

[¹⁸F]2-fluoro-2-deoxy-sorbitol PET imaging for quantitative estimation of blood-brain barrier permeability *in vivo*

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MATERIAL AND METHOD

Radiochemistry

Synthesis of [¹⁸F]2-fluoro-2-deoxy-sorbitol ([¹⁸F]FDS) from commercial [¹⁸F]FDG and quality control was described by Li et al. [13] and is reported as supplementary material. NaBH₄ (2 mg) was added to 4 mL [¹⁸F]FDG (180-200 MBq, Curium, Saclay, France). After 15 min reaction at room temperature, 10 µL acetic acid (0.15 mmol) was added. The mixture was passed through a Sep-Pak Alumina-N-Plus-Long cartridge (Waters, Guyancourt, France). Radiochemical purity was checked using radio-thin-layer chromatography using Silica gel-coated alumina plates (Merck, Guyancourt, France). The mobile phase consisted in acetonitrile/water (80/20, v/v). A single peak with retardation factor (R_f)=0.6 was observed. For comparison, R_f of ¹⁸F-FDG was 0.9.

Focused ultrasound protocol to induce hemispheric BBB disruption in mouse

Focused ultrasound (FUS) delivered by a transducer (active diameter 25 mm, focal depth 20 mm, axial resolution 5 mm, lateral resolution 1 mm, Imasonic, Voray sur l'Ognon, France) centered at 1.5 MHz was used to induce BBB disruption. The transducer was connected to a single-channel programmable generator (Image Guided Therapy, Pessac, France) and mounted on a motorized XYZ-axis stage and positioned above the mouse head maintained under anesthesia. The device was

coupled to the mouse skull using a latex balloon (filled with deionized and degassed water) and coupling gel. The distance between the transducer and the skull was adjusted by the displacement of the motorized axis (Z) and the filling of the balloon in order to get the center of the right brain hemisphere, at the focal distance (*i.e.*, 20 mm). SonoVue[®] microbubbles (Bracco, Italy) were intravenously administered in the tail vein via a bolus (50 μ L) before the beginning of the FUS (n=5) or Sham (no FUS, n=3) sessions. The FUS sequence was composed of ultrasonic waves transmitted for 3.5 s at 1.5 MHz with duty cycle of 71% and a peak negative pressure of 525 kPa (calibrated in deionized water). Therefore, the transmitted pressure in the mouse brain was estimated to be 420 kPa considering a transmission loss through the skull of 20% at 1.5 MHz. A mechanical scan (XY-axis) was synchronized to the generator output in order to induce a hemispheric brain BBB opening of 6 mm (anterior-posterior) $\times$ 3.6 mm (lateral right hemisphere). The sequence was repeated 36 times for a total exposure of 126.4 s.