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New Mn(II)-based MRI contrast agents

Background

MRI contrast reagents contain paramagnetic metals that respond to magnetic fields and modify the appearance of the image in the region where they have collected. The most common paramagnetic metal used in MRI is gadolinium. However, it has been discovered recently, that the use of Gd(III) ion based complexes has a possible toxic side effect in the living system and the gadolinium-containing contrast agent has become a suspected causal factor for Nephrogenic Systemic Fibrosis (NFS). Furthermore, the appearance and the growing concentration of Gd(III) substances derived from the sewage of medical institutes in surface and ground water is also a remarkable environmental problem (positive gadolinium anomaly).

Among the possible Gd(III) ion substitutes, clearly the Mn(II) cation has the greatest potential as an essential metal ion, which is better tolerated in the living systems, and biological organisms have efficient route to control its homeostasis. Mangafodipir was the only Mn(II) based contrast agent ever on the market, however it was withdrawn from both the US and the European market. Mangafodipir (sold under the brand name Teslascan) contained Mn(II)-ion as paramagnetic center, instead of Gd(III).

Technology

Researchers at the University of Debrecen have addressed the crucial need for new, Gd(III) contrast agent substitutes by designing new macrocyclic ligands for Mn^{2+} complexation. These ligands bind Mn^{2+} to form thermodynamically stable complexes as $[Mn(DOTA)]^{2-}$. Moreover, owing to the bound water molecule in these complexes their relaxivities were found to be similar or higher than the corresponding values of the most widely used Gd^{3+}-based CA's (r_{1p}=3.83 $mM^{-1}s^{-1}$ for the $[Gd(DOTA)]^{-}$ and r_{1p}=4.02 $mM^{-1}s^{-1}$ for the $[Gd(DTPA)]^{2-}$ vs. 3.20-5.67 $mM^{-1}s^{-1}$ at 25 and 2.70-4.37 $mM^{-1}s^{-1}$ 37 °C in the absence and the presence of 0.7 M HSA, 4.60-18.34 $mM^{-1}s^{-1}$ at 25 and 3.89-14.07 $mM^{-1}s^{-1}$ 37 °C, respectively at 20 MHz).

Competitive advantages

- High thermodynamic stability and kinetic inertness
- High relaxivity
- Can be applied safely in vivo
- Similar contrast enhancement to those obtained by using Gd^{3+}-based CAs
- The half-lives of dissociation are as long as 2.15×10^2 to 1.37×10^5 h
- Low production cost ($MnCl_2$ is nearly 50-times cheaper than $GdCl_3$)
- Environmental friendly

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Stage of development

- A number of new ligands have been synthesized, structurally verified and physicochemical properties including the relaxation parameters of their Mn(II) complexes have been experimentally validated.
- The basic ligand structures are being converted now to smart platforms that will allow us to follow important biological ions (cations like Zn(II)) and conditions (pH, hypoxia, etc.) by using safe Mn(II)-based CA's.
- Further development is focusing on the preclinical toxicity screening of three lead molecules as well as their testing in head and abdominal MRI scans in mice models. *In vivo* results are expected by the end of 2019.

IP status

- European patents are pending for three patent families.
- One US patent is pending
- Two US patents are granted.