《招待講演》

Use of a Human Liver Model in Prediction of the Metabolic Fate of PET and SPECT Radiotracers

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For brain imaging by PET and SPECT, radiotracers with high affinity to neurotransmitter receptors and transporters are required. The frequently associated problem, however, is the peripheral metabolism of radiotracers resulting in a reduced amount of radioactivity in the brain and a less clear image. Most metabolites have little or no affinity to receptors but some bind non-specifically while others even bind preferentially to different target receptors. Knowledge of drug metabolizing enzymes has rapidly expanded in the last decade and major enzymes and their isoforms have been fully characterized. The major site of drug metabolism is the liver and the *in vitro* use of human liver tissue has become commonplace. Two applications of this human liver model are described.

The first application is the screening for metabolically resistant radiotracers. Synthetic chemists can produce many analogues and derivatives of lead compounds for various receptors. The selection criteria of a successful radiotracer should be not only its high affinity for the receptor but also its resistance to peripheral metabolic degradation. The human liver model can recognize a radiotracer that is resistant to metabolism. Then, from among the metabolically resistant compounds (i.e. those with slow metabolism), receptor binding studies can identify the high affinity radiotracers. The order of these steps can be reversed.

The second application is to find inhibitors of peripheral metabolism of radiotracers that are suitable for co-administration. The classical example of an inhibitor of peripheral metabolism of a centrally active drug is carbidopa, which is combined with L-dopa and administered to Parkinson's patients. The human liver model can identify both the *in vitro* metabolic inhibitors of radiotracers and the metabolizing enzymes. Highly lipid soluble drugs including PET and SPECT radiotracers are often metabolized by cytochromes P450 (CYP) and systematic identification of CYP isoforms *in vitro* would be useful. Enzyme inhibitors when concomitantly administered would improve the imaging of many currently used radiotracers as well as increase the range of candidate compound for new radiotracers.

In conclusion, the results obtained *in vitro* are useful in predicting the *in vivo* metabolism of radiotracers and in selecting a favorable radiotracer. The human liver model can improve the *in vivo* clinical use of radiotracers.