Gadolinium contrast agents in magnetic resonance imaging (MRI)

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Abstract Magnetic Resonance Imaging (MRI) is one of the most powerful clinical diagnostic tools. Based on chemical principles discovered in the 1940s, MRI uses magnetic fields to excite bulk water protons throughout the body, creating an image from their responses. Although useful for the diagnosis of a variety of diseases and conditions, a lack of image clarity can result in incorrect or missed diagnoses. Due to the inherent challenges with MRI, gadolinium-based contrast agents (GBCAs) are used to modulate the response of the bulk water protons to the external magnetic fields, subsequently increasing the image contrast. Here, we discuss GBCAs and their role in overcoming the challenges with magnetic resonance (MR) image clarity.

INTRODUCTION

Magnetic Resonance Imaging (MRI) is one of the most vital technologies for diagnostic medical procedures, as well as disease detection and monitoring progression. Although there are limitations with cost, instrument size, and acquisition time, MRI remains one of the most effective non-invasive diagnostic methods. However, the clarity of magnetic resonance (MR) images may be impaired due to the lack of contrast between tissues, which can result in missed diagnoses (Leung, 2012). Image contrast is particularly important for the detection of certain cancers, notably breast cancer, in which tumors can be completely invisible to imaging (Wallace et al., 2005). This can be overcome through the use of paramagnetic gadolinium(III)-based contrast agents (GBCAs) to improve image clarity, diagnosis effectiveness, and patient care (Lin & Brown, 2007; Wahsner et al., 2019; Xiao et al., 2016). Approximately 40% of all MRI scans and 60% of central nervous system (CNS) MRI scans are administered with GBCAs, amounting to nearly 40 million total GBCA administrations worldwide annually (Runge, 2017). Two major limitations with GBCAs are their inherent toxicity and their potential to remain in the patient after the scan. From a clinician's perspective, understanding the function and limitations of these drugs is crucial for their proper use in hospital settings (Wahsner et al., 2019).

This review will begin by outlining the mechanisms of MRI and compare contrasted vs non-contrasted MR images. Then, an analysis of ligand design and the mechanisms of action of GBCAs will show how they increase the brightness of the images. Finally, this review will conclude with a discussion of the limitations of GBCAs and directions for future research.

FUNCTIONS OF MAGNETIC RESONANCE IMAGING

Since the experimental description of nuclear magnetic resonance (NMR) in 1946 by Bloch and Purcell, a Nobel Prize-winning discovery, the field of radiology has seen widespread advancement (Bloch, 1946; Leung, 2012). The first clinical use of magnetic resonance for diagnostic imaging was in the early 1980s and has since been used in nearly all fields of medicine (Hawkes et al., 1980; Smith et al., 1981).

Drawing from NMR technology, MRI makes use of the unique characteristics of hydrogen atoms to create images of internal tissues. Since humans are composed of approximately 70% water, there are many hydrogen atoms (each containing both a proton and an electron)

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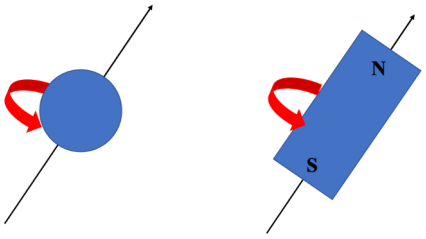

Figure 1 Water proton spin and bar magnet representation. Notice that the left spherical representation is a mathematical approximation of spin. Though this approximation allows for theoretical conclusions, other factors, such as angular momentum, are at play. More accurately, a proton can be visualized as a bar magnet with north and south poles. Although a water proton will not be labelled as such, we can imagine that the spin creates a magnetic moment which has polarity. This polarity is what causes the specific alignment of these protons when an external magnetic field is applied, releasing energy upon relaxation. This released energy can be detected and visualized as magnetic resonance images.

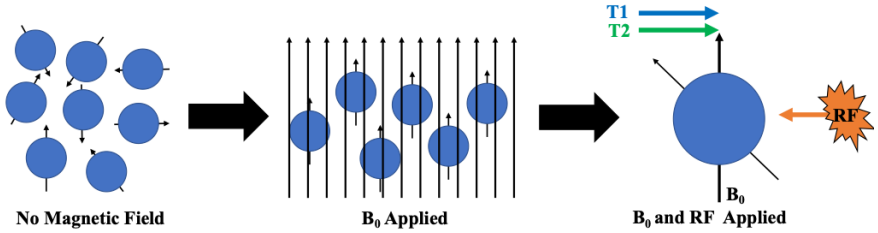

Figure 2 Bulk water protons aligning with the B_0 and RF magnetic fields. When no magnetic field is applied (e.g., normal human body), the hydrogen spins are all in different directions. After the initial B_0 magnetic field is applied, some of the hydrogen nuclei spins will line up with the direction of the applied magnetic field (about 4/1,000,000). During the pulsating RF magnetic field, the hydrogen nuclei's spin gets bumped off the B_0 axis (like tipping a spinning top), and subsequently returns via either T1 or T2 relaxation pathway.

present throughout nearly all tissues (Berger, 2002). The hydrogen protons have spin, which can be imagined as a vector with polarity, and will align itself parallel or anti-parallel to the magnetic field (Figure 1). Although there are no positive or negative ends of this imaginary vector, this intrinsic proton spin results in a magnetic moment, which causes a specific alignment of the bulk water protons when applied with a magnetic field (Huk & Gademann, 1984; Grover et al., 2015). MR images are created through slight polarization of proton spins by an external magnetic field, resulting in signals that can be picked up by the detection device (Lauterbur, 1973).

During an MRI scan, the patient is placed in a superconducting magnet which applies a strong magnetic field throughout the body part being analyzed. This applied magnetic field, B_0, orients some of the hydrogen atoms in the direction parallel to it, which places them in a low energy state (Figure 2) (Grover et al., 2015; Leung, 2012). Within the static magnetic field of B_0, the nuclei can be further excited upon the presence of pulsing radiofrequency (RF) waves, causing a secondary magnetic field. The RF is applied in bursts, and the absorption of this energy will bump the central axis of the hydrogen atom out of alignment with B_0, like tipping over a spinning top (Figure 2) (Huk & Gademann, 1984). Only a few protons line up in a low energy state with the magnetic field (approximately four per million in a high energy state). This means that the energy released by the water protons is not particularly strong however, an image can still be visualized due to the sensitivity of MRI detectors (Wahsner et al., 2019).

Once this occurs, there are two mechanisms through which the hydrogen atom can return to the lower energy state, through a T1 or T2 relaxation (Figure 2). T1 relaxation is the energy exchange between the proton and the surrounding water molecules during the return to thermal equilibrium, whereas T2 (or spin-spin) relaxation time refers to the interactions within the water molecules themselves (discussed further below). This relaxation time is the time that it takes for the central axis to re-align itself with B_0 (Grover et al., 2015; Lin & Brown, 2007). Depending on the type of scan that is conducted, either a T1 or T2 relaxation will be prioritized by the MRI (Wahsner et al., 2019). Although the endogenous relaxation times (without the addition of GBCAs) of bulk water protons will be sufficient for many diagnoses, there are limitations with contrast when MRI is used for CNS, gastrointestinal, and cancer diagnoses (Leung, 2012). This lack of contrast is due to the relative similarity of the water proton concentration between the tissue of interest and bordering tissues, making it difficult for the MRI machine to distinguish minor differences in signals (Burtea et al., 2008).

Over the first eight years of clinical use, the limitations of MRI with were realized. Beginning in 1988, bioinorganic drugs that could augment the contrast of the MR images became increasingly popular (Lohrke et al., 2016). These drugs are highly paramagnetic and can affect the relaxation times of protons, which affect the signal intensity picked up by the MRI detector (Wood & Hardy, 1993). These drugs have increased the effectiveness of MRI through improving image contrast, brightness, and clarity (Lohrke et al., 2016).

USE OF CONTRAST AGENTS IN MRI

Currently, paramagnetic drugs used in MRI are almost exclusively gadolinium(III) based chelates due to their ability to impact relaxation time of bulk water protons (Caravan et al., 1999). There are eight GBCAs that have been used in clinical settings, and 7 of these GBCAs are approved for imaging of the CNS (Kanal et al., 2014). Other contrast agents have also been investigated, including manganese(II)- and iron(III)-based drugs (Wahsner et al., 2019). These alternative contrast agents are less effective than gadolinium(III) based drugs, but they are less toxic (see Limitations) (Morcos, 2008).

GBCAs provide a non-invasive method to visualize deep anatomical structures. For example, analyzing vascular permeability to detect cancer, aneurysms, and blockages would otherwise require deep surgical intervention without GBCAs (Smith et al., 1981; Wahsner et al., 2019). In addition, GBCAs have an immediate effect on MRI clarity and do not release ionizing radiation, making them safe and clinically practical (Hermann et al., 2008). Lastly, GBCAs are effective due to their ability to shorten the speed of T1 relaxation pathways in bulk water protons (Weinmann et al., 1984). Shorter T1 relaxation times have a direct correlation to increases in image contrast (Wahsner et al., 2019).

Before discussing how GBCAs affect T1 relaxation, we must first address the chemical characteristics of gadolinium.

CHEMICAL CHARACTERISTICS OF GADOLINIUM

The structural and magnetic qualities of gadolinium allow it to fulfill its function of increasing MRI clarity and contrast. Although the following characteristics are interrelated, they both contribute specific effects to the bulk water protons.

Coordination Geometry

Gadolinium(III) is stable with a coordination number (CN) of 9, in part due to its small size compared to other lanthanide metals. This high CN allows for the attachment of highly chelating (polydentate) ligands, meaning there are numerous points of attachment to the central metal atom, while still leaving one attachment point for the water proton (Caravan et al., 1999; Wahsner et al., 2019). This is important because more attachment points between the metal and the ligand will increase the stability of the whole complex. Since gadolinium is a toxic heavy metal, this high affinity between the gadolinium atom and the attached ligands is crucial to avoid the dissociation of the ligands in vivo (Bellin & Van Der Molen, 2008). All the GBCAs that are approved by the US Food and Drug Association (FDA) have an octadentate polyaminopolycarboxylato-based ligand which is highly chelating and makes the overall molecule stable (Wahsner et al., 2019) (Figure 3).

Paramagnetic Qualities and Relaxation Time

In addition to gadolinium's ability to maintain a high CN, gadolinium is a paramagnetic f-block lanthanide metal. The gadolinium atom has 7 unpaired electrons, which allow the atom to interact strongly with an external magnetic field (Caravan et al., 1999; Wahsner et al., 2019). Gadolinium's high CN and its paramagnetic properties synergistically allow gadolinium-based drugs to influence the T1 and T2 relaxation times of water (Lin & Brown, 2007). After the RF pulse is administered, the central axis of the water proton is bumped out of alignment with B_0. As mentioned above, the T1 relaxation is the energy exchange between the water proton and the surrounding water molecules while it relaxes back to an equilibrium state. In pure water, the T1 relaxation is slow due to a high degree of water saturation; in human tissues, the T1 relaxation of water protons is faster due to water's interactions with macrocyclic biochemical molecules and endogenous paramagnetic compounds (Rooney et al., 2007;

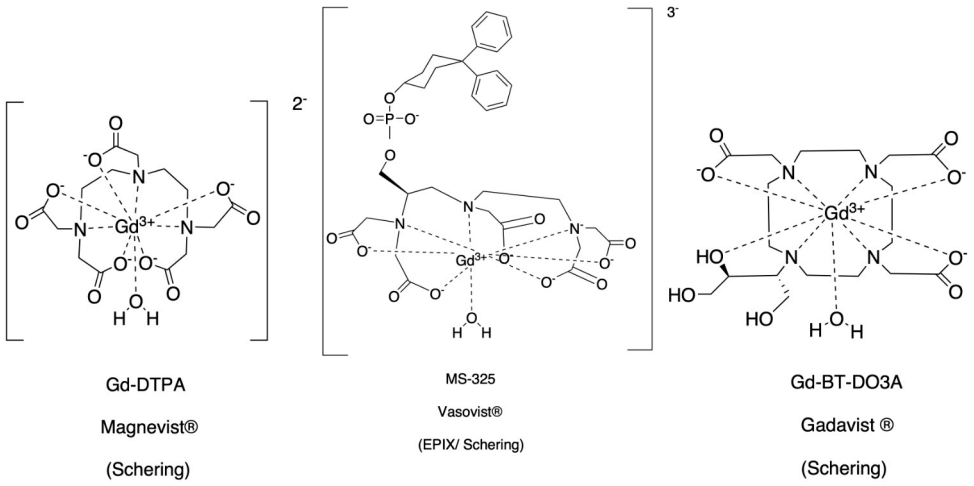

Figure 3 Three gadolinium(III)-based contrast agents, including their chemical codes, tradenames, and manufacturers. These examples depict the two ligand structures, linear and macrocyclic. Both Gd-DTPA and MS-325 have linear ligands, whereas Gd-BT-DO3A is macrocyclic. Further, MS-325 contains an extra biphenylcyclohexane group to interact with human serum albumin for cardiovascular-related MRI scans. Adapted from PubChem Compound Summary (National Centre for Biotechnology Information, 2020a, 2020b, 2020c).

Table 1 Clinically used Gadolinium(III)-Based Contrast Agents

Tradename	Chemical name and code	Ligand Structure	T1 Impacts (r_1/$mM^{-1}s^{-1}$)	Clearance/ Lifetime	Stability (logK)	Dosage
Dotarem®, Clariscan®	Gadoterate meglumine (Gd-DOTA)	Macrocyclic	4.2	Renal	25.3	0.1mmol kg^{-1}
ProHance®	Gadoteridol (Gd-HPDO3A)	Macrocyclic	4.4	Renal, 1.57h	23.8	0.1mmol kg^{-1}
Gadovist® (EU)/ Gadavist® (US)	Gadobutrol (Gd-DO3A-butrol)	Macrocyclic	5.3	Renal	20.8	0.1mmol kg^{-1}
Magnevist®	Gadopentetate dimeglumine (Gd-DTPA)	Linear	4.3	Renal, 1.60h	22.2	0.1-0.3mmol kg^{-1}
Omniscan®	Gadodiamide (Gd-DTPA-BMA)	Linear	4.6	Renal, 1.30h	16.8	0.1-0.2mmol kg^{-1}
Optimark®	Gadoversetamide (Gd-DTPA-BMEA)	Linear	5.2	Renal, 1.73h	16.8	0.1mmol kg^{-1}
Multihance®	Gadobenate dimeglumine (Gd-BOPTA)	Linear	6.7	Renal, Hepatic, 1.2-2h	18.4	0.05-0.1mmol kg^{-1}

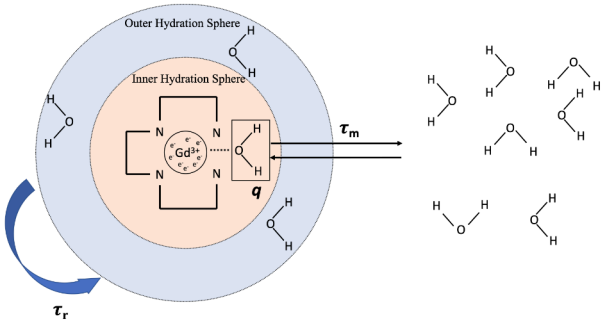

Figure 4 Mechanism of action of GBCAs. After injection into the patient, the GBCA affects bulk water protons throughout the body. There are effects on protons directly interacting with the gadolinium(III) centre (in the inner hydration sphere), as well as some secondary stabilization on protons in the outer hydration sphere. q refers to the number of protons interacting with the metal centre. τm refers to the time for water exchange. τr refers to the molecular rotation of GBCAs. τr has the greatest impact on the T1 relaxation times because molecular rotation creates a magnetic field that interacts with protons in the inner and outer spheres.

Wahsner et al., 2019). T2 (or spin-spin) relaxation time refers to the energetic interactions in the water molecules. T2 relaxation is faster than T1 relaxation and is governed by the different spins in the water molecule becoming out of phase after interacting with the RF magnetic field (de Graaf et al., 2006; Stanisz et al., 2005; Stevenson et al., 2000). MRI scans can be tuned such that they prioritize either T1 or T2 relaxation of the protons (Wahsner et al., 2019). In T1-weighted scans, tissue types with shorter T1 times result in brighter regions in the image, whereas in T2-weighted scans, tissue types with longer T2 times result in brighter regions. Thus, GBCAs are primarily used in T1 scans as they increase the contrast in T1 scans and decrease the contrast in T2 scans (Mitchell, 1996; Wood & Hardy, 1993). The paramagnetic qualities of GBCAs create local magnetic fields that increase the efficiency of T1 relaxation upon coordination with the bulk water protons, which will be discussed below.

GADOLINIUM CONTRAST AGENTS AND MECHANISMS OF ACTION

Since all clinically approved GBCAs interact with bulk water protons similarly, the following three examples were selected to depict the main ligand classifications (linear and macrocyclic) and the effects of attaching specific ligand groups (Figure 3).

These agents outline some of the key ligand design concepts of GBCAs. Gd-DTPA (Magnevist®; Schering) was the first GBCA and was developed in 1988 (Lohrke et al., 2016). This molecule has a linear pentetic acid (DTPA) ligand, which increases the kinetic activity of the drug (Wahsner et a., 2019). This drug is stable and has remained a staple in MRI clinics worldwide. MS-325 (Vasovist®; EPIX/ Schering) has a similar linear chelate to Gd-DTPA however, it also contains a biphenylcyclohexane group bound through a phosphodiester bond to the ligand base. Although prohibited for use in CNS scans (as it cannot pass the blood brain barrier), the biphenyl group in MS-325 can interact with human serum albumin protein in the blood (Hermann et al., 2008; Leung, 2012; Wahsner et al., 2019). Due to this interaction, MS-325 is used for MR angiography of the aorto-iliac vessels (Lauffer et al., 1998). Lastly, Gd-BT-DO3A (Gadavist®; Schering) makes use of a macrocyclic ligand to increase the stability of the metal-ligand complex (Morcos, 2008). Due to this stability, it is an ideal GBCA candidate and is frequently used in clinical settings (Hermann et al., 2008). Table 1 shows 8 GBCAs approved by the FDA, as well as their structures, their T1 impacts (ability to increase T1 relaxation time), their lifetime in the body, their measurements of stability, as well as their dosage (Gadavist and Gadovist are considered two drugs, but have the same structure) (Hermann et al., 2008). One notable aspect of all the GBCA candidates is their high dosages, due to their lack of tissue specificity in the body (Leung, 2012). As such, the thermodynamic stability of these drugs is crucial for safe clinical use due to the widespread toxicity resulting from the dissociation of the ligand from the metal centre (Hermann et al., 2008).

MECHANISM OF ACTION OF GADOLINIUM CONTRAST AGENTS

Once administered to the patient (either intravenously, orally, or by inhalation), the GBCA travels (non-specifically) towards the site of inflammation (Wahsner et al., 2019). The Brownian motion of the drug creates a changing magnetic field that alters the T1 relaxation time of the nearby protons (Hermann et al., 2008; Bellin & Van Der Molen, 2008; Caravan et al., 1999). There are 4 main metrics through which the efficiency of GBCA-mediated T1 relaxation is measured: (1) the number of water molecules bound to the complex (q); (2) the mean resistance time (τm); (3) the number and residence time of the water molecules in the second (outer) sphere; and (4) the rotational correlation time (τr) of the GBCA (Dumas et al., 2010). As depicted in Figure 3, GBCAs form complexes with one water molecule at a time (q = 1). Although possible to have cases where q = 2, this is uncommon due to the destabilization of the rest of the molecule (Lauffer, 1987; Lohrke et al., 2016).

Resistance time (τm) is the time of water exchange with the metal centre and is affected by the number and residency time of water molecules in the outer hydration sphere (Figure 4) (Wahsner et al., 2019). Increases in peripheral proton number (i.e. the number of protons around the GBCA) and residency time will facilitate the formation of a bond between the proton and the gadolinium(III) centre, causing faster T1 relaxation (Lohrke et al., 2016). This strength of the bond between the gadolinium centre and the proton needs to be deliberately tuned such that it allows the exchange process to occur (Grover et al., 2015).

The most important metric of T1 relaxation is the rotational correlation time (τr), or molecular tumbling, of the GBCA (Figure 4). Although variable, molecular tumbling induces proton relaxation through creating a fluctuating magnetic field (Caravan, 2006; Barrett et al., 2006; Jacques et al., 2010; Lauffer, 1987). To make this an effective process, the complex needs to create a fast and transient dative bond with water molecules (Figure 4) (Barrett et al., 2006; Lauffer, 1987). This bond occurs quickly, in the order of nanoseconds, such that the T1 relaxation of multiple water protons can be increased during the administration of these drugs (Wahsner et al., 2019).

LIMITATIONS OF GADOLINIUM-BASED CONTRAST AGENTS

Though GBCAs can affect T1 relaxation and hence MR image contrast, there are limitations to these drugs. During the first 20

years of GBCA usage in clinical settings, GBCAs showed minimal side effects and thus were considered to be some of the safest drugs (Lohrke et al., 2016). In 2006, GBCAs were linked to fatal nephrogenic systemic fibrosis (NSF) in patients with kidney failure (Grobner, 2006; Morcos, 2007; Wahsner et al., 2019). Since GBCAs lack tissue specificity, they travel the entirety of the bloodstream upon injection. Due to this, a high dosage (e.g., 0.1 mmol/kg) is required to achieve optimal imaging, resulting in the possibility of gadolinium(III) disassociation with its chelates and thus toxicity effects (Hermann et al., 2008). Although the disassociation is unlikely due to the high stability of the CN = 9 complexes, patients with kidney failure may not be able to excrete the drugs, rendering them susceptible to NSF (Marckmann et al., 2006). NSF symptoms in kidney failure patients arose 2-4 weeks after GBCA administration, indicative of a lack of excretion (Morcos, 2008).

In addition to the challenges with clearing these drugs from the body, there is inherent toxicity with injecting high dosages of heavy metals (Hermann et al., 2008). With GBCAs, there has been evidence of damage to the spleen and liver, inhibition of enzymes, and the blocking of calcium channels (Morcos, 2008). GBCAs may also accumulate in the brain, causing continued T1 shortening in deep gray matter (Tedeschi et al., 2018). Although no CNS health effects have been documented for gadolinium, more research needs to be done to analyze the effects of intercranial accumulation (Wahsner et al., 2019). Increasing tissue specificity of GBCAs will minimize dosage to reduce adverse side effects of the contrast agent. Alternatively, contrast agents that are more effective at increasing T1 relaxation times have shown promise in the development of lower dosage drugs (e.g., targeted agents, such as EP-2104R, that increase contrast in specific tissues of interest) (Caravan et al., 2007; Jacques et al., 2010; Spuentrup et al., 2007; Vymazal et al., 2009; Wahsner et al., 2019).

CONCLUDING REMARKS AND FUTURE DIRECTIONS

Gadolinium(III)-based contrast agents have demonstrated a productive application of inorganic chemistry to the field of medicine. Their ability to increase the T1 relaxation times of bulk water protons creates a greater image contrast, resulting in clearer images and better diagnoses. This has implications for certain diseases that would otherwise require highly invasive intervention, such as cancer (Gore et al., 2011). Nonetheless, GBCAs have significant limitations with toxicity and dosage, causing researchers to work towards finding other contrast agents. As mentioned previously, manganese(II), and iron(III) have been shown to effectively increase the T1 relaxation rate for bulk water protons (Lauffer, 1987). In addition, chemical exchange saturation transfer (CEST), redox transfer agents, neurotransmitter agents, and temperature responsive agents are found to be potential avenues for creating highly contrasted MRI images without adverse toxic effects (Klohs & Rudin, 2011; Wahsner et al., 2019). Nonetheless, GBCAs are currently the most effective contrast agents and provide a powerful method for clinicians to make non-invasive diagnoses.

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