Chemistry of Contrast Media

Small Molecules

Metabolic Probes for Nuclear Medicine

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Learning Objectives:

- Describe the features of metabolic probes for nuclear medicine in comparison with probes for other imaging modalities.
- Discuss and evaluate new design of metabolic probes for nuclear medicine.
- Examine how metabolic measurement can be realized using nuclear medicine technique.

Among the in-vivo molecular imaging technologies, nuclear medicine including positron emission tomography (PET) and single-photon emission tomography (SPECT) has extremely high sensitivity, which allows us to visualize metabolic processes without any toxicological side-effect. However, radioactivity signals themselves do not contain any information about the structure of radio-labeled molecules, so that biological information can be obtained only in an indirect manner, by kinetic/parametric analysis of radioactivity accumulation. This analysis requires rather long data acquisition time, so that metabolic parameters obtained are averages of several ten minutes. This point is totally different from MRI with hyperpolarized C-13-compounds, which allow us to obtain molecular structural information of C-13-compounds, but monitoring duration is limited to few ten seconds after injection. For quantitative measurement of metabolism using PET/SPECT, two probe-design approaches have been performed, namely selection of radio-labeling site of natural metabolic substrates, or use of modified metabolic substrates, to visualize a targeted metabolism. Recent researches mainly focus on the latter approach, such as metabolic trapping agent. The most widely used metabolic trapping agent is F-18-fluoro-deoxyglucose (FDG). It is transported by glucose transporter(s) and phosphorylated to G-6-P by hexokinase, but not metabolized further and trapped in the cell. In normal brain, glucose is a major energy substrate and phosphorylation to G-6-P is considered as a rate-limiting step of glycolysis, so that FDG accumulation can be evaluated as glucose metabolic rate in normal brain. At present, FDG is more popular in tumor diagnosis, but interpretation is not simple in tumor cells.

Recently, an amino acid analogue, F-18-amino-cyclobutane-carboxylic acid (FACBC) has moved to clinical trial in Japan. FACBC selectively accumulates into malignant tumor cells based on its affinity to amino acid transporter(s), but low accumulation in brain, kidneys and inflammatory tissues. In addition, F-18-ACBC accumulation is not affected by altered blood glucose levels, a major concern in FDG-PET.A precursor of protoporphyrin IX synthesis, 5-aminolevulinic acid (ALA), highly accumulates in tumor cells, and produced protoporphyrin IX is a therapeutic target of photodynamic therapy (PDT) or sonodynamic therapy (SDT). Accumulation of protophrphyrin IX can be visualized with fluorescence only when tumor mass is on the surface of body, or close to the surface of body. C-11-methyl-ALA (MALA) highly accumulated in tumor cells with protophorphyrin IX synthesis, but MALA is stable in tumor cells. MALA accumulation is closely correlated with ALAD expression, a first step enzyme for protoporphyrin IX synthesis. Thus, MALA is considered to be a marker of ALAD expression and useful for the prognosis of PDT/SDT with ALA.

There are several ways to visualize metabolic pathways with PET/SPECT, and molecular design of probes plays a crucial role to realize it.