PET-studies of methamphetamine enantiomers

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Introduction: Methamphetamine (METH) is a highly addictive stimulant drug which is toxic not only to brain but also to peripheral organs. d-METH, which produces a large elevation in extracellular dopamine through blockade of the dopamine reuptake site and the vesicular monoamine transporter, is about 5 times more potent than l-METH. Because high uptake and rapid brain entry of a drug is crucial in stimulant reinforcement and because peripheral organ toxicity is also a concern, we set out to determine (1) whether brain uptake and kinetics are consistent with the intense effects of d-METH and with differences between the two enantiomers and (2) to identify target organs for METH and its labeled metabolites. METH metabolism proceeds initially by both aromatic hydoxylation to p-hydroxymethamphetamine (pOHMETH) and by N-demethylation to amphetamine (AMPH). We developed a rapid assay of unchanged radiotracer in plasma, requiring the separation of the lipophilic labeled metabolite pOHMETH (logP=1.7)

Methods: d- and l-METH were prepared from d- and l-AMPH and [^{11}C]methyl iodide according to Inoue et al (1990). Anesthetized baboons (ketamine and isofluorane) were injected with 2-4 mCi of [^{11}C]d- or l-METH and anesthetized rats (ketamine/xylazine) were injected with 1.5-1.8 mCi of [^{11}C]d- or l-METH for dynamic PET or microPET scanning for 60-90 minutes. Plasma samples were analyzed by both High Pressure Liquid Chromatography (HPLC) and robotic solid phase extraction (rSPE) to determine metabolism. Plasma for rSPE was added to water on top of a CN (cyanopropyl) bonded-phase silica cartridge and pushed through the column. The cartridge was rinsed with water or methanol. All fractions and the cartridge were assayed for radioactivity. Labeled metabolites rinsed off the cartridge while [^{11}C]METH remained. Scans of a baboon torso were also carried out with [^{11}C]d-METH. Plasma protein binding (PPB) was also measured.

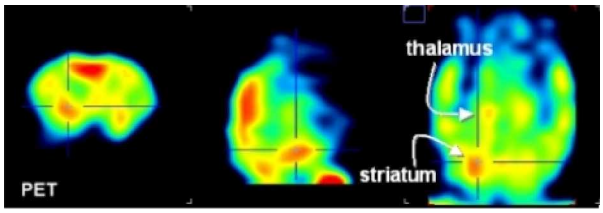

Fig. 1: microPET scan of [^{11}C]d-METH in a rat showing specific uptake. Cross-hairs intersect in the right striatum in all three planes.

Results: [^{11}C]d- and l-METH had a radiochemical purity of >99% and specific activities of 0.6-3.4 Ci/μmol. In baboons (n=5) average d-METH peak uptake occurred earlier for cerebellum (Cb) than striatum (Str) (4.1±2.7 vs 7.8±2.8 min; p=0.015) while there was no difference in peak uptake (0.033±0.008 vs 0.034±0.007 %dose/cc). The half time for clearance from peak was slower for Str vs Cb (81±14.7 vs 57.2±15.9); p=0.001). The ratio Str/Cb was 1.27± 0.05. Comparison of d- and l-METH in the same baboon (n=2) showed no significant difference in time to peak, %dose/cc, t1/2 or Str/Cb. MicroPET runs comparing d- and l-METH in the rat (n=2) were similar to baboon with Cb peaking earlier (5 vs 9 min) and clearing more rapidly (T½ 62 vs 71 min) than Str. Uptake in peripheral organs for baboon for d-METH was highest in the kidney »liver»spleen>heart>lung. There is a significant difference in the metabolic profiles of d- and l-METH (Fig. 3).

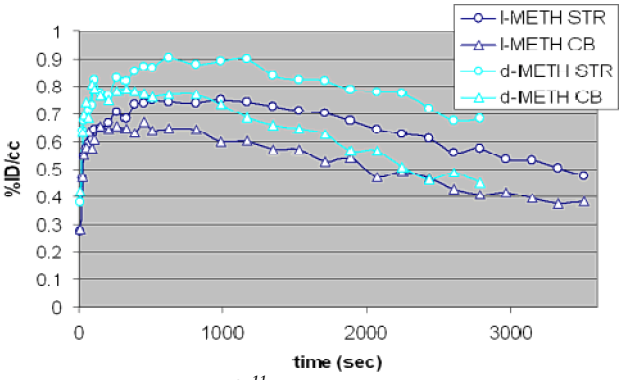

Fig. 2: Uptake kinetics of [^{11}C]d- and l-METH. Both enantiomers were injected in the same rat, one week apart. The profiles are very similar.

Conclusions: The high and rapid uptake of METH into the brain probably plays a role in its intense stimulant properties. However, since the brain uptake and kinetics of d-METH are similar to l-METH (Fig. 2), brain availability and pharma-cokinetics do not account for its more intense stimulant effects. The metabolism was the only remarkable difference found between d- and l-METH. High uptake in kidneys and liver indicate that these will be the target organs in dosimetry for future studies of [^{11}C]METH pharmacokinetics in humans.

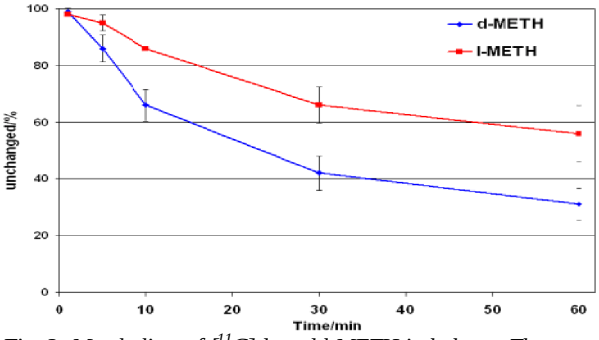

Fig. 3: Metabolism of [^{11}C]d- and l-METH in baboon. The curves show the results of rSPE analysis of [^{11}C]d-METH (N=6) and [^{11}C]l-METH (N=2) in baboon plasma.

References:

Inoue et al., Effect of reserpine on the brain uptake of [^{11}C]-METH. Eur J Nucl Med. 1990;17(3-4):121-6

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