ELSEVIER

European Journal of Radiology 67 (2008) 453–458

EJR
EUROPEAN JOURNAL OF RADIOLOGY

www.elsevier.com/locate/ejrad

Chemistry of paramagnetic and diamagnetic contrast agents for Magnetic Resonance Imaging and Spectroscopy pH responsive contrast agents

Elena Pérez-Mayoral [a,b], Viviana Negri [a], Jordi Soler-Padrós [a], Sebastián Cerdán [c], Paloma Ballesteros [a,*]

[a] *Laboratorio de Síntesis Orgánica e Imagen Molecular por Resonancia Magnética, Facultad de Ciencias, UNED, Paseo Senda del Rey 9, E-28040 Madrid, Spain*
[b] *Departamento de Química Inorgánica y Química Técnica, Facultad de Ciencias, UNED, Paseo Senda del Rey 9, E-28040 Madrid, Spain*
[c] *Laboratorio de Imagen Espectroscópica por Resonancia Magnética (LIERM), Instituto de Investigaciones Biomédicas "Alberto Sols", CSIC/UAM, c/Arturo Duperier 4, E-28029 Madrid, Spain*

Received 15 February 2008; accepted 27 February 2008

Abstract

We provide a brief overview of the chemistry and most relevant properties of paramagnetic and diamagnetic contrast agents (CAs) for Magnetic Resonance Imaging and Magnetic Resonance Spectroscopic Imaging. Paramagnetic CAs for MRI consist mainly of Gd(III) complexes from linear or macrocyclic polyaminopolycarboxylates. These agents reduce, the relaxation times T_1 and T_2 of the water protons in a concentration dependent manner, increasing selectively MRI contrast in those regions in which they accumulate. In most instances they provide anatomical information on the localization of lesions and in some specific cases they may allow to estimate some physiological properties of tissues including mainly vascular performance. Because of its ability to discriminate easily between normal and diseased tissue, extracellular pH (pH_e) has been added recently, to the battery of variables amenable to MRI investigation. A variety of Gd(III) containing macrocycles sensitive to pH, endogenous or exogenous polypeptides or even liposomes have been investigated for this purpose, using the pH dependence of their relaxivity or magnetization transfer rate constant (chemical exchange saturation transfer, CEST). Many environmental circumstances in addition to pH affect, however, relaxivity or magnetization transfer rate constants of these agents, making the results of pH measurements by MRI difficult to interpret. To overcome these limitations, our laboratory synthesized and developed a novel series of diamagnetic CAs for Magnetic Resonance Spectroscopic Imaging, a new family of monomeric and dimeric imidazolic derivatives able to provide unambiguous measurements of pH_e, independent of water relaxivity, diffusion or exchange.

Keywords: Magnetic Resonance Imaging; Magnetic Resonance Spectroscopy; Contrast agents; Paramagnetic chelates; Extracellular pH; pH probes

1. Introduction

Despite the fact that MR images were initially thought to provide enough endogenous contrast, the utilization of exogenous MRI contrast agents (CAs) has increased steadily to reach approximately 40–50% of the examinations currently performed. Reasons for this include the spectacular gain in resolution between normal and diseased tissues, their moderate cost and their adequate safety profile. This review will cover shortly the chemistry and properties of the paramagnetic CAs normally used in clinical practice emphasizing the more recent development of "responsive CAs" useful to visualize the properties of the extracellular environment with special reference to extracellular pH (pH_e). In addition we address in more detail the emerging field of diamagnetic CAs for Magnetic Resonance Spectroscopic Imaging, analyzing the progress achieved since the first generation of diamagnetic CAs for spectroscopic imaging of pH_e was proposed by some of us.

2. Paramagnetic contrast agents for MRI

MRI CAs are pharmaceuticals reducing the longitudinal (T_1) and transversal (T_2) relaxation times of water in those tissue regions in which they accumulate [1,2]. The reduction in water

* Corresponding author. Tel.: +34 913987320; fax: +34 913986697.
E-mail address: pballesteros@ccia.uned.es (P. Ballesteros).

0720-048X/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ejrad.2008.02.048

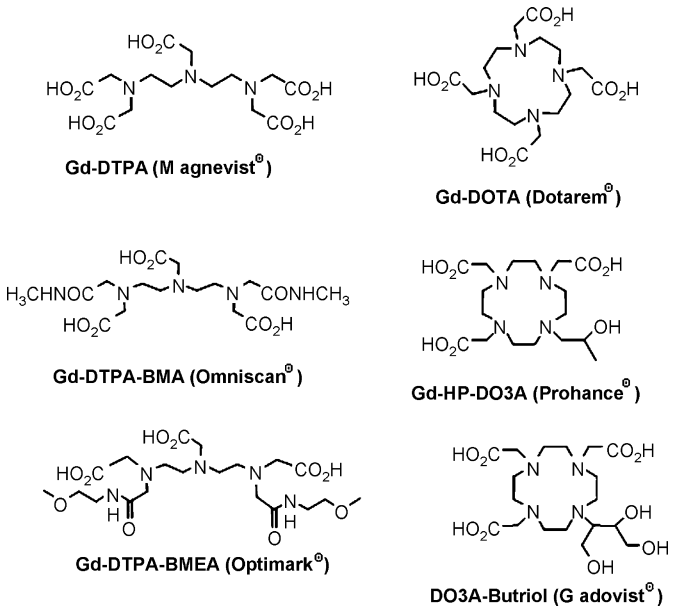

Fig. 1. Structures of Gd(III)-complexes commercially available and used in clinical practice.

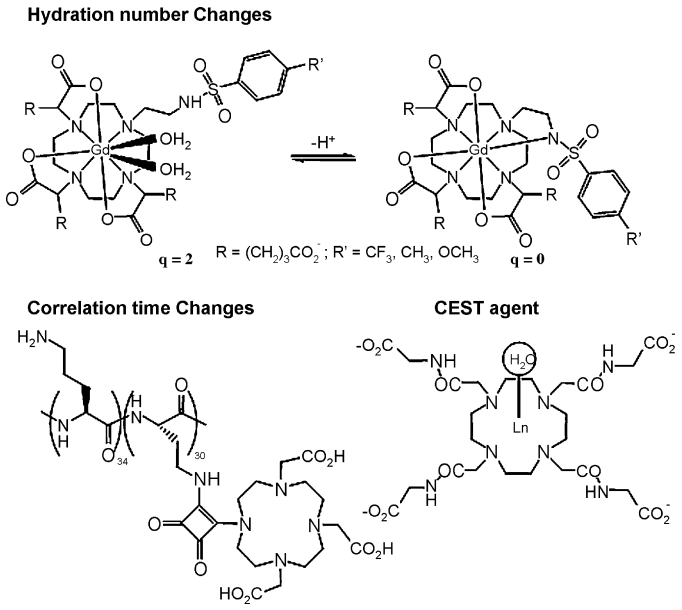

Fig. 2. Strategies to increase relaxivity and specificity in macrocyclic ligands. Increases in the hydration number q and restrictions in mobility such as those imposed through binding to macromolecules will increase relaxivity. pH specificity may be introduced by introducing appropriate CEST groups.

relaxation times is normally linear with concentration the slope being known as relaxivity, a magnitude that reveals the net increase the longitudinal ($1/T_1, r_1$) or transversal ($1/T_2, r_2$) relaxation rates of water, produced by 1 mM solution of the CA. The systemic administration of CAs may induce positive or negative contrast enhancement in T_1 or T_2 weighted images, delineating more clearly the pathological regions and reducing concomitantly the scanning time. These inherent advantages prompted the synthesis and characterization of novel generations of improved CAs, with more efficient relaxivity and sensitivity properties [3,4].

The majority MRI CAs are chelates of paramagnetic metals of the rare earth series, Gd(III) complexes being the most widely investigated [1]. Gd(III) is commonly used since it contains seven unpaired electrons with a relatively long electronic relaxation time, a circumstance resulting in the largest and longest lasting paramagnetic relaxation effect in water. However, free Gd(III) is a toxic in vitro an in vivo, and the use of Gd(III) chelates is mandatory to reduce its toxicity. The first generation of Gd(III) chelates was derived from linear or macrocyclic polyaminopolycarboxylates, such as diethylenetriaminepentaacetic acid ($[DTPA(Gd)(H_2O)]^{2-}$) and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid ($[DOTA(Gd)(H_2O)]^{-}$). Since then many reviews have addressed the chemistry and properties of these agents [3–9]. Fig. 1 summarizes the ligands most commonly used (Fig. 1).

Soon after the proposal of the initial complexes, researchers strived to increase their relaxivity in order to enhance their sensitivity and reduce the dose required [3–8]. Important increases in relaxivity were favoured by a deeper understanding of the theory of paramagnetic relaxation as proposed by Solomon, Bloembergen and Morgan (see Ref. [1] for a detailed description). In general, theory indicated that to increase relaxivity it became necessary to increase the number of water molecules in the first coordination sphere of the metal ion (q, hydration number), to decrease its rotational correlation time (τ_c), to favor faster water exchange (k_{ex}) on the complex, or a combination of these circumstances [4,6]. To comply with these requirements, several chemical manipulations of the original polyaminopolycarboxylate or macrocyclic structures were pursued. These improved by almost an order of magnitude the original relaxivities of 3–4 $mM^{-1}\,s^{-1}$ found in the initial Gd(III)DTPA or Gd(III)DOTA complexes, to the 30–40 $mM^{-1}\,s^{-1}$ determined in some CAs of the second generation. In particular, the rotational correlation time (τ_c) (a magnitude reflecting the molecular tumbling rate), was increased by coupling the complexes to slower tumbling macromolecules, a modification that increased significantly the relaxivity values [4,9,10]. In this sense, high molecular weight dendrimers of Gd(III)DTPA or Gd(III)DOTA or multiple adducts of these complexes with Bovine Seroalbumin (BSA) were synthesized. Our laboratory, an others, explored the additional possibility to increase relaxivity of the complex by

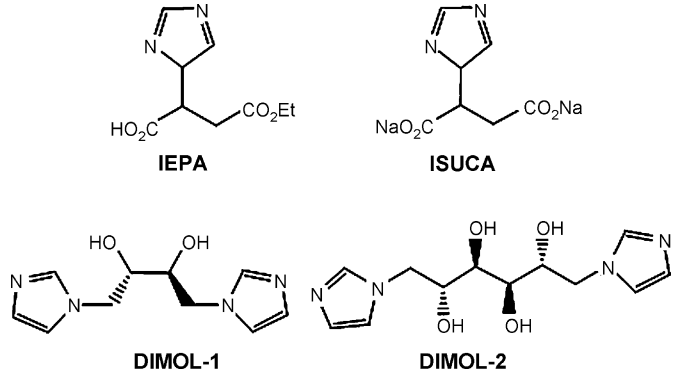

Fig. 3. pH sensitive indicators for ^1H MRSI. Monomeric IEPA and ISUCA (top). Dimeric DIMOL-1 and DIMOL-2.