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Review

Zn^{2+} detection by MRI using Ln^{3+}-based complexes: The central role of coordination chemistry

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ABSTRACT

This review deals with the rational design of Gd^{3+}-based complexes for Zn^{2+} detection. It describes the different possible mechanisms underlying Zn^{2+} detection with such responsive probes. Those probes are composed of three parts: the Gd^{3+} complex, the Zn^{2+} binding unit, and a linker. The role and the importance of each part will be described separately through various examples, and it will be shown how it affects the stability, affinity, and efficacy of the probes. Finally, it will be demonstrated how, knowing the mechanism of action of the complex for Zn^{2+} detection, such probes can be optimized. The aim is to try to establish relationships between the structure and the efficacy of the agents to design rationally more efficient contrast agents in the future.

Contents

Abbreviations: AMPA, 2-(aminomethyl)pyridine-*N*-acetate; BPEN, *N,N*-bis-(2-pyridyl-methyl)ethylene diamine; BPYREN, *N,N*-bis-(3-pyrazolyl-methyl)ethylene diamine; CEST, Chemical Exchange Saturation Transfer; DNA, Desoxyribonucleic acid; DPA, *N,N′*-bis-(2-pyridyl-methyl)amine; DO3A, 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; DOTAM, 1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane; DOTAM-Gly, *N,N′,N″,N‴*-[1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayltetrakis(1-oxo-2,1-ethanediyl)]tetrakis[glycine]; DTPA, 1,1,4,7,7-pentakis-(carboxymethyl)-1,4,7-triazaheptane; DTPA-BMA, 5,8-bis(carboxymethyl)-11-(2-(methylamino)-2-oxoethyl)-3-oxo-2,5,8,11-tetraazatridecan-13-oic acid; DTPA-NMA, 2,2′-(1-carboxy-2-(carboxymethyl)-10-oxo-2,5,8,11-tetraazadodecane-5,8-diyl)diacetic acid; HSA, Human Serum Albumin; IAPP, Islet Amyloid Polypeptide; MR, Magnetic Resonance; MRI, Magnetic Resonance Imaging; NMR, Nuclear Magnetic Resonance; NO2A, 1,4,7-triazacyclononane-1,4-diacetate; ParaCEST, Paramagnetic Chemical Exchange Saturation Transfer; SAP, Square Antiprismatic; TACN, 1,4,7-triazacyclononane; TSAP, Twisted Square Antiprismatic.

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1. Introduction

Metal ions play a fundamental role in living systems as they are involved in many essential biological processes. Their concentration is highly regulated by the cells through transporters and metallochaperones, to cite a few. Among them, zinc is the second most abundant d-block metal ion present in the body, after iron. This divalent cation is an essential micronutrient required for over 300 different cellular processes, including enzyme activity, signaling, DNA and protein synthesis. For example, it is a useful catalytic agent in enzymatic reactions involving carbonic anhydrase or carboxypeptidase. While it is not redox active under physiological conditions, zinc deficiency is known to cause increased oxidative stress contributing to human diseases such as cancer [1]. *In vivo*, zinc is present in the free and bound form. The content of zinc is particularly important in the brain, breast, prostate and pancreas [2]. Disruption of zinc homeostasis has been implicated in diabetes, cancer and neurodegenerative diseases.

It is now common knowledge that Zn^{2+} contributes to the formation of β-amyloid deposits in the brain, which are related to Alzheimer's disease [3]. Its role in type 2 diabetes is still an active area of research [4]. It has also been shown that inhibition of IAPP aggregation (implicated in type 2 diabetes) by insulin depends on the insulin oligomeric state, which is regulated by zinc concentration [5].

Zinc has also emerged as an important signaling ion and exposure to uncontrolled concentration of zinc can lead to excitotoxic neuronal death, particularly during epileptic seizures, head trauma, cerebral ischemia, reperfusion and situations of overintense neuronal activity. Very recent studies using electrochemical techniques have shown that zinc regulates chemical-transmitter storage in nanometric vesicles and exocytosis dynamics [6].

However, despite its importance, the detailed molecular mechanisms of intracellular zinc accumulation, trafficking, and function are still under debate. For example, there is still controversy about whether zinc levels are increased or decreased in prostate cancer compared to healthy prostate [7] and its role is still a current area of research [8]. Its role in pancreatic adenocarcinoma is still not entirely clear [9] even if evidence shows that the zinc levels are decreased in adenocarcinoma compared with normal pancreatic tissues [10] and more generally that decreased zinc levels are implicated in the development and progression of malignancy and that zinc could have a potential in the prevention and treatment of carcinomas [11].

It is therefore clear that imaging zinc by non-invasive techniques is of paramount importance to understand its role, and improve early-stage disease detection.

Zinc is not easily detected directly as it is not redox active, and it is diamagnetic. Nevertheless, with the recent development of molecular imaging, which aims at visualizing the expression and function of bioactive molecules representing often specific molecular signatures in disease processes, several imaging techniques have been used to detect Zn^{2+}.

2. Imaging techniques for Zn^{2+} detection

Among all the imaging techniques, nuclear imaging is characterized by an excellent sensitivity and a poor resolution. It is however not adapted to Zn^{2+} detection as it is not a responsive technique. Optical imaging is also characterized by a good sensitivity and several fluorescent zinc sensors have been developed. It is nowadays the major technique for zinc detection *in vitro* and in living systems [12]. Nevertheless this technique suffers from a lack of macroscopic resolution and is restricted to surface imaging as light does not penetrate in-depth.

MRI is a powerful non-invasive technique with an excellent spatial and temporal resolution. It is based on the observation of the proton of water molecules, and more precisely, on the relaxation properties of those water molecules, and the proton density. These parameters vary depending on the observed tissue, and its physical and chemical properties. However, MRI suffers from a lack of sensitivity, which can be compensated by the introduction of a contrast agent. It remains a method of choice for the *in vivo* whole body detection of metal ion in general. MRI contrast agents can be divided in two categories: T_1 (positive contrast) that have an effect on the longitudinal relaxation time of the surrounding water protons, and T_2 (negative contrast), that have an effect on their transversal relaxation time. T_2 agents are mainly iron oxide nanoparticles, and T_1 agents can be Mn^{2+} or Gd^{3+} complexes [13]. More recently, contrast based on chemical exchange saturation transfer (CEST) was proposed and has been exploited for Zn^{2+} detection (see Section 9). It should be mentioned that other MRI contrast agents based on heteronuclear magnetic resonance imaging have been developed for monitoring Zn^{2+}. Recently, ^{19}F probes

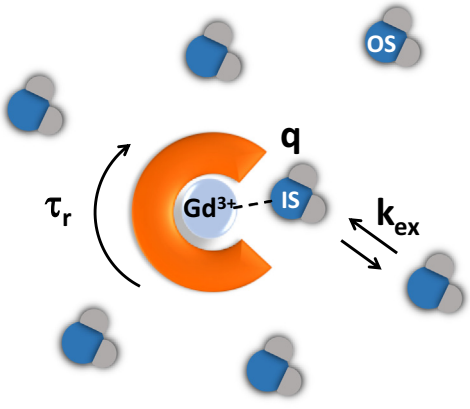

Fig. 1. Inner-sphere water molecule directly coordinated to Gd^{3+} and outer-sphere water molecules diffusing around the paramagnetic centre, illustrating the two mechanisms of relaxivity. The main microscopic parameters are indicated: the number of water molecules directly coordinated to Gd^{3+} (q), the exchange rate of this molecule with the bulk (k_{ex}), and the rotational correlation time of the complex (τ_R).