Tunable manganese porphyrin as Gd-free T1 contrast agents for broad applications

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TARGET AUDIENCE: contrast agent developer, perfusion imager, oncologist, radiologist

PURPOSE: MRI contrast agents currently approved for clinical use are largely based on gadolinium (Gd). Although Gd provides excellent positive contrast, its relaxivity decreases with field strength and toxicity may result if the Gd ion becomes free. From both an efficacy and safety perspective, there is a great need for Gd-free contrast agents. The purpose of this study is to report on a new class of manganese porphyrins (MnP) with high relaxivity, low toxicity, and tunability for different biomedical applications.

METHODS: Contrast agents: The two new compounds developed by the Zhang group are a small and polar MnP (MnP1) and a dimer (MnP2). Gd-DTPA and MnTPPS [1] are used as reference compounds. MnPs are safer, because Mn is an endogenous metal and is significantly less toxic than the Gd ion. Furthermore, the risk of metal dissociation is low, as Mn is tightly bound to the porphyrin ring. In-vitro study: Relaxivity measurements were made on a 3 T MRI scanner (Achieva TX, Philips) on solutions with concentrations of 0, 0.05, 0.1, 0.2, and 0.5 mM Mn. T1 was measured using a 2D IR TSE: nine TIs from 50 to 2000ms, TR=3000 ms. T2 was measured using a multi-echo SE: TR=2000 ms, 32 echoes from 7.74 to 248 ms. A T1-weighted TSE was also acquired: TR=122 ms, TE=18 ms, ETL=4, NSA=8. In-vivo study: Female rats were imaged on a 3 T MRI scanner using a 32-channel head coil. Rats were given a tail vein injection of contrast agent at a dose of 0.05 mmol/kg followed by a 2 mL saline chaser. T1-weighted SE images were acquired before injection and after injection at the following timepoints: 10 min, 20 min, 60 min, 1 day, and 2 days. Parameters for T1-weighted SE were: TR=353 ms, TE=11 ms, NSA=2, FOV = 120 mm, 2 mm slices, 0.6×0.6 mm in-plane, 20 slices.

RESULTS: Relaxivities of all contrast agents are shown in Table 1. Fig 1 shows a T1-weighted image of the different contrast agents in solution. Fig 2 shows T1-weighted images in rats acquired at different time-points before and after contrast injection.

DISCUSSION: The new class of MnPs has much higher T1 relaxivities than Gd-DTPA with a relatively weak T2 effect. They generate much greater positive signal contrast, meaning that signal enhancement comparable to Gd-DTPA can be obtained at a much lower dose. In-vivo results confirm in-vitro findings: MnP1 provides similar but slightly greater positive contrast than Gd-DTPA, while MnP2 provides significantly greater enhancement. MnP1 was rapidly cleared through renal filtration with a kinetic profile similar to Gd-DTPA. MnP2 was not cleared through the kidney and provided significant enhancement of the liver, heart, and blood, effects that were seen 2 days later.

CONCLUSION: The two novel MnPs provide much greater positive contrast than Gd-DTPA and are promising candidates for Gd-free MRI T1 contrast agents. MnP1 may be used as a Gd-DTPA surrogate for dynamic contrast-enhanced MRI, while MnP2 may be useful for angiography, cardiac, and liver imaging.

REFERENCES: 1. Chen CW et al. FEBS Letters 1984; 168: 70-4.

Table 1. Measured relaxivities at 3 Tesla

Contrast agent	r_1 (mM^{-1}s^{-1})	r_2 (mM^{-1}s^{-1})
Gd-DTPA	5.05	5.90
MnTPPS	8.63	10.4
MnP1	7.90	9.11
MnP2	14.1	18.0

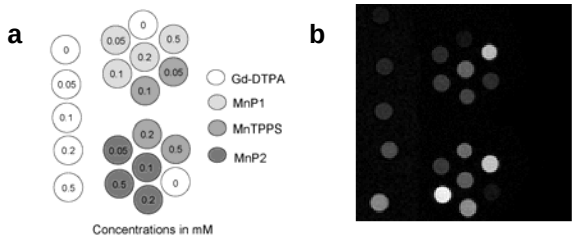

Fig 1. a) Schematic and b) T1-weighted TSE image of phantoms.

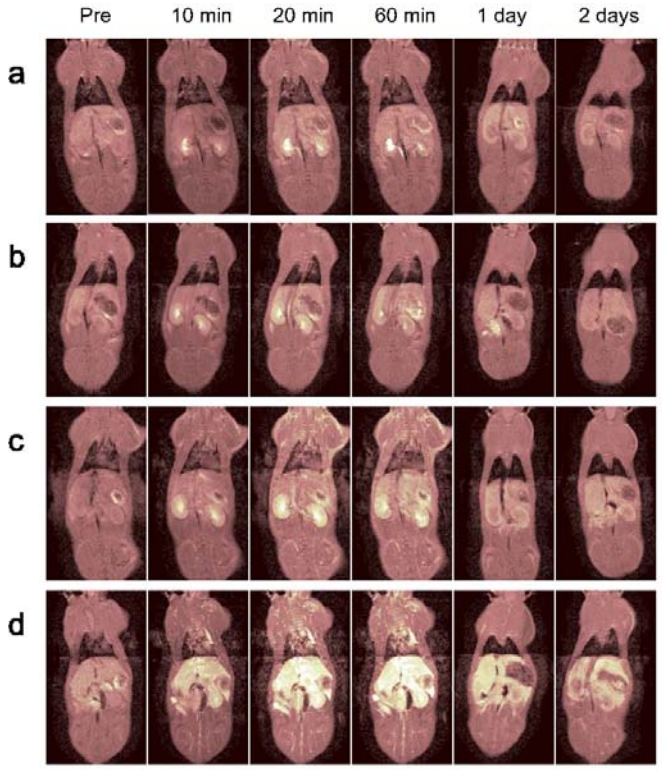

Fig 2. T1-weighted SE images in rats at different time-points post-injection: a) Gd-DTPA, b) MnP1, c) MnTPPS, d) MnP2.