PATHOPHYSIOLOGY AND MECHANISMS OF RADIOPHARMACEUTICAL LOCALIZATION

20140413 morning meeting 胡蓮欣

The Pathophysiological basis of Nuclear Medicine 2nd ed. Springer.

Cellular adaptation & cell injury

1. Normal cell
2. Atrophy
3. Hypertrophy
4. Hyperplasia
5. Metaplasia
6. Intracellular accur substances or abn
   - Lipids
   - Proteins
   - Glycogen
   - Pigment / Bilirubin
   - Calcium
7. Cell injury
8. Cell Death

Able to handle normal physiological & functional demands

In response to excessive physilogical conditions, or to some adverse or pathological stimuli
Escape from injury, neither normal nor injured, but has and altered steady state, and its viability is preserved
However, some normal function may be lost
Reversible

Unable to maintain homeostasis
Reversible or not reversible injury

Homeostasis maintained

Homeostasis Not maintained

Altered cellular and tissue biology

- Cellular adaptations
- Cellular injury
  - Biochemical mechanisms
    - ATP depletion
    - Oxygen & oxygen-derived free radiclas
    - Intracellular Ca2+ & loss calcium homeostasis
    - Mitochondrilal dysfunction
    - Defects in membrane permeability
  - Intracellular accumulation
- Cell death
  - Necrosis
    - Coagulation necrosis
    - Liquefaction necrosis
    - Caseous necrosis
    - Fat necrosis
  - Apoptosis

Radiopharmaceuticals

- Nuclear medicine, in the simplest terms, is the medical specialty based on examining the regional chemistry of the living human body.

NM diagnostic procedures involve 4 types of measurement:

1. regional blood flow, transport, and cellular localization of various molecules
2. metabolism and bioenergetics of tissues
3. physiological function of organs
4. intracellular and intercellular communication

Eight categories:

1. Radiolabeled particles
2. Radiolabeled gases
3. Radiolabeled chelates
4. Radiotracers as ions
5. Radiolabeled cells
6. Receptor binding radiotracers
7. Radiolabeled monoclonal antibodies
8. Radiolabeled metabolic substrates

Radiopharmaceutical	Application	Indication for imaging
Radiolabeled particles 微粒		
^{99m}Tc-MAA, 10 – 50 μm	Capillary blockade	Lung perfusion
^{99m}Tc-DTPA, aerosol, 1 – 4 μm	Sedimentation in bronchioles	Lung ventilation
^{99m}Tc-Sulfur colloid, 0.1 – 1.0 μm	Reticuloendothelial function	Liver, spleen, and bone marrow
^{99m}Tc-SC, filtered 0.1 – 0.3 μm	Lymphatic drainage	Breast cancer and melanoma
^{99m}Tc-HSA (nanocolloid), 0.02 μm	Lymphatic drainage	Breast cancer and melanoma
^{99m}Tc-Antimony sulfide colloid, 0.1 μm	Lymphatic drainage	Breast cancer and melanoma
Radiolabeled gases		
^{133}Xe, ^{127}Xe, ^{81m}Kr	Alveolar transit-capillary diffusion	Lung ventilation
^{99m}Tc-Technegas, 0.004 – 0.25 μ	Alveolar transit-capillary diffusion	Lung ventilation
Radiolabeled chelates		
^{99m}Tc-MDP, HDP	Bone formation	Metastatic bone disease, neuroblastoma, osteosarcoma
^{99m}Tc-DTPA	Blood brain barrier disruption	Brain tumors
	Renal function glomerular filtration	Renal blood flow and renogram
^{99m}Tc-MAG3	Renal function, tubular secretion	Renogram
^{99m}TcIII-DMSA	Binding to renal parenchyma	Renal scan
^{99m}TcV-DMSA	Tumor cell uptake	Medullary carcinoma of thyroid
^{99m}Tc-Disofenin and mebrofenin	Hepatobiliary function	Hepatobiliary imaging
^{99m}Tc-Ceretec and Neurolite	Blood flow	Brain imaging
^{99m}Tc-sestamibi and tetrafosmin	Blood flow	Myocardial perfusion
^{99m}Tc-sestamibi, and tetrafosmin	Tumor viability and multidrug resistance, MDR (Pgp expression)	Breast cancer, parathyroid adenoma, brain tumor
^{111}In-DTPA	CSF flow	Cisternogram
^{111}In-oxine	Radiolabeling white cells	Labeled leukocyte thrombus imaging
^{67}Ga-citrate	Tumor viability, capillary leakage	Tumor and infection imaging
Radiotracers as ions		
^{99m}Tc-pertechnetate (TcO_4^-)	Thyroid function (trapping)	Thyroid imaging
^{123}I,^{131}I-sodium iodide (I^-)	Thyroid function (trapping)	Thyroid uptake, imaging therapy
^{82}Rb-chloride, Rb^+	Blood flow	Myocardial perfusion
^{201}Tl-thallous chloride, $Tl(OH)_2^+$	Blood flow	Myocardial perfusion
	Tumor viability	Tumor imaging (brain, parathyroid, thyroid)

Cont.

Radiopharmaceutical	Application	Indication for imaging
Radiolabeled cells		
^{111}In-leukocytes	Cell migration and phagocytosis	Infection imaging
^{111}In-platelets	Cell incorporation in thrombus	Thrombus imaging
^{51}Cr-RBCs	Dilution in blood compartment	RBC mass and blood volume
^{99m}Tc-RBCs	Cardiac function	Cardiac ejection fraction, wall motion
	Blood pool	Hemangioma, GI bleeding
^{99m}Tc-RBC (heat denatured)	Spleen	Accessory splenic tissue
Receptor binding radiotracers		
^{111}In-pentetreotide, Octreoscan	Somatostatin receptors	Neuroendocrine tumors
^{99m}Tc-P829, Neotec	Somatostatin receptors	Lung cancer, NE tumors
^{99m}Tc-P280, Acutect	GP IIb/IIIa receptors	Thrombus imaging, DVT
^{99m}Tc-TRODAT-1	Dopamine transporter	Brain imaging-dopamine D2 receptors
^{123}I-VIP	VIP receptors	Gastrointestinal tumors
^{131}I-NP-59	LDL receptor, cholesterol metabolism	Adrenal carcinoma, adenoma, Cushing's syndrome
^{123}I- or ^{131}I-MIBG	Presynaptic adrenergic receptors	Myocardial failure
	Adrenergic tissue uptake	Tumor imaging (pheochromocytoma, neuroendocrine, neuroblastomas)
[^{11}C]Raclopride	Dopamine D2 receptors	Brain imaging-dopamine D2 receptors
^{123}I-IBZM	Dopamine D2 receptors	Brain imaging-dopamine D2 receptors, tumor imaging, malignant melanoma
[^{18}F]fluoro-estradiol (FES)	Estrogen receptors	Breast tumor imaging

Cont.

Radiopharmaceutical	Application	Indication for imaging
Radiolabeled monoclonal antibodies		
^{111}In-Oncoscint, B72.3 IgG	TAG-72 antigen	Colorectal and ovarian cancer
^{111}In-Prostascint, 7E11-C5.3 IgG	PSMA (intracellular epitope)	Prostate cancer
^{99m}Tc-CEA-Scan, IMMU-4 Fab'	CEA	Colorectal cancer
^{99m}Tc-Verluma, NR-LU-10 Fab'	Cell surface GP as antigen	Small cell lung cancer
^{99m}Tc-fanolesomab (CD15)	Granulocyte antigen CD15	Appendicitis
^{111}In-antimyosin	Antimyosin	Acute myocardial infarction, heart transplant rejection
Radiolabeled metabolic substrates		
^{18}F-Fluorodeoxyglucose, FDG	Tumor viability and metabolism	Tumor imaging
	Glucose metabolism	Brain and cardiac imaging
^{18}F-Fluorothymidine	Cell proliferation	Tumor imaging and monitoring treatment
^{11}C-choline	Cell proliferation	Brain tumors
[^{11}C] or ^{123}I-methyl tyrosine	Protein synthesis, protein upregulation	Brain tumors
^{11}C-methionine	Amino acid transport	Brain and pancreatic tumors
[^{11}C]-thymidine	DNA synthesis, cell proliferation	Brain tumors
[^{18}F] and ^{123}I-fatty acids	Myocardial metabolism	Cardiac imaging
[^{57}Co]-vitamin B_{12}	Vitamin B_{12} absorption	Pernicious anemia
^{18}F-fluoromisonidazole	Hypoxia and oxidative metabolism	Tumors selected for radiotherapy
^{18}F-fluoroethyltyrosine(FET)	Amino acid transporter	Brain tumors

Cont.

Table 2.3. Radiopharmaceuticals for therapy

Radiopharmaceutical	Application	Specific tumors
^{131}I-sodium iodide	Thyroid function	Differentiated thyroid carcinoma
^{131}I-MIBG	Adrenergic tissue	Colorectal cancer metastatic to liver and bladder cancer
^{131}I-anti B1 antibody	Anti CD22 antigen	Lymphoma
^{90}Y-MXDTPA-anti B1 antibody	Anti CD22 antigen	Lymphoma
^{32}P-chromic phosphate (colloid)	Cell proliferation and protein synthesis	Peritoneal metastases, recurrent malignant ascites
^{32}P-orthophosphate	Cell proliferation and protein synthesis	Polycythemia vera
^{89}Sr chloride	Exchanges with Ca in bone	Palliation of pain due to bony metastases
^{153}Sm-EDTMP	Binds to hydroxyapatite	Palliation of pain due to bony metastases
^{117m}Sn-DTPA	Binds to hydroxyapatite	Palliation of pain due to bony metastases
^{186}Re-HEDP	Binds to hydroxyapatite	Palliation of pain due to bony metastases
^{90}Y-DOTA-Tyr^3-octreotide	Somatostatin receptors	Neuroendocrine tumors
^{90}Y-DOTA-lanreotide	Somatostatin receptors	Neuroendocrine tumors
^{90}Yb-ibritumomab	Lymphocyte antigen CD20	Lymphoma

The mechanisms of radioisotope localization

- Isotope dilution
- Capillary blockade
- Physicochemical adsorption
- Cellular migration and sequestration
- Membrane transport
- Metabolic Substrates and Precursors
- Tissue Hypoxia
- Cell Proliferation
- Specific Receptor Binding
- Imaging Gene Expression

1. Isotope dilution

- $V_1 x C_1 = V_2 C_2$; V: volume, C: concentration
- Quantitation of:
  - RBC volume (mass)
  - plasma volume
  - Total blood volume
- Tc-99m RBC EF (MUGA); RBC scan for bleeding
- It is very important that the radiotracer remain only in the blood volume to be measured

血漿容量(Plasma Volume, PV)

- 常用tracers:
  - ^{131}I-HSA (^{131}I-人血清白蛋白)
  - ^{113m}In-Transferrin (^{113m}In-運鐵球蛋白)
- 靜脈注入示蹤劑後10分鐘它們在全身血漿中平衡分布，而不進入紅血球，抽血測定示蹤劑在PV或RV內稀釋後的濃度，按稀釋法原理，可計算出示蹤劑的被稀釋倍數
- 正常值
  - 男 BV = 21.18 x BH (cm) + 56.64 x BW (kg) – 2030
  - 女BV = 27.60 x BH (cm)+ 27.27 x BW (kg) - 2042
- 臨床上常見的失血、燒傷、高血壓、心力衰竭、貧血以及真性紅血球增多症等疾病都可以出現血容量的改變，實測血容量值有助於具體了解這些疾病或狀態的程度，對指導治療有重要意義。

From Website: 核醫學會/核醫文壇/簡明核醫學

紅血球容量(Red Blood Cell Volume, RV)

- Tracer: $Na_2{}^{51}CrO_4$
- 將血抽出以$Na_2{}^{51}CrO_4$ labeled後，靜脈注入後30分鐘(在全身血液中平均分布)後再抽血，按稀釋法原理，可計算出示蹤劑的被稀釋倍數

Main article: Isotopes of chromium

iso	NA	half-life	DM	DE (MeV)	DP
^{50}Cr	4.345%	$>1.3\times10^{18}$ y	$(\beta^+\beta^+)$	1.167	^{50}Ti
^{51}Cr	syn	27.7025 d	ε	-	^{51}V
			γ	0.320	-

BV，RV & PV 三者關係

$$BV = \frac{RV}{Htx0.96x0.91} \text{ 或 } \frac{PV}{1-(Htx0.96x0.91)}$$

0.96用以校正紅血球容積，因約4%的血漿粘附在緊壓的紅血球中

0.91校正全身紅血球容積約低於靜脈血紅血球容積9%

- 通常只需測定RV或PV任一項，換算出BV
- 也可同時測得PV和RV，二者相加為BV

From Website: 核醫學會/核醫文壇/簡明核醫學

紅血球壽命測定（Red Cell Survival）

- Tracer: $Na_2{}^{51}CrO_4$
- 放射性核素標記自身紅血球，返注入體內後，逐日測定標記紅血球在血循環中的消失率(標記紅血球在血循環中消失一半所需的時間，稱紅血球外表半壽期)，它在一定程度上可反映紅血球壽命的長短。
- 取靜脈血10ml，經抗凝離心，分離出紅血球，用^{51}Cr-鉻酸鈉溶液標記紅細胞。靜脈注入^{51}Cr-RBC後，10分鐘於對側肢體取靜脈血5ml，24小時再次採血，第2~7天間採血三次，以後每週二次。測定各血樣的放射性計數率，經衰變校正並換算成每毫升紅細胞計數率，於半對數紙上繪出紅血球存活曲線，通過外推法，計算出放射性計數率降低一半的天數，即紅血球外表半壽期。
- 在測定過程中要注意盡量保持受試者血容量和紅血球壓積的穩定。

From Website: 核醫學會/核醫文壇/簡明核醫學

紅血球破壞部位測定 (Detection of Sites of Red Cell Destruction)

- Tracer: $Na_2{}^{51}CrO_4$
- 靜脈注入^{51}Cr-RBC後30分鐘，測定心前區、脾區及肝區的放射性計數率，此後每日或隔日測定一次，測定條件和位置保持不變，直至心前區放射性減半或到達紅血球外表半壽期為止。
- 正常人：脾/心<1.5，肝/心<1，脾/肝<2.0。
- 脾/肝=2.1-2.3為輕度異常，脾/肝>2.3為明顯異常。
- 紅血球破壞部位測定與紅血球壽命測定同時進行有助於貧血的鑑別診斷、脾功能估計、脾切除適應症選擇和疾病預後判定。

From Website: 核醫學會/核醫文壇/簡明核醫學

2. Capillary blockade

- Microembolization
- To determine the perfusion of an organ
- Lung/ heart/ brain
- Tc-99m MAA: 10-50 um
  - Pulmonary capillary: 8 um
  - Arteriole: 20-25 um
- Gold standard for determination of perfusion
  - Microsphere
  - In experimental animal studies

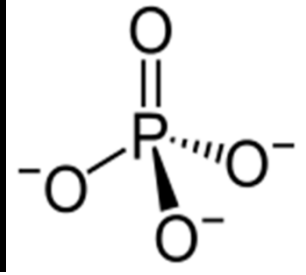
3. Physicochemical adsorption

- Tc-99m labeled phosphonates used in bone scan: MDP, HDP
- Phosphonates accumulate in hydroxyapatite (HA) crystal (contaning Ca2+ & phosphate ions) matrix or in the amorphous calcium phosphate (ACP, noncrystalline)

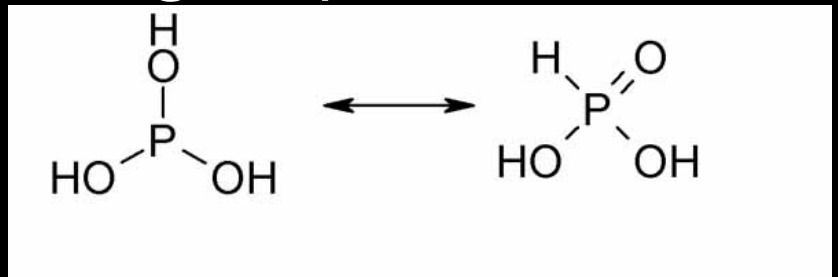
Phosphonate vs. Phosphate 磷酸鹽

- Inorganic phosphate: salt of phosphoric acid
- Organophosphate: ester of phosphoric acid

- Phosphoric acid 磷酸 H_3PO_4



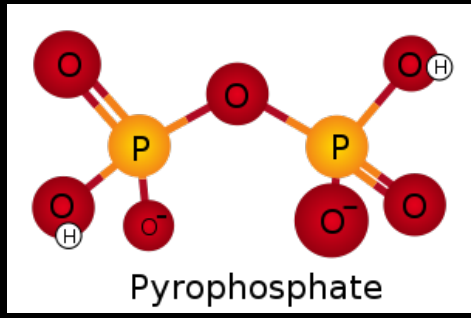
Phosphoric acid

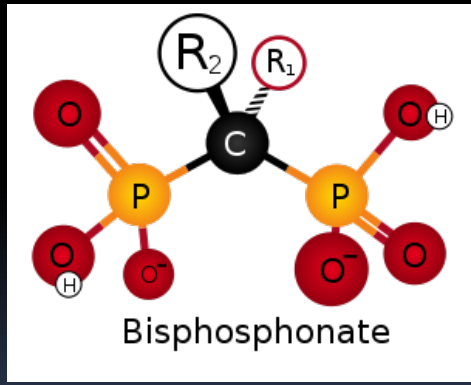


- H_3PO_3: Phosphorous acid 亞磷酸, phosphonic acid 膦酸 (因兩種形式可互相轉換,有時被當作同義字)

Phosphonate vs. Phosphate 磷酸鹽

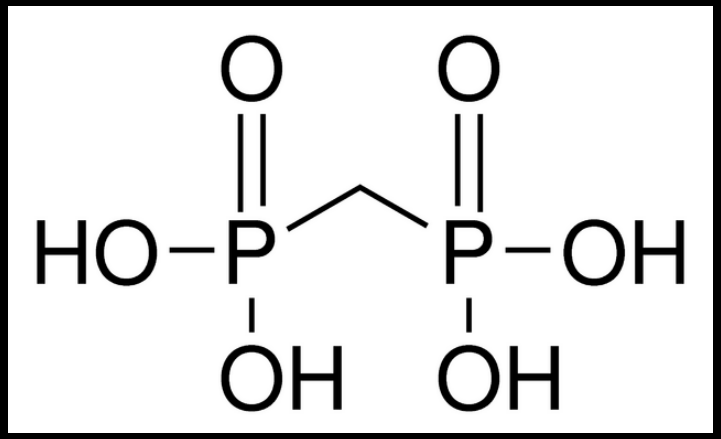
- Phosphate: P-O-P bond
  - 是alkaline phosphatase的substrate
  - 較不穩定
- Phosphonate: 有 P-C-P bond的化合物
  - C-PO(OH)$_2$ or C-PO(OR)$_2$
  - 不是alkaline phosphatase的substrate
  - 較phosphate穩定



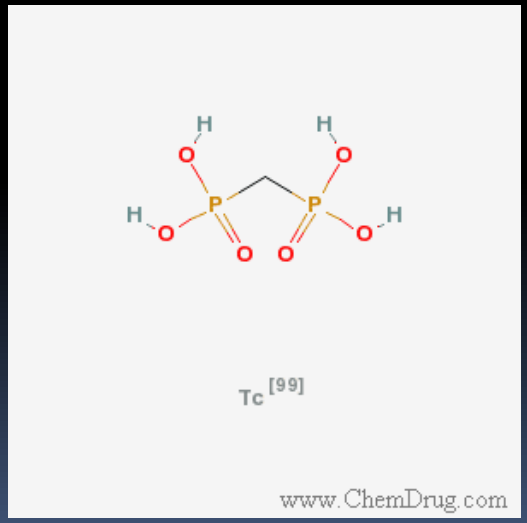


bisphospnonate = diphosphonate

Structure of MDP
(m**ethylene diphosphonic acid**)



Tc-99m MDP



From Website OPEN i beta

From Website QUALITY CONTROL IN THE HOT LAB

Hydroxyapatite (HA) crystal matrix

- Hydroxyapatite = hydroxylapatite
- $Ca_{10}(PO_4)_6(OH)_2$

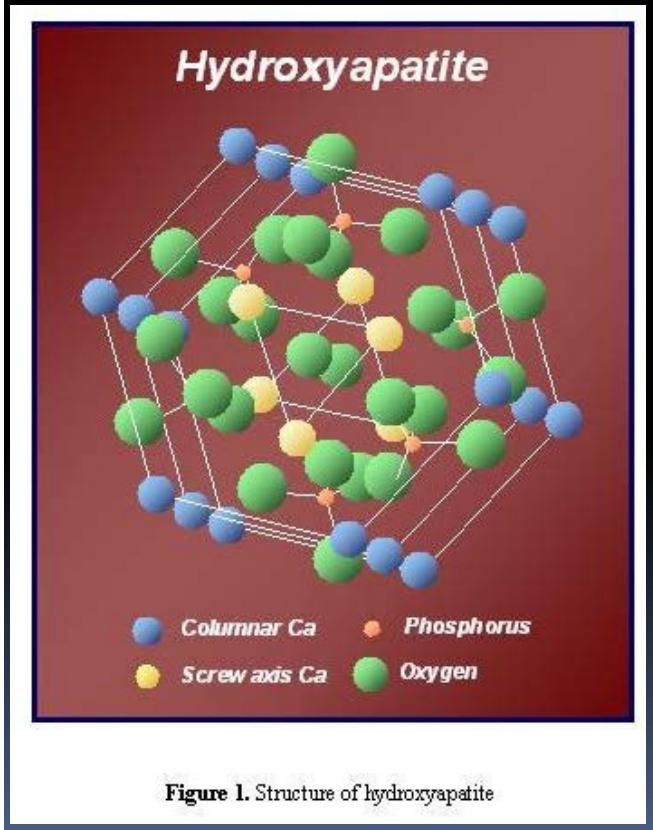
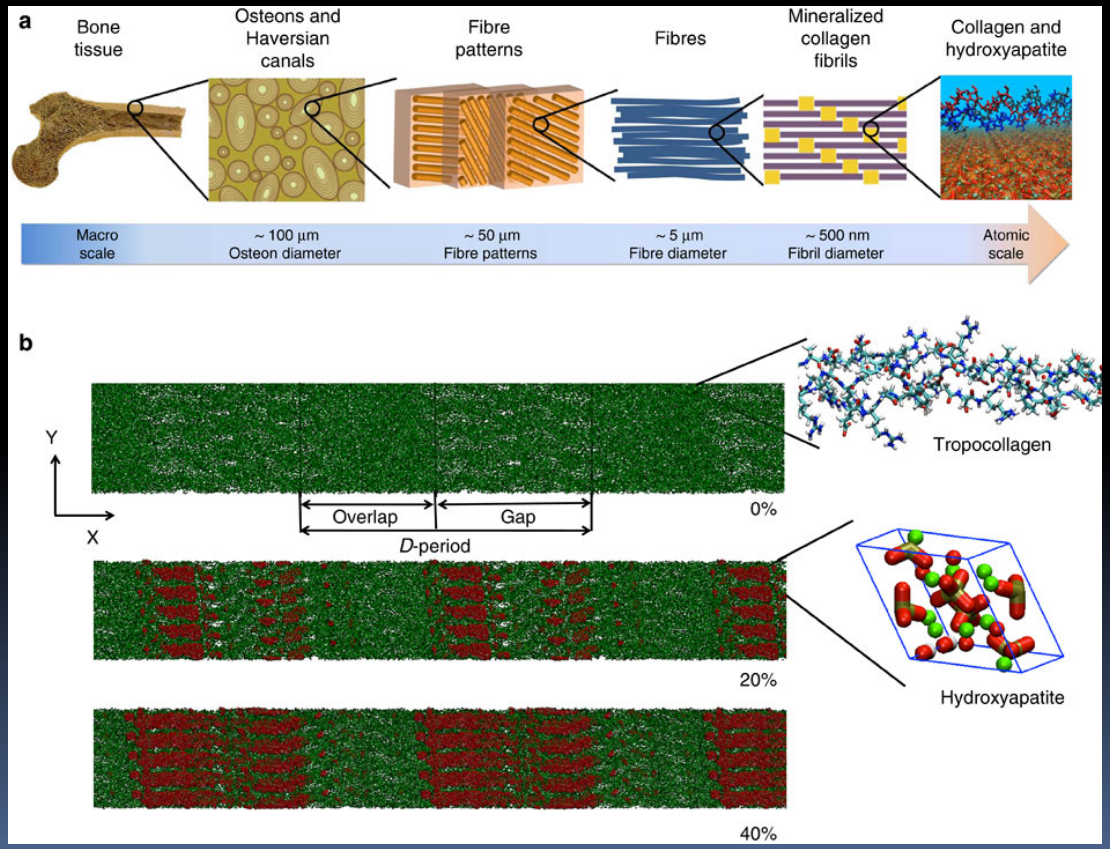


Figure 1. Structure of hydroxyapatite



Uptake mechanism of Tc-99m MDP

- Blood $\xrightarrow[?]{\text{endothelial cells}}$ extracelluluar fluid $\xrightarrow{?}$ HA/ ACP

- Physicochemical adsorption… in osteoblastic region
- In soft tissue… excess calcium
  - Chemisorption on the surface of calcium salts
  - Cell hypoxia & cell death would lead to increased deposition of calcium phosphates in ECF

4. Cellular migration and sequestration

- Chemotactic factors in infection sites…WBC
  - In the first 6-12 hrs, the predominant cells infiltrating a site of infection are PMNs
  - In-111-oxine-labeled WBC
  - Tc-99m-HMPAO-labeled WBC
  - 主要是PMNs (neutrophil)被labeled, but why?

- Active thrombus formation…Platelet
  - In-111-labeled platelet
- Accessory splenic tissue
  - Heat-damaged Tc-99m RBCs

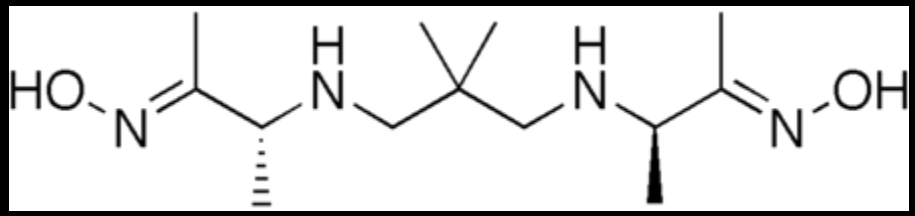
5. Membrane transport– Simple diffusion

- Concentration: high→ low
- Xe-133, Xe-127, Kr-81m
  - Inert lipophilic gases
  - Distribution proportional to ventilation

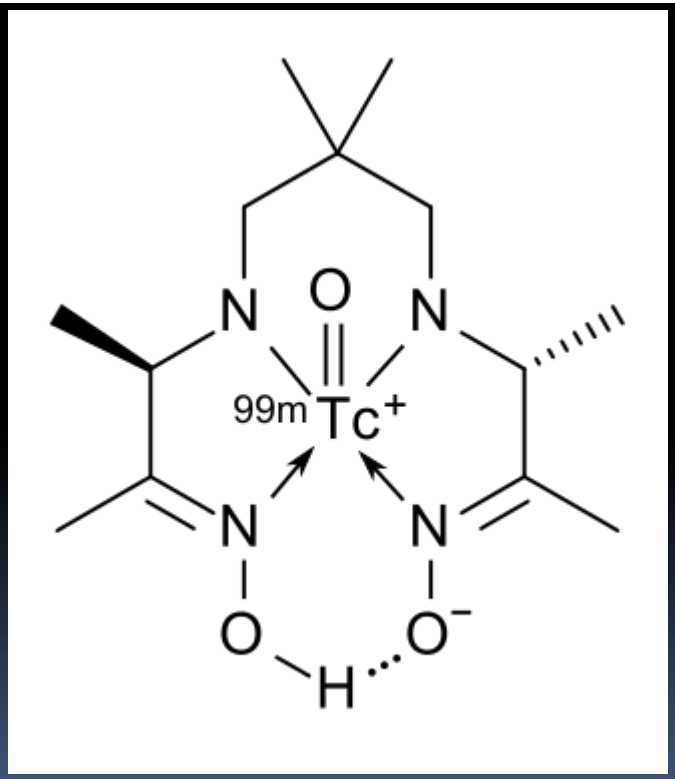
Membrane transport– Diffusion & intracellular metabolism/ binding

- Blood-brain barrier (BBB)
  - Endothelial cell of cerebral vessels, continuous layer w/o gap junctions
  - Preventing water-soluble molecules
    - Tc-99m pertechnetate, Tc-99m DTPA in brain scan
    - Only accumulate in lesions with defects in BBB
  - Allowance of small, neutral and relatively lipophilic molecules to cross BBB
    - I-123 IMP, Tc-99m HMPAO, Tc-99m ECD
    - Retention due to intracellular binding or metabolic degradation to polar metabolites/ charged complexes

HMPAO

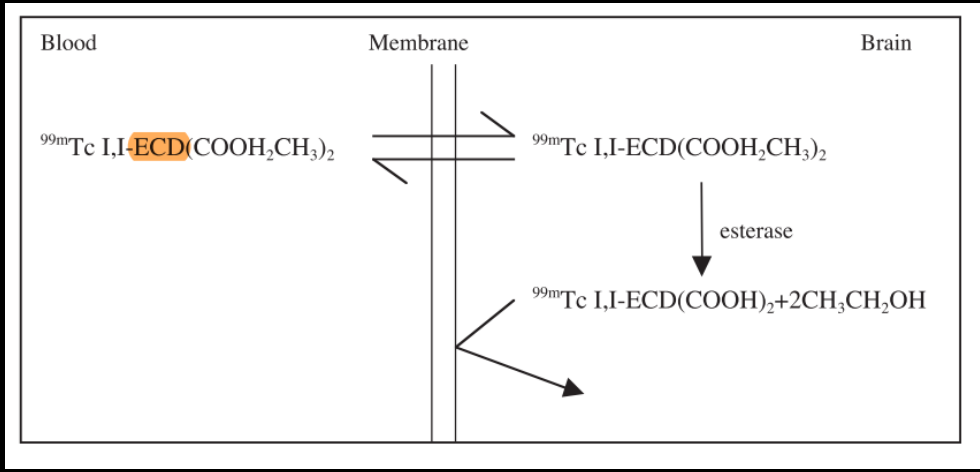


Tc-99m HMPAO

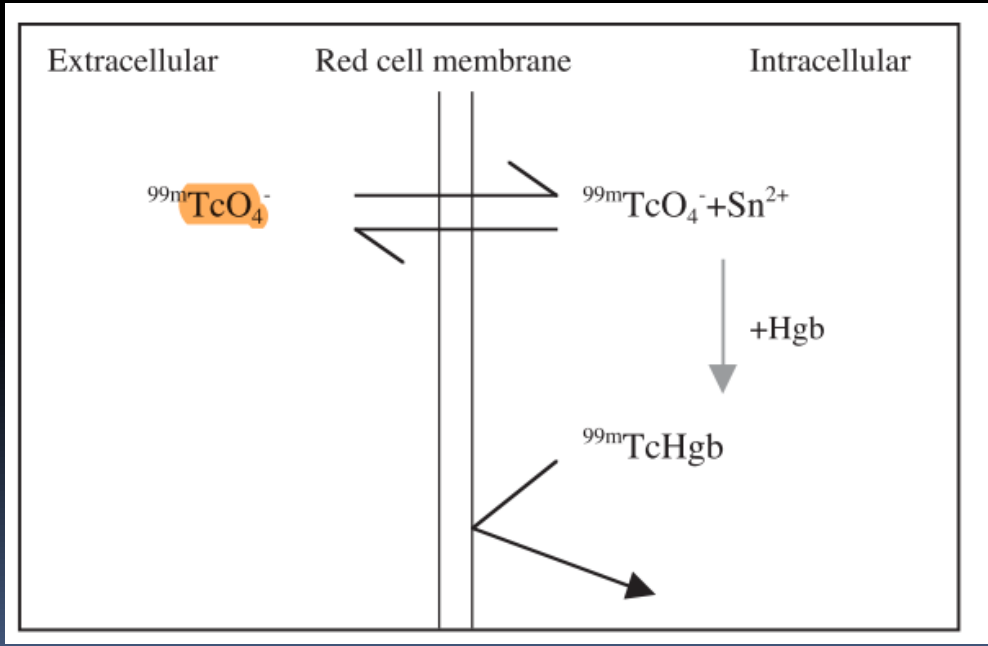


From website: wikipedia, Technetium (^{99m}Tc) exametazime

Tc-99m ECD



Tc99m-pertecnetate



Diffusion and mitochondrial binding

- Tc-99m MIBI, tetrofosmin and furifosmin vs. Tl-201
- Tc-99m MIBI vs. Tl-201:
  - Similar: cationic, cross cell membrane involving only passive diffusion (temperature dependent and non saturable)
  - Different: MIBI→ mitochondrial binding; Tl-201→ remain in cytoplasmic compartment

Tc-99m sestamibi and tetrofosmin

- Piwnica-Worms et al.:

  Cellular entry of MIBI (90%) is related to mitochondrial metabolism & negative inner membrane potential
  - Tetrofosmin: accumulated in cytosolic fraction
- MIBI metabolism: not organ/ tumor specific
- With irreversible ischemia, extracellular calcium enters cells and sequestered in the mitochondria→ mitochondria destruction→ block MIBI binding to mitochondria
- In tumors, uptake & retention (of Tc-cationic agentes, including MIBI & tetrofosmin) is related to back diffusion or efflux
  - Mediated by Pgp (P-glycoprotein)
  - 17-KD plasma membrane lipoprotein
  - Encoded by MDR (human multidrug resistance) gene

- To be continued.