

Basic Physics of MR Contrast Agents and Maximization of Image Contrast¹

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This review summarizes the physical basis of magnetic resonance (MR) imaging contrast agents, including both T1 agents, such as gadolinium-DTPA (diethylenetriaminepentaacetic acid), and T2 or T2* agents, such as superparamagnetic iron oxides. The maximization of image contrast and lesion visibility with contrast agents is described, and the use of contrast agents in MR angiography and perfusion imaging is discussed.

Index terms: Contrast enhancement • Contrast media • Gadolinium • Iron

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Abbreviations: CNR = contrast-to-noise ratio, DTPA = diethylenetriaminepentaacetic acid, FLASH = fast low-angle shot, 3D = three-dimensional.

MAGNETIC RESONANCE (MR) images are based on the signal from hydrogen nuclei contained in hydrogen-rich compounds in the body: water and lipids. Image contrast is based primarily on inherent properties of different tissues. These inherent tissue properties are hydrogen content (or hydrogen spin density) and hydrogen nuclei relaxation times (T1, T2, and T2*). MR contrast agents alter image contrast by selectively altering the hydrogen relaxation times of tissues containing the contrast agent.

In conventional radiography and computed tomography, contrast agents provide a direct effect. For example, the presence of iodine or barium contrast agents produces greater attenuation of the x-ray beam in agent-containing tissues. In MR imaging, the effect of contrast agents is indirect. No signal is derived from the contrast agents themselves; signal is still derived from hydrogen nuclei. Contrast agents work indirectly by altering the relaxation times of hydrogen nuclei that come in close proximity to the contrast agent.

In x-ray imaging, the most effective contrast agents are those that produce the greatest attenuation of x rays: materials with high atomic numbers (Z) and with photoelectric k-edge absorption peaks that match the energy of the x-ray beam. In MR imaging, the most effective contrast agents are those that produce the greatest alteration of hydrogen relaxation times. This in turn requires (a) that the MR imaging contrast agent be capable of readily exchanging with hydrogen nuclei through magnetic interactions and (b) that the contrast agent come in close physical proximity to water molecules. This second requirement is most readily achieved with MR imaging contrast agents that reversibly bind water molecules into their inner "coordination sphere," so that there is constant, rapid exchange of water molecules between binding sites near the agent and bulk water (1).

The driving force behind the use of contrast agents in MR imaging is to better delineate regions otherwise invisible to the imaging technique. This often occurs when a lesion is too small and is lost because of partial-volume averaging with other tissues or if its tissue properties are too similar to those of surrounding tis-

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Table 1
Properties of Some Transition and Lanthanide Metals

Element	Valence Shell Configuration	Unpaired Electrons	Net Magnetic Moment*	Electron Spin Relaxation Time (sec)
Transition metals				
Cr ³⁺	3d ³	3	3.8	10 ⁻⁹ –10 ⁻¹⁰
Cr ²⁺	3d ⁴	4	4.9	10 ⁻¹¹ –10 ⁻¹²
Mn ³⁺	3d ⁴	4	4.9	10 ⁻¹⁰ –10 ⁻¹¹
Fe ³⁺	3d ⁵	5	5.9	10 ⁻⁹ –10 ⁻¹⁰
Mn ²⁺	3d ⁵	5	5.9	10 ⁻⁸ –10 ⁻⁹
Fe ²⁺	3d ⁶	4	5.1	10 ⁻¹⁰ –10 ⁻¹¹
Co ²⁺	3d ⁷	3	4.1	10 ⁻⁹ –10 ⁻¹⁰
Lanthanide metals				
Gd ³⁺	4f ⁷	7	7.6	10 ⁻⁸ –10 ⁻⁹
Eu ²⁺	4f ⁷	7	7.6	10 ⁻¹² –10 ⁻¹³
Tb ³⁺	4f ⁸	6	9.5	10 ⁻¹²
Dy ³⁺	4f ⁹	5	10.6	10 ⁻¹² –10 ⁻¹³
Ho ³⁺	4f ¹⁰	4	10.4	10 ⁻¹² –10 ⁻¹³

* Net magnitude of the magnetic moment is given in units of magnetons; 1 magneton is the magnetic dipole moment of a single free electron.

sue. This review will address the effects of contrast agents and the consequences for lesion visibility in spin-echo and gradient-echo techniques.

• MAGNETIC PROPERTIES OF RELAXATION AGENTS

The first requirement cited above for an effective MR imaging contrast agent is to be able to interact magnetically with hydrogen nuclei. Because single, unpaired electrons have magnetic dipole moments that are 657 times stronger than the magnetic dipole moments of single, unpaired protons, the magnetic effects of unpaired electrons dominate the magnetic effects of the atom. Since magnetic relaxation properties (of hydrogen nuclei) vary as the square of the magnetic dipole moment (of the atom or molecule used as a contrast agent), it is the number of unpaired electrons in the outer electron shell of an atom that overwhelmingly determines its effect as a relaxation contrast agent.

Atoms with unpaired outer-shell electrons are either paramagnetic or ferromagnetic substances. Paramagnetic substances are those that manifest magnetic properties only when placed in an external magnetic field. When the external field is removed, the coherent effect of paramagnetic atoms is lost because of the return to random orientation of atomic dipoles.

Ferromagnetic substances remain magnetically polarized after an externally applied magnetic field has been removed, owing to a crystalline structure and nonmagnetic forces that promote the coherent alignment of atomic magnetic dipole moments. Only a few elements (iron, cobalt, and nickel) have ferromagnetic properties.

Superparamagnetic materials have a combination of paramagnetic and ferromagnetic properties. Because of crystalline structure, when an external magnetic field is applied, superparamagnetic materials set up magnetic domains among paramagnetic ions, similar to those of ferromagnetic materials. As a result, superparamagnetic materials can have net magnetic dipole moments far in excess of those of paramagnetic materials. However, unlike ferromagnetic mate-

rials, when the external magnetic field is removed, superparamagnetic materials return to zero magnetization because of the rotational freedom of particles making up the crystal. This rotational freedom allows the individual paramagnetic constituents to dephase by rotational motion once the externally applied magnetic field is removed. Some aggregates of iron, such as magnetite (Fe₃O₄), are superparamagnetic rather than ferromagnetic.

The chemical properties of atoms and ions (atoms with one or more electrons removed) are determined by the number of electrons in the outermost (valence) shell. Similarly, the magnetic properties of atoms or ions are determined by the number of unpaired electrons in the valence shell. Atoms with low atomic number have only a few unpaired electrons in their valence shells and hence have weaker magnetic effects. However, the transition series metals (where the 3d shell is the valence shell, holding as many as 10 electrons) and the lanthanide series metals (where the 4f shell is the valence shell, holding as many as 14 electrons) are characterized by having their lowest, preferred energy states with more than one unpaired valence electron. For example, ferric iron (Fe³⁺) is a transition metal that has five unpaired electrons in its valence shell. Gadolinium (Gd³⁺) is a lanthanide metal with seven unpaired electrons in its 4f valence shell. The metal ions from the transition series and lanthanide series have the highest numbers of unpaired electrons and, as a result, the highest atomic magnetic moments of all atoms or ions (Table 1) (2).

In addition to having larger numbers of unpaired electrons, successful relaxation agents must retain their electron spins collectively along the direction of the applied magnetic field for a sufficient duration. The duration of their collective relaxation effect is described by the electron spin relaxation time, listed for each metal in Table 1. Elements with the highest numbers of unpaired electrons and the longest electron spin relaxation times will have the strongest magnetic relaxation effects on hydrogen. Thus, Fe³⁺, Mn²⁺, and Gd³⁺ are the most likely candidates for MR imaging contrast agents. In elemental form, however,