Radiosynthesis and PET Imaging of [^{11}C]Valproic Acid, [^{11}C] Butyric Acid and [^{11}C]Phenylbutyric Acid

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Introduction: Three fatty acids, butyric acid (BA), 4-phenylbutyric acid (PBA), valproic acid (VPA) are bioavailable by the oral route and approved for the treatment of a variety of human diseases. They are also well-known as histone deacetylase (HDAC) inhibitors. For example, BA has been investigated for the treatment of colorectal carcinoma and PBA has been used in urea cycle disorder treatment and has recently been reported to increase the lifespan in drosophila, which was associated with the global alteration of histone acetylation pattern. Similarly, VPA has been used for the treatment of seizure disorders for many decades. Thus their pharmacokinetics are of intrinsic interest and we hypothesized that an examination of their pharmacokinetics and biodistribution of these compounds 'on the whole organism level' using PET would provide non-invasive insight into the involvement of epigenetics and other mechanisms on their therapeutic and side effects.

Experimental: [^{11}C]BA, [^{11}C]PBA were synthesized with the corresponding Grignard reagents, n-propyl magnesium chloride, 3-phenylbutylmagneisum bromide in anhydrous THF using carrier free [^{11}C]CO_2 at room temperature (decay-corrected radiochemical yield, 15-90% at EOB). The synthesis of carrier-added [^{11}C]VPA was performed by saturating a solution of THF with cold gaseous CO_2 at -78°C and subsequent trapping of [^{11}C]CO_2 which was then reacted with 4-heptylmagnesiumbromide. Following acidic hydrolysis afforded carrier-added [^{11}C]VPA in a radiochemical yield of 6-12%.

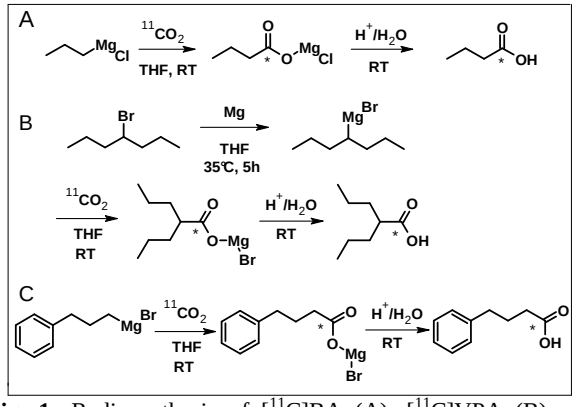

Fig. 1: Radiosynthesis of [^{11}C]BA (A), [^{11}C]VPA (B) and [^{11}C]PBA (C).

Purification was performed by semi-preparative RP-HPLC. Radiochemical purity was greater than 99%. Radiosynthesis was accomplished within 40 minutes from EOB including sterile formulation. The pharmacokinetics of all three acids was examined in baboons using PET.

Results: The determined log P value for [^{11}C]BA was 0.06 and for [^{11}C]VPA it was 0.26. The plasma protein binding was 74 % for [^{11}C]VPA and 18 % for [^{11}C]BA. Both [^{11}C]VPA and [^{11}C]BA showed low uptake in the brain. Peripherally, [^{11}C]VPA showed exceptionally high uptake in heart. [^{11}C]BA is rapidly metabolized to a radioactive metabolite within 10 min.

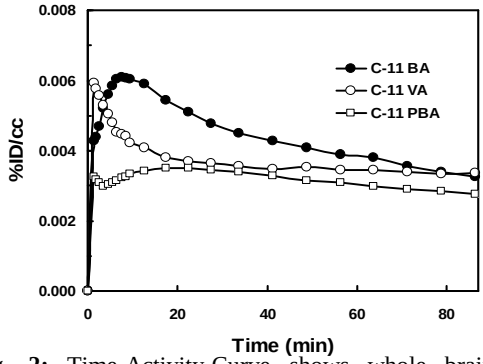

Fig. 2: Time-Activity-Curve shows whole brain uptake for [^{11}C]BA, [^{11}C]VPA and [^{11}C]PBA.

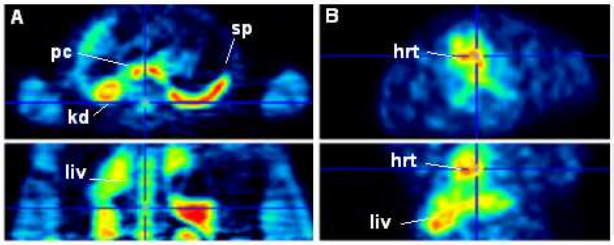

Fig: 3: PET images (body scan) after injection of [^{11}C]BA (A), [^{11}C]VPA (B) (avg. 30-90 min), top row: transaxial plane, bottom row: coronal plane, (liv): liver, (hrt): heart, (sp): spleen, (kd): kidneys, (pc): pancreas.

Conclusions: The three fatty acids showed totally different metabolism and pharmacokinetics. In order to validate the binding of the fatty acids as HDAC-specific additional studies are required. For [^{11}C]BA, the analysis of HDAC interaction is also complicated by the rapid metabolism. Additional studies are planned to determine the radioactive metabolites of [^{11}C]BA and to further investigate the pharmacokinetics and metabolism of the fatty acids.

References:

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