Kinetics And Metabolism Of [18-F]-Labeled-L-DOPA Analog PET Tracers

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Fluorinated analogs of L-3,4-dihydroxyphenylalanine (L-DOPA) have been investigated to assess their abilities to trace striatal dopamine metabolism in vivo with Position Emission Tomography (PET). One of the analogs studied, 6-[18-F]fluoro-L-DOPA (FDOPA), has been used with PET for over ten years. However, FDOPA is considered to be a suboptimal tracer due to the peripheral formation of 3-O-methyl-6-fluoro-L-DOPA (3-OMFD), which crosses the blood-brain barrier and reduces striatal contrast. For this reason tracers which have simpler metabolic characteristics have been studied. These include:

6-[18-F]-Beta-fluoromethylene-m-tyrosine(f-FMMT),
6-[18-F]Fluoro-L-m-tyrosine (6-FMT),
and 2-[18-F]Fluoro-L-m-tyrosine (2-FMT).

From PET studies performed on rhesus monkeys it was found that 6-FMT achieves more than double the striatal contrast of FDOPA at 90 minutes post injection (p.i.). FMMT and 2-FMT showed only about the same striatal contrast as FDOPA. Graphical analysis using a cortical input function revealed that all tracers have access to a slow clearing (trapped) compartment. To investigate how the apparent trapping occurs, the translocation of dopamine analogs was studied in two separate in vitro preparations. The uptake of monoamines into bovine chromaffin granule ghosts was studied as a model of vesicular storage.

Neuronal uptake was studied using C_6 glial cells transfected with a plasmid containing the cDNA for the human presynaptic dopamine uptake transporter. For both translocation processes 6-[18-F]Fluoro-L-m-tyramine (6-FMTA), showed a much lower affinity. An assay of cerebral FDOPA metabolites in stumptail monkeys showed that at 30 min. p.i., about 40% of the radioactivity in the striatum was due to FDA and about 20% was due to FDA metabolites. These metabolite fractions agree well with a model which allows for both rapid and slow turnover of FDA. FDOPA and 6-FMT were also found to respond differently with age. Straightforward models have been proposed for both FDOPA and 6-FMT metabolism, which are consistent with the results of our in vivo and in vitro studies.