NUCLEAR MEDICINE

Molecular Imaging + Endo-Radiotherapy

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DEFINITION OF NUCLEAR MEDICINE

Medical applications of unsealed radioisotopes for
Diagnosis – Therapy - Research
„Unsealed”: in the functions of the living organism
by iv., sc. injections, rare: per os, inhalation
Participation in organ-tissue-molecular functions!
(Brachytherapy, In vitro laboratory techniques: NOT)
Diagnosis + Therapy of diseases (not only imaging!)

Independent medical specialty (5 yr specialization)

HEVESY GYÖRGY
Georg von Hevesy

First use of radioactive isotopes
in biological systems (1924)
Tracer principle: to follow biological functions
small amount, labelled by
radioactive isotopes

„Father of nuclear medicine”
Nobel prize in chemistry, 1943

RADIOISOTOPES IN MEDICINE

Isotope: same number of protons
(bio)chemically the same element!
(e.g. C-11, O-15, I-123-124-125-127-131)
biochemically: no difference!
Proton : neutron. Optimal ratio: stability !
Unstable nucleus changes: radiations
Two types of isotopes :
plus protons or plus neutrons
Production (only arteficial isotopes are used):
plus proton: in cyclotron
plus neutron: in reactor

TYPES OF RADIATION

Plus protons:
- positron emission (positive beta)
meets electron : annihilation
2 x 511 keV electromagn.
- EC (K, L, M...): „avalanche”
characteristic Xray + gamma
- alpha particle (+gamma)

Plus neutrons:
beta („electron” from the nucleus)
+ gamma (immediately or metastable: „m”)

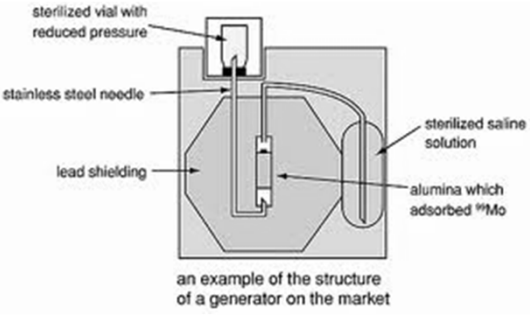
MOST IMPORTANT ISOTOPES IN NUCLEAR MEDICINE

Diagnostic: electromagnetic radiation (photons)
plus neutron:
Tc-99m, I-131, Xe-133: gamma (metastable)
plus proton:
- Ga-67, In-111, I-123, Tl-201: Xray +gamma
- C-11, N-13, O-15, F-18, Ga-68: annihilation

Therapeutic: particle (absorption in tissue: dosis)
plus neutron: beta: Y-90, I-131, Sm-153, Re-186,..
plus proton: alpha - At-211, Bi-212, Ra-223, ..

Tc-99m GENERATOR

Mo-99, Al-oxid, elution phys.saline, T1/2: 2.75 d



an example of the structure
of a generator on the market

ADVANTAGES OF Tc-99m

(m=metastable: energy slowly)
In 80 % of SPECT examinations

Physical (for detection)

140 keV: ideal for gamma camera (70-400 keV)
monoenergetic: easy for imaging

Biologic: low radiation dose

"pure" gamma radiation (metastable)
physical half-time 6 hours, optimal

Practical

from Mo-99 generator, elution by phys. saline (!)
stable complexes with many molecules

RADIOPHARMACEUTICALS

THE FUTURE OF NUCLEAR MEDICINE!

Organ- tissue- molecular-
function-specific labeled molecules
(sometimes the radioisotope alone
(e.g. I-131, Sr 89, Rb-82, Ra-223)
In diagnosis:
Functions: organ, tissue, molecular (quantitative)
Tissue characterization – identification
In therapy:
targeted, molecular (selective) endo-radiotherapy
(low dose rate, but high dose: continous radiation)
„targeted",„tailored", „personalized" therapy
„precision medicine"

THERANOSTICS CONCEPT

Function-specific molecules !

The role of radioisotope:

only for detection or for therapy

„Theranostics" concept: the same molecule!

e.g.	radioiod:	Dg: I- 123 -124 -125
		Th: I-131
	sms ligands:	Dg: In-111, Tc-99m, Ga-68,
		Th: Y-90, Lu-177, Bi-213,
	PSMA ligands	Dg: Ga-68, Tc-99m
		Th: Lu-177

BIOLOGICAL MECHANISM in living organism

Physical	SLN
Compartment	MUGA blood pool
Diffusion	DTPA, ventilation
Chemical reaction	MDP, PIB
Phagocytosis	colloid spleen
Cells	leucocyte
Excretion	HIDA, EC
MOLECULAR FUNCTIONS:	
Active transport	***thyroid, adrenerg***
Metabolism-nzymes	***FDG, FET, FCH, FLT,..***
Antigen	***antibody, fragments, peptides***
Receptor	***ligands***
Beta-amyloid	***florbetapir, …***
Others	***hypoxia,angiogenesis,apoptosis..***

DETECTION (MAINLY): IMAGING

Gamma camera (SPECT)

scintillation crystal, rectangular detectors
static and dynamic aquisitions
spot, whole-body images
planar or SPECT (emission CT: 64-128 projections)
ECG-gated myocardial perfusion
dedicated for organs (cardiac, breast, thyroid)
(new: semiconductors, multipinhole, small animal…)

Positron camera: PET („double-photon ECT")

BGO, GSO, LSO, LYSO,… crystals, semiconductors,
„ring detectors" (small block detectors)
16-21 cm axial FOV (whole-body: 5-6 bed positions)
coincidence detection, 3D data aquisition, time-of-flight

DETECTION: NON-IMAGING

Ex vivo measurements
- of biological samples
- renal clearance (blood), Schilling test (urine)

Small dedicated instruments
- Thyroid uptake test
  - before radioiodide therapy (dose?)
- Intraoperative gamma-probes for localization
  - sentinel lymph node detection

SPECT

Rotation: steps, continous
- circular, elliptic (close!)
- 64-128 projections

Reconstructions:
- filtered backprojection or iterative

Corrections:
- attenuation, Compton, detector-response (depth)

Slices:
- transverse (axial), coronal, sagittal
- 3 D, MIP, rotating

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PET ADVANTAGES (vs.SPECT)

double-photon vs. single-photon

1. More sensitive (no collimator!)
2. Spatial resolution is better (anatomic details)
   - SPECT: 8 - 10 mm, PET: 4 - 5 mm
   - (small animal: 1 mm!!)
3. Quantitation is easier. Relative is enough (%, SUV)
   - but absolute (mL/min/g, mol/min/g) is possible
4. **Biomolecules !!!**
   - C-11, N-13, O-15, F-18, Ga-68, Sc-44
   - (glucose, tyrosine, thymidine, H2O, etc…..)

„**SLICE OF LIFE”**

HYBRID SYSTEMS

Function + Morphology

on the same gantry: „simultaneous” (image fusion?)

Improvement of diagnostic capabilities

1 +1 = 3 !

PET/CT (only hybrid, no PET alone today)

SPECT/CT (the „good” SPECT is SPECT/CT)
- role of CT: localization + attenuation correction
- „low dose” ! (not diagnostic CT)

PET/MR
- no ionizing radiation (pediatry, serial)
- soft-tissue contrast (brain, oncology, ?)

PET/MR

Technology (PMTs in magnetic field)!
- Soft-tissue contrast excellent
- No ionizing radiation dose!
- Duration of the study (all sequences)?
- Clinical indications (both are indicated)?
- Cost-effectiveness?
- Research !

POTENTIAL INDICATIONS

- Pediatric patients
- Follow-up studies (e.g. lymphomas)
- Brain, breast, pelvic, cardiac
- Functional MR techniques ?
  - different sequences, STIR, DWI, ADC,..
  - arterial spin labeling
  - proton spectroscopy
  - diffusion-tensor imaging

NM ADVANTAGES IN DIAGNOSIS

TISSUE CHARACTERIZATION: IDENTIFICATION
- What is seen on the CT/MR?

FUNCTIONS!
- Organ- Tissue- Cell- Molecular Functions
- Quantitative e.g. renal: split, MTT, clearance
  thyroid uptake, I-131
  heart perfusion score
  PET: SUV, or mol/min/g

NON-INVASIVE
- i.v. injection and (small) radiation dose
- No toxic effects! Allergic reactions very rare.
- Nano-, picomolar amount!

DISADVANTAGES OF NM I.

1. Geometric resolution is limited
   - contrast (target/backgoround) is important
     like stars (size?? light!!)
   - „only" the function!
   - technical resolution of the instrument
     SPECT 8-10 mm, PET 4-5 mm
   - biologic resolution is different
     hot thyroid nodule vs. large liver mets
2. Anatomy, morphology, details, localization ??
   SPECT/CT, PET/CT, PET/MR, SPECT/MR?

DISADVANTAGES OF NM II.

3. Radiation dose
   - Gamma (SPECT) 1- 7 mSv
   - Annihilation (PET) 5-10 mSv
   - EC, conversion electrons (SPECT 15 mSv

Principles of radioprotection of the patient
- Indication!
- Non-ionizing (e.g. US) first!
- ALARA !
  (only reference levels)

Developments of hardware, software
Gravidity, lactation, small children: RISK-BENEFIT!

DIAGNOSTIC ROLE OF NM IMAGING

Functional imaging
- organ-, cell-, biochemical functions
- tissue characterization
- molecular imaging (at molecular level)

Radiology: morphology

Co-operation
- instrumentation: PET/CT, SPECT/CT
- in education (multimodality)
- in diagnostic algorhythms (changing)

IMPORTANCE OF MOLECULAR IMAGING

Disease: functional changes

Function before morphology !

Early diagnosis

Targeted diagnosis

Targeted therapy

Personalized/precision medicine

MOLECULAR IMAGING

Functions at molecular and cell levels
„Commodore" in molecular imaging
Nuclear medicine, mainly PET

Reasons:
- pico-nano-molar amounts
- not the substance, but radiation
- hundreds of biomolecules can be labelled
  all! But clinically today: 30-40 targets

(CT, MR, Optical, US…)

MOLECULAR NUCLEAR MEDICINE SELECTION OF TARGETS!

Enzyms – substrates
FDG, FLT, FET, FEC, FDOPA,…
Receptors – ligands
D2, Somatostatin,…
Antigens – antibodies (fragments)
PSA, CEA, TAG72, CD20,…
Transzport proteins – substrates
NIS, NET,…
Deposits – bindings molecules
beta-amyloid, tau-protein,…

F-18-FLUORO-DEOXY-GLUCOSE

FDG is the most important molecular imaging radiopharmaceutical

F-18 is the most frequently used PET-nuclide

FDG is the most frequently used PET radiopharmaceutical

Clinical use:	Oncology	85 %
	Neuropsychiatry	5 %
	Cardiology	5 %
	Others	5 %

WHY FDG?

- „Sugar scan”
- Tumors need sugar – energy (Warburg)
  - Only uptake of glucose (hexokinase)
  - F-18-FDG-phosphate intracellular
  - Success of PET is because of FDG !
    - cost-effectiveness in oncology!
      - reimbursement!
    - (however not tumor-specific!)

FDG: GENERAL INDICATIONS IN ONCOLOGY

Tumor – non-tumor	e.g.SPN
Staging	Mets
Restaging	
Therapeutic effectiveness?	interim
Therapy follow-up	Effect?
Recidiv or recurrent tumor ?	CEA, Tg..
Planning radiotherapy	tumor!

RADIONUCLIDE THERAPY GENERAL CHARACTERISTICS

- Specific (targeted, molecular)
- Effective
- Low dose rate but high dose
- Low side-effects (hematological, renal
- Excellent palliation (but ecen curative)
- Repeatable

THERAPEUTIC APPLICATIONS I.

- Hyperthyreosis: I-131
  - (molecular, targeted, individual, personal)
  - Grave’s disease, toxic adenoma,…
- Thyroid cancer: I-131
  - (ablation, then follow-up: serum-Tg)
  - Papillar and follicular ca. recidives, mets,
- Bone metastasis: Sm-153- Re-186-phosph.
  - Prostate, breast, lung: palliative
  - Alpha emitters: Ra-223, high LET, curative

THERAPEUTIC APPLICATIONS II.

- Radioimmunotherapy Lu-177-PSMA, Y-90-anti-CD20 (B-cell lymphoma),,…
- Adrenerg receptor: I-131-MIBG, pheo, neuroblastoma,…
- Neuroendocrine tumors: Y-90-, Lu-177- SMS PeptidReceptorRadioTherapy (PRRT)
- Radiosynovectomy Y-90, Re-186, Er-169 colloids (local, not systemic!)
- Microspheres Y-90, intraarterial, liver, mets
- And….

PERSPECTIVES OF NM molecular

■ Apotosis	Annexin V,
■ Angiogenesis	VEGF, integrin antibodies
■ Hypoxia	Misonidazol, FMISO
■ ….	
■ Oncogens	F-18 oligonukleotides
■ Genexpressions	Gen therapy:reporter gen HSV-Tk co-expression with F-18-deoxytimidine

etc. !!!!!

THANK YOU