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Development and Evaluation of Potential MRI Contrast Agents

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Complexes of paramagnetic transition and lanthanide ions have received much attention as potential contrast agents. Generally Gd(III), Mn(II), and Fe(III) ions have the highest relaxivity by virtue of the large magnetic moments and long T_{1e}s. In particular the Gd chelates, like Gd-DTPA and Gd-DOTA, have been used clinically to enhance the image contrast between normal and diseased tissue or to indicate the status of organ function or blood flow. The relaxivity, specific in vivo distribution, thermodynamic and kinetic stability as well as lack of toxicity are most demanding properties for a contrast agent. In this presentation, our work on this direction is reported.

Gd-DTPA derivatives. GdDTPA is the most common used contrast agent. But the high-osmolality charged, unspecific extracellular fluid distribution and rapid renal excretion limited its use. Some kind amide modification of the ligand may result Gd complex of low-somolality as well as liver specificity. Four neutral gadolinium complex of DTPA bisamide derivatives, Gd(DTPA-BDMA), Gd(DTPA-BDEA), Gd(DTPA-BIN) and Gd(cyclic -DTPA-1, 2-pn) were synthesized and characterized. In vitro and in vivo evaluation showed that three bisamide derivatives are of favorable liver-specific except Gd(DTPA-BDEA), in which Gd(cyclic-DTPA-1, 2-pn) demonstrates more powerful hepatic specificity, while Gd (DTPA-BIN) provides the stable contrast for several hours. Binding Gd-DTPA to biological macromolecules may result a conjugate of high relaxivity and certain organ specificity. Conjugates of Gd-DTPA and three natural polysaccharides, AGPS-Gd-DTPA, PQPS-Gd-DTPA, and GAPS-Gd-DTPA, were synthesized and characterized. The higher relaxivities of 7.6-9.2 $mM^{-1}\cdot s^{-1}$ in D_2O were observed. MR imaging in rats showed remarkable signal enhancement in liver and kidney, which is 2-3 times that of Gd-DTPA, and the strong enhancement in liver parenchyma persisted much longer time, which is 2-3 times that of Gd-DTPA.

Gadolinium polyoxometalates (Gd-POM). Transition metal heteropoly complexes were regarded as purely inorganic analogs of porphyrins, which are the promising tissue specific contrast agent. Four Gd-POM, $K_9GdW_{10}W_{36}(GdW_{10})$, $K_{11}[Gd(PW_{11}O_{39})_2]$ $(Gd(PW_{11})_2)$, $K_{15}[(GdO)_3PW_9O_{34}]_2$ $(Gd_3(PW_9)_2))$ and $Gd_2(P_2W_{18}O_{62})$ $(Gd_2P_2W_{18})$ were evaluated by in vitro and in vivo test. GdW_{10}, $Gd(PW_{11})_2$ and $Gd_3(PW_9)_2$ manifested very close enhancement in liver and kidney, on the contrary Gd-DTPA mainly enhances intensity in kidney, the enhancement is four time that in liver. $Gd_2P_2W_{12}$ is of the largest relaxivity of 28.4 $mM^{-1}\cdot s^{-1}$

in D_2O but low utilization factor in body limited its use as contrast agent.

Endohedral gadolinium fullerenols. Endohedral metallofullerens have unique molecular structure and great potential applications. The Gd fullerenols were synthesized by reaction of gadolinium fullerenes with potassium directly and characterized by using various spectrometric methods. Four this kind of novel agent, the carbon polyhedron not only keep the toxic Gd ion in the cage, but also enlarge the surface of the central metallic ion, while the polyhydroxyls can deliver the paramagnetic effects of the central gadolinium ion to the bulk water via the fast proton chemical exchange. In this way, the conflict between the relaxation efficiency and the toxicity is solved. Its excellent relaxivity of 47.0 ± 1.0 $mM^{-1} \cdot s^{-1}$ (an order of magnitude higher than that of Gd-DTPA) will make them to be the efficient and potential contrast agent for MRI.

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