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V OKVIRU DOKTORSKEGA ŠTUDIJA
KEMIJSKE ZNANOSTI

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z naslovom:

Positron emission tomography

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Vljudno vabljeni!

Operacija se izvaja v okviru Operativnega programa razvoja človeških virov za obdobje 2007-2013, razvojne prioritete 3 : »Razvoj človeških virov in vseživljenjskega učenja«; prednostne usmeritve 3.3 »Kakovost, konkurenčnost in odzivnost visokega šolstva«.

Abstract

In our quest to find a cure for diseases which are the major health concerns of our age (e.g. diabetes mellitus, neurodegenerative diseases, and cardiovascular diseases) we are often faced with the stark reality: we rarely can determine for each patient how much damage of vulnerable cell populations, vital for normal physiological functioning of the affected organ, they have. Medical diagnosis often relies on measuring functional viability of the specific organ in question, including measuring plasma values of nutrients, ions in fluids, detection and quantification of certain molecules which are surrogate markers of vital enzymes and transporters. Very often such molecules include metabolites of normally occurring endogenous and exogenous substances with physiological activity.

Medical imaging provides the ability to look into the living body and detect disease related changes in the affected organs. Which method to use and how to interpret the results depends heavily on what we need to measure in the body. X-ray based techniques e.g. computer aided tomography (CAT), which deliver X-rays from outside of the body and measure their absorbance in different tissues are suitable for visualization of bones and soft tissues of different densities but provide very little functional information. Magnetic resonance imaging (MRI) delivers radio frequency energy pulses to the tissues in strong magnetic fields and looks for relaxation properties of different nuclei. It can distinguish different soft tissues from each other in terms of anatomy but can be also applied for a limited number of functional studies, e.g. for brain activation studies.

Positron emission tomography (PET) and other similar types of medical imaging differ significantly from MRI and CAT scanners in that sense that the camera by itself does not provide any energy to the body (as is the case of X-rays in CAT scanners or radio waves in MRI scanners). These methods rely on injection of different types of radioactive atoms either alone or attached to organic molecules. These cameras measure either gamma rays emitted by gamma emitting radionuclei (scintigraphy, SPECT) or gamma rays resulting from annihilation of positrons emitted by positron emitting radioisotopes. Use of these nuclear medicine techniques (called so because of use of radioactive materials) is heavily dependent on radiolabeling of the organic molecule to be used (radioactive molecular imaging probe or radiotracer) and on proper understanding of the interactions such molecular imaging probe has with proteins that are their intended targets.

Due to the flexibility in radiotracer design we can prepare different radiotracers and perform scans of functional expression of different proteins (receptors, enzymes, transporters) involved in pathophysiology of each disease.

Commonly used short living positron emitters include carbon-11 (half-life ~20 min), nitrogen-13 (half-life ~10 min), oxygen-15 (half-life ~2 min) and fluorine-18 (half-life ~110 min). An excellent example of fluorine-18 labelled organic molecule is 2-[F-18]fluoro-2-deoxy-D-glucose, 2-[F-18]FDG, which is used for PET visualization of tumors in oncology and in for determination of changes in regional brain glucose utilization indicative of neurodegenerative diseases. These tissues depend on glucose as one of their major sources of energy. The basic mechanism of radiotracer (2-[F-18]FDG) accumulation in these tissues is based on phosphorylation of its 6-OH group by the enzyme hexokinase. Unlike D-glucose 6-phosphate which is further degraded by other glycolisis enzymes 2-[F-18]FDG 6-phosphate cannot be further degraded because of its lack of 2-OH group.

Development of new radiotracers is a complex process in which chemists play a crucial role in several steps. This includes synthesis by the molecule in non-radioactive form and of the molecule which can be used as a starting material for [F-18]radiofluorination, determination of biochemical constants of interaction between the tracer and its intended protein target in collaboration with physiologists and pharmacologists,

determination of metabolites and their structures in collaboration with pharmacologists and bio-mathematicians during the pre-clinical stages.

Once the radiotracer reaches clinical use (after receiving all required regulatory approvals) radiochemists are vital part of the PET team because tracers have to be prepared for every scan due to the short half-life of these positron emitting isotopes.

Further applications of this technology and its scope and limitations will be discussed including [F-18]FDDNP, a radiotracer for insoluble protein aggregates, developed in collaboration with Dr. Andrej Petrič.