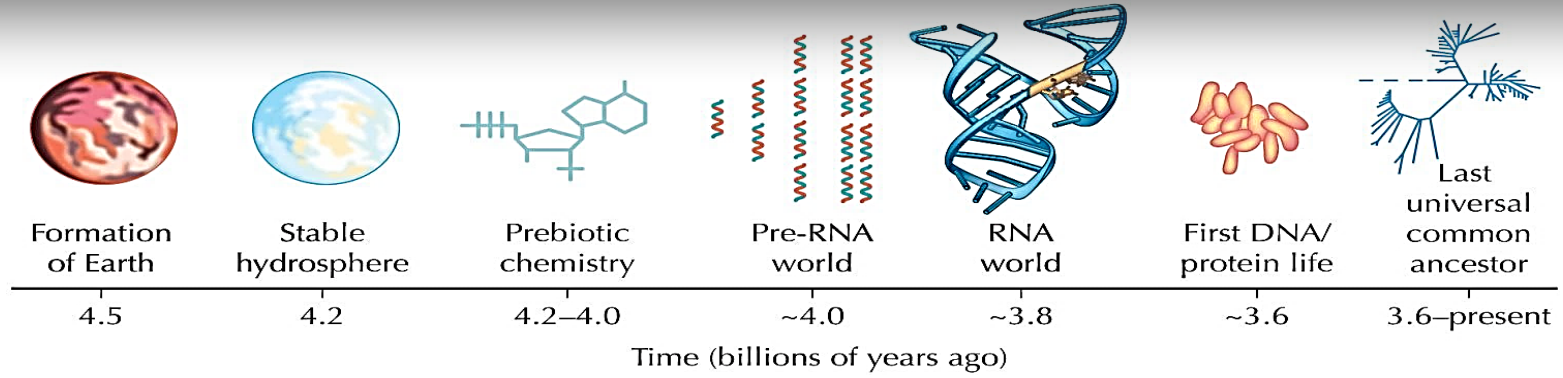


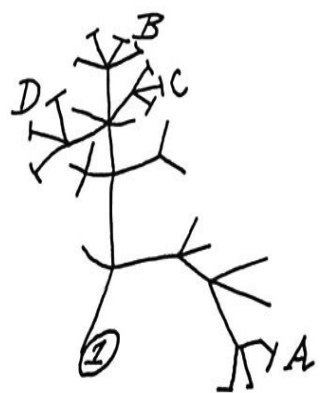
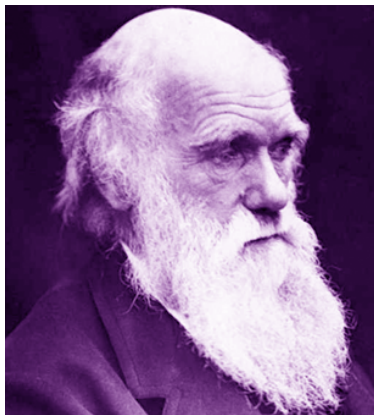
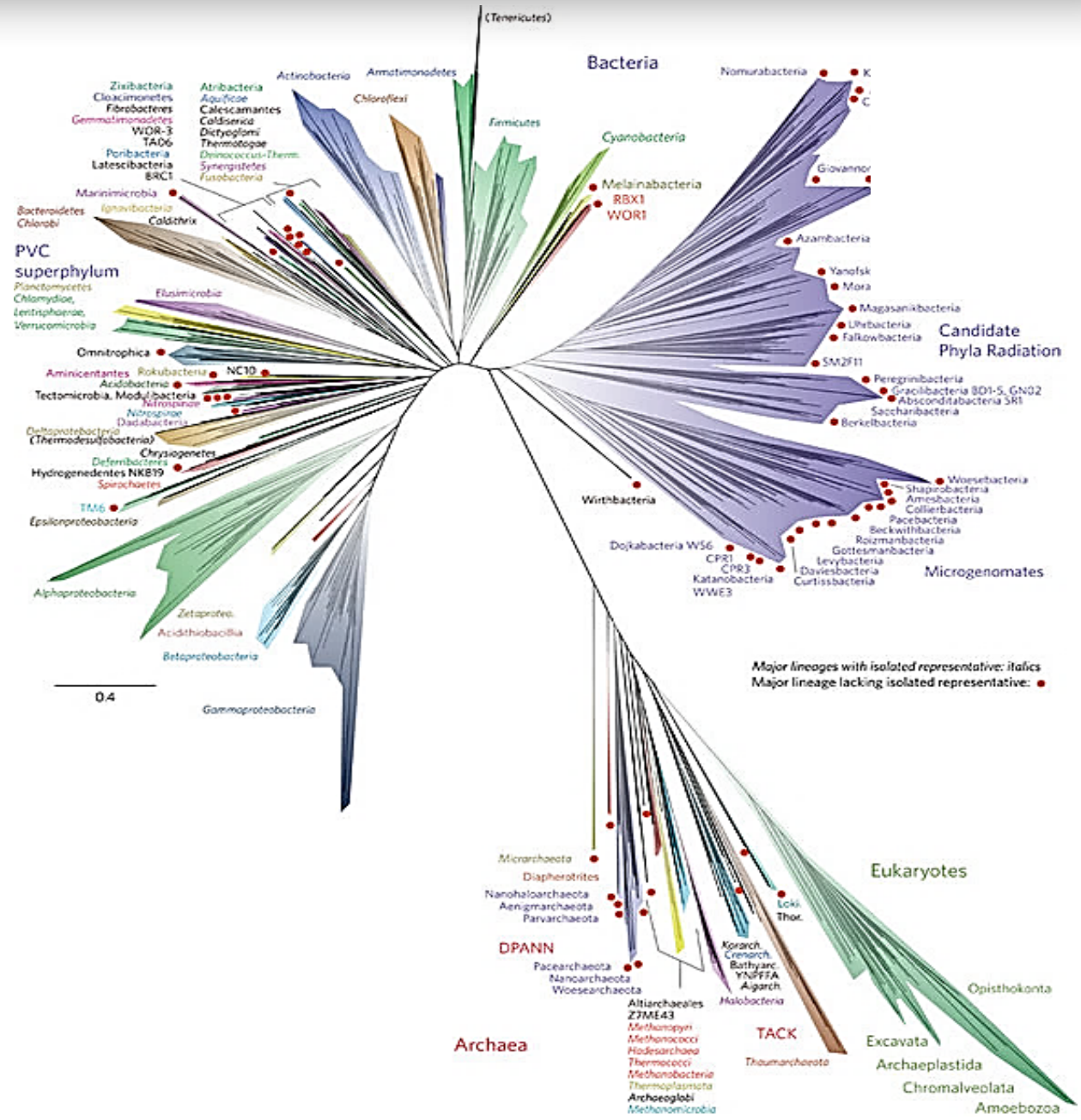
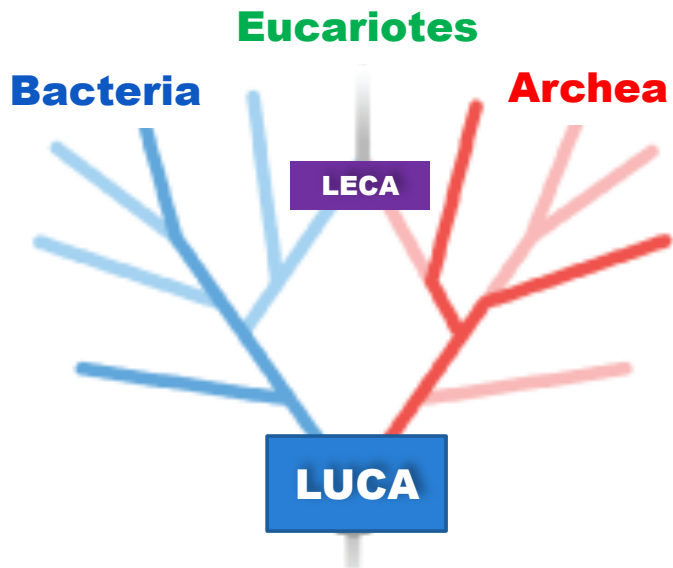
Stanley Miller



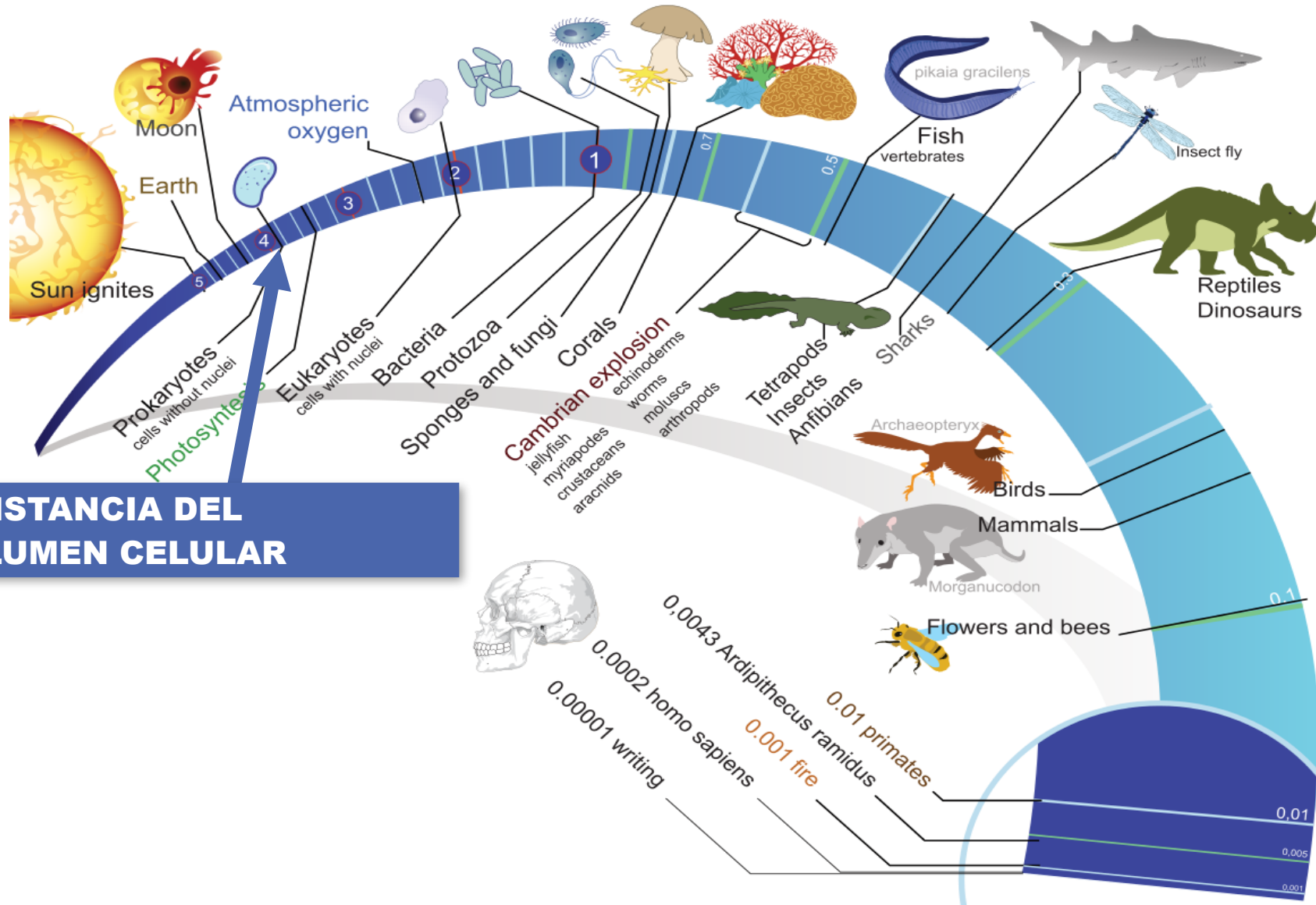
LUCA

(Last Universal Common Ancestor)





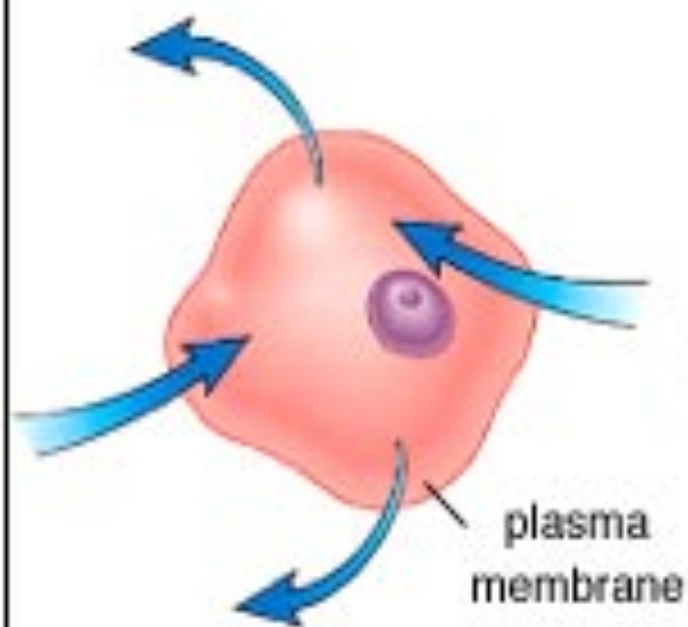
RETOS OSMOREGULATORIOS



1. CONSTANCIA DEL VOLUMEN CELULAR

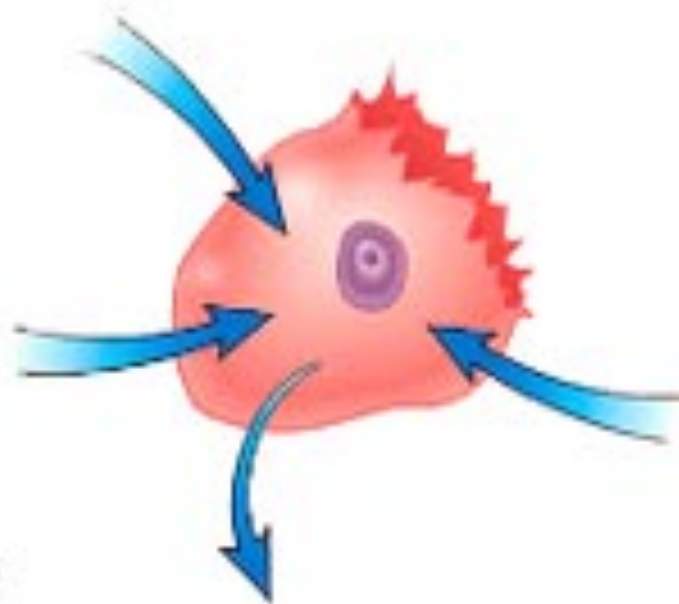
Animal Cells

Isotonic
Conditions



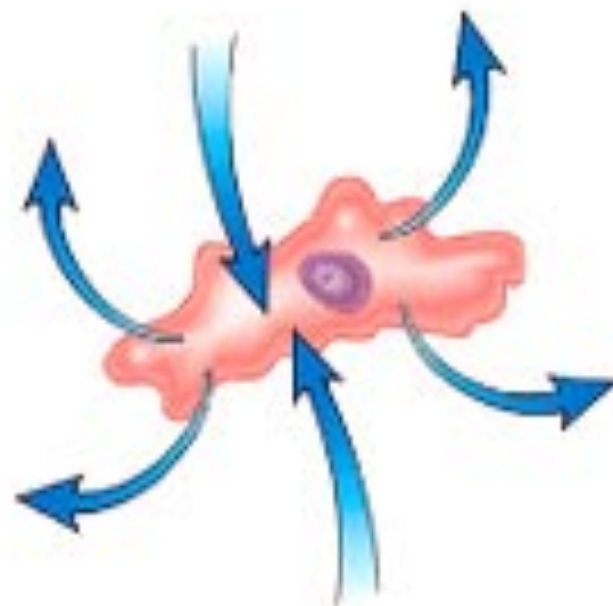
No net movement of water
into and out of the cell.

Hypotonic
Conditions



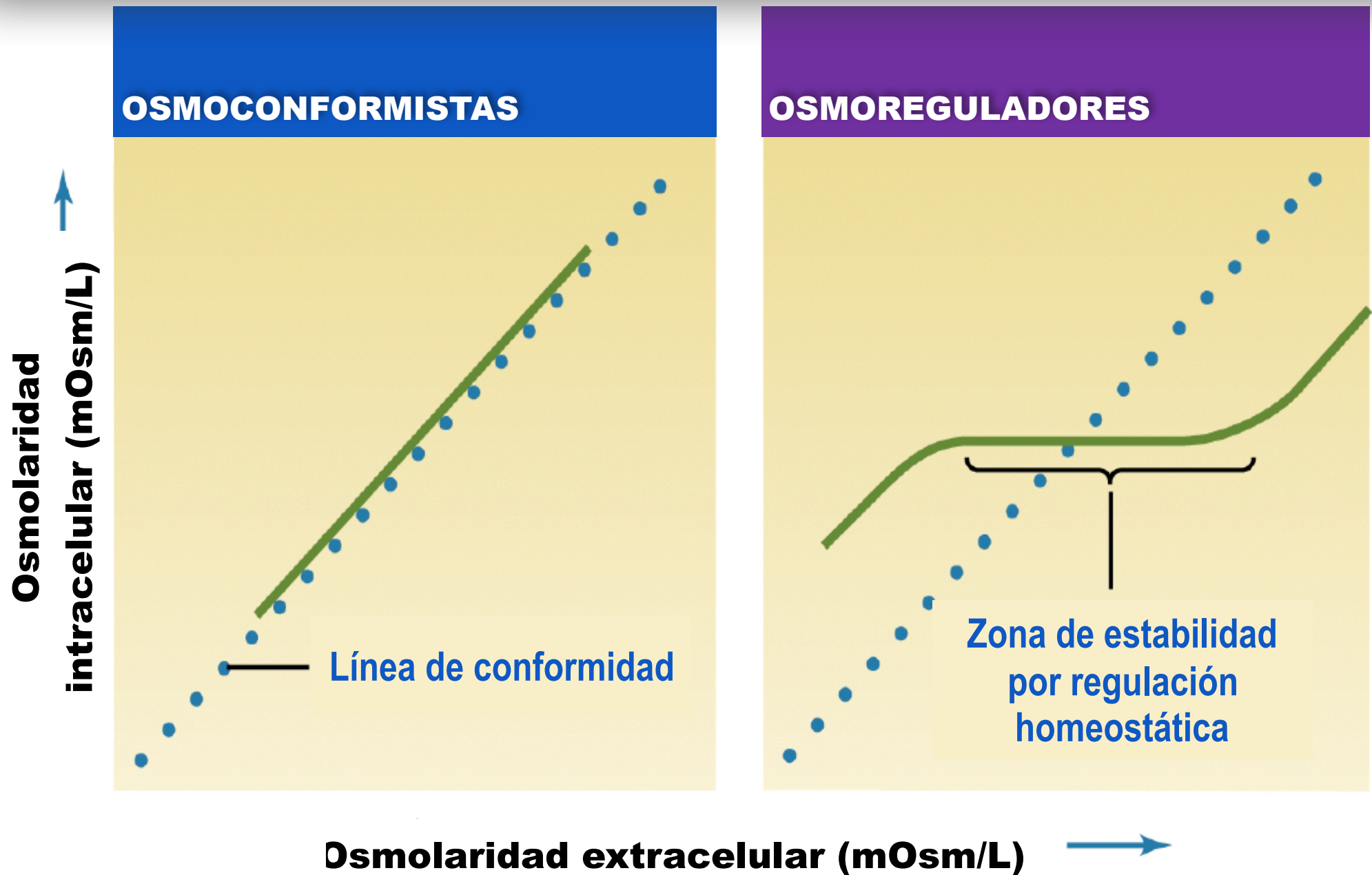
Water enters the cell, which
may burst (lysis) due to
osmotic pressure.

Hypertonic
Conditions



Water exits the cell, which
shrivels (crenation).

ADAPTACIONES A LA OSMOLARIDAD EXTERNA



Physiology of Cell Volume Regulation in Vertebrates

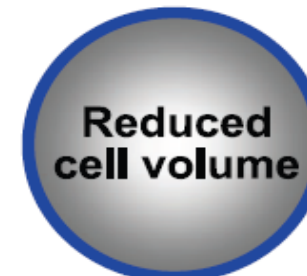
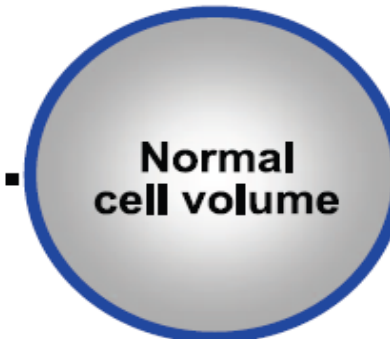
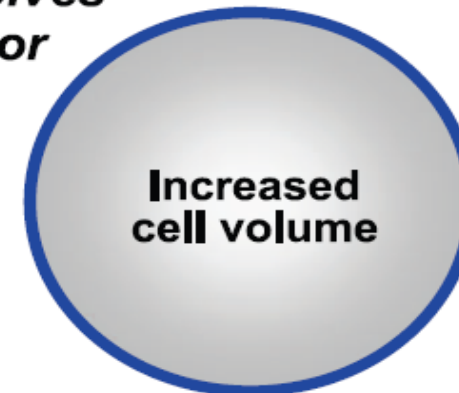
ELSE K. HOFFMANN, IAN H. LAMBERT, AND STINE F. PEDERSEN

Physiol Rev 89: 193–277, 2009;

Physiological conditions that involves a change in cell volume as a sensor

- Transepithelial transport – absorption
- Regulation of metabolism – anabolism
- Hormone / Transmitter release – stimulation
- Excitability and contraction
- Cell proliferation
- Cell migration
- Oxygen transport in RBCs
- Necrosis

-
- Transepithelial transport – secretion
 - Regulation of metabolism – catabolism
 - Cell differentiation
 - Programmed cell death



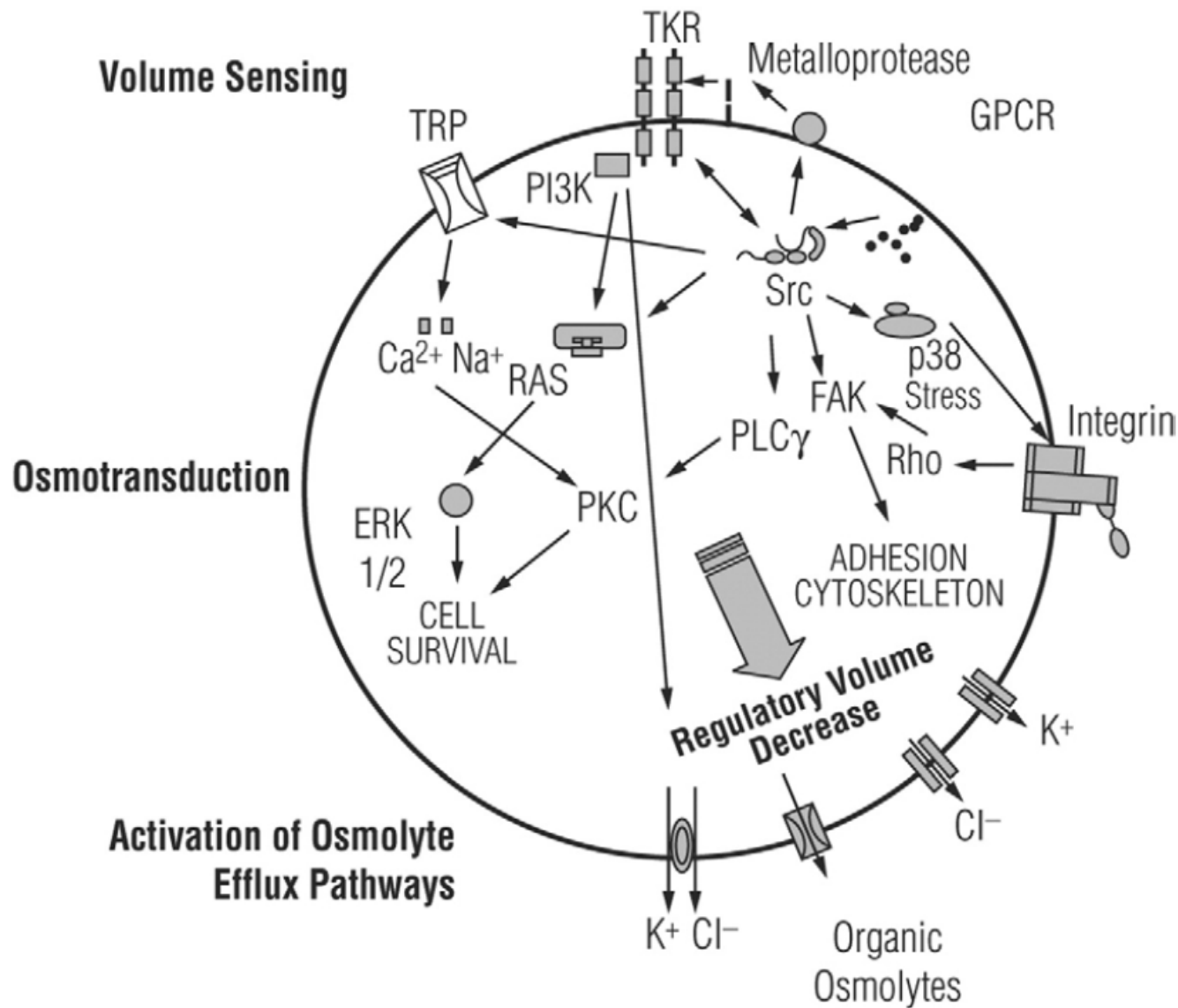


Mechanisms of Cell Volume Regulation in Hypo-osmolality

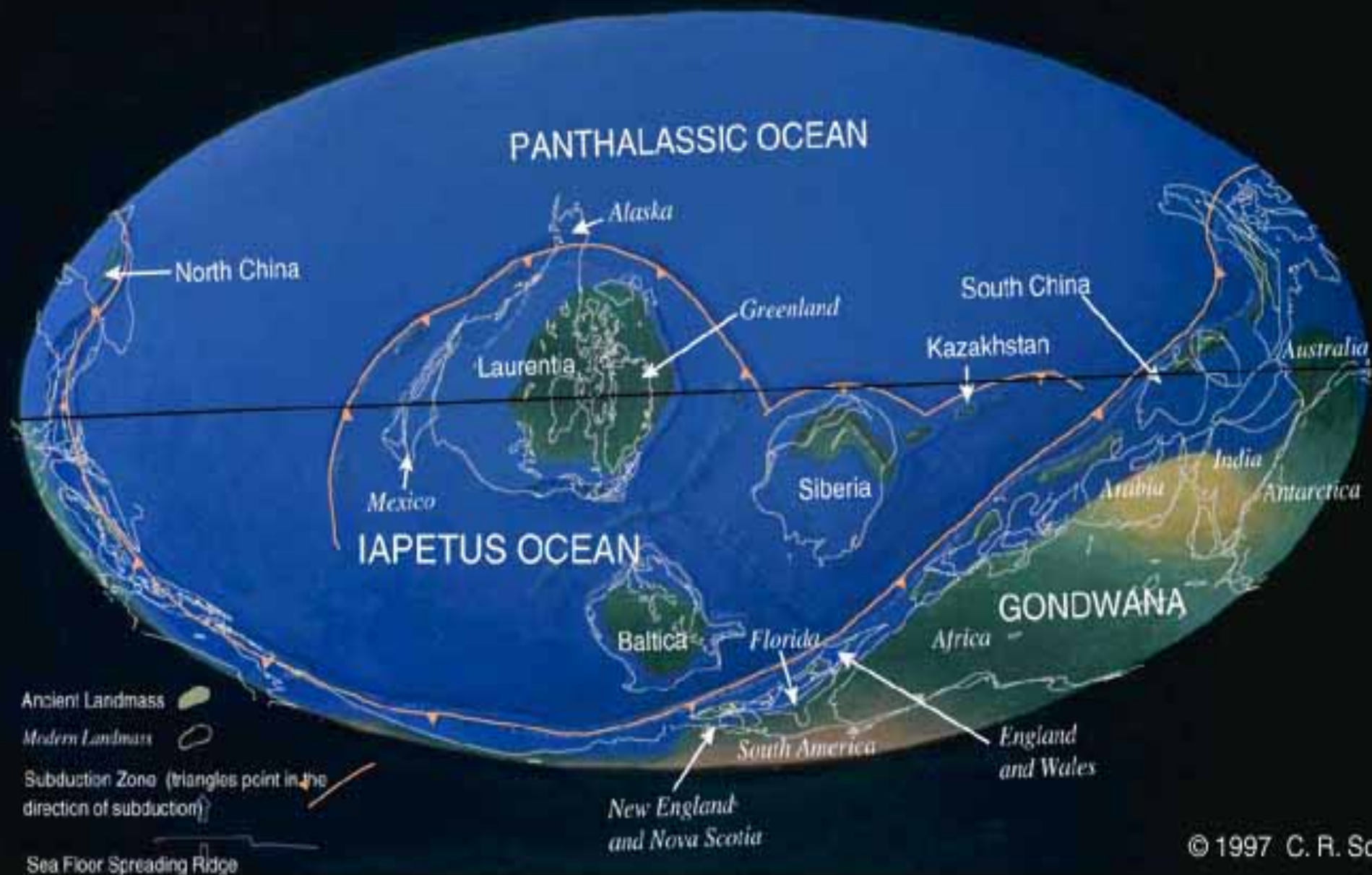
Herminia Pasantes-Morales, PhD,* Ruth A. Lezama, PhD, Gerardo Ramos-Mandujano, PhD, Karina L. Tuz, PhD

Department of Biophysics, Institute of Cell Physiology, National University of Mexico, Mexico City, Mexico

The American Journal of Medicine (2006) Vol 119 (7A), S4-S11



Late Cambrian 514 Ma

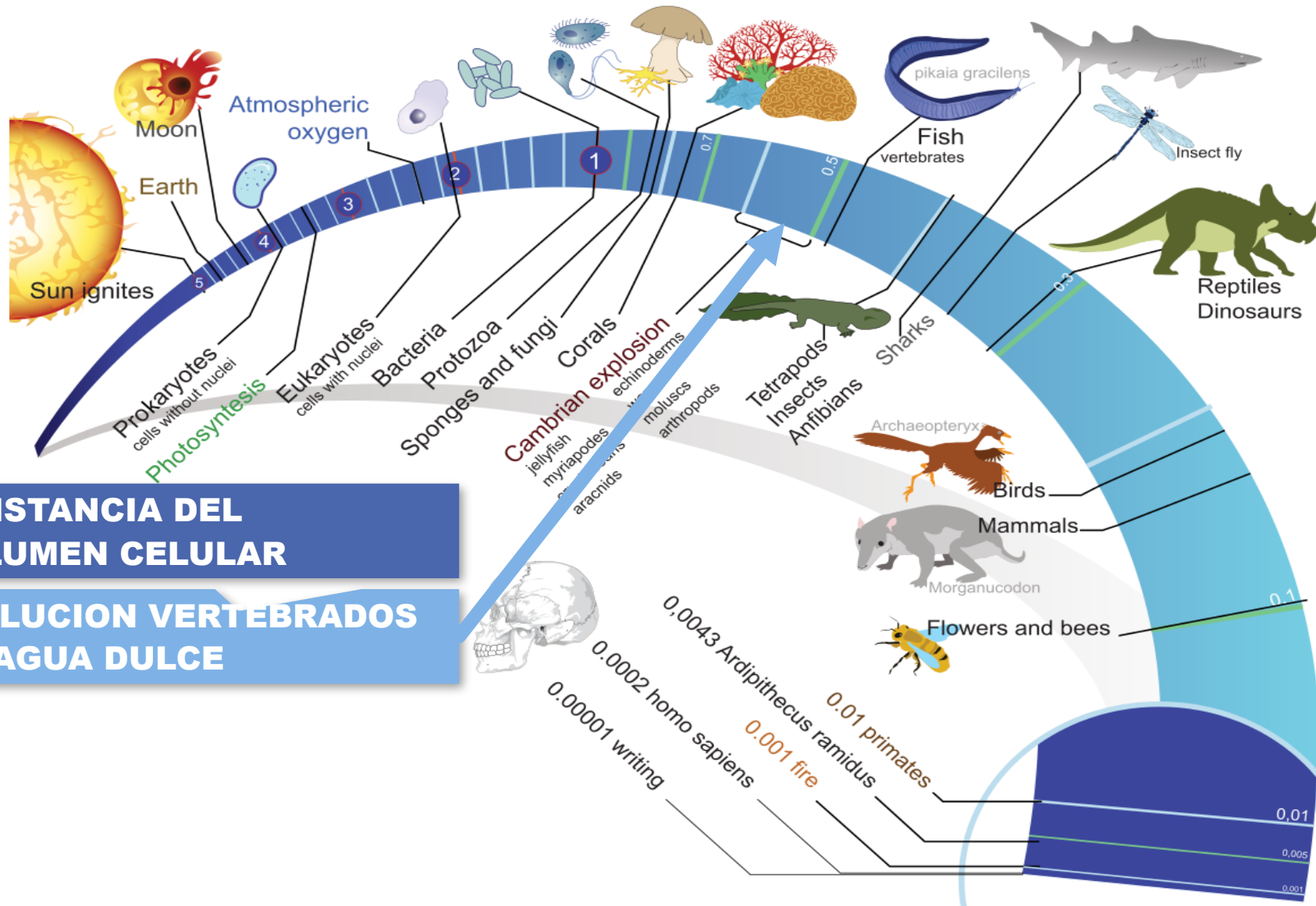


Mundo Precámbrico

(hace 600 millones de años)



RETOS OSMOREGULATORIOS



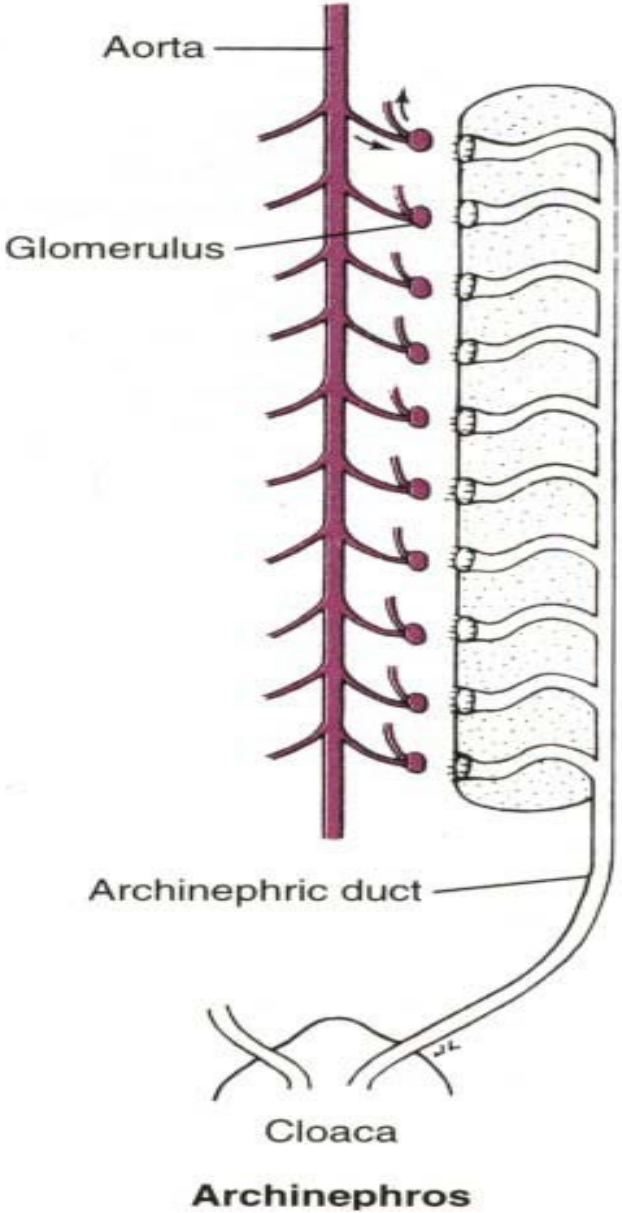
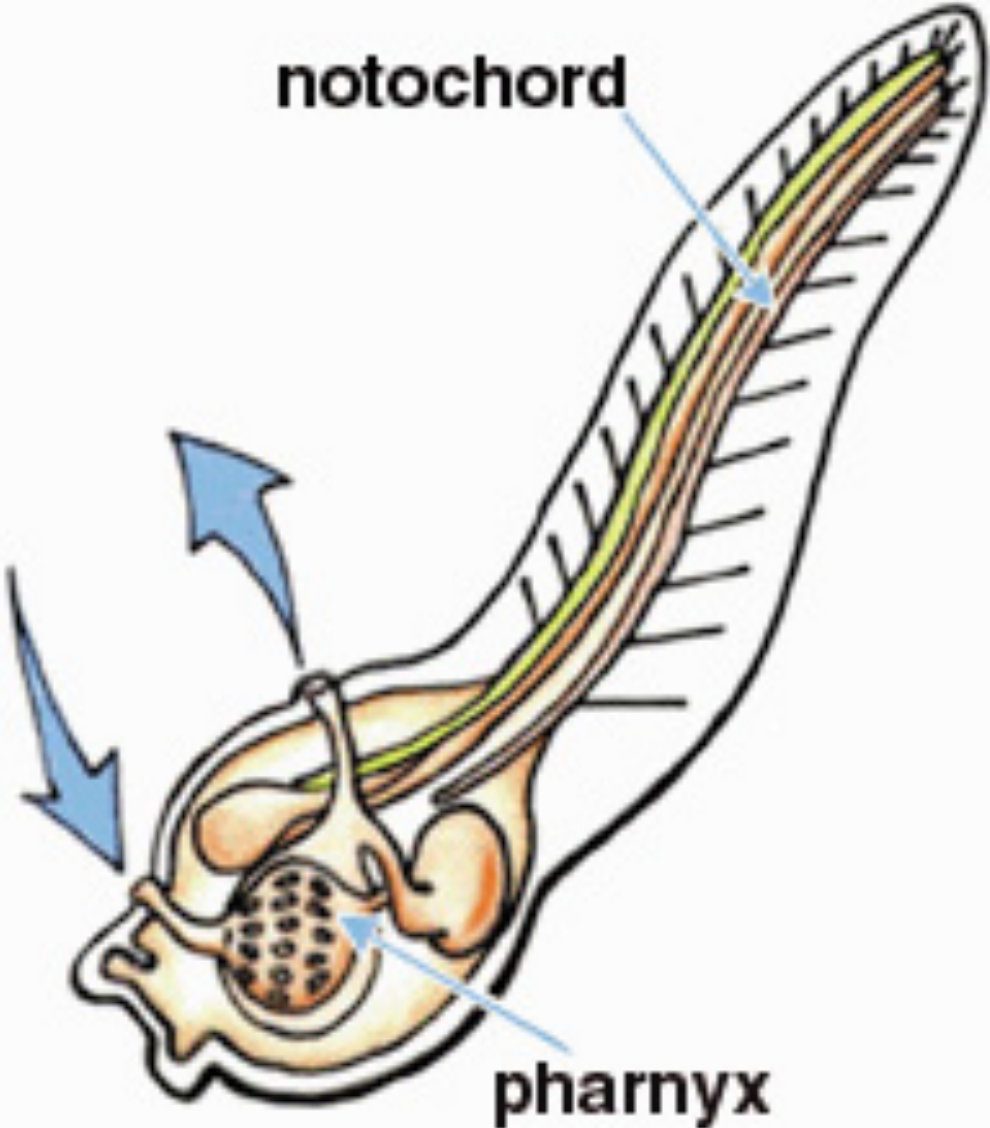
1. CONSTANCIA DEL VOLUMEN CELULAR

2. EVOLUCION VERTEBRADOS EN AGUA DULCE

Composición iónica de diversos ambientes acuosos

Iones (mM/kg de agua)	Agua Marina (media)	Mar Muerto	Agua de Río (media)	Agua de Río Dura	Agua Lacustre Blanda
Sodio	478.3	1955	0.39	6.13	0.17
Magnesio	54.5	2028	0.21	0.66	0.1
Calcio	10.5	481	0.52	5.01	0.22
Potasio	10.1	219	0.04	0.11	-----
Cloruro	558.4	7112	0.23	13.44	0.03
Sulfato	28.8	5.3	0.21	1.40	0.09

Protovertebrado

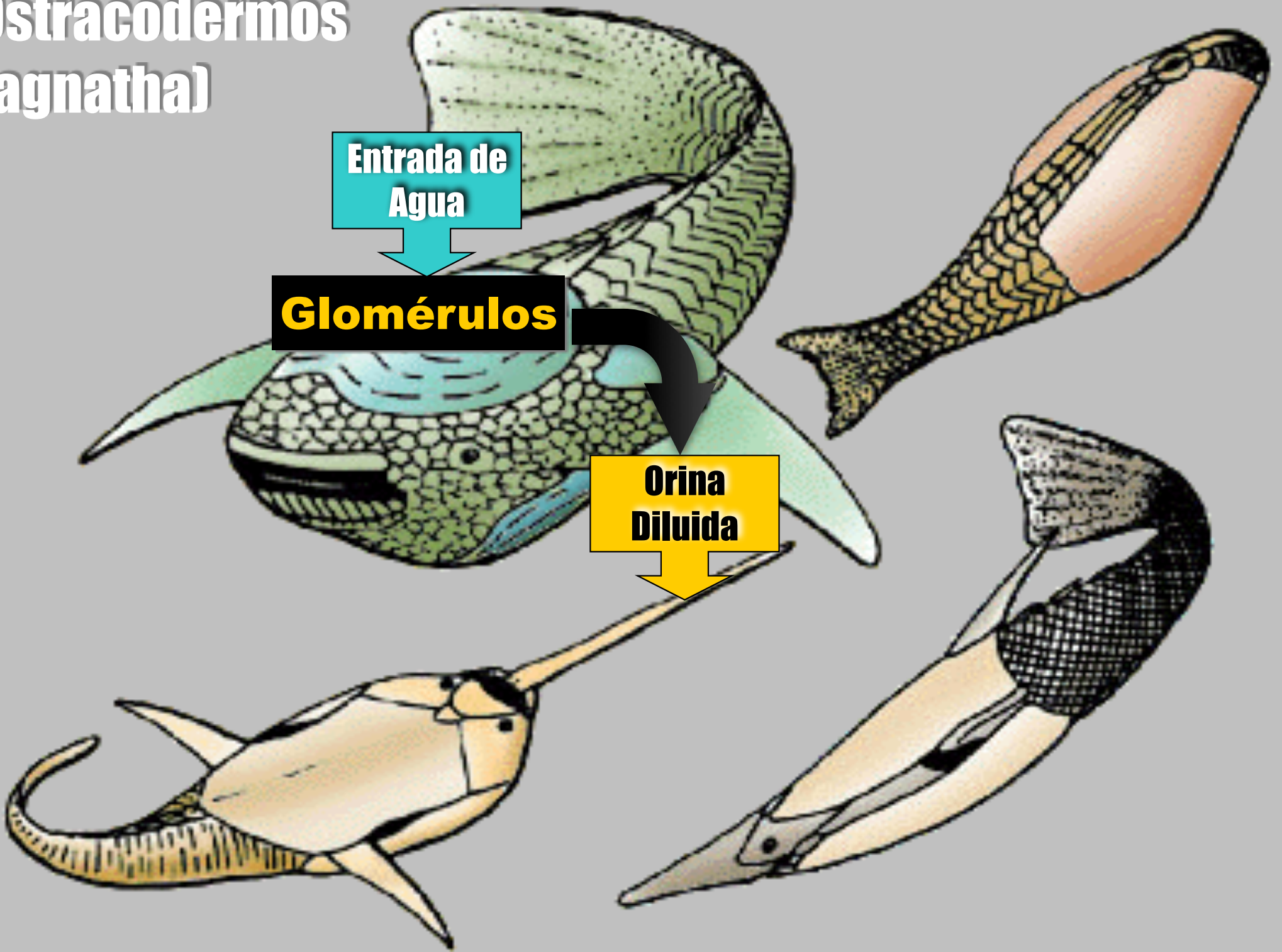


Ostracodermos (agnatha)

Entrada de
Agua

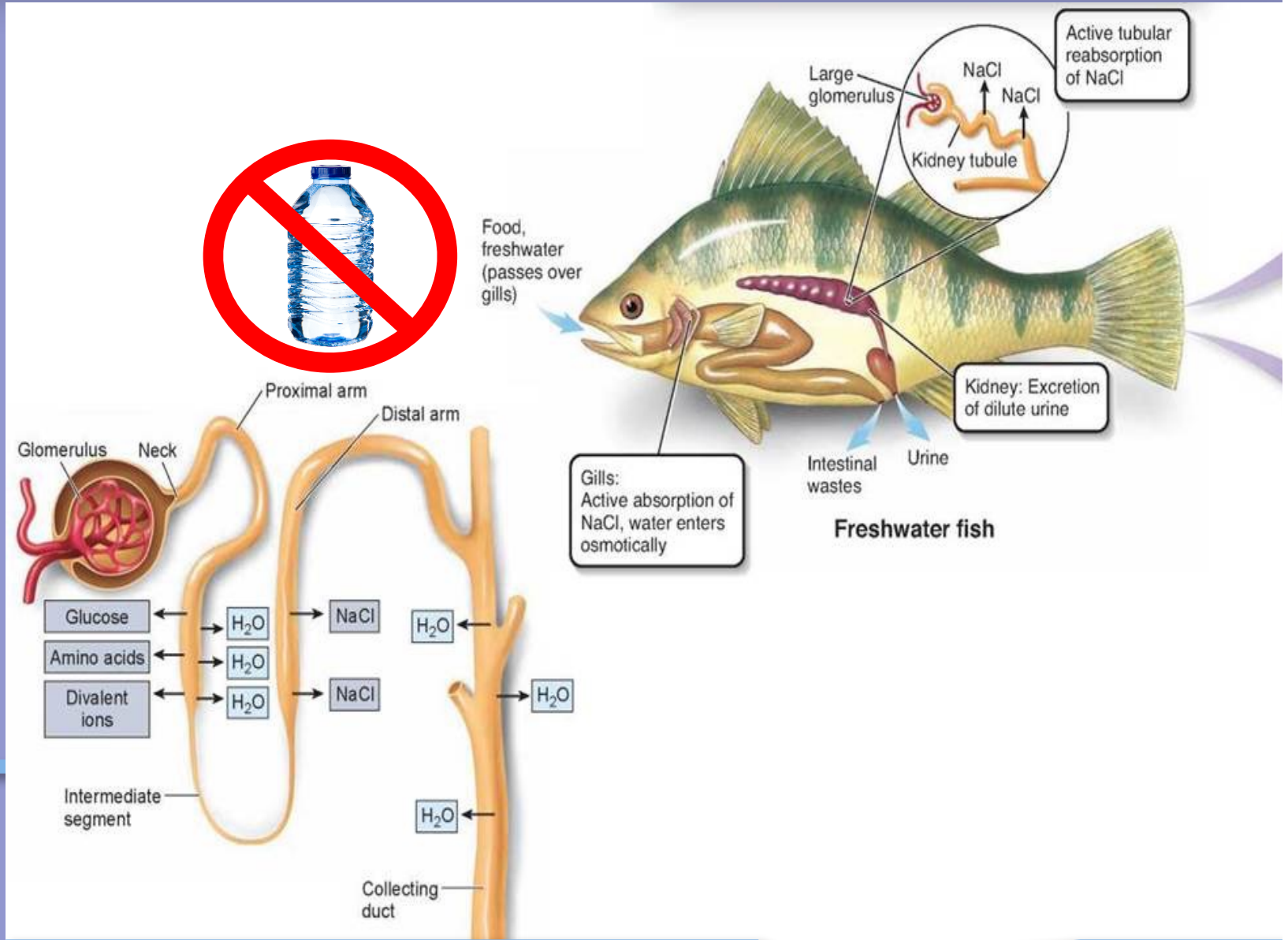
Glomérulos

**Orina
Diluida**



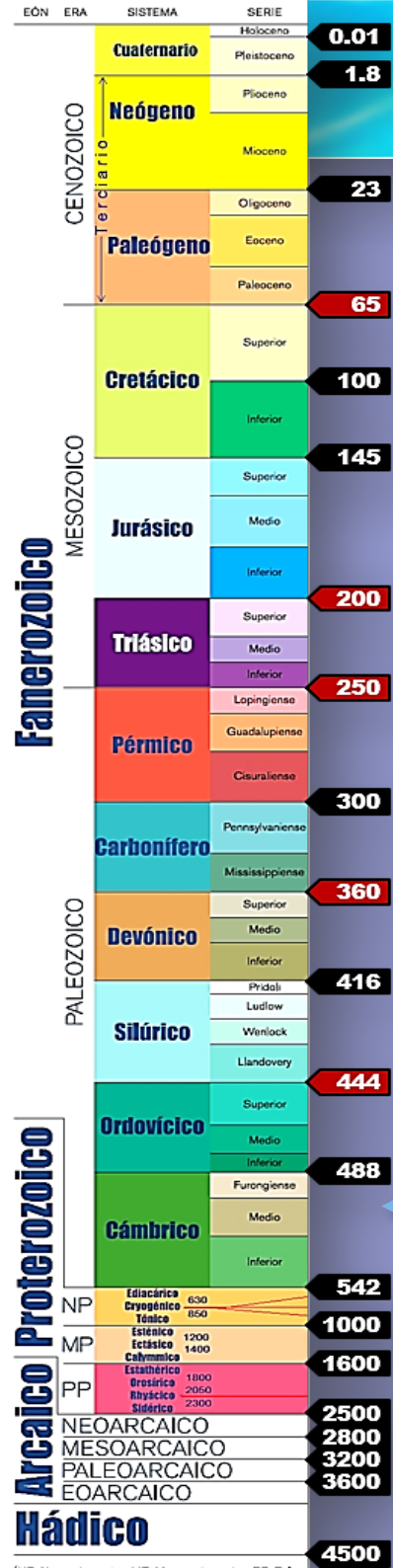
RETOS OSMOREGULATORIOS

ERA	SISTEMA	SERIE	TIEMPO (Ma)
CENOZOICO	Cuaternario	Holoceno	0.01
		Pleistoceno	1.8
	Neógeno	Plioceno	
		Mioceno	
	Paleógeno	Oligoceno	23
		Eoceno	
		Paleoceno	65
	MESOZOICO	Cretácico	Superior
Inferior			145
Jurásico		Superior	
		Medio	
Triásico		Inferior	200
		Superior	250
Pérmico		Lopingiense	
		Guadalupiense	
		Cisuraliense	300
PALEOZOICO		Carbonífero	Pennsylvaniense
	Mississippiense		360
	Devónico	Superior	
		Medio	
Silúrico	Pridali	416	
	Ludlow		
	Wenlock		
	Llandovery	444	
Arcaico Proterozoico	Ordovícico	Superior	
		Medio	488
	Cámbrico	Inferior	
		Medio	
Arcaico Proterozoico	NP	Ediacárico	630
		Cryogénico	850
	MP	Toniaco	1200
		Estárico	1400
	PP	Calyménico	1600
		Estathérico	1800
	NEOARCAICO	Brosárico	2050
		Rhyárico	2300
	MESOARCAICO		2500
			2800
PALEOARCAICO		3200	
		3600	
Hádico		4500	



2. EVOLUCION VERTEBRADOS EN AGUA DULCE

RETOS OSMOREGULATORIOS

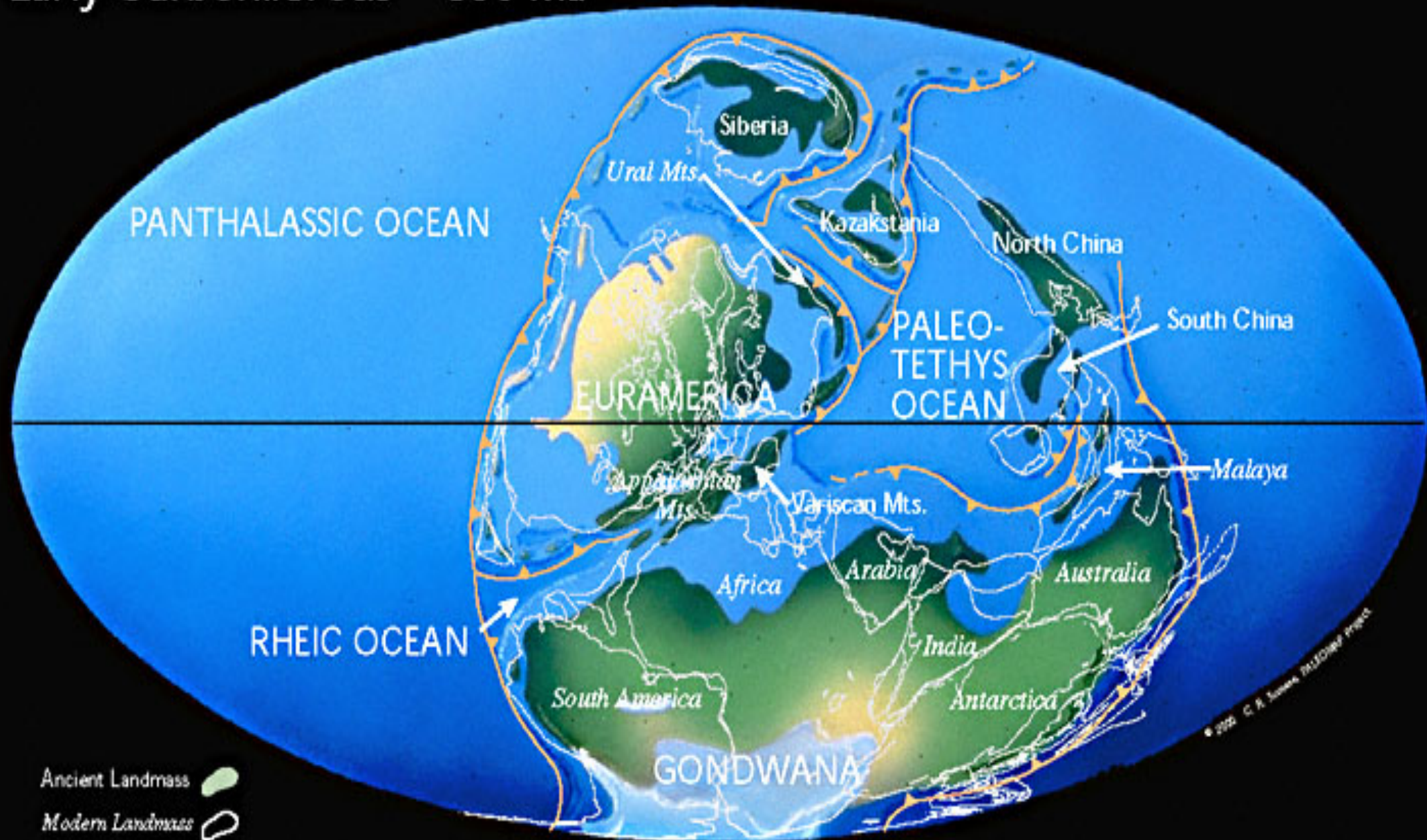


3. REGRESO DE LOS VERTEBRADOS AL AGUA DE MAR

2. EVOLUCION VERTEBRADOS EN AGUA DULCE

1. CONSTANCIA DEL VOLUMEN CELULAR

Early Carboniferous 356 Ma



Ancient Landmass



Modern Landmass

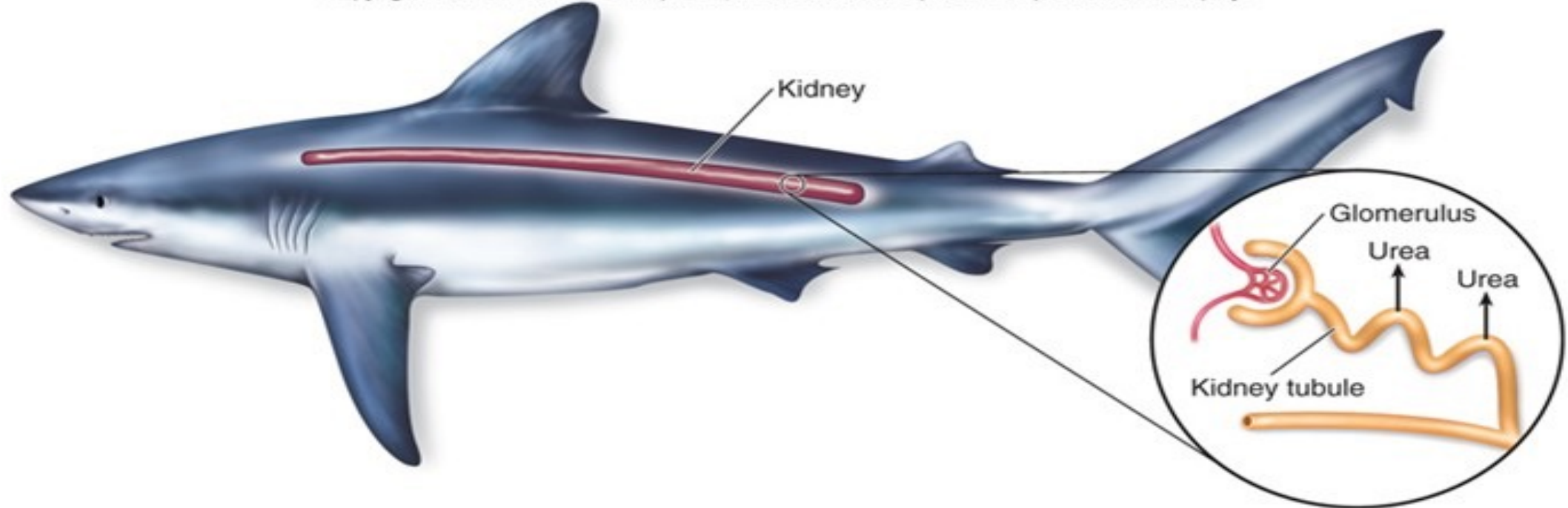


Subduction Zone (triangles point in the direction of subduction)



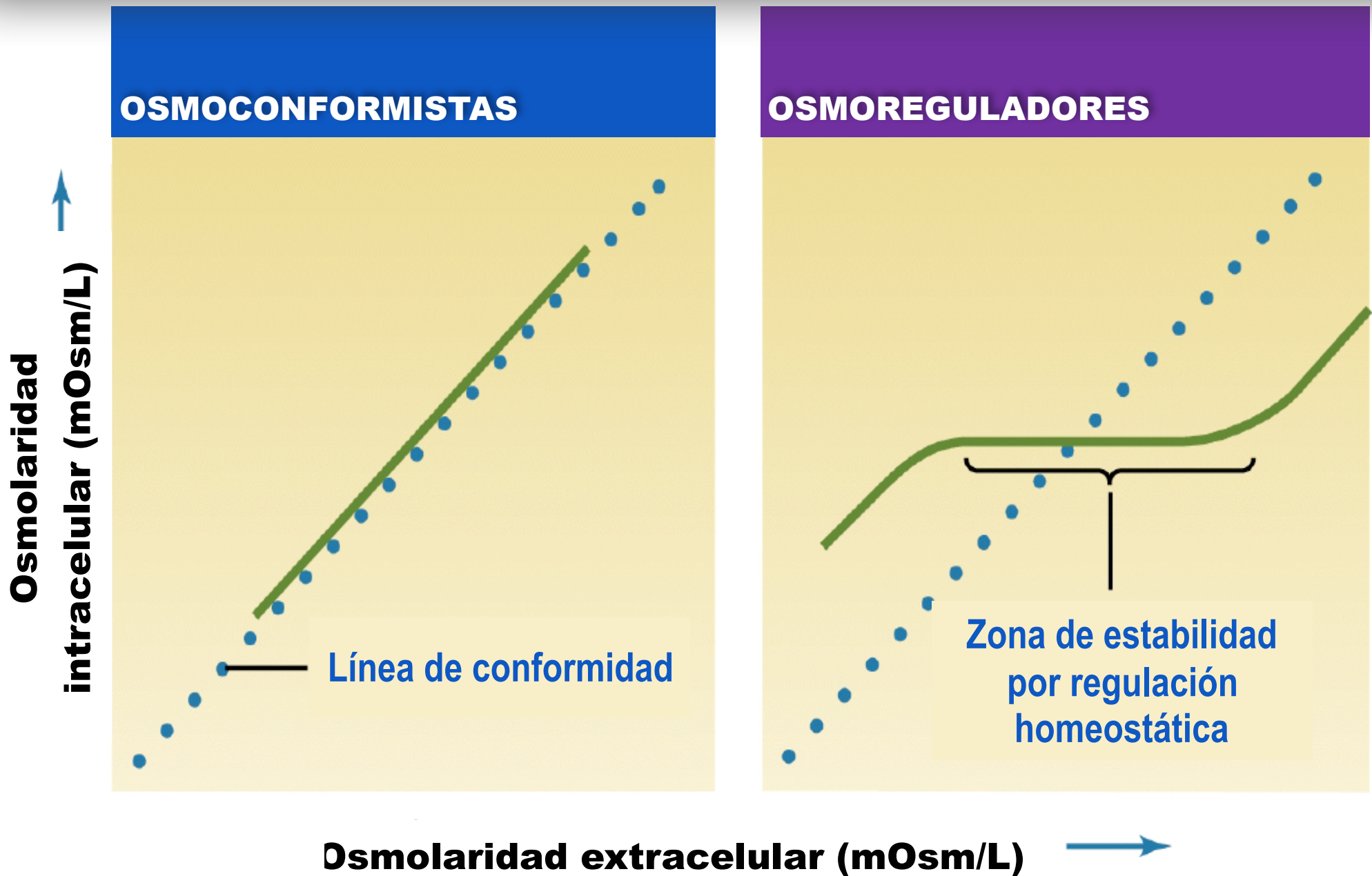
Sea Floor Spreading Ridge

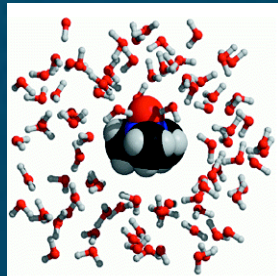
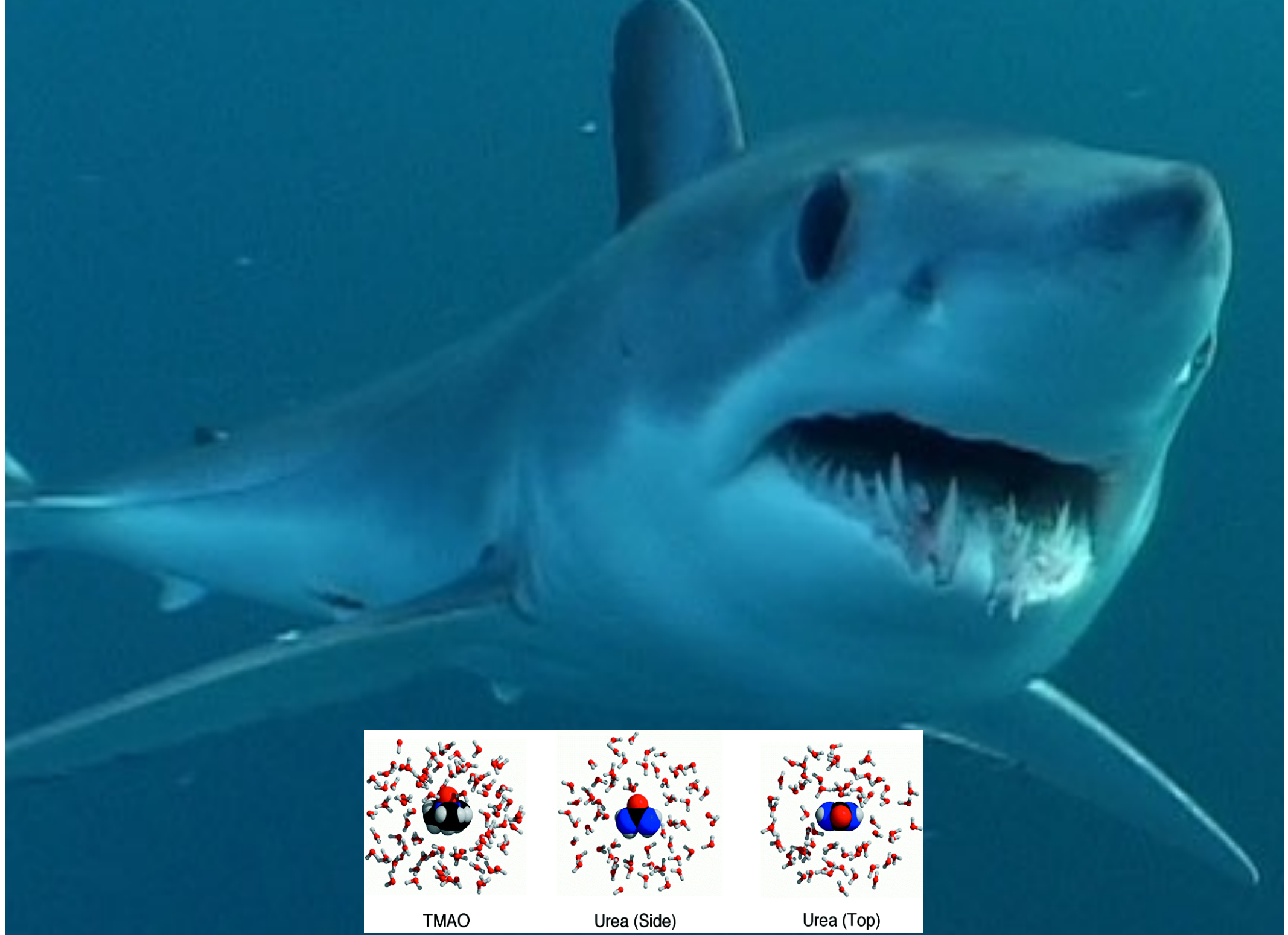




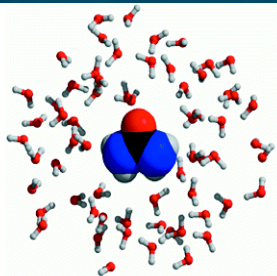
Orina Diluida

ADAPTACIONES A LA OSMOLARIDAD EXTERNA

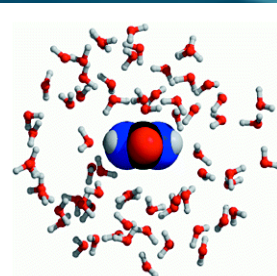




TMAO



Urea (Side)

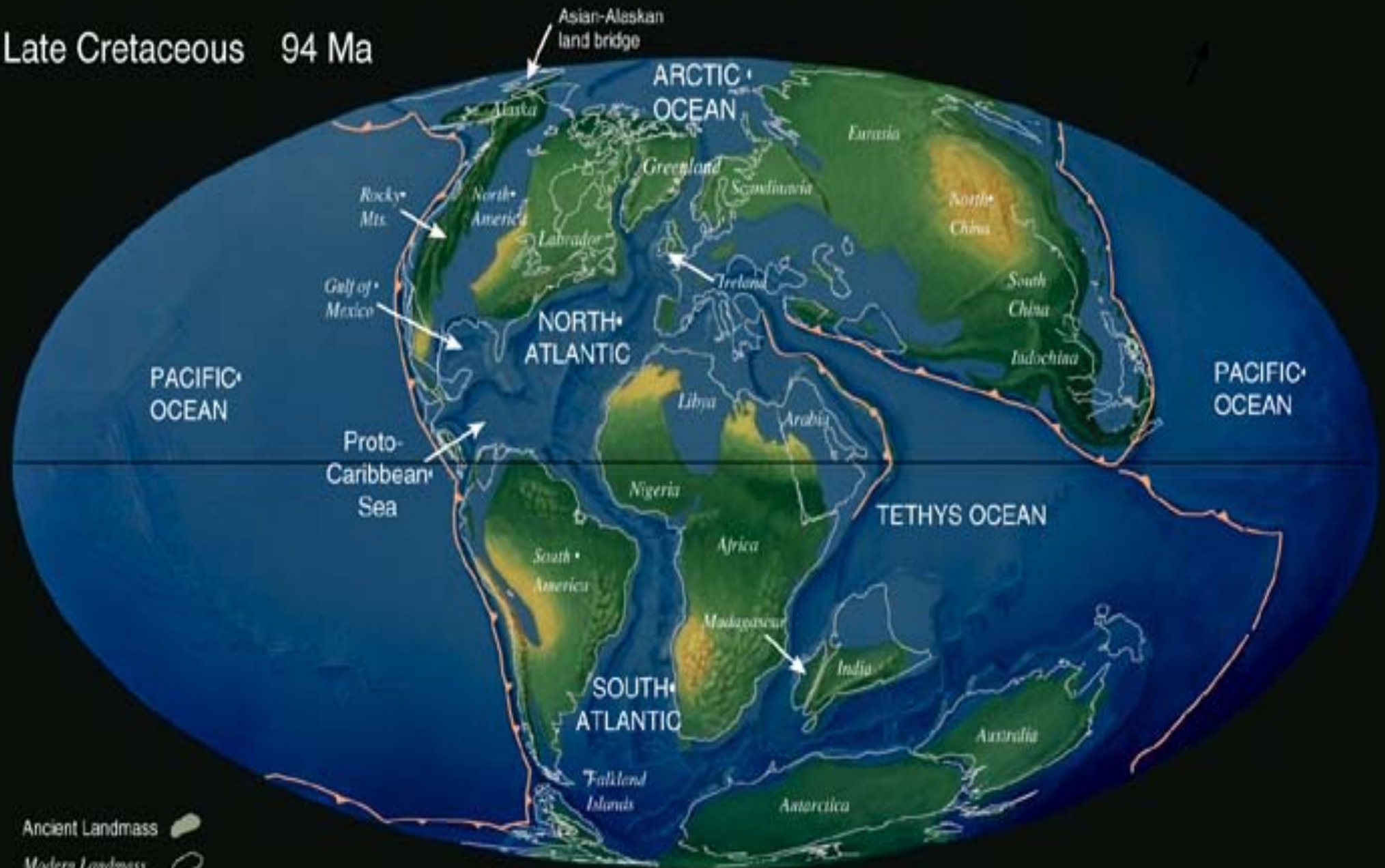






Urea (Top)

Carcharodon carcharias



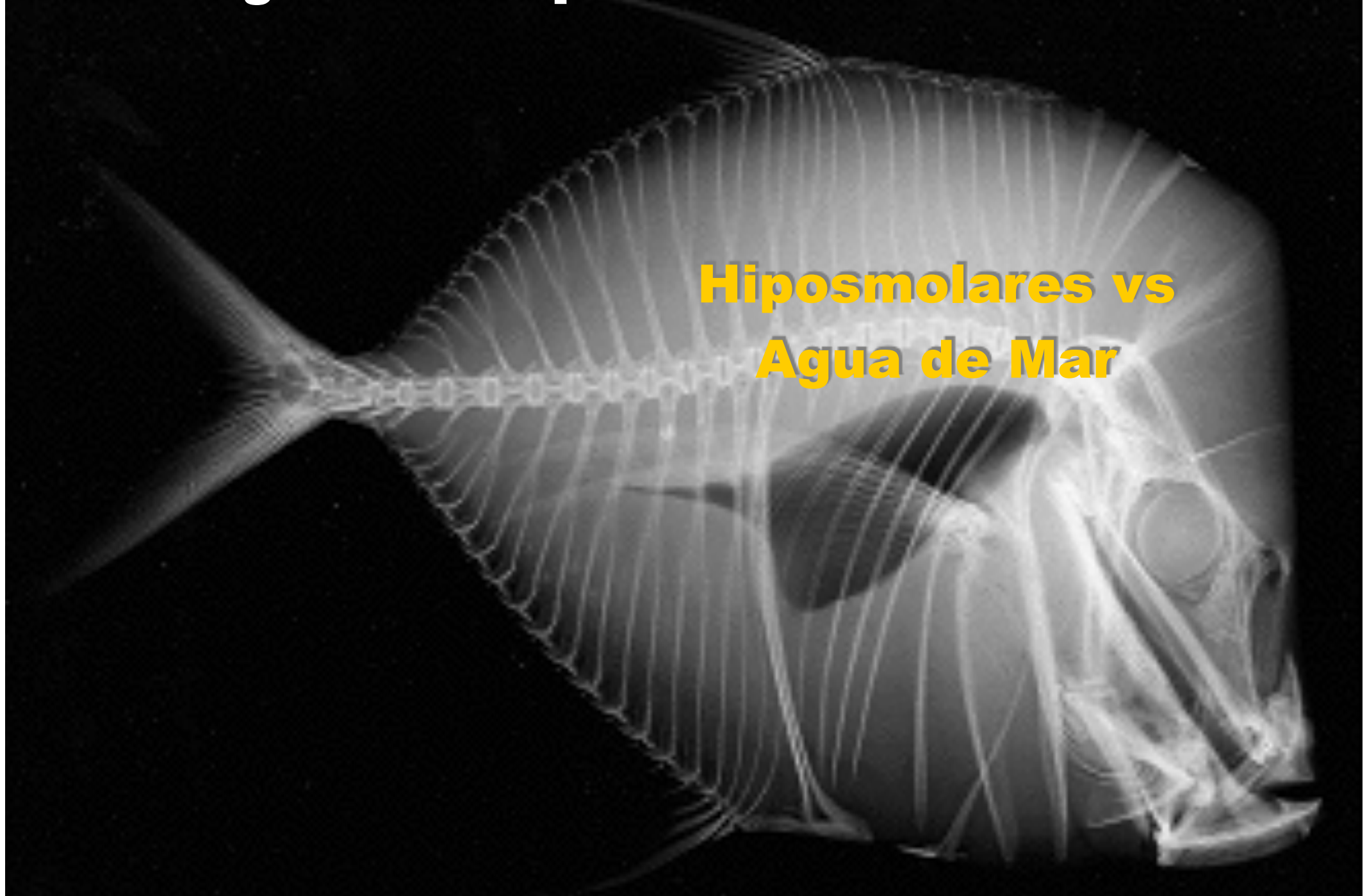
Late Cretaceous 94 Ma



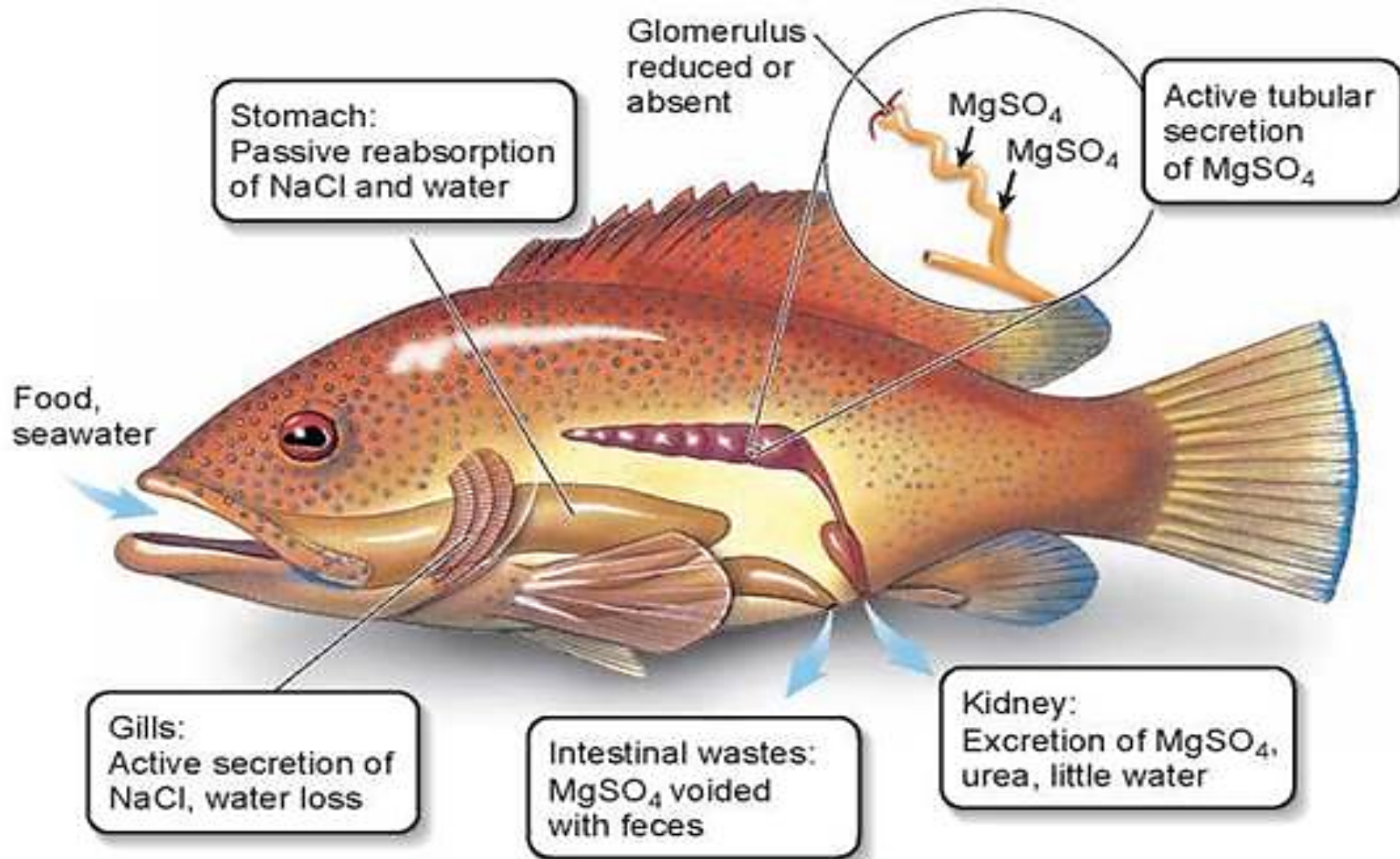
- Ancient Landmass 
- Modern Landmass 
- Subduction Zone (triangles point in the direction of subduction) 
- Sea Floor Spreading Ridge 

Pez de agua marina (pez oseo)

**Hiposmolares vs
Agua de Mar**



Osmorregulación en agua marina (pez oseo)



RETOS OSMOREGULATORIOS



4. EVOLUCION OSMOREGULATORIA EN TIERRA FIRME

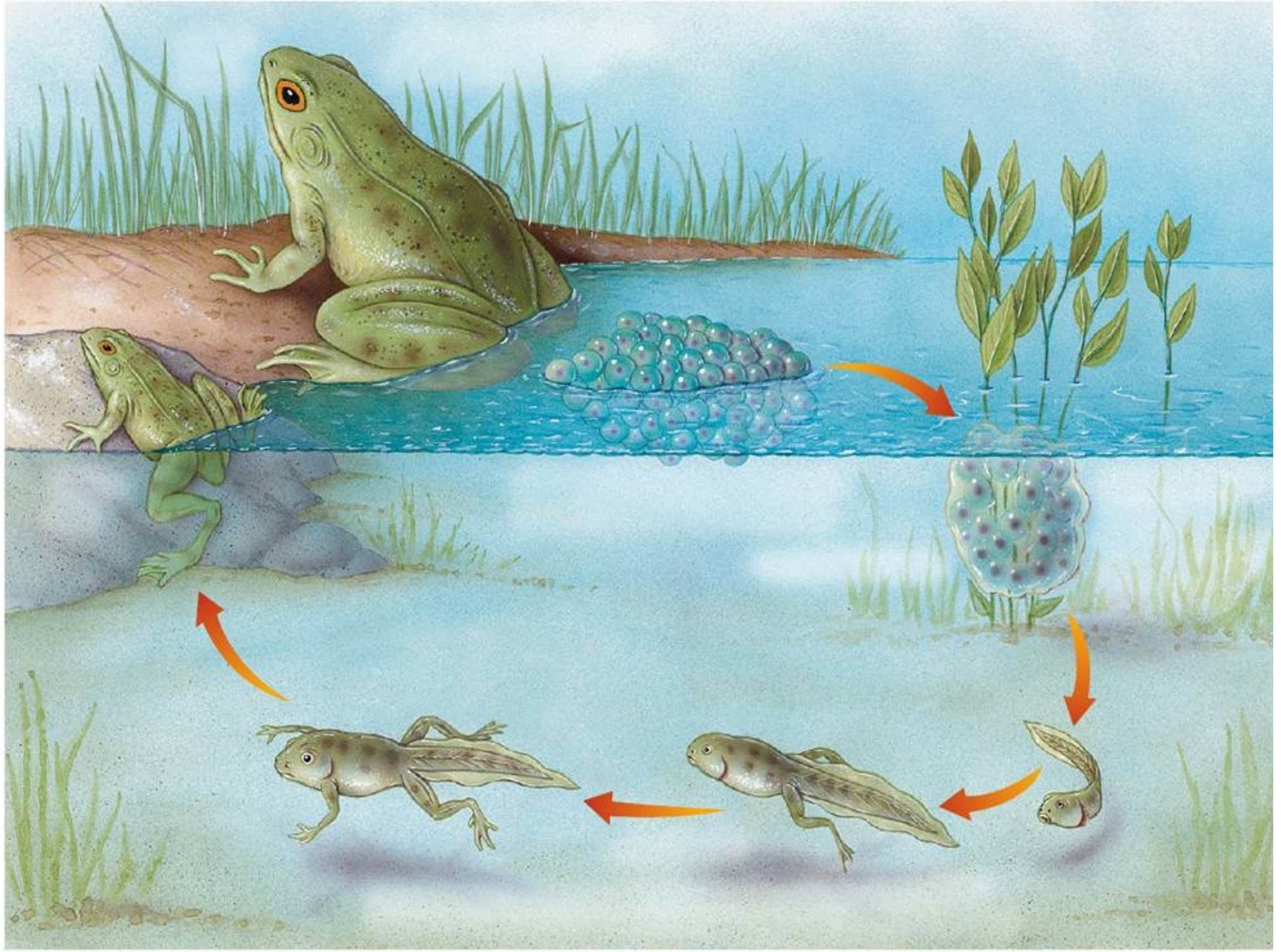
3. REGRESO DE LOS VERTEBRADOS AL AGUA DE MAR

2. EVOLUCION VERTEBRADOS EN AGUA DULCE

1. CONSTANCIA DEL VOLUMEN CELULAR

Tiktaalik roseae (Devónico/375 Ma)

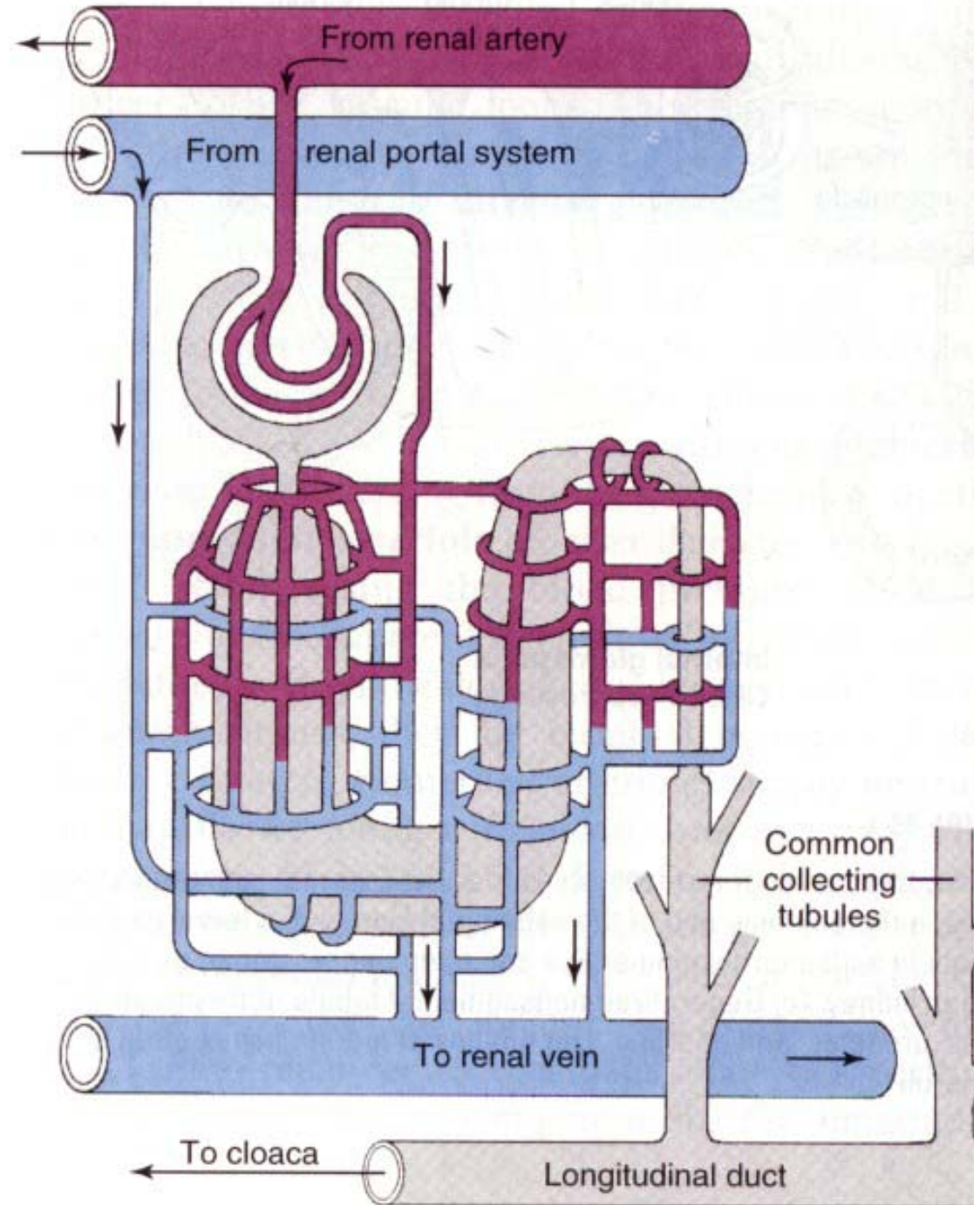
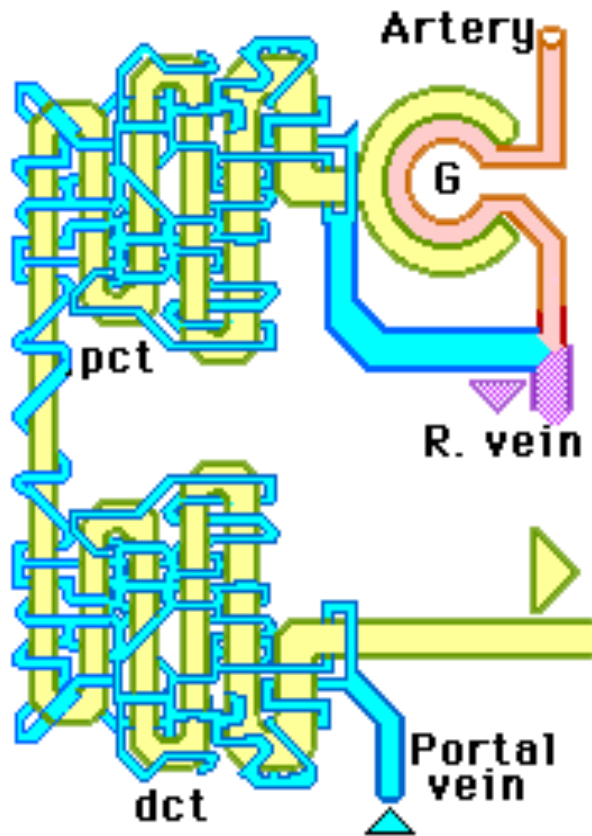




Familia Peptídica de la Oxitocina

	1	2	3	4	5	6	7	8	9	
Oxytocina	Cys	Tyr	Ile	Gln	Asn	Cys	Pro	Leu	Gly(NH ₂)	Placentados, marsupiales,
Mesotocina	*	*	*	*	*	*	*	Ile	*	Marsupiales, nomamíferos tetrapodos,
Isotocina	*	*	*	Ser	*	*	*	Ile	*	Osteichthyes
Glunitocina	*	*	*	Ser	*	*	*	Gln	*	Rayas (Chondrichthyes)
Valitocina	*	*	*	*	*	*	*	Val	*	Tiburones (Chondrichthyes)
Aspargtocina	*	*	*	Asn	*	*	*	*	*	Tiburones (Chondrichthyes)
Asvatocina	*	*	*	Asn	*	*	*	Val	*	Tiburones (Chondrichthyes)
Phasvatocina	*	*	Phe	Asn	*	*	*	Val	*	Tiburones (Chondrichthyes)
Cephalotocina	*	*	Phe	Arg	*	*	*	Ile	*	<i>Octopus vulgaris</i> (Moluscos)
Annetocina	*	Phe	Val	Arg	*	*	*	Thr	*	<i>Eisenia foetida</i> (Anélidos)
Vasotocina	*	*	*	*	*	*	*	Arg	*	No mamíferos vertebrados, cyclostomes
Vasopressina	*	*	Phe	*	*	*	*	Arg	*	Mamíferos
Lysipressina	*	*	Phe	*	*	*	*	Lys	*	Cerdos, marsupiales
Phenypressina	*	Phe	Phe	*	*	*	*	Arg	*	Macropodids (marsupiales)
Locupressina	*	Leu	*	Thr	*	*	*	Arg	*	<i>Locusta migratoria</i> (Insectos)
Arg-conopressina	*	Ile	*	Arg	*	*	*	Arg	*	<i>Conus geographicus</i> (Moluscos)
Lys-conopressina	*	Phe	*	Arg	*	*	*	Lys	*	<i>Lymnaea stagnalis</i> (Moluscos)

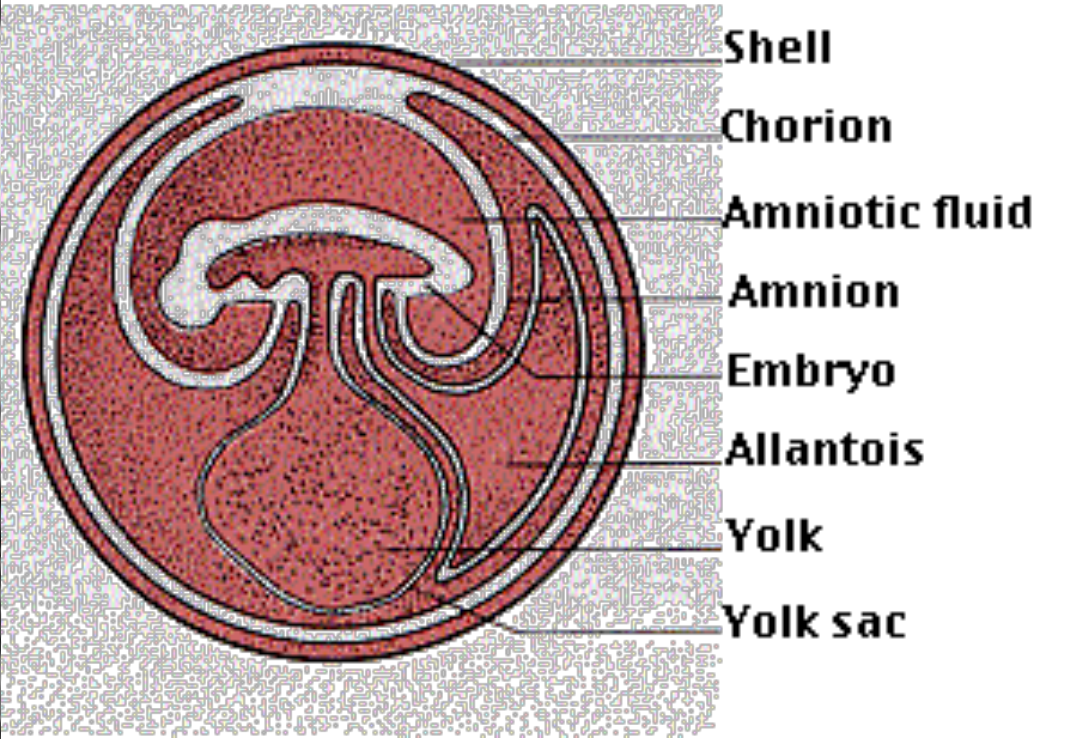
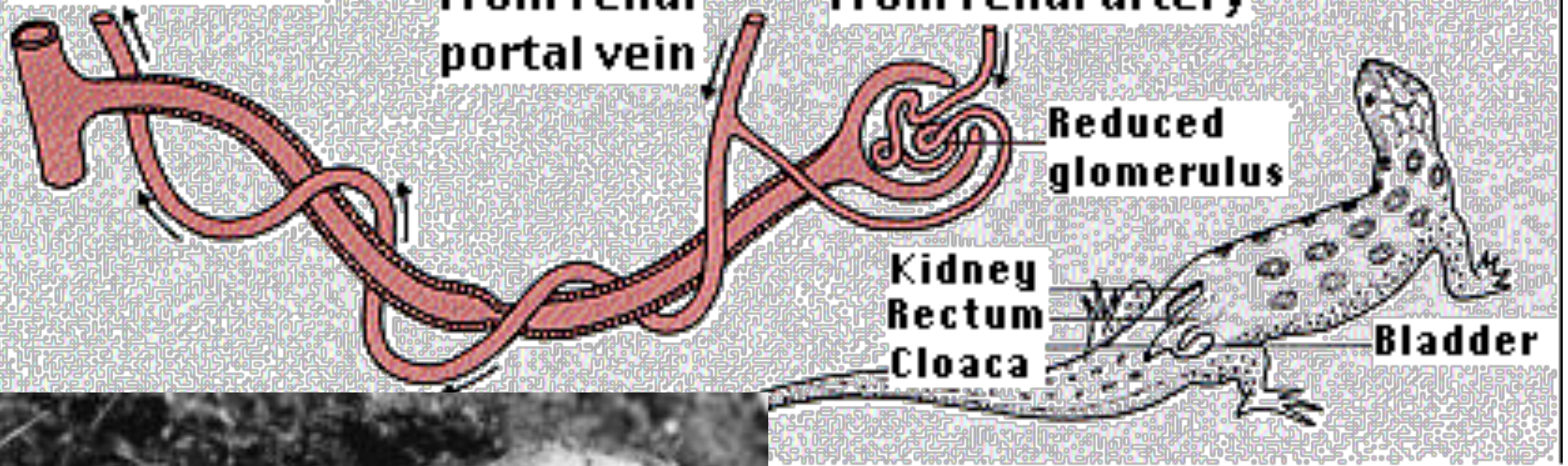
Sistema Renal Portal



To renal vein

From renal portal vein

From renal artery



EXCRECION DE COMPUESTOS NITROGENADOS

Amino acids and nucleic acids

1 Catabolism

Ammonia by-product

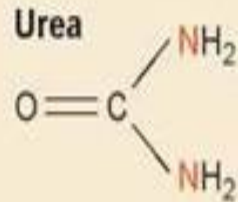
2 Eliminated directly

Ammonia
 NH_3



Most fish

3 Converted to urea



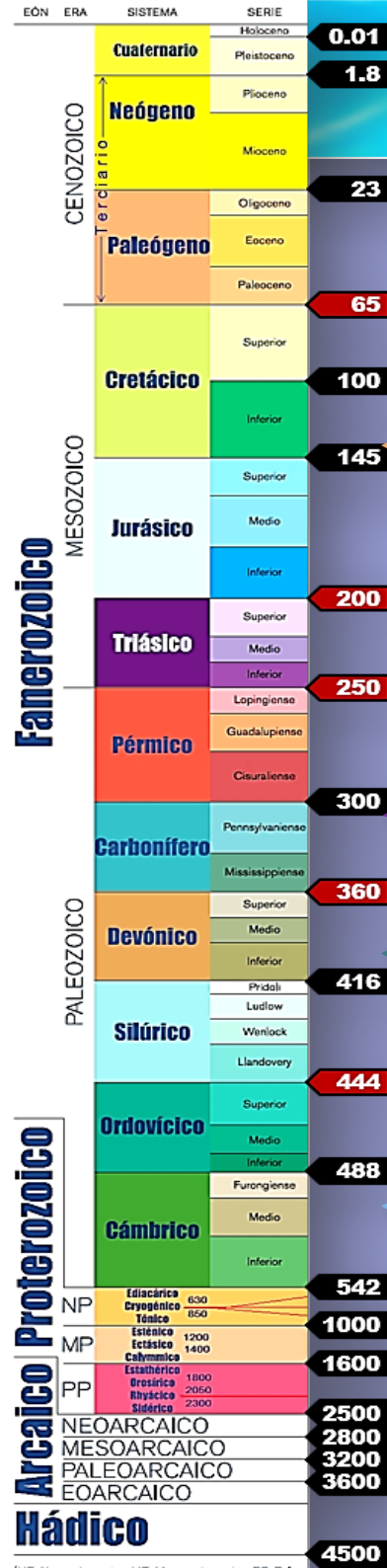
Mammals, some others

4 Converted to uric acid



Reptiles and birds

RETOS OSMOREGULATORIOS



5. NEFRONA SUPERCONCENTRADORA DE LOS MAMIFEROS

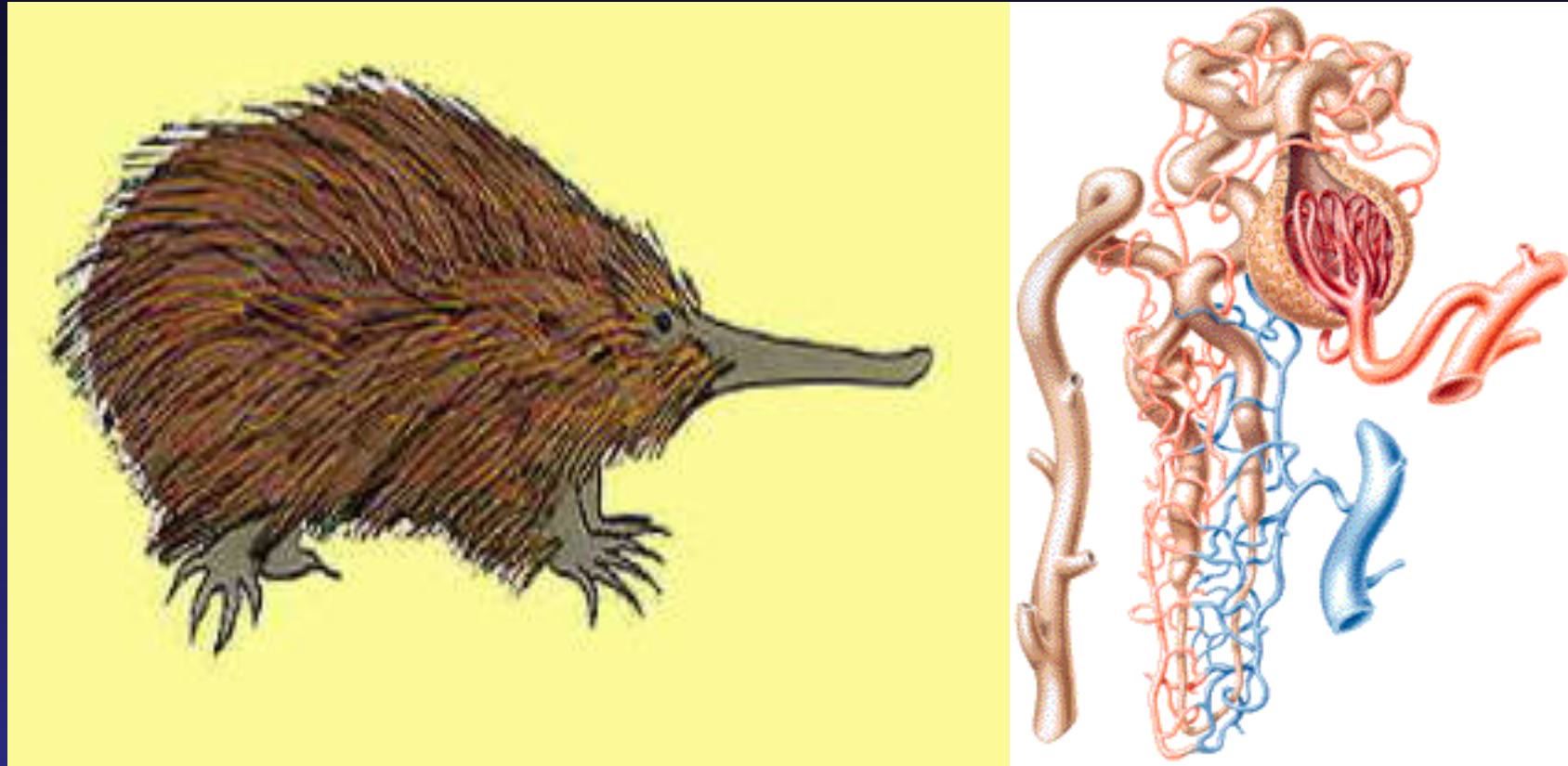
4. EVOLUCION OSMOREGULATORIA EN TIERRA FIRME

3. REGRESO DE LOS VERTEBRADOS AL AGUA DE MAR

2. EVOLUCION VERTEBRADOS EN AGUA DULCE

1. CONSTANCIA DEL VOLUMEN CELULAR

Nefrona “superconcentradora” de los mamíferos



From Fish to Philosopher
The Story of Our Internal Environment

Homer W. Smith



CIBA Edition, Revised and Enlarged



The Author

All physicians, especially those treating edema with diuretic agents, will read this book on the evolution of our internal environment with profit and pleasure.

In this perceptive and philosophical treatise, Dr. Homer W. Smith, the distinguished physiologist, describes the evolution of the kidney from "fish to philosopher." He shows quite clearly how this hard-working regulator of our "internal environment" has come to work the way it does. "The composition of the blood is determined not by what the mouth takes in but what the kidneys keep." In fact, at every stage in man's ascent, the structure of the kidneys was modified (by natural selection) to cope with the changing requirements of life in water, on land, in trees; and finally the requirements of an erect bipedal, bimanual, talking and thinking organism. Here, indeed, the author has written another masterpiece in keeping with his *Kamougo* and *Man and His Gods*.

Role of the Diuretics in Maintaining the "Internal Environment"

And when, as often happens, the internal environment is upset because of heart failure or renal disease, and edema occurs—what measures can be taken to restore the physiological balance?

Until recently, the parenteral mercurial diuretics, because of their direct and specific action on the renal tubules, were used to restore the internal environment by eliminating excess salt and water. Since 1958, however, these drugs have been virtually replaced by the oral diuretics, such as *Lasix*® (hydrochlorothiazide caps), the improved analog of chlorothiazide. Unlike the mercurials, these drugs are not only pain-free and convenient measures, but they are also free of the dangers of mercurialism.

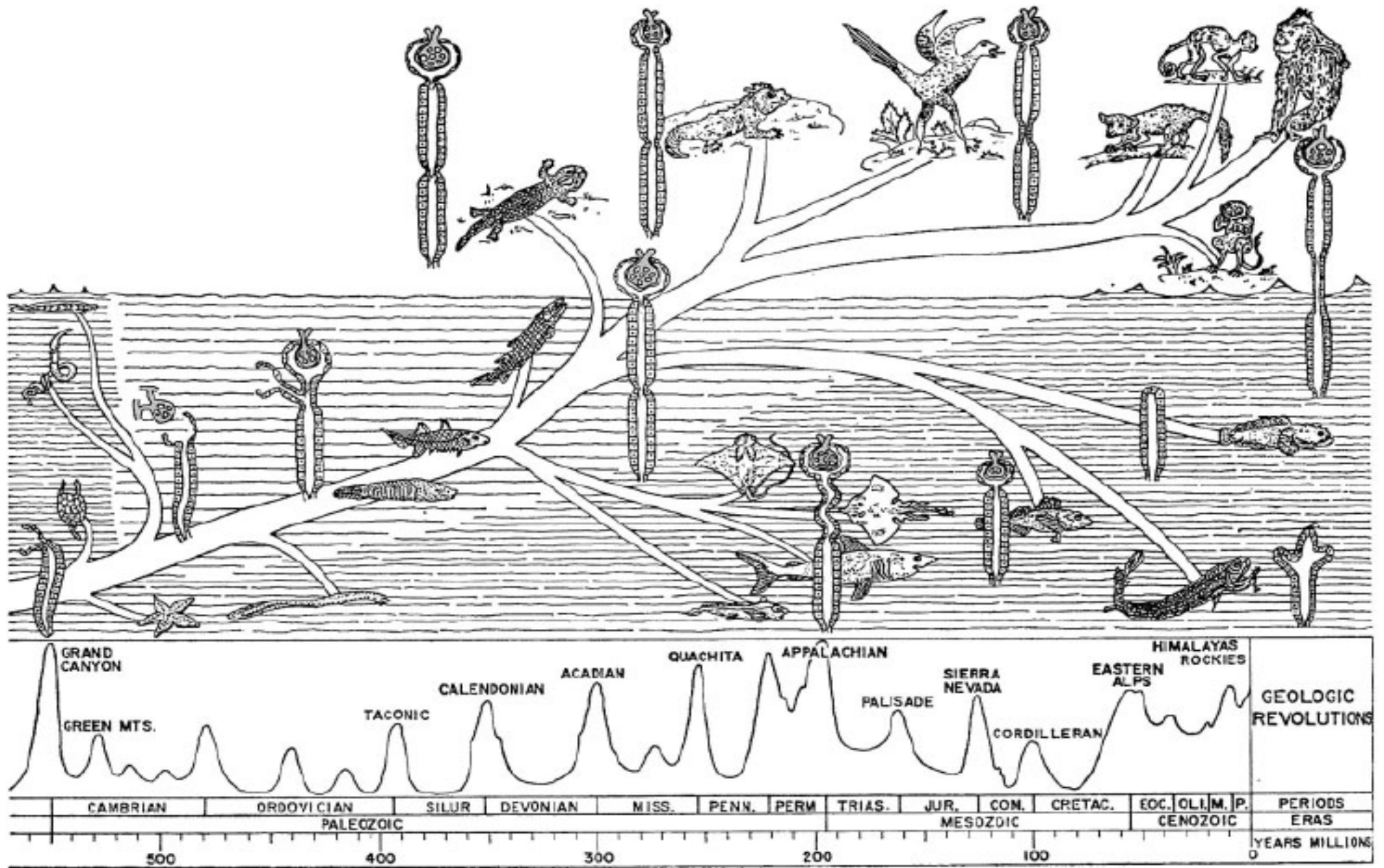
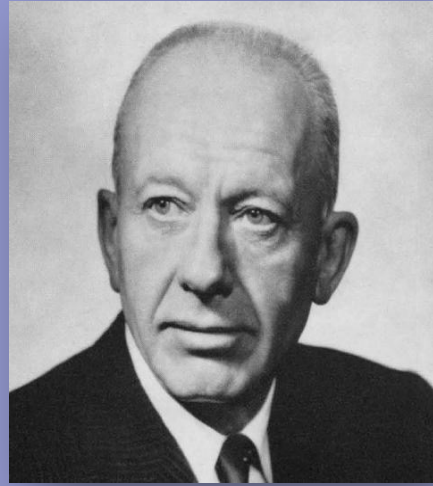
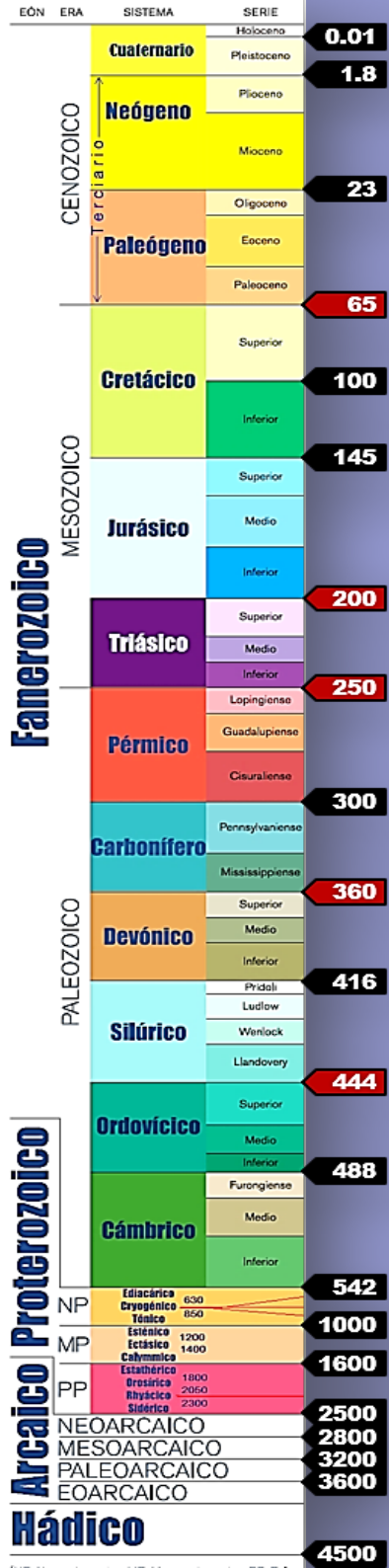


Fig. 1. Synopsis of the evolution of the vertebrates in relation to saltwater (darkly shaded) and freshwater (lightly shaded) habitat. The irregular curve illustrates mountain-building episodes (geologic revolutions) which have influenced this evolutionary history. The time scale is such that the Pleistocene era and recent time are compressed.



Homer Smith

“ ... casi un siglo ha trascurrido desde que Claude Bernard propuso que el verdadero **medio** en el cual vivimos no es la tierra o el aire, sino el **líquido de la sangre** que baña nuestros tejidos ... “

“ ... este **milieu intérieur** se encuentra totalmente aislado y las variaciones atmosféricas no pueden alterarlo o penetrarlo ... “

“ ... fue una visión de Bernard ... “



Claude Bernard

“ La constancia del milieu intérieur es la condición de nuestra existencia libre e independiente “