Manganese PET enables the same contrast as Manganese Enhanced MRI

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Target audience – Scientists interested in PET-MRI multi-model imaging as well as those interested in transferring manganese MRI studies in animal models into clinical stages.

Purpose – Manganese has been used as a contrast agent in many MRI studies, due to the ability of Mn^{2+} ions to enter cells through the activity of channels and transporters that indicate function. Manganese enhanced MRI (MEMRI) has been used in animals to image different organs including liver, kidneys, pancreas, heart and brain, following simple systemic administration of manganese[1-4]. MRI studies in animals have also shown that administration of Mn^{2+} into a specific regions enable neuronal tract tracing. In particular administration of Mn^{2+} into the nostril traces the olfactory pathway as far as the amygdala over several days due to its ability of transported along axons in the brain and cross synapses[5]. A major limitation for the use of manganese as an MRI contrast agent in humans is its cellular toxicity and therefore the need to use as low a dose as possible. The much higher sensitivity of PET over MRI, and therefore the ability to use a much lower concentration of manganese for imaging, may enable the use of manganese as a radiotracer in humans. Here we studied the use of manganese-51 (^{51}Mn), and manganese-52 (^{52}Mn), positron-emitters with a physical half-life of 46.2 min and 5.6 days respectively, for PET imaging in both rats and monkeys to compare to MEMRI results.

Method – ^{51}Mn was infused intravenously at a dose of 0.3-0.7 mCi for rats (~1.0 ml volume) and 9 mCi (15 ml) for monkeys over several minutes. ^{52}Mn was also infused intravenously at a dose of 0.2-0.5 mCi for rats. Furthermore, ^{52}Mn was administrated into the nostrils of a monkey on three separate occasions, at a dose of 0.2-0.6 mCi (0.5ml). Dynamic PET imaging was performed on a High Resolution Research Tomography (HRRT) scanner, starting with injection and continuing for up to 2.5 hours. Maximum intensity projection (MIP) images were generated for different time periods following injection and time activity curves (TACs) were obtained for various organs. Imaging of nasal administration in monkey study was performed on a Siemens mCY® PET/CT scanner. PET images were co-registered to MRI images of the same monkey (3D T_1 weighted, acquired on 3T Philips scanner).

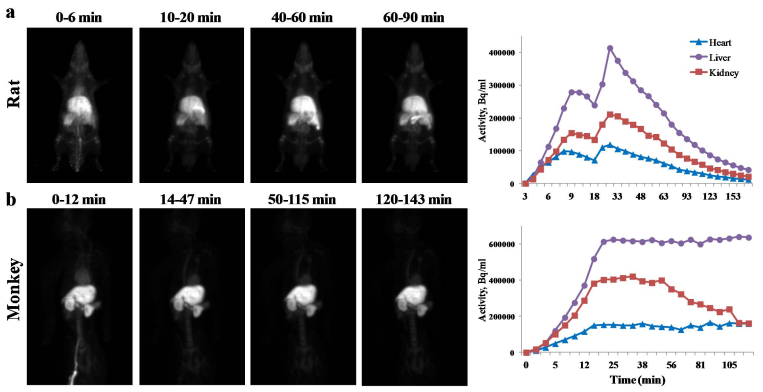

Fig. 1 – PET MIP image sequence and the corresponding time-activity curves following ^{51}Mn infusion for a rat (a) and a monkey (b).

Results – Representative MIP images during ^{51}Mn infusion in rat and monkey and the corresponding TACs are shown in Fig. 1a and b, respectively. In both species, ^{51}Mn was detected in different tissues: liver, kidneys, stomach, spleen and heart. For rats, the highest ^{51}Mn activity was detected in liver, then kidney, and then in heart. This is consistent with MRI results that use a much higher dose of Mn[3,4]. High activity was also detected in the different tissues of the monkey, with highest activity in liver, similar to rats. The longer half life of ^{52}Mn allow for imaging at longer time points following tracer infusion as seen in Fig. 2. MIP images 24 and 48 hours after iv ^{52}Mn infusion show in addition to the accumulation of the tracer in the different organs of the body (as in ^{51}Mn) an accumulation of the radiotracer in the brain. This is consistent as well to MEMRI results in the rodent brain[1]. Fig. 3 shows the co-registered images of PET tracer from the nose into the brain following ^{52}Mn administration into the nostril of a monkey, at 1 day, 3 days and 6 days following administration. One day after administration the ^{52}Mn was detected in the OB was than traced to the OB tract and into the area corresponding to the piriform cortex. The intensity of the tracer increased with increased time from administration. At the later time points the tracer was also detected in the cortex and in areas corresponds to the amygdala.

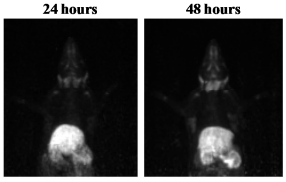

Fig. 2 – PET MIP images following ^{52}Mn infusion for a rat

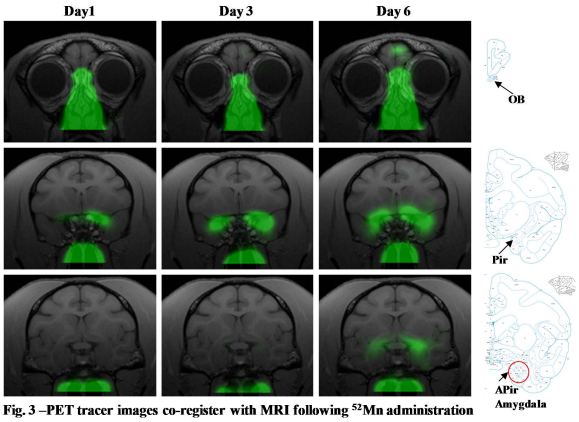

Fig. 3 –PET tracer images co-register with MRI following ^{52}Mn administration in to the nostrils of a monkey and the corresponding atlas images (Paxinos[7]).
OB-olfactory bulb, Pir – piriform cortex, APir- amygadalpiriform transition area

Discussion – This study demonstrates that manganese based radiotracers give contrast consistent to when manganese is used as contrast agent in MRI. This is true despite the large concentration differences (~100 mM Mn range for MRI compare to ~0.05 mM range for PET), indicating that similar uptake and transport mechanism hold even at low PET doses. ^{51}Mn and ^{52}Mn in PET imaging in both rodents and monkeys showed that the accumulation of activity in different organs is similar to that observed in MRI studies in rodents following systemic administration. Furthermore, the longer-lived Mn radiotracer, ^{52}Mn (half life 5.6 days), can be used to trace neuronal connections analogous to MEMRI neuronal tracing studies[6] This opens a wide variety of potential applications for the use of a manganese based radiotracer in both pre-clinical and clinical studies, that has been demonstrated with MEMRI. This includes the detection of heart ischemia, liver metastases and other tumors, and the assessment of renal and pancreatic function as well as imaging of neurological disorders in the brain.

References – 1.Akoi I. et al, NeuroImage 2004 2.Antkowiak PF. et al, AJB Endocrinol Metab 2009 3.Hu TC. et al, MRM 2005 4.Kang YS. et al, Invest Radiol 1984 5. Pautler and Koretsky, NeuroImage 2002 6.Topping GJ. et al, Med Phys 2013. 7. Paxinos G, The Rhesus Monkey Brain in Stereotaxic Coordinates,2nd addition.